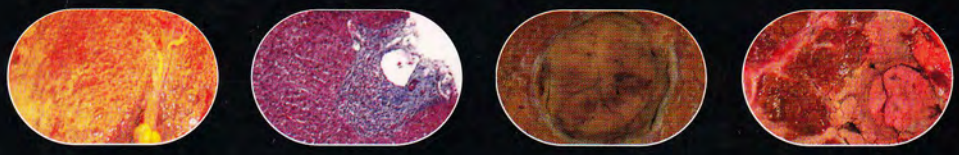

Clinical Dilemmas in Viral Liver Disease

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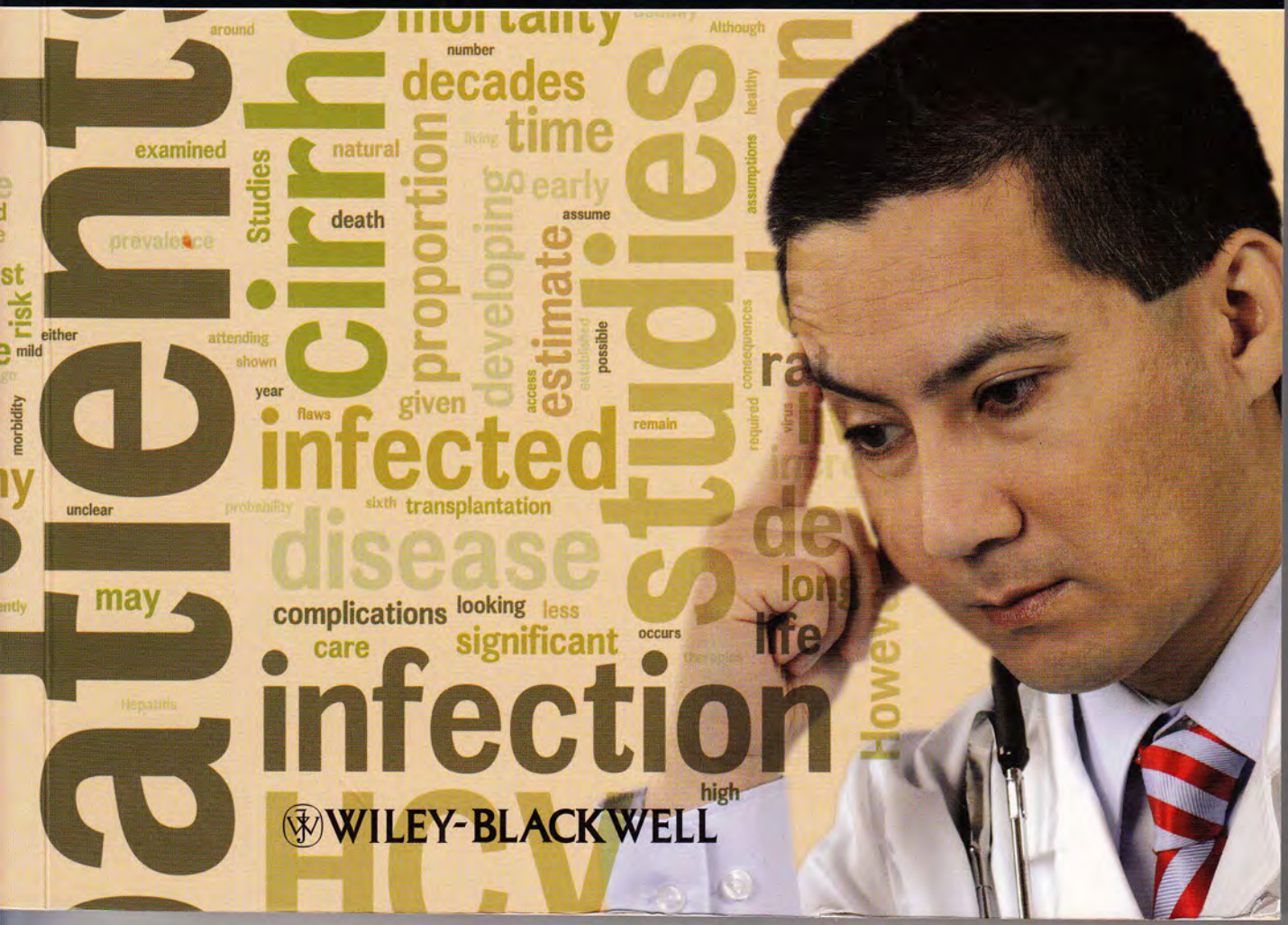

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Preface

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Viral hepatitis is a global problem of enormous magnitude and the consequences of chronic liver disease due to hepatitis B virus (HBV) and hepatitis C virus (HCV) have significant economic implications. Globally, approximately 170 million people are estimated to be infected with HCV and another 350–400 million with HBV. Chronic hepatitis and cirrhosis evolve to a varying degree and the propensity to devolop cirrhosis and its consequences is variable and depends on several factors. Suffice to say that with HBV infection, approximately 15–40% develop cirrhosis, liver failure or hepatocellular carcinoma, whereas HCV infection generally requires two to three decades to evolve into cirrhosis and its consequences, albeit in 20–30% of patients over this time period. The leading predisposing cause for hepatocellular carcinoma in the Western world is HCV cirrhosis, with an annual incidence of approximately 1–1.5%, while HBV regardless of the presence of cirrhosis is the leading cause in areas where this infection is endemic.

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Although hepatitis, perhaps manifesting as jaundice, has been recognized for over 2000 years, dating back to several centuries BC, the advances made over the past few decades have been fundamental to the proper classification of viral hepatitis. Ingenious molecular biology techniques have led to the identification of HCV. Diagnostic assays, including viral molecular assays, are reliable in the diagnosis of these hepatitis virus infections and, further, help in monitoring therapeutic response. Screening, diagnosis and therapeutic algorithms and recommendations have been made by experts from various parts of the world but these are inevitably based on the highly selected populations that participate in seminal clinical studies. Many patients present with complications or characteristics that have not been adequately researched and evidence-based medicine cannot be applied. In these controversial areas there is considerable debate about the most appropriate management. This book, *Clinical Dilemmas in Viral Liver Diseases*, has been compiled to address these controversial understudied questions that arise in our day-to-day practice while dealing with patients with viral hepatitis. This is not intended to be an exhaustive review of a specific topic but to be a focused approach, supported by literature and expert opinion, looking at the controversial questions and topics where there is divergence of opinion. We have assembled a number of globally recognized investigators and clinicians to address these issues in viral hepatitis B and C. Readers will find the issues tackled to be unique and not readily accessed in standard textbooks. The style is simple and has key learning points. This book was assembled in a few months, making the material up to date in this rapidly moving area that frequently has new developments. We believe the reader will have a rewarding experience while going through the various sections.

Graham R. Foster, FRCP, PhD

K. Rajender Reddy, MD, FACP, FACG, FRCP

2 Liver biopsy in hepatitis C patients with easy-to-treat characteristics: should we bother or just do biomarkers?

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LEARNING POINTS

- The utility of routine liver biopsy in chronic HCV is debated.
- Biomarkers are excellent alternatives to liver biopsy in HCV patients with easy-to-treat characteristics.
- HCV patients with easy-to-treat characteristics are defined as those with genotype 2 or 3 or with three or more of the following characteristics: Caucasian or Asian race, pretreatment viral load < 250 000 IU/mL, fibrosis stage 0–3, BMI < 30, no insulin resistance, age < 40 years, and female.
- The two indications for liver biopsy in chronic HCV patients with easy-to-treat characteristics are (i) determination of the stage of fibrosis in cases where the treatment course is undecided and biomarker values are indeterminate and (ii) determination of the presence of concomitant diseases and the degree to which these conditions contribute to the liver disease.

Liver biopsy and hepatitis C: role, indications and limitations

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the USA, with approximately 3.2 million persons chronically infected [1]. Of chronically infected persons, 60–70% develop chronic liver disease. While most patients undergo liver biopsy prior to treatment of chronic HCV infection, the utility of routine biopsy continues to be debated. A survey conducted in 2004 asked 61 expert hepatologists whether they would recommend a liver biopsy in 12 clinical scenarios of chronic HCV [2]. The survey found great divergence of management opinion, with most of the experts recommending liver biopsy in four to eight of the 12 clinical scenarios.

Liver histology is useful for determining the stage and prediction prognosis of the disease. Patients with cirrhosis, for example, should undergo screening for hepatocellular carcinoma according to the American Association for the Study of Liver Diseases (AASLD) guidelines and upper endoscopy every 2 years to evaluate for varices. When considering a difficult treatment with toxic side effects, the stage of disease and the chance of success of treatment are both very important factors to consider. Advanced fibrosis and a high chance of success both provide impetus to treat, whereas minimal fibrosis and a low chance of success tip the decision scales the other way.

Once treatment has started, the threshold for discontinuing therapy may be relatively high in patients who have advanced histological features. In addition to staging, a liver biopsy is also useful in establishing the presence of concomitant diseases, such as iron overload or fatty liver disease, and the degree to which these conditions contribute to the liver disease.

The limitations of liver biopsy include cost, its invasive nature with the accompanying risk of complications, and sampling error. Minor biopsy complications such as pain occur in up to 30% of patients, with more severe complications like bleeding or perforated viscus occurring in 0.3% and mortality rates approaching 0.01% [3]. The third and perhaps most important limitation of liver biopsy is its significant sampling error. Bedossa *et al.* [4] examined the sampling variability of liver biopsy in chronic HCV. Image analysis of liver biopsies showed a coefficient of variation

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of 55% for 15-mm biopsies and 45% for 25-mm biopsies. Using the Metavir scoring system, the variation improved to 35% and 25% for the respective biopsy sizes. Poynard *et al.* [5] found that only 13.8% of 537 liver biopsies performed at an experienced medical centre were greater than 25 mm. In addition to the issues with biopsy size, there is also variablity in sampling that can lead to incorrect staging of disease. A study compared percutaneous biopsy with laparoscopic biopsy and demonstrated that cirrhosis was missed in almost 30% of cases by percutaneous biopsy [6]. The potential for error in staging disease can be as high as 35% and even cirrhosis can be missed in 30% of patients. These findings reflect the heterogeneity of liver disease in HCV, the small sampling size of biopsy (1 in 25 000 to 1 in 50 000 of the liver) and interobserver variability in interpreting biopsy results. Because of the many limitations of liver biopsy, there has been ongoing research to seek better alternatives.

Biomarkers in hepatitis C

Commercially available serological biomarkers in the USA include FibroSure, FibroSpect and Hepascore. These biomarkers and others are available to varying degrees in other parts of the world as well. They consist of combinations of several blood and clinical parameters that are optimized to reflect the stage of liver fibrosis. While all these tests have demonstrated acceptable accuracy in differentiating early from advanced disease [7–9], they lack sensitivity for quantifying the amount of fibrosis and monitoring fibrosis progression and regression. For this reason, biomarkers are excellent alternatives to liver biopsy for patients in whom we need to determine whether or not cirrhosis is present. Therefore, they are valid approaches for assessing for significant fibrosis or cirrhosis in the following HCV patient groups: (i) patients who will always be treated (e.g. those with easy-to-treat characteristics), (ii) those with obvious cirrhosis, and (iii) those with absolute contraindications to treatment. The role of these biomarkers is more limited for patients in whom more detailed information on exact stage of fibrosis is necessary for management of disease. Besides the commercially available serological markers mentioned above, a large number of other serological markers and elastography have been evaluated for the assessment of liver fibrosis. The strengths and limitations of these noninvasive markers are all similar in that they are excellent for evaluating the presence or absence of significant fibrosis, but lack sensitivity for quantifying the amount of fibrosis [10].

Patients with easy-to-treat characteristics in hepatitis C

What are easy-to-treat characteristics?

For each patient it is important to weigh the chance of a sustained virological response (i.e. cure) and the risk of disease progression against the risks of treatment. The major predictors of a sustained virological response (SVR) are HCV genotype, race or ethnic group, viral load, and degree of liver fibrosis. Multivariate analyses have identified two major predictors of SVR among all populations studied: the viral genotype and pretreatment viral load [11–13]. SVR rates were higher in patients infected with genotype non-1 (mostly genotype 2 and 3) and in those with a viral load of less than 250 000 IU/mL [13]. In the VIRAHEP-C (Viral Resistance to Antiviral Therapy of Chronic Hepatitis C) study of patients infected with HCV genotype 1, sponsored by the National Institutes of Health, black race was associated with lower rates of SVR (28%) compared with Caucasian race (52%) [14]. Other less consistently reported baseline characteristics associated with a favourable response include female gender, age less than 40 years, lower body weight (< 75 kg), the absence of insulin resistance, and the absence of bridging fibrosis or cirrhosis on liver biopsy (Table 2.1) [11,12,15].

Recommended management approach (Figure 2.1)

For the purposes of management, we define HCV patients with easy-to-treat characteristics as those with genotype 2 or 3 or with three or more of the following characteristics: Caucasian or Asian race, pretreatment viral load less than 250 000 IU/mL, fibrosis stage 0–3, body mass index (BMI) less than 30, no insulin resistance, age under 40 years, and female. In patients meeting these criteria, we recommend biomarkers to assess for advanced fibrosis prior to initiating treatment.

TABLE 2.1 Characteristics that predict response to treatment.

Characteristics	Easy to treat	Hard to treat
Genotype	2 or 3	1 or 4
Race/ethnicity	Caucasian, Asian	Black, Hispanic
Pretreatment viral load	< 250 000 IU/mL	≥ 250 000 IU/mL
Fibrosis stage	0–3	4
BMI	< 30	≥ 30
Insulin resistance	Absent	Present
Age (years)	< 40	≥ 40
Gender	Female	Male

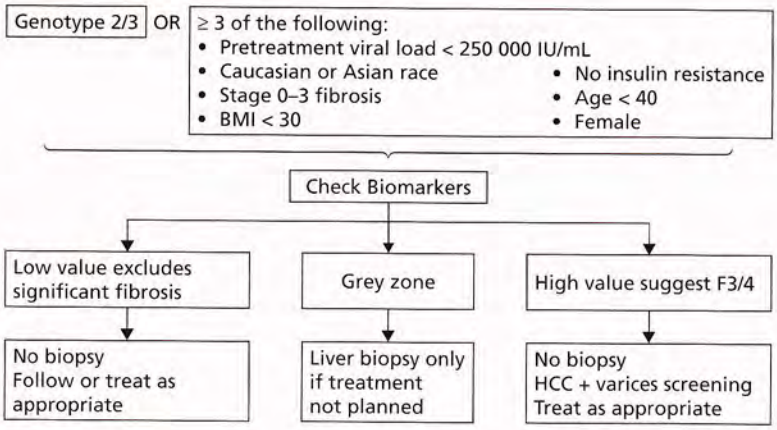

FIG. 2.1 Algorithm for HCV patients with easy-to-treat characteristics. HCC, hepatocellular carcinoma.

If the biomarkers indicate advanced disease, regular screening for hepatocellular carcinoma and varices should be initiated.

There are two indications for liver biopsy in this subgroup of HCV patients. One is to determine the stage of fibrosis in cases where the treatment course is undecided and biomarker values are indeterminate. Another indication is to establish the presence of concomitant diseases (such as haemochromatosis, alcoholic hepatitis and hepatic sarcoidosis) and the degree to which these conditions contribute to the liver disease.

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4 Genomic investigations in viral hepatitis: likely to help or hinder?

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LEARNING POINTS

- Host genetic background plays an important role in determining the outcome of viral hepatitis infections.
- A number of genetic associations have been reported but only a few are reproducible.
- Identification of disease susceptibility genes tells us a lot about the biology of these infections but has not yet been translated into clinical practice.

Introduction

Infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV) may result in a number of different outcomes, ranging from asymptomatic self-limited (*acute*) infection to persistent (*chronic*) infection with liver cirrhosis, liver failure or hepatocellular carcinoma (HCC). While it has been shown that viral factors such as genotype, sub-genotype, viral variation and viral load have an important influence on the outcome of HBV and HCV infection, it is also evident that host genetic background plays a major role in determining many aspects of viral liver disease including early viral clearance, disease progression, vaccine efficacy and response to interferon. None of the genetic associations reported to date are simple Mendelian traits and they should be considered as complex traits where viral (or vaccine), environmental and host genetic variables contribute to the outcome. Furthermore, unlike simple Mendelian traits, many polymorphic genes will exert effects on the outcome, rather than one major gene. Thus we may expect the influence of any particular gene to be small and, if odds ratios are used as the measure of increased susceptibility conferred by possession of an allele, then values in the range of 1.2–2 would be expected [1].

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Genetic mapping by linkage and association studies

Viral clearance/chronicity

HBV infection

Self-limiting infection with either HBV or HCV is associated with a vigorous polyclonal and multispecific $CD4^+$ T-helper cell responses, in contrast to the weak responses seen in persistent infection. Therefore, polymorphism in the major histocompatibility complex (MHC) class II region is a potential explanation for the variation in outcome. The alleles DRB1*1301/2 are consistently associated with resistance to persistent HBV infection in sub-Saharan African, Oriental and Caucasian populations. Other alleles such as DRB1*07 and DRB1*0301 have also been associated with persistent HBV infection. DRB1*0901, DQA1*0301, DQA1*0501 and DQB1*0301 are consistently associated with persistent HBV infection in different ethnic populations [2]. Several population studies have also revealed that some non-human leucocyte antigen loci, including interferon (IFN)-γ, tumour necrosis factor (TNF)-α, vitamin D receptor (VDR), interleukin (IL)-10, estrogen receptor α (ESR1),

MHC class II transactivator (C2TA) and T-bet (TBX21), are associated with persistent HBV infection or HBV clearance [3].

Recently, in a cohort of 200 sibling pairs with persistent HBV infection from Gambia, a genome-wide scan has been conducted for susceptibility genes. The initial scan revealed linkage of markers on chromosome 21. Fine-mapping with additional markers revealed a maximum linkage located within a cluster of cytokine receptor genes. Family association studies using pedigree disequilibrium analysis revealed an IL-10 receptor B (IL10-RB) haplotype that includes the minor allele at both the IL-10RB-K47E and IFN-α receptor 2 (IFNAR2)-F8S loci, which conferred resistance to persistent HBV infection [4].

HCV infection

Several consistent associations have been observed between MHC alleles and HCV outcomes. Perhaps the most interesting and consistent finding has been the association of the human leucocyte antigen (HLA) class II allele DQB1*0301 and self-limiting HCV. In a meta-analysis of the effects of DQB1*0301 and DRB1*11 employing molecularly genotyped studies conducted among Caucasians, DQB1*0301 had a relatively strong correlation with self-limiting HCV infection [summary estimates of 3.0 (95% CI 1.8–4.8) and 2.5 (95% CI 1.7–3.7) for DQB1*0301 and DRB1*11, respectively]. Other non-HLA loci, such as IL-10, TNF-α and IFN-stimulated genes (*MxA*, *PKR* and *OAS1*), are also reported to associate with HCV clearance or persistence [2].

Disease progression

The outcome of chronic HBV infection is variable, with 80% of cases reaching a stable and relatively safe disease state with low viral loads, normal liver biochemistry and no histological evidence of necroinflammatory disease. In contrast, 20% of cases will progress to cirrhosis and HCC [5]. In chronic HCV infection the rate of disease progression varies such that probably the majority of patients will die with, rather than from, their infection [6]. The rate of disease progression varies substantially between individuals; while it is influenced by a number of demographic and environmental factors, these account for only a small proportion of the variability. Numerous case–control, candidate gene, allele-association studies have examined the relationship between host single-nucleotide polymorphisms (SNPs) or other genetic mutations and disease progression in patients with HBV or HCV infection.

HBV infection

In East Asian populations, it is consistently demonstrated that IL-10 gene promoter polymorphisms influence disease progression (acute liver failure, liver cirrhosis and HCC), mode and sequelae of HBeAg seroconversion in patients with chronic HBV infection [7]. Recently, Chong *et al.* [8] demonstrated that low-expression promoter haplotypes of *MBL* were associated with the occurrence of cirrhosis and HCC in patients with HBsAg persistence and disease progression. Deng *et al.* [9] identified a regulatory SNP, G201A, in the promoter region of *CXCL10* that was associated with susceptibility to disease progression of chronic HBV infection, while Zhai *et al.* [10] reported that estrogen receptor α gene haplotypes were associated with HBV-related HCC.

Numerous studies have demonstrated strong familial clustering of cirrhosis and liver cancer. Formal segregation analysis of HCC, performed by several groups, consistently demonstrate a sibling risk of 3.9 or higher. However, the predicted mode of inheritance varies between datasets, with some studies finding evidence of a major gene with a recessive effect and others predicting an autosomal dominant gene with incomplete penetrance [11].

HCV infection

Studies of the MHC and the progression or severity of HCV have largely been inconsistent. However, there is a trend towards an association with DRB1*11 alleles and 'less severe' liver disease. Hellier *et al.* found a protective role for CCR5-Δ32 carriage against severe fibrosis and CCR5-Δ32 homozygotes had milder portal inflammation, while Knapp *et al.* observed an association between the low-IL-10-producing genotype and haplotype with fast fibrosis progression. TNF variants have also been studied with respect to the progression of HCV-related liver disease, and the results have been inconsistent. Wright *et al.* [6] found that median fibrosis rates were higher among patients who were heterozygotes for the factor V Leiden variant, while Promrat *et al.* [12] examined six chemokine system polymorphisms and demonstrated that HCV-seropositive Caucasians with the RANTES-403A allele were less likely to have severe hepatic inflammation compared with those without. Recently, it has been reported that IFN regulatory factor 7 (*IRF-7*) polymorphisms are associated with increased risk of cirrhosis in Japanese patients with chronic hepatitis C [13].

Huang *et al.* [14] tried to identify clinically significant SNPs in 433 patients with chronic HCV infection through a

low-resolution genome-wide scan (consisting of 24 823 SNPs, 68.3% coding functional SNPs, 24.9% non-coding putative regulatory SNPs, and 6.8% other types of SNPs) covering 12 248 genes and tried to validate their findings in a separate cohort of 483 patients. A missense SNP in the DEAD box polypeptide 5 gene causing an amino acid replacement at position 480 (S480A) in exon XIII was associated with an increased risk of advanced fibrosis, while a missense SNP in the carnitine palmitoyltransferase 1A gene caused an amino acid change with a decreased risk for advanced fibrosis. Seven SNPs (one in the antizyme-inhibitor-1 gene, one in the Toll-like receptor-4 gene, and five in five other genes of unclear function) with the highest predictability for cirrhosis (odds ratio 1.86–3.23) were used to build a cirrhosis risk score (CRS) signature. CRS offered a better prediction of cirrhosis compared with clinical factors (age, gender and alcohol abuse): area under the receiver operating characteristic curves 0.73–0.75 for CRS, 0.53 for clinical factors and 0.76 for CRS and clinical factors together. Two cut-off CRS values (range 0–1) were eventually suggested as potentially identifying the majority of low-risk (< 0.50) and high-risk (> 0.70) patients for development of cirrhosis.

Response to interferon therapy

HBV infection

Currently, predictive factors for responsiveness to IFN-α-based treatment include viral genotypes, baseline alanine aminotransferase level, serum HBV DNA, female gender, fibrosis on liver biopsy and pre-existing T-cell immune responses. King *et al.* [15] examined genes in the IFN pathway involved in antiviral and signalling activities and demonstrated that SNPs of *eIF-2α* and *MxA* affected IFN response in patients from Taiwan. Chen *et al.* [16] developed a new approach for identifying whole-genome short tandem repeat (STR) markers that allowed the prediction of IFN response in HBV-infected patients. The study subjects could be divided into six groups based on 11 STR markers, which correlated with IFN response rate.

HCV infection

Studies of the MHC and responsiveness to anti-HCV therapy have yielded conflicting results. Conflicting observations have also been observed with respect to CCR5-Δ32 variant and HCV therapy. Several studies have demonstrated a lack of association between TNF variants and the response to anti-HCV therapy. Hijikata *et al.* observed the presence of *MxA* –88G/G homozygotes to be lower in sustained type I IFN responders (31%) than in non-responders (62%). These effects appeared to be independent of HCV genotype. Knapp *et al.* reported that the *MxA* gene –88G/G genotype was also correlated with non-response to IFN. A similar association was found in an independent Japanese population. The –88MxA SNP lies in a region that is highly homologous to the IFN-stimulated response element consensus sequence, with T substitution increasing the homology [2]. Persico *et al.* reported that SNPs of SOCS3 (suppressor of cytokine signaling 3) were positively and negatively associated with response to antiviral therapy in HCV genotype 1-infected patients. The concept of SOCS3 being involved in modulating antiviral response mechanisms is appealing, because it acts as a negative regulator of the cytokine-induced JAK/STAT pathway. Asselah *et al.* reported that the expression of three genes (*IFI-6-16*, *IFI27* and *ISG15*) coding for IFN-inducible proteins are upregulated in non-responders to anti-HCV therapy. They further showed that a two-gene signature including one of these three genes (*IFI27*) predicts treatment outcome reasonably well [17]. Wada *et al.* [18] demonstrated that genetic polymorphisms in IFN signalling pathway-related genes were associated with IFN-induced neutropenia (10848A→G and 4757G→T) and thrombocytopenia (789G→A) in chronic HCV-infected patients.

Chen *et al.* [19] conducted genome-wide linkage disequilibrium screening for loci associated with genetic differences between responder and non-responder HCV patients by using 382 autosomal STR markers. They identified 19 STR markers displaying different allele frequencies between the two patient groups. In addition, based on their genomic location and biological function, the authors selected the CD81 and IL-15 genes to perform SNP genotyping. Four SNPs of the CD81 gene region and three SNPs in the IL-15 gene region showed significant association, with *P*-values ranging from 0.0135 to 0.0013 and from 0.0168 to 0.0034, respectively.

Recently, three independent genome-wide association studies (GWAS) identified *rs12979860* (located ~3 kb upstream of *IL28B*) [25] and *rs8099917* (located ~8 kb upstream of *IL28B*) [26,27] in the *IL28B* region as the variant most strongly associated with sustained virological response to pegylated interferon-alpha/ribavirin treatment among HCV-infected individuals of European, African and Asian ancestry. The specific causal variant(s) accounting for this effect remains to be determined, however, this seems a biologically plausible candidate for a role in HCV infection. *IL28B* encodes a protein also known as interferon-λ3,

which is found adjacent to *IL28A* (interferon-λ2) and *IL29* (interferon-λ1) [28]. The significantly different responses to interferon-alpha/ribavirin therapy between European, African and Asian patients with HCV now seems in partly due to population differences in the frequency of the advantageous *IL28B* genotype. This exciting discovery raises the possibility of personalized therapy for HCV, and encourages a combination treatment regimen including both interferon-alpha and interferon-λ.

Vaccine efficacy

The alleles DRB1*0701 and DRBI*0301 have been associated with failure to respond to HBsAg-based vaccine, although this finding needs to be replicated in other populations [2]. Hennig *et al.* [20] analysed 715 SNPs across 133 candidate genes in 662 infant vaccinees from the Gambia, assessing peak vaccine-induced anti-HBs level and core antibody (anti-HBc) status. A replication study comprised 43 SNPs in a further 393 individuals assessing genetic determinants of HBV vaccine-induced immunity. A coding change in *ITGAL*, which plays a central role in immune cell interaction, was shown to exert beneficial effects on induction of peak antibody level in response to HBV vaccination. Variation in this gene does not appear to have been studied in relation to immune responses to viral or vaccine challenges previously. The findings suggest that genetic variation in loci other than the HLA region affect immunity induced by HBV vaccination.

Hohler *et al.* [21] aimed to assess the heritability of the HBsAg (anti-HBs) and anti-hepatitis A virus (anti-HAV) immune response and to estimate the effect of the HLA-DRB1 locus and other genetic loci unlinked to HLA. They did an open prospective study and vaccinated 202 twin pairs with a combined recombinant HBsAg/inactivated HAV vaccine. Anti-HBs and anti-HAV showed heritabilities of 0.61 and 0.36, respectively. For the anti-HBs immune response, 60% of the phenotypic variance was explained by additive genetic and 40% by non-shared environmental effects. The heritability of the HBsAg vaccine response accounted for by the DRB1* locus was estimated to be 0.25, leaving the remaining heritability of 0.36 to other gene loci. Their results demonstrate that genetic factors have a strong effect on the immune response to HBsAg. Although genes encoded within the MHC are important for this immune response, more than half the heritability is determined outside this complex. Hohler *et al.* [22] further investigated the influence of IL-10 promoter polymorphisms on anti-HBs and anti-HAV responsiveness. In the multiple regression analysis accounting for smoking, gender, body mass index and age, the ACC haplotype (−1082, −819 and −592) had a strong influence on anti-HBs production. Individuals carrying the ACC haplotype had anti-HBs titres almost twice as high as individuals without this haplotype. In contrast, anti-HAV production was suppressed by the presence of the −1082A allele in comparison with individuals homozygous for the −1082G allele. The contribution of the shared IL-10 promoter haplotype accounted for 27% of the genetic influence on anti-HBs antibody response.

Dilemmas and lessons

Genetic association studies are fuelled in almost every disease by the unlimited availability of SNPs, the relative ease and low price of performing genotyping assays based on polymerase chain reaction technology, and the desire to identify major disease susceptibility genes. However, genetic association studies generate enthusiasm, suspicion and even confusion among readers and reviewers. Many results have generally been unrepeatable and disappointing because of small sample size, poor study design, and diverse viral or environmental confounding factors [23]. For viral hepatitis there are a number of confounding factors that need to be taken into account when assessing genetic mapping studies.

Diversity of viral genotypes and sub-genotypes

One major problem in genetic association studies in viral hepatitis is that different genotypes and subtypes of HBV and HCV are prevalent in different ethnic populations, and parallel evolution of virus–host interactions occurs in geographically distinct areas [24]. It is not feasible to replicate genetic association results in different major ethnic groups for the same genotype or sub-genotype of hepatitis viruses because there are only one or two genotypes prevalent in most geographical regions. On the other hand, we have to collect at least twice the number of samples to maintain statistical power, if there are two or more viral genotypes in the same ethnic population.

Effect sizes for common variants are typically modest

Studies so far indicate that for the vast majority of common variants, the estimated effects are small, mostly increases in risk by a factor of 1.2–1.5 per associated allele. Furthermore, the frequency of a genetic variant is not related to the magnitude of its effect nor to the potential clinical value that may be obtained [25].

Confounding factors are heterogeneous

The age at infection and the age of disease onset are important determinants for outcome, but are difficult to identify and match. Outcome is also significantly different between male and female viral carriers. Host DNA is stable throughout life and easy to measure. However, the viral sequence varies and evolves with age and with clinical stages of disease (e.g. HBeAg/eAb seroconversion and precore/core mutation in HBV).

Links between genetic association and disease biology

Although genetic association studies show that a particular gene might be important in the pathogenesis of viral hepatitis, many of them are unable to reveal anything about the links between these associations and disease mechanisms. Gene products are subject to several levels of regulation from transcription to elaboration of final protein, which might suppress, attenuate or amplify the functional consequences of a given polymorphism [17].

Translation into clinical practice

Many genetic associations are difficult to translate into clinical and therapeutic benefit, such as association with MHC class II alleles. At present, only few results are expected to be applied in clinical practice, such as the seven-gene-signature CRS established by Celera Diagnostics, and a clinical trial of warfarin anticoagulation in patients transplanted for HCV-related diseases (arising from the genetic association study which demonstrated that the thrombophilic factor V Leiden mutation conferred susceptibility to rapid fibrosis).

Prospects for the future

The outcome and course of HBV/HCV infection are determined by a complex interplay of genetic, immunological, virological and environmental factors. The successful determination of genetic signatures for outcomes of HBV/HCV infection will require multicentre collaborations using genome-wide association studies with large, phenotypically well-defined sample sets. Although these studies will require a significant financial commitment, a successful understanding of the genetic architecture is essential not only to gain better and new insight into the mechanisms of viral hepatitis, but also to offer the potential for personalized therapy and better patient management. Additionally, genetic mapping for previously unidentified phenotypes, such as HBV/HCV-exposed uninfected individuals, HAV and hepatitis E, may open new windows onto the mechanisms of viral hepatitis. Finally, translation of genetic risks into biological mechanisms is here with us today, but translation into clinical practice for patients with HBV/HCV infection remains an aspirational goal rather than a reality.

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5 Affective and cognitive disorders in hepatitis C infection: are they real and what are the mechanisms?

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LEARNING POINTS

- Chronic HCV infection is associated with significant impairment in quality of life.
- Cognitive dysfunction and aberrant neuroimaging using a variety of different techniques have confirmed that patients with chronic HCV have altered higher cerebral function.
- The mechanisms underlying this impairment remain unclear, although intracerebral infection and/or virus-induced cytokine release remain the most attractive models.

Introduction

Most textbooks state that chronic hepatitis C virus (HCV) infection is an asymptomatic disease. However, both general *physical complaints*, such as fatigue and musculoskeletal and right upper abdominal discomfort, and *neuropsychological complaints*, including depression, mental clouding ('brain fog') and a perceived inability to function effectively, are common and have led to a number of published reports documenting the prevalence of such symptoms and their impact on quality-of-life scales in cohorts of patients with HCV infection. Hepatic encephalopathy is the most obvious neurological consequence of chronic HCV infection in the context of advanced liver disease. Vasculitic neurological complications of HCV-associated mixed cryoglobulinaemia are uncommon and present as a peripheral sensory or motor neuropathy, although there are sporadic case reports of cryoglobulin-related central nervous system (CNS) vasculitis. The possibility of HCV infection *itself* leading to cerebral dysfunction in the absence of a vasculitic process or advanced liver disease has been the subject of intense debate.

The presence of neuropsychological symptoms in the context of HCV infection does not imply causality, since there are many associated factors that may independently affect patients' perceptions of well-being, such as anxiety regarding diagnosis, prognosis and treatment, previous or ongoing substance abuse and associated emotional problems or personality traits [1]. In addition to epidemiological evidence linking HCV infection with neuropsychological impairment, there is emerging evidence from imaging, neurophysiological, neuropsychological and virological studies demonstrating a biological effect of HCV on cerebral function.

Health-related quality of life, fatigue and depression

The results from several large studies challenge the perception that HCV infection is an asymptomatic disease, with general agreement that physical and mental health-related quality of life (HRQL) is significantly reduced in HCV-infected patients compared with published normative data [2]. This reduction in HRQL appears independent of the severity of the liver disease and is seen in all domains of

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HRQL, including mental health. In one study, SF-36 scores were lower in patients with HCV infection compared with both healthy controls and patients with chronic hepatitis B virus (HBV) infection. These findings, together with large studies, which have shown significant improvements in HRQL in combined cohorts of many thousands of patients after successful antiviral therapy, suggests that the viral infection itself is an important determinant of reduced HRQL [3]. However, whether a biological mechanism underlies this remains controversial. Other relevant determinants of HRQL, which have been described in the literature, include medical comorbidity, the effect of the diagnosis, depression and labelling [4]. Importantly, many studies did not blind their subjects to HCV polymerase chain reaction status and the impact of diagnosis or knowledge of antiviral response is likely to affect reported HRQL.

Fatigue is often said to be the commonest symptom in patients with chronic HCV infection, affecting up to 80% of patients referred for treatment. It is an important determinant of reduced HRQL. Although improvements in fatigue have been reported after treatment [5], it appears to persist in some individuals despite a virological response. Fatigue in chronic HCV infection is a multidimensional symptom and is influenced by multiple interrelating social, behavioural, psychological and personality factors [6]. Indeed, it has been argued that because most studies have been methodologically flawed in some way and fail to take account of all confounding factors, there is no evidence of a causal association between HCV infection *per se* and fatigue [7]. It is likely that the fatigue reported by HCV-infected patients is due to multiple coexistent causes and the relative contribution of a biological mechanism remains unclear.

Depression is a common and clinically important finding in HCV-infected patients [8]. Antiviral therapy with interferon alfa may precipitate or exacerbate depression [9] and hence this symptom may limit the tolerability of treatment and reduce compliance [10]. The relationship between HCV and depression is undoubtedly complex. The greatest reservoir of HCV infection is in intravenous drug users, many of whom have clinical depression [11]. Conversely, depression may exist as a secondary phenomenon to HCV infection. This may take the form of a reactive depression, related to the diagnosis and concerns over long-term health or may be associated with symptoms such as fatigue and cognitive impairment [12].

It has become clear that objective measures of cerebral function are needed in order to elicit more precisely the nature and extent of CNS dysfunction in HCV infection. In recent years, significant advances have been made and a number of published studies have focused on cognitive function, brain metabolism and neurophysiological parameters in HCV-infected patients. There is increasing evidence of measurable biological abnormalities, which are summarized below:

Evidence for impaired cognitive function in HCV-infected individuals

Impairments in the domains of psychomotor speed, visual perception and attention are common in otherwise asymptomatic patients with cirrhosis, constituting the syndrome of minimal hepatic encephalopathy [13]. Clinical studies of cognitive function in HCV infection therefore need to exclude or control for the effect of cirrhosis. Forton *et al.* [14] used a computer-based cognitive testing battery and reported selective impairments in attention, concentration and working memory in a cohort of patients with biopsy-proven minimal HCV hepatitis attending a tertiary treatment centre. These impairments were significantly less common in a comparable group of patients who had recovered from HCV infection. The findings were independent of depression and fatigue scores and were not related to the presence or absence of a history of substance abuse. In an expanded cohort of HCV patients with mild liver disease, the same investigators demonstrated impaired cognitive testing scores in 38% of HCV-infected individuals.

Hilsabeck *et al.* [15] found evidence of mild cognitive impairment in up to 49% of HCV-infected patients with varying stages of liver fibrosis. The same group of researchers used a similar testing battery in an independent cohort of HCV-infected individuals to test the relationship between neuropsychiatric symptoms (e.g. complaints of cognitive dysfunction) and objective neuropsychological test performance. Similar rates of impairment in complex attention, concentration and working memory were reported, but no significant differences on any of the cognitive measures were found between individuals reporting high or low levels of fatigue, depression or perceived cognitive function, raising questions about the clinical significance of the measured impairments. Weissenborn *et al.* [16] addressed this issue in a study designed to determine whether patients' subjective impression of fatigue was associated with objective evidence of cerebral dysfunction; 30 HCV-infected patients with normal liver function, 15 with mild and 15 with moderate

to severe fatigue on the fatigue impact scale, underwent a battery of well-validated neuropsychological tests, which again revealed deficits in attention and higher executive function. These deficits were more pronounced in the more severely fatigued patients.

The clinical significance of cognitive impairment in HCV was questioned by McAndrews *et al.* [17], who studied a highly selected cohort of HCV-infected patients with minimal liver disease; patients with cirrhosis, depression and substance misuse were excluded. They reported less cognitive dysfunction than in the earlier studies, detecting impaired learning efficiency in only 13% of 37 patients. Likewise, Cordoba *et al.* [18] showed no cognitive impairment in HCV-infected patients without cirrhosis and in those who had compensated cirrhosis. Cognitive impairment was only detected in those patients who had had previous episodes of hepatic decompensation (almost certainly explained by hepatic encephalopathy). Patients in this study were enrolled after a diagnosis of HCV infection had been made at blood donation, which means this cohort may have been positively selected for good health and is therefore probably not comparable to groups of patients recruited from hospital-based treatment centres.

Neuroimaging in chronic HCV infection

Neuroimaging has been employed in an attempt to provide an objective measure of cerebral function in HCV infection. Proton magnetic resonance spectroscopy (^{1}H-MRS) is an established imaging technique that has been used in the investigation of hepatic encephalopathy and CNS infections such as HIV. This technique gives information on brain metabolism. Forton *et al.* [19]. showed that HCV-infected patients with mild liver disease had significantly elevated choline to creatine ratios in the basal ganglia and frontal white matter compared to patients with chronic HBV infection and also healthy controls. These findings were unrelated to previous substance use. In a later study [20] of a similar patient cohort, the same group of researchers demonstrated elevated myoinositol/creatine ratios in the frontal white matter, which were associated with impairments in working memory.

Similarly, Weissenborn *et al.* [16] used ^{1}H-MRS to study 30 HCV-infected patients with normal liver function who also had cognitive testing. They found decreased *N*-acetylaspartate (NAA)/creatine ratios in occipital grey matter compared with healthy controls, but no abnormalities in any other brain regions or in choline-containing compounds. There were no significant associations between the MRS data and the neuropsychological or fatigue scores. McAndrews *et al.* [17] studied 37 HCV-positive patients with minimal hepatitis and found elevated cerebral levels of choline and reduced levels of NAA in the central white matter, in keeping with the previous studies by Forton and Weissenborn. There was also no statistical correlation between cognitive dysfunction and cerebral metabolite ratios in this study.

Elevated myoinositol/creatine and choline/creatine ratios have been demonstrated in HIV-related minor cognitive–motor disorder and are thought to represent CNS immune activation. In early HIV disease, elevations in white matter myoinositol/creatine are the most consistently found MRS abnormalities associated with abnormal cognitive processing. The MRS data from the studies in HCV infection suggest that cerebral immune activation may also occur in this setting and may underlie some of the mild neurocognitive impairment seen in a proportion of HCV-infected patients.

This has been studied further in a study combining cerebral positron emission tomography, using a selective ligand for microglial/brain macrophage activation, [^{11}C](*R*)-PK11195, and MRS [20]. Mean PK11195 binding potential was significantly increased in the caudate nucleus of 11 patients with histologically mild HCV infection compared with controls. This was more significant in the subgroup of six patients with genotype 1 HCV infection and correlated with viral load. Again, elevations were seen in cerebral myoinositol/creatine ratios. These data provide further *in vivo* evidence for immune activation within the CNS as a consequence of HCV infection.

Possible underlying mechanisms

The pattern of neurocognitive dysfunction in HCV patients is consistent with the involvement of subcortical brain systems. Similar impairments have been reported in the asymptomatic stages of HIV infection. The ^{1}H-MRS findings in HCV-infected subjects are similar to those that are well documented in HIV infection, where viral infection of microglia is well established. The recent demonstration of *in vivo* microglial activation in HCV infection raises the question of whether this virus, like HIV, also infects the CNS.

Although the hepatocyte is the major cell for HCV replication, there is evidence of low-level replication in extrahepatic sites. Different HCV quasi-species have been detected in liver

and peripheral blood monocuclear cells [21], supporting the concept of independent viral replication in different compartments. This methodology has been applied to the CNS and distinct viral quasi-species have been identified in post-mortem brain samples, suggesting that brain-specific variants of HCV may replicate within brain [22]. Furthermore, Radkowski *et al.* [23] detected negative-strand HCV RNA, the replicative intermediate, in post-mortem brain tissue. Most recently, negative-strand HCV RNA has been detected in microglia/macrophages derived from post-mortem brain tissue of HCV-infected patients [24]. It is therefore possible that, in certain individuals, the immune response to viral proteins within the CNS may constitute the underlying mechanism leading to cognitive dysfunction.

An alternative hypothesis is that peripherally derived cytokines may result in CNS immune activation and/or changes in neurotransmission. The therapeutic use of cytokines such as interferon alfa is associated with the induction of depressive symptoms in patients with viral hepatitis. Interferon alfa increases serum kynurenine concentrations and reduces serum serotonin and tryptophan concentrations and these changes have been shown to correlate with depression ratings. Interactions between the immune system and serotonergic neurotransmission have been demonstrated at a number of levels, both peripherally and within the CNS [25]. However, there are few data on the role of endogenous cytokines and CNS effects in chronic HCV infection.

Alterations in monoaminergic neurotransmission in patients with HCV infection have been documented using single-photon emission computed tomography: reduced serotonin and dopamine receptor binding capacity was associated with impaired performance on cognitive testing [26]. These novel findings were interpreted as implicating a role for disturbed monoaminergic neurotransmission in the pathophysiology of HCV-associated cerebral dysfunction. It is therefore conceivable that some individuals, possibly predisposed as a result of HCV neuroinvasion, may develop neuropsychological symptoms and cognitive impairment as a consequence of both central and peripheral immune activation, mediated by disturbances in serotonergic neurotransmission.

In summary, there is increasing evidence for CNS dysfunction in HCV infection which is associated with abnormal metabolism within brain structures. It is hypothesized that, as in HIV, HCV neuroinvasion may lead to the observed CNS abnormalities, even though progressive disease, as in HIV dementia, is not seen. The mechanisms which may mediate these CNS abnormalities remain unclear and need to be investigated further.

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6 Acute hepatitis: treat immediately or give a chance to spontaneously clear?

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LEARNING POINTS

- Acute HCV infection is defined as new occurrence of viraemia with conversion from HCV antibody negative to positive status.
- Symptomatic acute HCV infection occurs in only 25–30% of patients; acute HCV infection is rarely fulminant.
- Symptomatic patients have a higher chance of spontaneous viral resolution by 12–24 weeks after exposure.
- Antiviral treatment with pegylated interferon monotherapy is extremely effective in treating acute HCV infection, with sustained virological response rates over 80% when initiated within 48 weeks of infection.
- Duration of therapy is controversial; however, most authorities recommend treatment for 12–24 weeks with longer duration of treatment advised for patients with genotypes 1 and 4 or those with HCV/HIV co-infection.

Introduction

The lack of universal diagnostic criteria, the asymptomatic nature of most acute cases of hepatitis C virus (HCV) infection, and a lack of screening programmes result in the vast majority of HCV diagnoses being made when the infection is in the chronic state [1,2]. However, detection of acute HCV, often defined as HCV viraemia of shorter than 6 months' duration, affords clinicians an opportunity to intervene and prevent long-term complications of HCV infection.

The majority of HCV infection in the acute phase remains subclinical, with only 25–30% of patients presenting with symptoms [1]. An estimated 15% of all symptomatic cases of acute liver injury in the USA result from acute HCV. Acute HCV infection should be suspected in patients with (i) new-onset elevation of serum aminotransferases, (ii) documented HCV viraemia, (iii) exclusion of other causes of acute hepatitis, (iv) optimally in the setting of documented seroconversion from hepatitis C antibody (HCVAb) seronegative to seropositive status, and (v) a risk factor for exposure. However, many patients have never been previously tested for HCVAb and up to 20% do not have clearly identifiable risk factors such as parenteral drug use or high-risk sexual behaviour. Ancillary findings that may be considered for the diagnosis include the receipt of graft tissue or blood products known to be contaminated with HCV, large fluctuations of HCV RNA titres (> 1 log), and documentation of persistently normal liver-associated enzymes prior to the acute episode.

After needlestick exposures, HCV RNA can generally be detected in the serum within 1–2 weeks but clinical hepatitis does not occur until 6–8 weeks after exposure. Antibody seroconversion usually also occurs after 6–8 weeks; however, seroconversion can be delayed in immunocompromised patients. Sensitive HCV RNA polymerase chain reaction (PCR) testing should be used to confirm the diagnosis of acute HCV infection in patients with clinical suspicion who remain HCVAb-negative on initial evaluation. During the acute phase, spontaneous clearance occurs in 16–46% of patients usually by 12–16 weeks after exposure [1,2].

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While in established chronic infection interferon-based antiviral therapy only cures 46–54% of patients, therapy in the acute phase has a much greater chance of success, with greater than 80% sustained virological response (SVR) rates [3]. The timing of therapy (in light of fairly high spontaneous resolution rates) and the composition and duration of therapy (standard vs. pegylated interferon, the use of ribavirin, 24 vs. 48 weeks) remain debated.

Epidemiology

A precise estimation of the incidence of acute HCV infection is difficult to determine since most acute infections remain undiagnosed and the rates of spontaneous resolution are variable. The epidemiology of acute HCV has changed over the past decade, particularly in the western world. In the USA, the incidence of acute HCV decreased from 130 per 100 000 in the 1980s to 0.2 per 100 000 in 2005, with approximately 40 000 acute HCV cases reported per year [4]. The falling incidence of acute HCV is attributed to improvements in blood donor screening, needle exchange programmes, and education among injection drug users. As a result of these efforts, other modes of transmission such as needlestick injuries and sexual and perinatal transmission have gained relative importance.

Injection drug use accounts for about 25–54% of acute HCV cases in Europe and the USA. The risk of HCV transmission via contaminated needlestick injuries is 0.3%. Acquisition of HCV infection via perinatal transmission occurs in approximately 6.5% of infants born to HCV-infected mothers. The role of sexual transmission of HCV remains controversial. In approximately 15% of individuals diagnosed with acute HCV infection, sexual transmission is the only identifiable risk factor. This is of particular concern in HIV-positive men who have sex with men, associated with traumatic sexual practices and concomitant sexually transmitted diseases. Blood transfusions from unscreened donors and unsafe therapeutic procedures remain the major modes of transmission of HCV in the developing world [5].

Clinical presentation and diagnosis

Diagnosing acute HCV with certainty can be difficult given the high proportion of asymptomatic cases as well as the absence of a reliable IgM-based serological test. However, a series of clinical features can lead to the diagnosis of acute HCV infection, including known or likely exposure to HCV during the previous 2–12 weeks, development of symptoms (particularly jaundice) in a previously healthy individual, and an acute increase in alanine aminotransferase (ALT) levels to more than 10–20 times the upper limit of normal coupled with detectable HCV RNA by PCR-based techniques. HCV-specific antibodies are detected 6–8 weeks after infection, although seroconversion may often be delayed or absent in the immunocompromised host.

Acute HCV infection is rarely fulminant (<< 1%). Symptoms occur in about 25–30% of patients with acute HCV. Flu-like symptoms, fever, jaundice, dark urine, fatigue, nausea, vomiting, anorexia and abdominal pain are commonly reported by symptomatic patients. Symptoms when present usually develop 6–8 weeks after exposure and may last for 3–12 weeks in self-limited disease, subsiding as ALT and HCV RNA titres decline. Most patients with self-limiting infection experience HCV RNA clearance within 3 months of disease onset. Detectable HCV RNA titres beyond 6 months after infection is usually associated with chronic evolution.

Spontaneous clearance

Spontaneous clearance occurs in up to one-third of patients with acute HCV infection. Although no reliable predictors of spontaneous resolution of acute HCV have been identified, several clinical features have been associated with spontaneous viral clearance. The presence of jaundice, HCV genotype 3 infection, female gender, white ethnicity, low peak viral load and a rapid decline in viral load within the first 4 weeks of diagnosis are associated with spontaneous viral clearance. Factors associated with viral persistence include co-infection with HIV or *Schistosoma mansoni*, and infection at the time of receipt of an organ transplant [6].

Cellular immune responses seem to play a crucial role in the spontaneous resolution of acute HCV infection. Clearance of HCV is associated with the development of vigorous and multispecific $CD4^+$ and $CD8^+$ T-cell responses in the blood and the liver that can be maintained for years following recovery from acute disease. It has been suggested that viral clearance occurs more frequently in patients with acute HCV infection whose peripheral blood mononuclear cells proliferate well and display a Th1 phenotypic profile, associated with secretion of interleukin (IL)-2 and interferon-γ, compared with those who express a Th2 phenotype (associated with secretion of IL-4 or IL-10) [7].

Treatment of acute HCV infection (Figure 6.1 and Table 6.1)

There are several factors providing a rationale for treating patients with acute HCV infection, including the high rate of chronic evolution, the lack of reliable factors to predict the outcome of acute infection, and high treatment success rates.

Large randomized controlled trials in acute HCV infection do not exist to guide therapeutic decisions. Studies in this field show considerable heterogeneity in trial design, inclusion criteria, patient characteristics, duration between exposure and treatment onset, and treatment dosages and duration.

In a sentinel study by Jaeckel *et al.* [8] assessing the outcomes of 44 patients with acute HCV treated with standard

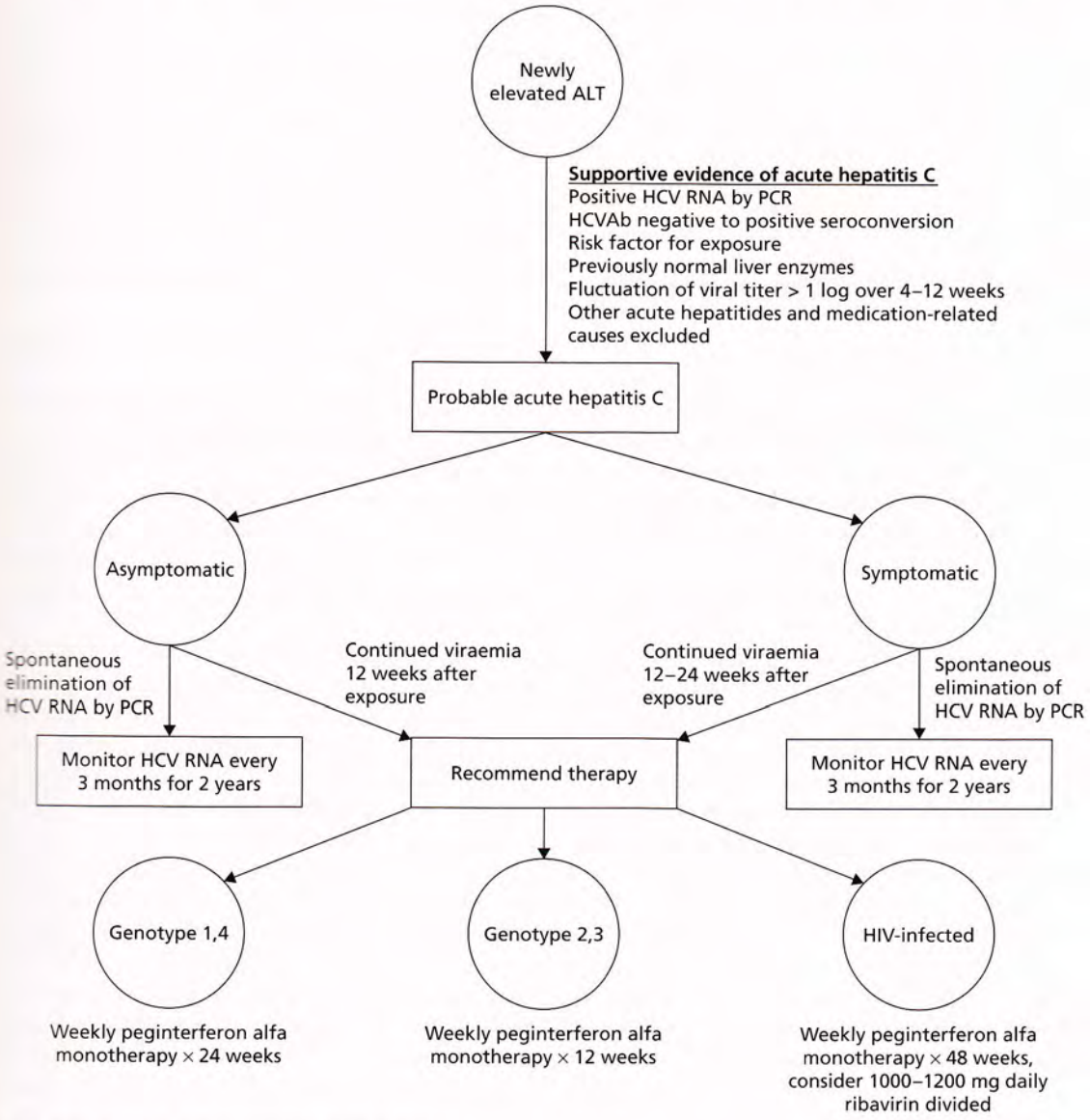

FIG. 6.1 Algorithm for treatment of acute HCV infection.

TABLE 6.1 Trials comparing therapies for acute HCV infection.

Study	Design	No. of patients	Regimen	Time to initiation of therapy	Treatment duration	SVR
Jaeckel *et al.* [8]	Non-randomized	44	Interferon alfa-2b 5 MU/day for 4 weeks followed by interferon alfa-2b 5 MU three times weekly	89 days from infection	24 weeks	98%
Wiegand *et al.* [9]	Non-randomized	89	Peginterferon alfa-2b 1.5 μg/kg	76 days after infection	24 weeks	71%
Kamal *et al.* [11]	Randomized controlled trial	173	Peginterferon alfa-2b 1.5 μg/kg per week	12 weeks	8 weeks 12 weeks 24 weeks	68% 82% 91%
Dominguez *et al.* [12]	Non-randomized	25 (HIV/HCV)	Peginterferon alfa-2a 180 μg/week and ribavarin 800 mg/day	3–24 weeks	24 weeks	71%

MU, million units.

interferon alfa monotherapy (5 million units daily for 4 weeks followed by 5 million units three times weekly for 20 weeks), 43 subjects (98%) attained SVR. In this study, the average time from infection to the start of therapy was 89 days. The effectiveness of standard interferon monotherapy has been confirmed in a number of other studies, with SVR rates between 75 and 100%. With the introduction of pegylated interferon alfa (peginterferon alfa), a preferred medication due to the once-weekly dosing schedule and lower side effects, several randomized and non-randomized studies were conducted to assess its efficacy in acute HCV. Monotherapy with peginterferon alfa-2b (1.5 μg/kg per week) for a duration of 24 weeks has been shown to result in SVR rates of 71–94%, with significant impact on outcomes related to patient adherence to therapy [9]. One randomized controlled trial reported by Kamal *et al.* [10] showed no benefit with the addition of ribavirin to peginterferon alfa in the acute setting.

The optimum duration of therapy remains debated, but as in chronic infection viral genotype plays a critical role. A study comparing treatment duration of 8, 12 and 24 weeks using peginterferon alfa-2b monotherapy (1.5 μg/kg per week) suggested an incremental improvement in SVR rates from 67.6 to 82.4 to 91.2%, respectively. However, all genotype 2 or 3 patients achieved SVR irrespective of treatment duration, suggesting that as few as 8 weeks of therapy could be sufficient in these genotypes. In contrast, SVR rates for genotype 1 patients were highly influenced by duration, ranging from 38 to 60 to 88% with 8, 12 and 24 weeks of therapy, respectively. Similar findings were identified in genotype 4 patients [11]. Adherence to prescribed therapy is a strong predictor of virological response [9]. The role of measuring early viral kinetics in acute HCV infection remains unclear.

The optimal timing of treatment for acute HCV infection remains controversial. Reasonably high spontaneous resolution rates make treatment unnecessary in a significant proportion of patients with acute HCV infection, but identifying such patients early in the course remains challenging. Excessive delay in initiation (> 48 weeks) clearly reduces treatment efficacy relative to early initiation of therapy (after < 12 weeks of infection). However, there are few data regarding the efficacy of therapy initiated at time points between weeks 12 and 48. Many patients who remain viraemic at week 12, but few who remain viraemic at week 24, will nonetheless resolve without therapy. Thus, some experts in the field suggest waiting for 12–24 weeks prior to initiating antiviral therapy, especially in symptomatic cases due to higher spontaneous clearance in this subgroup. Other experts recommend immediate therapy prior to 12 weeks. The authors recommend individualizing the treatment decision based on patient preference, comorbidities and early

virological trends, but initiating treatment at the latest by week 24 if spontaneous resolution has not occurred [12].

Treatment in special populations

Several studies have suggested that SVR rates in patients with acute HCV co-infected with HIV are lower than in HIV-negative patients, ranging from 59 to 71%. Higher treatment response rates have been observed in patients treated for 48 weeks versus 24 weeks. Some co-infection authorities also advocate the addition of ribavirin, at a cost of increased adverse effects (anaemia and thrombocytopenia), possible interaction with antiretroviral agents, and greater pill burden. Further studies are warranted to evaluate the efficacy and safety of acute HCV therapy in patients infected with HIV and to elucidate the optimal duration of therapy in acute HCV/HIV superinfection [13].

Summary

Acute HCV infection is an under-recognized clinical entity due to its mostly asymptomatic nature and variable rates of spontaneous resolution. Symptomatic patients are more likely to spontaneously clear the virus, although approximately 70% of patients will develop chronic HCV infection. Acute HCV infection therefore represents an important window during which therapeutic intervention is highly successful. Antiviral therapy can be delayed for at least 12 weeks, possibly up to 24 weeks, from the date of exposure or onset of symptoms to allow for spontaneous resolution. Antiviral therapy with peginterferon monotherapy (for 12–24 weeks depending on genotype) achieves SVR rates over 80% in this setting. Patient adherence with therapy remains a key determinant of response rates. In acute HCV in HIV-infected persons, 48 weeks of peginterferon plus ribavirin should be considered. Further research should be directed at optimizing cost-effective methods for improving the early detection of acute HCV infection and for preventing spread of infection in high-risk populations.

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7 Management of HCV genotype 1 non-responders/relapsers: a European perspective

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LEARNING POINTS

- A large proportion of patients with genotype 1 chronic HCV infection will not respond to current therapies.
- An accurate assessment of the reasons for treatment failure and a full understanding of the nature of the virological response is essential when considering further therapy.
- For patients who have had an inadequate course of therapy, retreatment with peginterferon and ribavirin should be strongly considered.
- For patients who had a post-treatment relapse after their first course of therapy, it may be reasonable to consider a further course of therapy with prolonged duration of peginterferon and ribavirin, perhaps for 72 weeks.
- Long-term maintenance therapy with peginterferon is of no benefit for the majority of patients, although some patient subgroups may derive some benefits from this approach.

Introduction

Chronic hepatitis C virus (HCV) is a major cause of liver cirrhosis and its sequelae. The aim of antiviral therapy is a sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after the end of therapy. Sustained elimination of HCV by antiviral therapy improves liver histology and patient outcome. However, in patients with genotype 1 chronic HCV infection undergoing therapy with the current standard of care (peginterferon alfa in combination with ribavirin), almost 50% of patients fail to achieve an SVR after antiviral therapy and options for retreatment of these patients are clearly needed.

Consistent with the decline of HCV RNA during treatment, four different patterns of treatment failure can be distinguished.

1 Non-response: < 2 $\log_{10}$ IU/mL decline in HCV RNA from baseline to treatment week 12. Null response: < 0.5 $\log_{10}$ IU/mL decline in HCV RNA at any time point.
2 Partial virological response: ≥ 2 $\log_{10}$ IU/mL decline in HCV RNA from baseline to treatment week 12 with detectable HCV RNA at week 24.
3 Breakthrough: detectable HCV RNA during treatment after an initial virological response.
4 Relapse: recurrence of HCV RNA after the end of therapy in patients who achieved and maintained undetectable HCV RNA during treatment.

The exact classification of these response patterns is important when retreatment is being considered as the response to subsequent courses of therapy is influenced by the initial response.

Correctable reasons for treatment failure

When assessing a patient who does not achieve SVR during the initial course of therapy, the reason for this treatment failure should be determined. Correctable reasons for treatment failure include non-compliance, medication errors, missed opportunities to manage adverse events, or treatment

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that has not been continued for a sufficient period of time. Patients who have a known and correctable reason for their previous treatment failure are good candidates for retreatment with peginterferon alfa and ribavirin therapy.

If patients are true non-responders with no clear correctable reasons for treatment failure, the potential success with a further course of standard peginterferon and ribavirin retreatment is much less promising and there are a number of potential treatment options, which are discussed below.

Retreatment with peginterferon and ribavirin

In the EPIC3 study, non-responders and relapsers to previous therapy with interferon alfa ($N = 1203$) or peginterferon alfa-2a/b ($N = 820$) with or without ribavirin were retreated with peginterferon alfa-2b (1.5 μg/kg per week) and ribavirin (800–1400 mg daily) [1]. The treatment duration was 48 weeks. All patients had F2 to F4 fibrosis (Metavir). The overall rate of SVR in retreated patients was 22%. The rate was higher in prior relapsers compared with prior non-responders (38% vs. 14%) and the lowest SVR rate was observed in non-responders to prior peginterferon alfa/ribavirin combination therapy (6–7%, all HCV genotypes). An early virological response at week 12 was achieved in 35% of patients. The majority of patients with an early virological response at treatment week 12 achieved SVR (56%). The results of the EPIC3 study show that retreatment of non-responders and relapsers is an option that should be considered in patients who achieve an early virological response (see also Chapters 9 and 10 for a review of the EPIC study relating to other HCV genotypes).

Increased dose of peginterferon and/or ribavirin

A small prospective study of 10 (treatment-naive) patients with HCV genotype 1 infection and high baseline viral load (> 800 000 IU/mL) showed the feasibility of treatment with even higher doses of ribavirin without major treatment interruption [2]. Ribavirin dose was calculated from a pharmacokinetic formula based on renal clearance to achieve a steady-state ribavirin concentration above 15 μmol/mL. After dose adjustments, at week 24, the average daily ribavirin dosage was 2540 mg (range 1600–3600 mg). Following this regimen, individualized ribavirin dosing with standard peginterferon alfa-2a therapy yielded SVR in 9 of 10 patients. However, prophylactic and as-needed administration of erythropoietin and blood transfusions were required in single patients.

A recent study by Fried *et al.* [3] demonstrated an improvement in SVR in genotype 1-infected patients with body weight above 85 kg treated with a higher dose of ribavirin, especially in conjunction with a higher dose of peginterferon. Patients treated with peginterferon alfa-2a 270 μg and ribavirin 1600 mg daily showed an SVR of 47% compared with 28% in patients treated with the standard dosing regimen. This improvement was driven mainly by a marked reduction in relapse in the high-dose group compared with the standard-dose group (19% vs. 40% respectively). However, the use of a higher dose regimen was associated with an increased rate of haematological adverse events.

Extended treatment duration

Intensified treatment with higher fixed-dose induction of peginterferon and/or longer treatment duration may increase SVR rates in patients with prior non-response to peginterferon alfa and ribavirin treatment. The REPEAT trial compared both strategies in prior non-responders to peginterferon alfa-2b and ribavirin [4]. Patients ($N = 942$) were randomized into four arms: those in arms A and B received peginterferon alfa-2a induction (360 μg/week) for 12 weeks followed by peginterferon alfa-2a 180 μg/week for a further 60 or 36 weeks (total duration 72 and 48 weeks, respectively); those in arms C and D received peginterferon alfa-2a 180 μg/week for 72 and 48 weeks, respectively. All patients were treated with ribavirin 1000–1200 mg/day. The overall SVR rates were 16% and 7% in the peginterferon alfa-2a induction arms for 72 and 48 weeks of therapy, respectively, and 14% and 9% in the peginterferon alfa-2a non-induction arms for 72 and 48 weeks, respectively. The SVR rate was higher for pooled 72-week arms versus pooled 48-week arms ($P = 0.0006$, odds ratio 2.22), while no difference was found between the induction and non-induction arms. The results of the REPEAT trial show that retreatment of non-responders with extended treatment duration improves SVR rates while induction therapy has no beneficial effect.

In this trial the overall early virological response (EVR) rates were 62% and 58% in the peginterferon alfa-2a induction arms for 72 and 48 weeks of therapy, respectively, and 49% and 42% in the peginterferon alfa-2a non-induction arms for 72 and 48 weeks, respectively. The corresponding SVR rates were 57% and 35% in the 72-week and 48-week

arms (induction, non-induction). The SVR rates in patients without EVR were 4.5% and 4.7%, respectively [5]. Multiple logistic regression analysis indicated that EVR at week 12 consistently predicts SVR regardless of favourable or unfavourable baseline prognostic factors in non-responders to peginterferon alfa-2b/ribavirin when retreated with peginterferon alfa-2a/ribavirin [5].

Maintenance therapy with low-dose peginterferon alfa

Two large multicentre trials have evaluated the potential benefits of maintenance therapy: the COPILOT (Colchicine vs. Peginterferon alfa-2b Long-Term) study [6] and the HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) trial [7].

The scope of the COPILOT study was to determine the effect of treatment on 4-year survival or hepatic transplantation; variceal or portal (hypertensive) bleeding; development of jaundice, ascites, encephalopathy or hepatocellular carcinoma (HCC); and deterioration of the Child–Pugh–Turcotte score. A total of 555 patients with prior failure to interferon-based antiviral therapy were randomized to peginterferon alfa-2b (0.5 μg/kg per week) ($N = 286$) or colchicine (0.6 mg twice daily) ($N = 269$); 20% of patients showed a clinical end-point within the study period. Development of HCC was more often observed in patients on peginterferon alfa-2b ($N = 26$) than in patients on colchicine ($N = 12$). Complications of portal hypertension, above all variceal haemorrhage, were more common in the colchicine ($N = 39$) than in the peginterferon alfa-2b ($N = 26$) group. Only in patients with portal hypertension was peginterferon alfa-2b superior to colchicine with respect to event-free survival at 2 and 4 years.

The HALT-C trial was a prospective, randomized, controlled study of long-term maintenance therapy with peginterferon alfa-2a in patients with chronic HCV infection and advanced fibrosis or cirrhosis (Ishak 3–6) who did not achieve SVR after treatment with interferon alfa or interferon alfa plus ribavirin [7]. A total of 1050 patients were randomly assigned to receive either peginterferon alfa-2a 90 μg/week ($N = 517$) or no treatment ($N = 533$) for 3.5 years. By the end of the study period, after 3.5 years, there was no difference between the control and treated groups in the frequencies of study end-points, such as death, hepatic decompensation or development of HCC (33.8% vs. 34.1%, respectively) [7]. Although mean serum alanine aminotransferase and HCV RNA levels decreased significantly with treatment ($P < 0.0001$), as did necroinflammatory changes on liver biopsy ($P < 0.0001$), no significant difference was observed in rates of any of the primary outcomes between the groups. The risk for development of HCC was further evaluated in a later analysis of the HALT-C study cohort [8]. The cumulative 5-year incidence was not significantly different between treated and untreated patients (5.7% and 5.1%, respectively; $P = 0.91$). Overall the COPILOT and HALT-C trials show that long-term peginterferon alfa maintenance therapy does not reduce the rate of clinical disease progression over periods of up to 4 years.

STAT-C

Studies on the structures of key replication enzymes encoded by HCV, such as NS3/4A protease and NS5B polymerase, have enabled the development of specifically targeted antiviral therapy against HCV (STAT-C). Several compounds are currently under investigation in clinical trials and show high antiviral activity in patients with chronic HCV infection [9,10]. The development of agents in different classes may allow construction of antiviral combinations that enhance the effectiveness of antiviral treatment in current non-responder patients. Safety issues and the rapid emergence of resistant mutations in monotherapy currently limit the use of anti-HCV-specific drugs [11] (see Chapter 44 for further discussion of new drugs in development for HCV).

Conclusion

Patients with treatment failure to interferon alfa-based standard therapy can be classified into non-responders, partial responders, patients with breakthrough, and relapsers. Strategies for retreatment comprise the modification of interferon alfa and ribavirin dosage and elongation of treatment duration to improve clinical outcomes. Adherence to treatment is also an important factor for attaining SVR. Failure rates after retreatment of non-responders are high for HCV genotype 1 patients, particularly those with additional poor predictive characteristics such as high baseline viraemia or advanced fibrosis. Patients with treatment failure should be carefully assessed for correctable reasons for treatment failure such as non-compliance, medication errors, missed opportunities to manage adverse events, or treatment that has not been continued for a sufficient period of time. Patients who have a correctable reason for

previous treatment failure are good candidates for retreatment with peginterferon alfa and ribavirin. For patients who do not have correctable factors that may improve the response to a second course of therapy, several trials have shown that retreatment of non-responders with peginterferon/ribavirin is associated with reasonable SVR rates, particularly when patients achieve an EVR at week 12. Retreatment of non-responders with peginterferon/ribavirin for 72 weeks is associated with higher SVR rates compared with 48 weeks' retreatment and should be considered. Long-term maintenance therapy with low-dose peginterferon does not improve the clinical outcome of patients with chronic HCV infection, although some subgroups, such as patients with portal hypertension, may benefit from long-term maintenance therapy.

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8 HCV genotype 1: how are you managing the non-responders and relapsers? A North American perspective

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LEARNING POINTS

- Non-sustained responses to peginterferon and ribavirin comprise a heterogeneous group of antiviral responses (non-responders and relapsers). Relapsers can be further defined by the time point at which they achieved undetectable viraemia.
- Numerous fixed and correctable factors identified during the previous course of treatment must be considered when counselling about retreatment. Patients with correctable factors, such as extreme dose reductions or discontinuation of ribavirin, may be most likely to benefit from retreatment if these issues can be better managed.
- The change in HCV RNA during a prior course of therapy has important implications for the likelihood of response to retreatment.
- Optimized dosages of ribavirin and extending duration of therapy for slow virological responders may modestly improve rates of sustained virological response during retreatment.
- Preliminary data of triple combination regimens including a direct antiviral agent, such as telaprevir or boceprevir, are promising for the treatment of prior non-sustained responders but must be confirmed in Phase III clinical trials.

Introduction

The goal of antiviral therapy for chronic hepatitis C virus (HCV) infection is sustained virological response (SVR), defined as undetectable HCV RNA in serum for at least 6 months after stopping therapy [1]. Non-sustained virological response encompasses a spectrum of outcomes, including relapse and non-response. Clinicians are faced with an increasing number of patients who have been previously treated with combination antiviral therapy but who have not achieved SVR. Treatment with peginterferon and ribavirin is rigorous and is associated with numerous side effects that diminish quality of life [1]. Therefore, clinicians and patients must make an informed choice about whether to repeat a course of peginterferon and ribavirin or wait until new triple-therapy regimens become available. Thus, a concise individualized strategy for managing these patients based on currently available evidence would be helpful. As discussed below, it is especially important to keep in mind that 'those who cannot remember the past are condemned to repeat it', as stated by the philosopher George Santayana.

Manage correctable factors

Numerous host and virological factors can influence the outcomes of antiviral therapy. Fixed factors are those intrinsic to HCV, such as genotype or pretreatment level of HCV RNA, or to the patient, such as race or severity of liver disease. It is well established that genotype 1 has a lower rate of virological response than other genotypes. Similarly, African-Americans and Hispanic patients have significantly lower rates of SVR compared with Caucasian patients when treated with the same medications. Other fixed factors, such as cirrhosis, hepatic steatosis and insulin resistance, can also diminish rates of SVR. Thus, it is apparent that patients with a constellation of fixed factors that negatively impact on therapeutic outcome would be at greatest disadvantage during a second course of treatment.

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Correctable factors are those that occurred during initial treatment but which may be amenable to intervention during a second course of therapy. Identifying correctable factors that may have contributed to prior treatment failure can help inform decisions about retreatment and subsequent management. Thus, detailed discussion with patients about their tolerance and adherence to previous therapy and a review of past records to identify factors that may be mitigated during subsequent treatment is warranted. Transient discontinuation of ribavirin and/or peginterferon could significantly diminish rates of SVR. The most common correctable factors and potential solutions include the following.

1. Extreme dose reductions or interruptions due to side effects such as anaemia, neutropenia or depression: close monitoring, modest dose reductions earlier during treatment, the judicious use of growth factors, and other adjunctive therapies, such as prophylactic antidepressants, could minimize dose reductions and premature discontinuation of treatment.
2. Lack of adherence to the prescribed medication regimen: patients must have realistic expectations about outcomes and potential adverse events before embarking on another course of therapy. The importance of complete adherence should be stressed and a plan for monitoring adherence developed with the patient.

Definition of non-response and relapse

Patients who remain with detectable HCV RNA throughout a course of therapy are considered to be *non-responders*. Within the non-responder category, *null responders* achieve the least reduction in HCV RNA, usually less than 1-log decrease in HCV levels, and are considered the most refractory to peginterferon and ribavirin therapy. *Partial responders* may have multiple log-fold decreases in HCV RNA in viraemia but always have detectable viraemia in serum during treatment.

In contrast, *relapsers* are those who do achieve undetectable HCV RNA during treatment, as measured by a sensitive standardized assay, but then HCV RNA again becomes measurable in serum after the end of a prescribed treatment regimen. Relapsers can be further categorized based on the time point at which they cleared virus for the first time (Table 8.1). Rapid virological responders achieve undetectable viraemia by week 4 of treatment. These patients have the highest chance of achieving an SVR (> 90%) during the initial course of therapy [2]. Patients who achieve undetectable viraemia for the first time at week 12 have had a *complete early virological response*, whereas those whose HCV RNA decreased by at least 2-logs at this point but remained detectable are considered to have had only a *partial early virological response*. Patients with a partial early virological response who then become undetectable by week 24 are considered to have a *slow virological response* (Table 8.1).

Importance of previous antiviral response

The likelihood of SVR during subsequent courses of treatment is associated with the previous response achieved by the patient during the first course of combination therapy. Therefore, it is imperative that clinicians review past records, specifically the change in HCV viraemia, to categorize patients broadly as null responders, partial responders or relapsers and further try to determine at which week of treatment they first became undetectable, according to the definitions provided above (Table 8.1). As might be expected, previous null responders are least likely to benefit from another course of therapy similar to their earlier treatment. SVR rates during retreatment rarely surpass 15% in this population, and may be lower when there are predominant unfavourable treatment factors present. Unless other compelling reasons

TABLE 8.1 Definitions of on-treatment virological response.

Response	Definition
Rapid virological response	HCV RNA negative (< 50 IU/mL) at week 4
Early virological response (EVR)	
Complete EVR	HCV RNA positive at week 4 but negative at week 12
Partial EVR	HCV RNA positive at week 4 but ≥ 2 $\log_{10}$ by week 12 and undetectable by week 24
Non-EVR	< 2 $\log_{10}$ drop from baseline at week 12

exist to treat these patients (such as control of extrahepatic manifestations), the best option may be observation while waiting for triple-therapy combinations.

Prior relapsers have the best chance of achieving SVR during a second course of treatment. SVR rates as high as 50% have been reported when previous relapsers to combination therapy have been retreated with peginterferon and ribavirin. Poynard *et al.* [3] retreated over 2300 prior non-responders and relapsers (all with advanced fibrosis) with peginterferon alfa-2b and ribavirin (800–1400 mg/day) for 48 weeks. The SVR rate was 38% among prior relapsers but only 14% among prior non-responders. Genotype non-1, HCV RNA below 600 000 IU/mL, and lower fibrosis stage were associated with improved treatment response. This marked difference in success rates between relapsers and non-responders further emphasizes the importance of investigating prior treatment response.

Prolonged therapy for slow virological responders

The rationale for extending the duration of treatment in some patients has been examined in several studies [4]. Extending the duration of therapy beyond 48 weeks appears to be a promising approach for a select group of prior relapsers. Slow virological responders are those who achieve undetectable HCV RNA in serum for the first time between weeks 12 and 24 of therapy. In this group, treatment with a standard 48-week course of treatment has been associated with a high rate of virological relapse on treatment cessation. Several randomized controlled trials comparing 48 weeks of treatment to 72 weeks of treatment among those with slow virological response have been performed. While all of these studies have differed somewhat in study design, such as different doses of ribavirin and different criteria for randomization to extended treatment, the message has been very consistent: prolonged therapy can significantly improve rates of SVR, largely by decreasing the rate of relapse, among slow virological responders. In one study performed in the USA, notable for its inclusion of numerous patients with difficult-to-treat characteristics (African-Americans, high viral levels, overweight, advanced fibrosis), SVR rates for slow virological responders treated for 72 weeks was 38%, compared with only 18% for those treated for 48 weeks [5]. Relapse rates were inversely proportional to the duration of therapy (20% vs. 59% when treated for 72 or 48 weeks, respectively). Thus, one could surmise that slow virological responders who relapsed to a previous course of treatment might benefit from extending therapy to 72 weeks during a second treatment course in order to diminish the chances of relapse. However, it should be noted that one large study recently reported from Europe failed to demonstrate an advantage to prolonged combination therapy in slow responders. Furthermore, extending therapy has been regularly associated with a high rate of premature discontinuation beyond 48 weeks of treatment, which must temper this approach in many patients.

Optimizing ribavirin dosing during retreatment

The importance of ribavirin in the treatment of HCV infection has always been underestimated. Ribavirin monotherapy has negligible antiviral activity; however, when combined with peginterferon, it is critical to preventing relapse after treatment cessation. In general, higher doses of ribavirin measured on a milligram per kilogram basis are associated with improved rates of SVR. Ribavirin dosing in the range 13–15 mg/kg appears to be the best balance between optimized efficacy and intolerable haemolytic anaemia that develops at higher doses. SVR is significantly diminished when dosing is below approximately 11 mg/kg. Therefore, maximizing ribavirin dosing, particularly in overweight patients, has the potential to improve SVR during a second course of treatment and is another important factor to consider.

Similarly, numerous studies have also established that poor adherence to ribavirin significantly decreases the rate of SVR and that this effect is evident throughout the course of treatment. Reddy *et al.* [6] retrospectively analysed a large database of patients treated with peginterferon and ribavirin and demonstrated that ribavirin dose reductions generated a stepwise decrease in SVR. A cumulative ribavirin dose below 60% expected resulted in the most striking decline in SVR. As the most extreme example from a randomized trial, patients on combination therapy with undetectable HCV RNA who discontinued ribavirin in the latter 24 weeks of treatment had higher rates of virological breakthrough and relapse than those who continued on dual therapy [7]. Thus, major dose reductions or discontinuation of ribavirin during an initial course of therapy may have compromised sustained response and must be avoided, if possible, during subsequent treatment.

Increased peginterferon dose or consensus interferon

From the above discussion, it may be inferred that non-responders should be retreated with higher doses of

peginterferon and ribavirin in order to maximize SVR. Unfortunately, studies of intensified regimens of combination therapy have demonstrated only modest increases in SVR. A recent four-arm study compared standard dose versus higher induction dosing of peginterferon in combination with ribavirin for either 48 or 72 weeks [8]. The highest rate of SVR was attained in the induction dose group treated for 72 weeks (16%), although a similar rate was also achieved with standard dosing of peginterferon for 72 weeks (14%), both of which were higher than the 48-week treatment arms, suggesting that the duration of therapy rather than the induction dose of peginterferon was of greater importance.

In a study of consensus interferon in previous peginterferon/ribavirin non-responders that included many patients with unfavourable treatment factors such as advanced fibrosis and high viral load, the SVR rate was 7% and 11% when patients were treated with either 9 or 15 μg of consensus interferon daily, respectively, combined with ribavirin [9]. SVR rates were higher (32%) if patients had demonstrated at least a 2-log decrease in viraemia during their previous course of peginterferon/ribavirin.

Role of maintenance therapy

Patients with advanced fibrosis who fail to respond to interferon-based therapies are at highest risk for complications of cirrhosis. The HALT-C study treated a large cohort of these patients with a low dose of peginterferon alfa-2a for 3.5 years to determine if maintenance therapy would decrease the rates of fibrosis progression, hepatic decompensation and hepatocellular carcinoma [10]. In a rigorously controlled trial, there were no differences in the rates of these events between the treated group and an observational control group. Interestingly, in a small subgroup of patients who had viral suppression from low-dose maintenance therapy, there was a suggestion of histological benefit, although the study design and small sample size precluded any meaningful post hoc analysis. At this point, maintenance therapy cannot be endorsed for prior non-responders to therapy.

Triple-combination therapies in prior non-sustained responders

The protease inhibitors telaprevir and boceprevir are direct-acting antiviral agents that have shown great promise in recent Phase II studies [11,12]. SVR rates in previously untreated patients are significantly improved when these agents are combined with peginterferon and ribavirin. Limited data exist on their use in prior peginterferon/ribavirin non-responders but it is anticipated that SVR rates will also significantly improve. Assuming the results of Phase III trials currently underway are similar, clinicians may have additional therapeutic options to consider for their prior non-responders in the next 2–3 years, which may affect selection of candidates and the urgency for retreatment.

Practical approach to retreatment of non-sustained virological response

1 Assess patient's motivation for another course of therapy: patients must be highly motivated to undergo another treatment regimen with attendant side effects, particularly since the likelihood of SVR is substantially lower than in treatment-naïve patients.
2 Assess severity of liver disease (clinical, biochemical, histological if applicable): patients with minimal fibrosis may opt to defer treatment until triple therapies become available. It is expected that these triple regimens will improve the chance for SVR in both non-responders and relapsers.
3 Determine virological response to previous treatment course: null responders are unlikely to benefit from a second, similar treatment regimen and intensified regimens of peginterferon have demonstrated only modest improvements in SVR. Slow virological responders who have relapsed may benefit from extending the duration of therapy for up to 72 weeks.
4 Examine prior dosing regimens and adherence: optimizing ribavirin dosing on a milligram per kilogram basis, minimizing dose reductions, and avoiding interruptions to therapy are important goals during a second course of treatment.
5 Identify correctable factors and make a plan for vigilant monitoring and/or management.

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9 Management of HCV-2 and HCV-3 non-responders and relapsers

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LEARNING POINTS

- Patients with HCV-2 and HCV-3 have differing outcomes from therapy.
- Treatment failure is uncommon in patients with HCV-2 and HCV-3.
- Factors that predispose to treatment failure include obesity, insulin resistance, advanced fibrosis and high pretreatment viraemia.
- Retreatment in patients with HCV-2 and HCV-3 should be considered as response rates are reasonable, particularly with prolonged duration of treatment.

Introduction

Therapy of chronic hepatitis C virus (HCV) infection is currently based on the combination of peginterferon and ribavirin [1]. The response to such treatment depends on several virus and host variables that determine the need for a more or less aggressive schedule and which are associated with a higher or lower chance of achieving a sustained virological response (SVR). Patients infected with HCV genotype 2 (HCV-2) or genotype 3 (HCV-3) have traditionally been considered easier to treat than those with HCV genotype 1 (HCV-1) or genotype 4 (HCV-4). Response rates are indeed higher in the former and, according to current international guidelines, need shorter therapy. Most published series have reported SVR rates above 80% in HCV-2/HCV-3 infection compared with SVR rates below 60% in HCV-1 infection, and current treatment guidelines recommend 24 weeks of therapy in the former and 48 or 72 weeks in the latter [1,2]. However, a subgroup of patients with HCV-2 or HCV-3 infection do not develop an SVR and are termed 'relapser' or 'non-responder', and there is evidence that these patients behave somehow differently. In this chapter we describe the factors that have been associated with reduced response to antiviral therapy in patients with HCV-2 and HCV-3 infection and the prospects for improving response in such patients.

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HCV-2 and HCV-3: the easy-to-treat HCV genotypes

In 2004, Hadziyannis *et al.* [3] provided clear evidence that HCV-2/HCV-3 infection is easier to treat than HCV-1/HCV-4 infection and requires only 24 weeks of therapy, without significant overall gain in benefit when combination therapy is given for 48–52 weeks. In most clinical trials SVR rates in patients with HCV-2/HCV-3 infection, considered as a single group, have been in excess of 80% [2]. The most recent American Association for the Study of Liver Diseases (AASLD) guidelines recommend treating patients with HCV-2 or HCV-3 infection with peginterferon for 24 weeks plus ribavirin 800 mg daily. Patients who are intolerant of a planned 24-week course of therapy can discontinue the antiviral therapy between weeks 12 and 16 if they have achieved a rapid virological response (RVR). However,

patients should be informed that this schedule is associated with a higher relapse rate [1].

HCV-2 and HCV-3 have different responses to therapy

Most clinical trials have pooled treatment response rates in patients with HCV-2 and HCV-3 infection. However, in 2004 Zeuzem *et al.* [4] reported that SVR rates after a 24-week course of peginterferon alfa-2b plus ribavirin were 93% for HCV-2 but only 79% for HCV-3. Reduced response in HCV-3 infection was associated with a higher incidence and degree of liver steatosis and higher rates of post-treatment relapse. High viral load at baseline was also an important factor in reducing SVR in HCV-3 but not HCV-2 infection. Zeuzem and collegues calculated an overall rate of SVR as 80–89% for HCV-2 and 66–80% for HCV-3 [2]. This has been recently confirmed in a meta-analysis by Andriulli *et al.* [5], who estimated an 8.7% difference in SVR rates between the two genotypes after 24 weeks of treatment. The difference was not influenced by the type of peginterferon, but was significantly affected by viraemia at baseline.

Factors associated with relapse, poor response or non-response in HCV-2 and HCV-3 infection

Primary non-response to peginterferon and ribavirin is a very rare event in patients with HCV-2 and HCV-3 infection, as in the vast majority of treated patients a significant reduction in HCV RNA is usually observed with adequate therapy. On the other hand, a non-negligible subgroup of patients may show only partial response or virological relapse after therapy withdrawal. Factors that may influence the response to antiviral therapy in patients with HCV-2 and HCV-3 infection have been described in several recent studies. Baseline HCV RNA levels influence SVR rates. Indeed, patients with HCV-2 and HCV-3 infection with low viraemia respond equally well to both 12 and 24 weeks of therapy [6–10]. The ACCELERATE study has shown that high baseline viral load (> 600 000 IU/mL) is associated with a high rate of virological relapse (23%) in HCV-3 infection [7]. The NORDynamIC study found that age and HCV RNA levels on days 7 and 29 were independent predictors of SVR [8]. RVR (i.e. undetectable HCV RNA in serum 4 weeks after initiation of therapy) is a well-known predictor of virological response to antiviral therapy. Indeed, patients with HCV-2 and HCV-3 infection who do not achieve RVR have significantly lower SVR rates with antiviral therapy. The ACCELERATE study has clearly shown that only 49% of those patients infected with HCV-2 and HCV-3 who did not achieve RVR attained an SVR [7]. In the study by Yu *et al.* [9], which enrolled only patients with HCV-2 infection, achievement of RVR and patient's age were independent factors associated with SVR. In the study by Dalgard *et al.* [10], age 40 years or less, male gender and baseline viraemia 400 000 IU/mL or less were independent predictors of RVR. Since high rates of relapse occur with 24-week therapy in HCV-2 and HCV-3 patients not achieving RVR, it is conceivable that these patients may benefit from longer therapy, but this remains to be proven in well-conducted clinical trials. Metabolic factors such as steatosis, obesity and insulin resistance have been reported to have a significant negative influence on the response to antiviral therapy in HCV infection. In the study by Zeuzem *et al.* [4], a significant difference in terms of SVR was observed between patients with HCV-2 and HCV-3 infection and this was associated with a higher amount of hepatic steatosis among the latter group of patients. In the study by Poustchi *et al.* [11] on 82 patients with HCV-2 or HCV-3 infection, the role of insulin resistance in influencing the SVR was investigated. In this study, patients able to achieve SVR had lower mean serum insulin measured by homeostasis model (HOMA) at baseline, indicating that insulin resistance was associated with reduced response. Body mass index (BMI) and fibrosis stage were independently associated with HOMA baseline values. After adjusting for fibrosis stage, patients with HOMA level less than 2 were 6.5 times more likely to achieve SVR than those with HOMA level 2 or more. Thus it is clear from these data that even in easy-to-treat HCV-2 and HCV-3 infection, insulin resistance leads to reduced response to peginterferon and ribavirin combination therapy. Since obesity and insulin resistance have been shown to have a negative impact on progression of fibrosis and on response to antiviral therapy in patients with HCV infection, including those with HCV-2 or HCV-3, it is appropriate to counsel those who are overweight about losing weight and reducing, as much as possible, insulin resistance before initiation of antiviral therapy.

A recent study by Mangia *et al.* [12] has investigated the determinants of relapse after a short (12-week) course of antiviral therapy in 718 patients with HCV-2 or HCV-3 infection. The RVR patients who were most likely to relapse after an abbreviated course of therapy were those with higher

BMI and lower platelet count. Indeed, a BMI of 30 or higher and a platelet count of 14×10^9/L or lower were independently associated with relapse. In this analysis, factors associated with relapse did not differ between HCV-2 and HCV-3 infection. When patients without SVR were analysed individually, at least one of the following unfavourable factors was always present: cirrhosis, age over 50 years or BMI greater than 30 kg/m^2. The authors concluded that shortening of antiviral therapy for less than 24 weeks in patients with HCV-2 or HCV-3 infection should be considered only for young patients with RVR, providing they present with no advanced fibrosis and low BMI.

The observation that patients with HCV-2 and HCV-3 infection and severe fibrosis are less likely to achieve RVR or SVR and show higher relapse rates has been described in numerous reports. In the study by Dalgard *et al.* [13], pretreatment liver histology showing no or minimal fibrosis was a solid predictor of SVR and all patients who relapsed after 14 weeks of therapy had severe fibrosis. In another study, patients with HCV-2 infection and low pretreatment levels of alanine aminotransferase were more likely to relapse following shorter treatment duration [14].

Retreatment of HCV-2 and HCV-3 infection

Several recent studies have addressed the issue of whether retreatment with peginterferon plus ribavirin could result in SVR in patients who have failed previous therapy as relapsers or non-responders (or partial responders). These studies indicate that the probability of achieving SVR with retreatment is higher in previous relapsers compared with non-responders and in HCV-2/HCV-3-infected patients compared with HCV-1-infected patients. According to available data, in patients with HCV-2/HCV-3 infection, retreatment for 48–52 weeks can achieve SVR in more than 60% of previous relapsers and in more than 30% of previous non-responders [2,3]. These figures are clearly higher than those obtained with the same retreatment schedule in patients with HCV-1 infection and mainly reflect the fact that most patients with HCV-2 and HCV-3 had received only 24 weeks of therapy during the previous unsuccessful course while those with HCV-1 had already been treated for 1 year. It is unclear whether success rates with retreatment differ between patients with HCV-2 and HCV-3 infection, as most retreatment studies pooled the two genotypes. On the basis of these findings it seems reasonable to consider retreatment with a 48–52 week course of peginterferon and ribavirin in HCV-2 and HCV-3 patients who had been relapsers, partial responders or non-responders during previous antiviral therapy, particularly when they had received 24-week therapy. Recently, it has been suggested that patients with HCV-3 infection and advanced liver fibrosis or cirrhosis should be treated from the very beginning for at least 48 weeks, based on the observation that many of them obtain an end-of-therapy response but then relapse after therapy discontinuation when treated for only 24 weeks [2]. Further studies are needed to prove or disprove the real benefit of such approach.

STAT-C development for HCV-2 and HCV-3 infection

A number of direct antiviral agents against HCV (STAT-C) are now in the final phases of clinical development. The most promising ones include protease inhibitors and nucleoside and non-nucleoside inhibitors of the viral polymerase [2]. Most of these new compounds have been designed to target patients with HCV-1 infection, simply because this is the largest pool of individuals who fail to respond to currently available therapies. Some of these new compounds may be active on genotypes other than HCV-1; for example, telapravir has been recently shown to have significant antiviral activity against HCV-2 but not HCV-3 [15]. While there are no doubts that HCV-1 deserves priority as a target for STAT-C development, antiviral compounds active against HCV-2 and particularly HCV-3 will also need to be developed in the future, despite the more limited numbers of potential candidates.

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10 Management of HCV infection in patients with thalassemia and sickle cell disease

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LEARNING POINTS

- Chronic HCV infection is common in patients with blood dyscrasias and should be managed jointly by specialists in hepatology and haematology, preferably in a joint clinic.
- Liver biopsy is needed for histological assessment and chemical quantitation of liver iron content.
- Patients with thalassemia major should be optimally chelated before starting antiviral therapy, with liver iron maintained in the range 2–7 mg/g dry weight. Patients with sickle cell disease may require regular transfion during anti-viral therapy to reduce the risk of severe haemolysis and acute sickle crisis.
- Combination therapy with peginterferon and ribavirin induces sustained virological responses in about 50% of patients with thalassemia and should be considered if there is evidence of active inflammation or fibrosis on biopsy.
- During treatment, careful monitoring of side effects, transfusion frequency and iron chelation is required.

Introduction

Regular or intermittent red blood cell transfusion is often required for patients with inherited anaemias, and this has resulted in a proportion becoming infected with HCV as a result of receiving contaminated red cell donations. Chronic HCV infection in these patients causes particular management problems and there are no large-scale clinical trials to provide definitive guidance. Here we discuss the management options for patients who also suffer from either thalassemia major or sickle cell disease.

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Thalassemia and sickle cell disease

Thalassemia major and sickle cell disease are common conditions in non-northern European populations and present particular management problems. Both are inherited as autosomal recessive conditions with mutations affecting the β-globin gene. β Thalassemia mutations reduce or abolish the production of β-globin, causing a deficiency of haemoglobin, severe anaemia and ineffective erythropoiesis with intramedullary and extramedullary erythroid marrow expansion. Patients with thalassemia major require regular transfusions for normal growth and development. In the case of sickle cell disease, there is an abnormal β-globin chain with a substitution of valine for glutamic acid at position 6. This structural haemoglobin variant tends to form polymers when deoxygenated, leading to haemolytic anaemia, acute large- and small-vessel occlusion and chronic tissue damage.

Transfusion-transmitted HCV infection

These patients require intermittent or regular transfusion therapy, and are at increased risk of infection because of exposure to multiple blood donors. The highest risk is in thalassemia major, which requires regular long-term transfusion therapy, usually given every 2–4 weeks. It is less prevalent in sickle cell disease, with about 10–20% of patients being regularly transfused, mostly in childhood for stroke prevention.

If recommended blood donor selection and screening procedures are implemented, the risk of HCV transmission is now very low. In the UK, the estimated risk of an infected

it entering the blood supply in 2002–2003 was 0.05 per ion donations [1]. Most patients in the UK with persist- infection acquired HCV prior to implementation of ective HCV screening of blood donors. Some continue to at risk through transfusion while resident in a country ere exclusion of infected donors is less secure. In some ltitransfused patients, there is evidence of multiple past posures to HCV [2].

Prevalence of HCV antibody positivity in adult patients h thalassemia major varies from 30 to over 70%, with h proportions reported in Italy compared with the UK d North America. More than 50% of antibody-positive ients have evidence of chronic infection [3,4]; the nainder are persistently serum HCV RNA negative, and pear to have cleared the virus spontaneously.

ver disease

gression of liver disease is influenced by the pathological cts of the conditions themselves. In the case of thalas- nia major, the dominant disease-altering factor is iron ding of hepatic parenchymal cells. There is increased estinal absorption of iron in non-transfused thalassemia alassemia intermedia), which can result in very heavy n loading [5]. The liver is also the major site of iron position in transfusion-dependent (thalassemia major) ients and hepatic iron concentration is linearly related otal body iron load [6]. Progression of hepatic fibrosis is luenced by the degree of hepatic iron overload and is st rapid in patients with heavy iron overload (> 15 mg/g weight) who are HCV RNA positive [7,8]. Cirrhosis d hepatocellular carcinoma are well documented, even in ng patients [3,9].

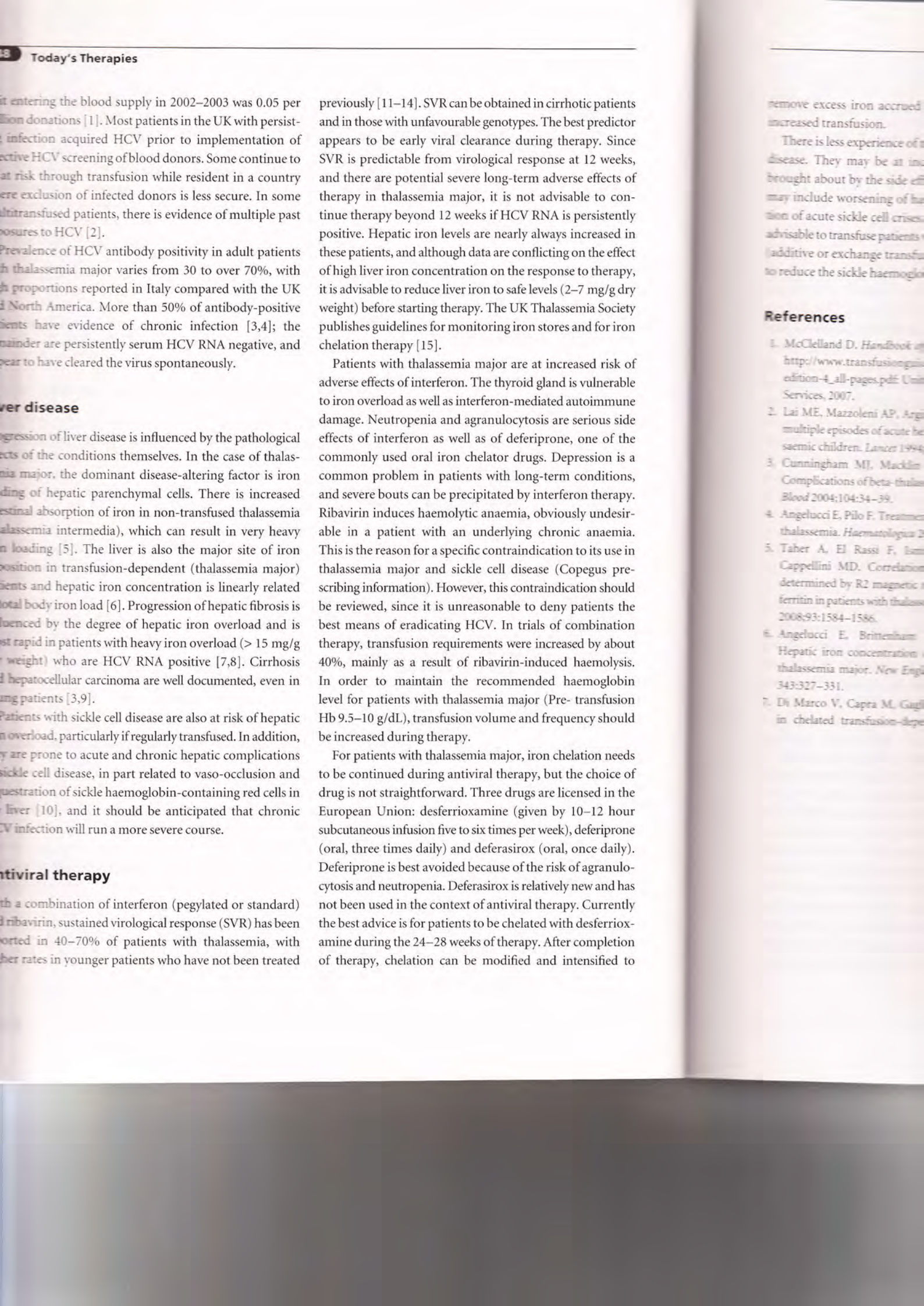
Patients with sickle cell disease are also at risk of hepatic n overload, particularly if regularly transfused. In addition, y are prone to acute and chronic hepatic complications sickle cell disease, in part related to vaso-occlusion and uestration of sickle haemoglobin-containing red cells in liver [10], and it should be anticipated that chronic CV infection will run a more severe course.

ntiviral therapy

th a combination of interferon (pegylated or standard) d ribavirin, sustained virological response (SVR) has been orted in 40–70% of patients with thalassemia, with her rates in younger patients who have not been treated previously [11–14]. SVR can be obtained in cirrhotic patients and in those with unfavourable genotypes. The best predictor appears to be early viral clearance during therapy. Since SVR is predictable from virological response at 12 weeks, and there are potential severe long-term adverse effects of therapy in thalassemia major, it is not advisable to continue therapy beyond 12 weeks if HCV RNA is persistently positive. Hepatic iron levels are nearly always increased in these patients, and although data are conflicting on the effect of high liver iron concentration on the response to therapy, it is advisable to reduce liver iron to safe levels (2–7 mg/g dry weight) before starting therapy. The UK Thalassemia Society publishes guidelines for monitoring iron stores and for iron chelation therapy [15].

Patients with thalassemia major are at increased risk of adverse effects of interferon. The thyroid gland is vulnerable to iron overload as well as interferon-mediated autoimmune damage. Neutropenia and agranulocytosis are serious side effects of interferon as well as of deferiprone, one of the commonly used oral iron chelator drugs. Depression is a common problem in patients with long-term conditions, and severe bouts can be precipitated by interferon therapy. Ribavirin induces haemolytic anaemia, obviously undesirable in a patient with an underlying chronic anaemia. This is the reason for a specific contraindication to its use in thalassemia major and sickle cell disease (Copegus prescribing information). However, this contraindication should be reviewed, since it is unreasonable to deny patients the best means of eradicating HCV. In trials of combination therapy, transfusion requirements were increased by about 40%, mainly as a result of ribavirin-induced haemolysis. In order to maintain the recommended haemoglobin level for patients with thalassemia major (Pre- transfusion Hb 9.5–10 g/dL), transfusion volume and frequency should be increased during therapy.

For patients with thalassemia major, iron chelation needs to be continued during antiviral therapy, but the choice of drug is not straightforward. Three drugs are licensed in the European Union: desferrioxamine (given by 10–12 hour subcutaneous infusion five to six times per week), deferiprone (oral, three times daily) and deferasirox (oral, once daily). Deferiprone is best avoided because of the risk of agranulocytosis and neutropenia. Deferasirox is relatively new and has not been used in the context of antiviral therapy. Currently the best advice is for patients to be chelated with desferrioxamine during the 24–28 weeks of therapy. After completion of therapy, chelation can be modified and intensified to



remove excess iron accrued during therapy as a result of increased transfusion.

There is less experience of treating patients with sickle cell disease. They may be at increased risk of complications brought about by the side effects of antiviral therapy. This may include worsening of haemolytic anaemia and induction of acute sickle cell crises. In most cases, it would seem advisable to transfuse patients with sickle cell disease regularly (additive or exchange transfusion) during therapy in order to reduce the sickle haemoglobin percentage below 30.

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11 Management of HCV in dialysis patients

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LEARNING POINTS

- HCV infection remains frequent in patients on maintenance haemodialysis.
- HCV infection plays a detrimental role on survival in haemodialysis patients and renal transplant recipients.
- No optimal antiviral therapy of chronic HCV infection in dialysis populations exists.

Introduction

Chronic hepatitis C virus (HCV) infection remains prevalent in the haemodialysis population despite elimination of HCV from the blood supply, partly reflecting nosocomial spread within haemodialysis units [1,2]. Although there is increasing information on the detrimental impact of HCV on survival in patients with chronic kidney disease (CKD), the treatment of HCV infection in this population remains a challenge to clinicians.

The treatment of HCV infection in patients on chronic haemodialysis is predicated on the premise that HCV is associated with decreased patient survival. Some information on the association between positive anti-HCV serological status and survival in dialysis populations already exists [3], even if an accurate assessment of the natural history of HCV in dialysis patients is difficult [1]. A recent meta-analysis on the impact of HCV on mortality (seven observational studies enrolling 11 589 unique patients on maintenance haemodialysis) showed that the summary estimate for adjusted relative risk (RR) of all-cause mortality with anti-HCV was 1.34 (95% CI 1.13–1.59) [3]. Liver dysfunction has been implicated in lower survival of seropositive patients; the summary estimate for RR of liver-related mortality with anti-HCV was 3.75 (95% CI 1.93, 17.99) [3]. These results are consistent with evidence from other sources. A large survey (DOPPS) of patients on long-term dialysis in three continents reported an independent and significant association between positive anti-HCV serological status and mortality (RR 1.17; $P < 0.02$) (reviewed in ref. 4).

Antiviral therapy of HCV in dialysis patients: rationale

The information in the literature on the antiviral therapy of HCV in dialysis populations is not abundant. Clinicians have so far been reluctant to offer interferon-based therapy for HCV infection in dialysis populations as it was felt to be too toxic in this setting. The immunomodulatory activity of interferon supports a large spectrum of side effects in patients with chronic HCV infection and normal renal function, including alopecia, depression, fever/flu-like syndrome, and infections. Dialysis patients are typically older and have several comorbidities (including cardiomyopathy, malnutrition and gastrointestinal abnormalities).

The decision to treat HCV infection in the CKD patient should be based on liver histology, age, comorbidities, and ability to tolerate therapy. Potential benefits of successful therapy include aborting the progression of liver disease and reducing the risk of post-transplant complications associated with HCV. Positive anti-HCV serological status after kidney transplantation is implicated in the pathogenesis of acute glomerulopathy, *de novo* graft-associated nephropathy, new-onset diabetes mellitus after transplantation, and

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increased incidence of infections. In some patients, there are good data to support antiviral treatment, for example in the pretransplant patient. For HCV-infected dialysis patients who are kidney transplant candidates, antiviral therapy is suggested in order to prevent extrahepatic complications even in those with a pattern of histological injury that does not meet the recommended degree of fibrosis to qualify for therapy in the general population (i.e. Metavir score < 2 and Ishak score < 3) [4]. Given the generally indolent progression of HCV, treatment is not recommended for the dialysis patient with less than a 5-year estimated survival due to comorbidities such as cardiovascular disease. This is particularly the case if liver histology shows an absence of extensive fibrosis. The decision to treat an HCV-infected patient on regular dialysis must be made in the context of the patient's clinical situation. The patient should be appropriately informed of the risks and benefits of antiviral therapy and should also participate in the decision-making process.

With regard to the question of liver biopsy prior to treatment, the information derived from a liver biopsy in haemodialysis patients may be particularly useful, as clinical and biochemical findings may underestimate severity of liver disease. Pretransplant liver biopsy provides useful prognostic information. Staging of disease severity may guide considerations for antiviral therapy as patients identified with advanced fibrosis should be considered for liver–kidney transplantation.

Although genotype does not predict the outcome of infection, it has been shown to predict the probability of response to, and determine the necessary duration of, therapy. Infections with HCV genotypes 1 and 4 are less responsive to interferon-based therapy and require 48 weeks of treatment. In contrast, genotypes 2 and 3 are far more responsive to treatment and require only 24 weeks of therapy to achieve a sustained virological response (SVR). HCV genotype 5 appears to have a response similar to genotypes 2 and 3 but requires 48 weeks of therapy. Genotype 6 responds better than genotype 1 but not so well as genotypes 2 and 3. These results have been obtained in patients with HCV infection and normal kidney function. In a meta-analysis of patients on maintenance haemodialysis, the overall summary estimate for SVR was 37% in the whole group and 30% in those patients with HCV genotype 1 [5]. In another review, the pooled SVR rate was 33% in the whole group and 26% in those with HCV genotype 1 [6].

Interferon monotherapy

Numerous clinical trials have been published on antiviral therapy (conventional or pegylated interferon alone) for chronic HCV infection in dialysis populations but most of these have an uncontrolled design; also, the size of the study groups is rather small. At this time, there are data, albeit very limited, supporting peginterferon as monotherapy for the treatment of HCV infection in patients receiving long-term dialysis [7–21].

A recent meta-analysis identified 24 clinical trials enrolling 429 unique patients on maintenance dialysis who received conventional interferon monotherapy; the summary estimate for SVR rate was 39% (95% CI 32, 46) and the drop-out rate was 19% (95% CI 13, 26) [5]. The most frequent side effects requiring interruption of treatment were flu-like symptoms and gastrointestinal and haematological changes. A relationship between age and drop-out rate was found, even if no statistical significance was reached ($P = 0.064$). The studies were heterogeneous with regard to SVR and drop-out rate. No publication bias was found. The conclusion of the authors was that one-third of dialysis patients with chronic HCV infection were successfully treated with conventional interferon monotherapy.

The viral response to monotherapy with standard interferon in maintenance haemodialysis patients (summary estimate of 39%) is higher than that observed in patients with chronic HCV infection and normal kidney function (7–16%) who received conventional interferon monotherapy. Several mechanisms account for the relatively higher response to interferon in subjects receiving regular haemodialysis: dialysis patients with HCV infection usually have a lower viral load; the infection is frequently associated with milder forms of histological liver disease; clearance of interferon is lower in dialysis than in non-CKD patients; and an increase in endogenous interferon release from circulating white blood cells during haemodialysis procedures has been reported. Marked and prolonged synthesis of hepatocyte growth factor (or other cytokines) caused by haemodialysis could play an additional role [4].

Although response rates to conventional interferon are better in the dialysis population, tolerance to interferon monotherapy appears lower in patients on maintenance haemodialysis than in non-CKD individuals. The summary estimate for drop-out rate was 19% in dialysis patients who received standard interferon monotherapy, whereas the frequency of side effects requiring interferon discontinuation ranged

between 5 and 9% in non-CKD patients with chronic HCV infection who received a usual dose of standard interferon monotherapy (3 million units thrice weekly for 6 months). The altered pharmacokinetic parameters of interferon in the haemodialysis population may, to some extent, explain the higher frequency of side effects leading to interferon discontinuation. The interferon alfa half-life was longer in dialysis than in normal controls (9.6 vs. 5.3 hours; $P = 0.001$) and the area under the curve was twice that seen in patients with normal kidney function. Additional mechanisms were older age and high rate of comorbid conditions in haemodialysis populations [5].

Combination therapy

The information on combined antiviral therapy (i.e. conventional interferon plus ribavirin) in the CKD population is preliminary in nature [22] and the data on peginterferon plus ribavirin are even more sparse [23–27]. The quality of evidence on this issue is very low. The results provided in some trials have been encouraging in terms of efficacy and safety, but the limited size of the study groups does not allow definitive recommendations (Table 11.1). Very little ribavirin is removed via dialysis so there is a propensity for the drug to accumulate, exacerbating haemolysis in the dialysis population already at significant risk for anaemia. Ribavirin therapy in this setting is not recommended.

We feel that if a decision is made to use ribavirin in patients on maintenance haemodialysis, it should be used very cautiously and only after the implementation of several precautions, including (i) very low doses of ribavirin (200 mg thrice weekly), (ii) weekly monitoring of haemoglobin levels, and (iii) high doses of erythropoietin to treat anaemia. This will typically be performed at specialized centres [4].

Limitations and research recommendations

There is still concern about the applicability of the results of these studies to all dialysis patients, as most of the subjects included were on the waiting list for kidney transplantation and were younger and probably healthier than the general dialysis population. Furthermore, only a few studies were from North America, where many CKD patients are African-American. This is of special relevance, as there are racial differences in the response to interferon therapy in subjects with normal kidney function.

Early virological response (i.e. virological response obtained 12 weeks after initiation of antiviral therapy with at least a 2-log fall in the HCV viral titre) has been demonstrated to be highly predictive of SVR in HCV-infected patients with normal kidney function. There are studies which have formally addressed the predictive value of early viral response in evaluating the response of HCV-infected CKD patients to antiviral therapy. Many dialysis patients who receive antiviral therapy are potential renal transplant candidates, but they cannot be assigned to a transplant waiting list while receiving antiviral therapy. Thus, the failure to achieve a virological response 12 weeks after the initiation of antiviral therapy can support an early interruption of antiviral treatment, giving the patient the possibility of rapid inclusion in the waiting list for transplantation. Prospective studies on the clinical utility of early changes in the viral load, measured as absolute viral loads or change in viral load from baseline, are required in CKD-infected patients who receive antiviral therapy.

Information on the rate of adverse effects during interferon therapy in dialysis patients is unsatisfactory. It remains unclear whether the adverse effects in dialysis patients with

TABLE 11.1 Peginterferon in combination with ribavirin in patients with chronic HCV infection on maintenance haemodialysis: clinical trials.

Reference	SVR	Antiviral agent
Bruchfeld *et al.* 2006 [23]	50% (3/6)	Peginterferon alfa-2a ($N = 2$) or peginterferon alfa-2b ($N = 4$) plus ribavirin
Rendina *et al.* 2007 [24]	97% (34/35)	Peginterferon alfa-2a plus ribavirin
Schmitz *et al.* 2007 [25]*	50% (3/6)	Peginterferon alfa-2b plus ribavirin
van Leusen *et al.* 2008 [26]	71% (4/7)	Peginterferon alfa-2a plus ribavirin
Carriero *et al.* 2008 [27]	29% (4/14)	Peginterferon alfa-2a plus ribavirin

Results have been calculated according to an intention to-treat analysis.
* This study concerned liver–kidney transplant recipients.

HCV are related to interferon activity *per se* or to the high prevalence of comorbid conditions typical of dialysis patients. Prospective controlled studies in dialysis patients are required to compare the rate of adverse effects during interferon-based therapy with those patients who do not receive antiviral therapy. Prospective trials involving the treatment of HCV-infected patients on peritoneal dialysis are needed. Essentially, all information available on the treatment of dialysis patients comes from studies in haemodialysis patients.

The higher efficacy of combined antiviral therapy compared with interferon monotherapy for HCV infection in patients with normal renal function is likely related to the synergistic activity played by ribavirin. However, the activity of ribavirin appears to be dose-dependent, and the effective role of low-dose ribavirin in enhancing the antiviral activity of interferon in dialysis patients remains to be determined. Controlled studies designed to answer this question should be performed.

Prospective studies are needed to assess whether the benefit of therapy in terms of lower mortality is realized in a patient population with significantly reduced long-term survival.

Conclusions

Combined therapy with peginterferon and ribavirin is the gold standard of treatment in the general population. However, ribavirin is not recommended in those patients with glomerular filtration rate less than 50 mL/min per 1.73 m^2. We recommend that standard interferon (3 million units thrice weekly subcutaneously) be used for the treatment of HCV-infected maintenance haemodialysis patients. For the kidney transplant candidate with HCV, we suggest a liver biopsy. For HCV-infected dialysis patients who are kidney transplant candidates, antiviral therapy is recommended even for those with a lesser degree of fibrosis on biopsy than is generally recommended for the non-CKD population. The data on combined antiviral therapy (standard or pegylated interferon plus ribavirin) in patients undergoing regular dialysis appear encouraging but more studies are needed to confirm these early findings before clear recommendations can be made.

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12 Management of HCV in patients with a renal transplant

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LEARNING POINTS

- HCV infection reduces both graft and patient survival in recipients of renal transplants.
- Progression of liver disease after renal transplantation is unpredictable, but liver disease remains a major cause of death.
- New-onset diabetes and renal lesions are both common after transplantation in patients infected with HCV.
- Historically, antiviral therapy has been avoided after renal transplantation due to risks of precipitating graft rejection. Recent small studies have challenged this dogma.

Background

The prevalence of antibodies against hepatitis C virus (HCV) varies between 10 and 49% in patients who have undergone kidney transplantation. Country, race and mode of dialysis treatment (haemodialysis vs. peritoneal dialysis) all have effects on this figure [1]. The frequency of HCV infection has steadily declined in patients on haemodialysis, and so has the prevalence of HCV infection in transplant recipients. A retrospective study of patients receiving allografts in Spain during 1990, 1994 and 1998 demonstrates a progressive decline in prevalence of HCV antibody, from 29.5% in 1990, 19% in 1994 to 10% in 1998 [2].

Although HCV infection influences graft and patient survival, it should not be considered a contraindication to renal transplantation. Sezer *et al.* [3] showed that the 5-year survival rates for HCV antibody-positive patients are significantly better if they receive a transplant rather than remaining on haemodialysis (85.2% vs. 74.5%).

The KDIGO (Kidney Disease: Improving Global Outcomes) clinical guidelines for HCV infection in chronic kidney disease recommend that antiviral therapy should be given to patients, even with mild fibrosis, who are being considered for renal transplantation [4]. This is discussed in Chapter 11. In those patients for whom therapy is inappropriate or for those who fail to respond to therapy, HCV infection can lead to potential complications in the renal allograft, the development of liver disease, and other health consequences (Table 12.1). These areas are discussed below.

Effect of HCV on graft and patient survival

HCV infection adversely affects both graft and patient survival. The increase in mortality has been demonstrated in many studies and appears to be a delayed effect, occurring between 5 and 10 years after transplantation [1]. Mathurin

TABLE 12.1 HCV-related complications after renal transplantation.

General
Reduced allograft survival
Reduced patient survival
Liver
Liver failure
Hepatocellular carcinoma
Fibrosing cholestatic hepatitis
Renal
Membranoproliferative glomerulonephritis
Membranous glomerulonephritis
Other
New-onset diabetes after transplantation

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et al. [5] published a case–control study in which 10-year survival was significantly lower in HCV-positive recipients compared with HCV-negative ones (63.5% vs. 85.3%; $P < 0.001$). Similarly, delayed effects on graft survival have been shown in many studies. Morales *et al.* [2] compared 10-year graft survival between the two groups and demonstrated a significant reduction (69% vs. 79%; $P < 0.0001$) in the HCV-positive patients.

Effects of transplantation on HCV-related liver disease

The increase in patient mortality is predominantly liver related. Death from hepatocellular carcinoma and liver failure is significantly higher in HCV-positive recipients than HCV-negative recipients [6]. However, the rate of fibrosis progression after transplantation is unclear. One case–control study of serial biopsies has shown a slower rate of progression compared with immunocompetent controls [7], whereas another matched study has shown a faster rate of fibrosis [8]. It is not clear whether different immunosuppression regimens alter fibrosis progression. With the increasing availability of non-invasive markers of fibrosis, such as liver stiffness measurement, it will become easier to assess fibrosis progression and the risk of end-stage liver disease in individual patients.

The time of acquisition of HCV influences the natural history of the associated liver disease. Although uncommon because of effective screening of donor blood and renal graft, infection at or around the time of renal transplantation is associated with a rapidly progressive course, leading to a 20% rate of hepatic decompensation within 7 years [9]. The reasons behind this observation remain unclear, but might relate to the level of immunosuppression in the early stages of the infection. Another small series describes how the rapidly progressive lesion, fibrosing cholestatic hepatitis, evolves more commonly in patients who acquire the virus at the time of transplantation. In a small series of four such patients, two died of liver failure within 18 months and two survived following dramatic reductions in immunosuppression [10].

Non-hepatic effects of HCV following renal transplantation

In addition to problems with liver disease, patients with HCV infection undergoing renal transplantation are at increased risk of developing new-onset diabetes and have a higher incidence of severe septic episodes. As in non-transplanted patients, renal lesions are common in the allograft and include both acute glomerulopathy and *de novo* immune complex glomerulonephritis.

The rates of new-onset diabetes after transplantation in HCV-positive recipients are threefold to fivefold higher than non-infected recipients, with an overall prevalence of 10–65%. It typically occurs within 3 months of transplantation and the risk of diabetes appears to be higher in tacrolimus-based immunosuppression regimens [4]. New-onset diabetes is a significant risk factor for major cardiac events and mortality following renal transplantation [11].

Renal lesions and proteinuria are more common in allografts in HCV antibody-positive recipients. Membranoproliferative glomerulonephritis (MPGN) is commonly observed in kidney allograft biopsies in HCV-infected patients with proteinuria and may be associated with both chronic allograft nephropathy and either *de novo* disease or post-transplant recurrence of the native kidney lesion [12]. Thus a biopsy of the kidney allograft should be performed in HCV-infected patients with proteinuria to look for evidence of cryoglobulinaemic MPGN [4], as there might be a role for rituximab therapy in such cases to rescue declining renal function [13].

Antiviral therapy after renal transplantation

Treatment of HCV infection in renal transplant patients remains controversial. Historically, it has been associated with both poor efficacy and an increased risk of interferon-induced allograft rejection. Interferon-based therapy has only been advocated in fibrosing cholestatic hepatitis where the potential benefits of treatment outweigh the risks of graft loss. Trials of monotherapy with ribavirin or amantadine have been disappointing and have shown no benefit in either reducing viral load or halting fibrosis.

The majority of the published studies of interferon-based treatment of HCV infection in renal transplant recipients have been observational studies of small patient numbers. It is therefore difficult to draw conclusions as to both efficacy of therapy and associated risks. A meta-analysis published in 2004 included 12 interferon-based treatment trials comprising 102 patients [14]. Treatment was discontinued in 35% of these patients, the majority due to graft dysfunction, and only 18% of them obtained a sustained

virological response (SVR). In nine of the trials, interferon was used as monotherapy, mainly at very high doses. Of the three trials that used interferon and ribavirin, one looked at acute HCV infection acquired at the time of transplantation and the other two included only 23 patients of whom seven had an SVR and three had graft dysfunction.

More recently, two studies have reported treatment with peginterferon and ribavirin, one in combined liver and kidney transplant recipients and the other in renal transplant alone. Both studies are small (six and eight patients respectively), and in both 50% obtained an SVR [15,16]. Appropriate dose reductions and use of growth factors were employed. Most importantly, there was no renal graft rejection reported in any of the patients included, although one patient developed haemolytic–uraemic syndrome.

The timing of treatment is also likely to be of importance. There appears to be an inverse relationship between the median time therapy is commenced after transplant and the risk of precipitating graft rejection. Although later treatment might not be as beneficial to the underlying liver disease or HCV-related renal disease, it may prove safer in terms of allograft survival.

In the future, STAT-C therapy will be valuable in the post-renal transplant patient with HCV infection. The side-effect profiles and interaction with immunosuppressant drugs will be a challenge and lessons are likely to be learned from the management of HCV recurrence after liver transplantation.

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13 Management of HCV in patients with psychiatric comorbidity

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LEARNING POINTS

- Psychiatric comorbidity is common in patients with chronic HCV infection.
- Psychiatric side effects are common following treatment with interferon alfa therapy.
- Treatment of patients with HCV infection and psychiatric comorbidity requires an interdisciplinary team approach including hepatologists and psychiatrists.
- Prospective clinical trials suggest that within an interdisciplinary team approach, patients with HCV infection and psychiatric comorbidity can be safely and effectively treated with antiviral regimens including interferon alfa.
- Early intervention with antidepressant therapy may attenuate/prevent major depressive episodes in those patients at risk of worsening depressive symptoms.

Introduction

One of the commonest challenges in the treatment of hepatitis C virus (HCV) infection is the management of a patient presenting with current or a past mental illness. Interferon, with its known neuropsychiatric side effects, is relatively contraindicated in these patients. However, this recommendation is based on the reporting of adverse events, as opposed to robust clinical trials conducted with patients suffering from psychiatric comorbidity. The occurrence of neuropsychiatric illness in patients with HCV infection is common; various studies have reported a prevalence of up to 60% of infected patients having concurrent significant psychiatric comorbidity [1,2]. This is perhaps unsurprising in view of the association between HCV and intravenous drug use, which is independently associated with a high prevalence of psychiatric comorbidity [3].

By inference patients with psychiatric illness represent an important reservoir of undiagnosed and untreated HCV infection [4]. One study reported the prevalence of HCV in patients with severe mental illness to be 20%, while half of those studied with both a substance use disorder and a psychiatric disorder were seropositive for exposure to HCV [1,5].

Neuropsychiatric side effects of Interferon therapy

The standard of care for the treatment of chronic HCV infection is currently a combination of peginterferon (alfa-2a or alfa-2b) and ribavirin. Importantly, emerging studies suggest that interferon-alfa will remain a key component of regimens incorporating the new HCV protease inhibitors [7]. The established psychiatric side effects of interferon therapy increase the complexity of treating patients with mental health problems as interferon may both exacerbate underlying symptoms and trigger new ones. Interferon alfa therapy has been associated with many neuropsychiatric side effects, including psychosis, mania, anxiety, suicidal ideation leading to suicide, anhedonia, irritability, cognitive disturbances, delirium and depression [8,9]. Studies estimate that neuropsychiatric side effects occur in up to 50% of all patients receiving treatment with peginterferon alfa and ribavirin, the commonest of which is depression. In trials from which subjects with significant unstable psychiatric illness were excluded, reported rates of depression vary widely, with up to 41% described in some series [6]. Mania and psychosis are much less common side effects of therapy; one study reported that 9 of 121 patients (7%) treated with interferon alfa developed these side effects. Importantly none of these

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tients had previous psychiatric illness and all their symp-ms resolved with cessation of therapy.

evious guidelines on the treatment of CV infection in patients with psychiatric morbidity

view of these established neuropsychiatric side effects, ny hepatologists are understandably reluctant to provide erferon to patients with HCV infection and psychiatric morbidity despite the relatively high prevalence of HCV this patient group. Indeed, consensus opinion from both European Association for the Study of the Liver and the tional Institutes of Health (NIH) in the 1990s recom-nded that pre-existing mental disorders were a con-ndication to antiviral therapy [10,11]. However, in the decade recognition of the prevalence of psychiatric morbidity in patients with HCV infection allied to a desire improve access to treatment has led to clinical trials for se patients. This shift in emphasis was reflected in the H consensus statement of 2002, which stated that efforts uld be made to increase availability of best current treat-nt for patients with chronic HCV infection who were ligible for trials because of neuropsychiatric comorbidity]. This statement also encouraged collaboration between atologists and mental health clinicians as a means of rdinating treatment for these patients.

eatment of HCV infection in patients th psychiatric illness: the evidence

s not surprising that there are few clinical trials which spectively address the issue of interferon alfa therapy atients with pre-existing psychiatric comorbidity. The lished trials are prone to limitations of small sample , heterogeneous patient populations and high drop-out s. However two small, prospective, controlled clinical ls published in 2003 and 2007 showed that both controls patients who had pre-existing psychiatric comorbidity erienced comparable rates of neuropsychiatric side effects, erence to treatment and sustained virological response R) in response to standard or pegylated interferon and virin [3,13]. These publications also describe no differ-e in the rates of new major depressive episodes during tment in these groups. Although these trials recruited tively small numbers of subjects (81 and 100), they llenge the preconception that patients with psychiatric orbidity are at increased risk of severe psychiatric side effects during therapy. The more recent of these trials, which treated patients with peginterferon, used a structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV diagnoses. The scale used for assessment of depression (Montgomery–Asberg Depression Scale, MADRS) and that used for assessment of psychosis (Brief Psychiatric Rating Scale, BPRS) are among the most widely used and psychometrically validated in psychiatric research, enhancing the impact of this paper. The authors of this study emphasize the importance of an interdisciplinary team approach involving hepatologists and mental health physicians in the successful treatment of these patients. Indeed, in this study all patients had at least three appointments with hepatologists and three appointments with psychiatrists prior to commencing interferon alfa-based therapy. Other studies have highlighted the importance of close collaboration between HCV specialists and psychiatrists in the treatment of patients with significant psychiatric comorbidity [4,14]. While these results support the widening of access to treatment for patients with mental health problems, it is important to note that patients who were deemed to have an unstable psychiatric disorder were appropriately excluded from these trials. Furthermore, those included had been subjected to extensive psychiatric assessment.

Schaefer *et al.* [3] reported an interesting observation which indicated that there was no increased incidence of depression in patients with psychiatric comorbidity compared with controls, during treatment with peginterferon alfa therapy. This was despite higher baseline depression scores in patients with psychiatric comorbidity at treatment initiation. One of the explanations for this was intervention with antidepressants prior to and during treatment, which may prevent or attenuate depressive reactions. This theory is supported by other studies. A stepwise logistic regression performed in this study suggested that genotype alone was predictive of SVR and the factors influencing response did not differ between patients with psychiatric comorbidity and the controls. This study supports other work suggesting that stable treated psychiatric comorbidity does not impact on adherence to antiviral therapy or rates of SVR [15].

Because patients with psychiatric comorbidity are common among those with chronic HCV infection, their treatment is crucial if the incidence and prevalence of HCV are to be reduced long term. It is also clear that patients with psychiatric comorbidity suffer significant morbidity and mortality from their untreated HCV infection, supporting the need for these patients to receive treatment wherever possible.

Conclusions

Psychiatric comorbidity is common in patients with chronic HCV infection. A formal psychiatric assessment requires expertise and is an important step prior to reaching decisions about the management of patients in whom psychiatric illness is suspected. Ideally, all patients with known psychiatric comorbidity should be assessed by a healthcare professional trained in psychiatric assessment who understands both the impact of HCV infection and the benefits and adverse effects of interferon-based regimens. Where this is not possible, hepatologists and clinical nurse specialists should receive training in the assessment of these patients. The use of formal psychometrically validated tools such as MADRS or BPRS will standardize and objectify assessment and improve the ability of the hepatologist to assess these patients.

In the absence of adequate psychiatric assessment and support for these patients, many of them will be excluded from access to interferon alfa-based therapy due to the fear of exacerbating or inducing severe psychiatric illnesses. While this prudent approach is entirely appropriate, it has long-term implications, not just for the individual patients who are denied access to effective treatment but also for the long-term prevalence and incidence of chronic HCV infection in the population. It is clear from the limited evidence available that a significant proportion of patients with chronic HCV infection and stable psychiatric comorbidity can be safely and effectively treated with antiviral regimens that include interferon alfa therapy.

Following assessment, patients who are deemed suitable to receive therapy with interferon should be closely followed through a course of antiviral therapy by both hepatologists and mental health professionals as part of a multidisciplinary team. Specialist clinics for patients with chronic HCV infection should ideally have a named psychiatrist with experience in this field attached to the team with regular scheduled multidisciplinary meetings to discuss the care of individual patients. Through close collaboration between hepatologists and mental health professionals, those patients with stable, well controlled, psychiatric comorbidity can be treated for their HCV infection safely and effectively.

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14 Morbid obesity and HCV: management strategies

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LEARNING POINTS

- Obesity is common in patients with chronic HCV infection.
- Obesity is associated with a reduced chance of viral clearance with antiviral therapy.
- Insulin resistance, the severity of which correlates with BMI in chronic HCV infection, is one mechanism by which response to antiviral therapy is reduced.
- Interventions targeted at reducing obesity and/or insulin resistance may improve treatment outcome.
- Antiviral therapy tailored to body weight improves rates of SVR.

Introduction

Obesity – a body mass index (BMI) of 30 kg/m^2 or above – is a global health problem affecting approximately 300 million people worldwide. Obese individuals with a BMI of 40 or above (World Health Organization class III obesity) are considered morbidly obese. The prevalence of obesity in patients with chronic hepatitis C virus (HCV) infection attending a single tertiary hospital setting has been estimated as 28.8% [1]. Obesity promotes hepatic fibrosis and is associated with more rapid progression to advanced liver disease, liver failure and hepatocellular carcinoma [2]. Higher morbidity and mortality is also demonstrated in the obese compared with non-obese in the liver transplant setting [3].

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Obese individuals with HCV infection have a lower chance of clearing the virus with antiviral therapy compared with individuals whose BMI is in the normal range when matched for genotype, viral load and severity of liver disease [4]. Obesity is independently associated with insulin resistance (IR) in patients with HCV infection who do not have cirrhosis. Obesity and IR predispose patients to the non-hepatic health problems of the metabolic syndrome and diabetes, and the latter is also associated with increased risk of hepatocellular carcinoma in HCV infection. The prevalence of IR increases with higher BMI and is associated with reduced response to antiviral therapy [5]. Thus, obesity in patients with HCV infection needs to be addressed prior to the start of antiviral therapy.

Obesity and sustained virological response

Three main mechanisms for the poor response to antiviral therapy in obese individuals with chronic HCV infection have been proposed: the actions of inflammatory cytokines (adipokines), IR and reduced interferon bioavailability.

Inflammatory cytokines

Central obesity is now recognized as a low-grade proinflammatory condition as evidenced by elevation in serum levels of inflammatory cytokines (adipokines) such as tumour necrosis factor (TNF)-α and interleukin (IL)-6 produced by adipocytes and stimulated macrophages and biologically active proteins (or hormones) including adiponectin and leptin. TNF-α induces suppression of SOCS3 (cytokine signaling protein 3), leading to reduced interferon signalling and thereby interfering with treatment efficacy in the obese with chronic HCV infection [6]. There

is a reciprocal association between BMI and adiponectin; low levels of adiponectin are associated with reduced HCV-specific CD4 and CD8 T-cell responses in patients with chronic HCV infection [7]. Leptin induces the production of TNF-α, IL-6, IL-12 and IL-1β, stimulating the Th1 immune response through which interferon mediates some of its antiviral effects. Although obese individuals have high circulating leptin levels, it has been suggested that leptin resistance contributes to a failure of Th1 immune stimulation; this may account for the poor response to interferon in obese patients with chronic HCV infection [8].

Insulin resistance

IR is associated with a lower rate of treatment-induced viral clearance [5]. The HCV core and NS5A proteins act directly to mediate IR [9]. Both obesity and HCV-induced TNF-α production induce IR through serine phosphorylation of the insulin receptor substrate subunit of the insulin receptor by c-jun terminal amino kinase (JNK) and IKβ/NF-κB, by acting directly on pancreatic β cells and via increased expression of SOCS3 [10]. While upregulation of SOCS3 may be partly genotype dependent, it may be that all obese individuals with HCV have increased expression of SOCS3 compared with their lean counterparts, accounting for the higher rate of IR and lower rates of sustained virological response (SVR) in obese patients independent of genotype effects [6].

Interferon bioavailability

Absorption of high-molecular-weight compounds occurs predominantly via the lymphatics as opposed to via capillaries [11]. Obese individuals may have impaired lymphatic drainage, potentially resulting in lower drug bioavailability and reduced access to the vascular space.

Management of obesity and insulin resistance in chronic HCV infection

An instinctive approach to the management of HCV infection in the obese is to target weight loss through lifestyle intervention, thereby potentially enhancing response to antiviral therapy. A collateral benefit of such interventions may be a reduction in the prevalence of metabolic syndrome (and therefore vascular risk). Modest weight loss achieved by diet and exercise in overweight patients with chronic HCV infection improves liver histology and fasting insulin levels [12]. An important future direction of the management of HCV in the obese will be to evaluate the rate of SVR following antiviral therapy in obese and/or insulin-resistant subjects with chronic HCV infection who have lost weight and/or reduced their IR through pretreatment lifestyle intervention.

Insulin-sensitizing agents have been used in attempts to both reduce IR and improve response to antiviral therapy; however, limited efficacy and side effects may preclude their use in chronic HCV infection. Metformin successfully improved (but did not reverse) IR in genotype 1 infected patients being treated concurrently with peginterferon and ribavirin, although no significant difference was achieved in rate of negative HCV PCR at weeks 12, 24, 48 or 72 compared with the patients not receiving metformin [13]. Similarly, while pioglitazone (a thiazolidinedione) improved IR in 3 of 5 non-responders to prior antiviral therapy, no patient achieved an early virological response at week 12 [14]. The use of insulin-sensitizing medications to enhance antiviral treatment response cannot be universally recommended at this time, but this is certainly an area for further study.

Management of HCV in the obese

Tailored antiviral therapy using weight-based dosing algorithms may overcome the problems with reduced drug delivery in the morbidly obese. Morbidly obese individuals at the extreme of body weight are unlikely to be receiving equivalent systemic drug dosages (particularly agents distributed outside the vascular space) when compared with their lean counterparts.

Of the two commercially available drugs, peginterferon alfa-2b is dosed by weight because, due to the 12-kDa polyethylene glycol (PEG) moiety, its volume of distribution varies substantially according to body weight; this is in contrast to peginterferon alfa-2a which has a molecular mass of 60 kDa (40-kDa PEG moiety) and therefore a volume of distribution that is not affected by body weight [8]. Both peginterferon alfa-2a and alfa-2b are coadministered with ribavirin, which although already dosed on weight category to some degree, may be limited by the dose that is prepackaged with peginterferon.

A handful of studies have investigated the role of weight-based dosing regimens in patients with HCV (Table 14.1).

TABLE 14.1 Outcomes of studies examining effects of weight-based antiviral therapy dosing on SVR and relapse rates.

Study population	Treatment regimen		Treatment duration	Outcomes (%)	
	Peginterferon (μg/week)	Ribavirin (mg/day)		SVR	Relapse
Hoffman et al. [15]					
Genotype 1	Peg-IFN alfa-2b 1.5 μg/kg	13.3 mg/kg	48 weeks	29	36
		13.3 mg/kg + EPO		19	40
		15.2 mg/kg + EPO		49*	8*
Jacobson et al. [16]					
Genotype 1	Peg-IFN alfa-2b 1.5 μg/kg	FD	48 weeks	28.9	29.6
		WBD		34†	23.0
Genotype 2/3	Peg-IFN alfa-2b 1.5 μg/kg	FD	24 or 48 weeks	59.5	8.3
		WBD		61.9‡	7.0
Fried et al. [17]					
Genotype 1, weight > 85 kg, high viral load (> 8×10^5 IU/mL)	Peg-IFN alfa-2a 180 μg	1200 mg	48 weeks	28.3	40
	Peg-IFN alfa-2a 180 μg	1600 mg		31.9	42
	Peg-IFN alfa-2a 270 μg	1200 mg		36.2	46
	Peg-IFN alfa-2a 270 μg	1600 mg		46.8§	19¶

† Significant compared with ribavirin 13.3 mg/kg ± EPO.
‡ $P = 0.005$ compared with FD group.
§ $P = 0.252$ compared with FD group.
¶ $P = 0.09$ compared with Peg-IFN alfa-2a 180 μg + RBV 1200 mg group.
¶ $P = 0.0001$ compared with Peg-IFN alfa-2a 180 μg + RBV 1200 mg group.
Peg-IFN, peginterferon; EPO, epoetin alfa.
FD, flat dose: 65–125 kg, ribavirin 800 mg.
WBD, weight-based dose: < 65 kg, ribavirin 800 mg; 65–85 kg, ribavirin 1000 mg; 85–105 kg, ribavirin 1200 mg; 105–125 kg, ribavirin 1400 mg.

Peginterferon in combination with high-dose ribavirin (15.2 mg/kg) with the support of epoetin alfa reduced relapse rates and increased the rate of SVR compared with low-dose ribavirin (13.3 mg/kg) [15]. There is evidence to suggest that weight-based dosing of ribavirin (800 mg for patients weighing < 65 kg, 1000 mg for patients weighing 65–85 kg, 1200 mg for patients weighing 85–105 kg, and 1400 mg for patients weighing > 105 but < 125 kg) is safe, and leads to higher rates of SVR compared with flat-dosed ribavirin in genotype 1 (but not genotype 2 or 3) patients [16]. The use of high-dose peginterferon alfa-2a (270 μg weekly) and ribavirin (up to 1600 mg daily) in difficult-to-treat patients with chronic HCV infection (genotype 1, high viral load, weight > 85 kg) leads to a numerically higher SVR rate (47% vs. 28%; $P = 0.09$) and lower relapse rate (19% vs. 40%; $P = 0.0001$) compared with patients receiving standard-dose regimens; however, high-dose treatment was less well tolerated, which may limit its universal use [17]. Most studies evaluating the efficacy of antiviral therapy have only a small proportion of obese patients, and even fewer who are morbidly obese. It is therefore not possible to provide evidence-based algorithms for antiviral therapy in the morbidly obese and it is clearly important that the optimum treatment regimen for these individuals is further investigated. Considerations for further investigation may include (i) the assessment of the safety of higher ribavirin dosages in individuals with body weight in excess of 125 kg and the efficacy of such doses in combination with peginterferon and (ii) drug dosage and/or duration of therapy based on presence and degree of IR.

Summary

Obesity impacts adversely on overall survival in patients chronically infected with HCV, because they are less likely to achieve SVR with antiviral therapy, disease progression

is more rapid (therefore risk of liver failure and hepatocellular carcinoma higher) and the outcome following liver transplant is worse. Obesity (and concomitant IR) may be managed with lifestyle interventions (including diet and physical activity) and/or insulin-sensitizing medications; however, the benefits of these approaches remain unproven. Further research is required to develop evidence-based antiviral treatment algorithms for such patients at the extreme of body weight and BMI.

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15 Management of cytopenias during chronic hepatitis C therapy

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LEARNING POINTS

- Clinical trials suggest that the use of erythrocyte colony-stimulating growth factors is efficacious in raising the haemoglobin concentration, maintaining ribavirin doses and improving quality of life. However, a favourable impact on SVR has not been observed.
- If used, the goal of erythropoietin therapy should be to maintain haemoglobin in the range 11–12 g/dL.
- G-CSF has been shown to be successful at maintaining neutrophil counts and avoiding dose reduction of peginterferon.
- Given the importance of therapy adherence for maximal virological response, it is appropriate to use G-CSF as an adjuvant therapy in order to allow the continuation of antiviral therapy. However, there is no consensus on the absolute neutrophil count (ANC) threshold at which it should be used. An ANC threshold of 500×10^6/L for the use of G-CSF appears reasonable.
- Thrombocytopenia exacerbated by interferon therapy is managed by dose reduction or discontinuation of interferon. The threshold for the platelet count for dose modification or drug discontinuation is dependent on the experience of the treating physician. Bleeding rarely evolves at platelet counts above 20×10^9/L.
- Thrombopoietin receptor agonists may provide an alternative to medication reduction or cessation but are currently under investigational use only.

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Introduction

The current standard of care for the treatment of chronic hepatitis C virus (HCV) infection focuses on treatment with peginterferon alfa and ribavirin [1,2]. The combination of these agents has been shown to produce a sustained virological response (SVR) in up to 46% (range 34–46%) of those with genotype 1 disease [1,2]. It has also been demonstrated that the chances of achieving an early and sustained virological response are higher when patients receive at least 80% of both their total interferon and ribavirin doses for at least 80% of the duration of therapy [3]. Recently, it has been established that maintenance of an adequate ribavirin dose throughout the entire treatment course may be the pivotal factor in the achievement of high SVR rates [4].

Despite this knowledge, our use of combination therapy for HCV infection is often limited by the development of adverse effects. Chief among these are the development of cytopenias, which can lead to dose reductions in up to 25% of patients [1,2].

Anaemia

The anaemia that develops as a result of treatment with peginterferon and ribavirin is primarily mediated by ribavirin-induced haemolysis and secondarily by interferon-mediated bone marrow suppression. The mechanism for ribavirin-induced red cell haemolysis is the accumulation of phosphorylated ribavirin within erythrocytes. The red cells are unable to break down these phosphates, which accumulate and lead to oxidative injury and cell lysis [5]. Concurrent bone marrow suppression from interferon

treatment renders the bone marrow unable to compensate for this haemolysis. Typically, the anaemia occurs within the first few weeks of therapy initiation [6].

It has been observed that median haemoglobin decreases seen with combination therapy are around 2.5 g/dL [1,2]. Likewise, significant anaemia (< 10 g/dL) has been reported in up to 13% of patients receiving combination therapy [1]. The package insert from the manufacturer of ribavirin recommends a dose reduction when the haemoglobin falls below 10 g/dL and discontinuation when it falls below 8.5 g/dL [7].

Since the anaemia experienced while on combination therapy is dose dependent, dose reduction of ribavirin has been a primary tactic to combat unacceptable levels of anaemia. However, we know that full-dose therapy yields maximal results. Therefore, the goal of the prescribing practitioner should be to maintain ribavirin and peginterferon doses for the duration of therapy. To that end, the use of recombinant human erythropoietin has been evaluated in the management of anaemia.

Epoetin alfa

Epoetin alfa is a recombinant form of erythropoietin, a glycoprotein normally produced by the kidney to stimulate red blood cell production by the bone marrow. The role of epoetin alfa has been established in the management of anaemia due to chronic renal disease, in HIV patients treated with zidovudine and in those who receive chemotherapy [8]. Given its efficacy in improving anaemia in these populations, its use has been evaluated in the management of anaemia due to treatment with interferon and ribavirin.

The use of epoetin alfa in the management of ribavirin-induced anaemia was evaluated in 185 patients with haemoglobin of 12 g/dL or less undergoing treatment with combination therapy for chronic HCV infection [9]. The authors found that in those patients randomized to receive weekly subcutaneous erythropoietin injections, the average haemoglobin increased by 2.2 g/dL and ribavirin doses were maintained in 88% of patients versus only 60% in the placebo group. Quality of life was also assessed and found to be significantly better in the group receiving epoetin alfa. Clearly, an improved perception of quality of life has implications for therapy maintenance and achievement of an SVR.

Most recently, Shiffman *et al.* [10] examined the rates of virological response in treatment-naive genotype 1 patients treated with combinations of peginterferon alfa-2b, weight-based ribavirin and epoetin at the outset of therapy. While there were no significant differences in rapid, early or end-of-treatment responses between groups, there were differences in the sustained responses. The group treated with high-dose weight-based ribavirin (15.2 mg/kg body weight daily), peginterferon and epoetin alfa had a significantly lower relapse rate and thus improved SVR. These results suggest that although epoetin alfa co-therapy is costly, it may improve our ability to treat with high-dose ribavirin and achieve improved SVR.

Of note, while adjuvant therapy with epoetin alfa is generally thought to be safe, there are potentially serious side effects associated with its use, including a risk of hypertension, thrombosis and cardiovascular events [8]. There have also been reports of pure red cell aplasia in conjunction with antibodies to erythropoietin in those treated for chronic HCV infection [11].

Darbepoetin

Darbepoetin is an erythropoiesis-stimulating protein that has effects similar to those of epoetin alfa. The advantage of darbepoetin is that it has a longer half-life and is given as a weekly or biweekly drug. It is currently indicated in the treatment of anaemia due to chronic renal disease and chemotherapy [12]. A 2007 Phase II study examined the role of darbepoetin and a granulocyte colony-stimulating factor (G-CSF) in the outcome of combination therapy for chronic HCV infection [13]. Darbepoetin was given on a biweekly basis to patients who developed haemoglobin concentrations less than 10.5 g/dL. Of the patients who received darbepoetin, 58% achieved SVR compared with 37% of those who did not receive darbepoetin. These findings suggest that the use of growth factors may improve our ability to maintain treatment, thereby improving rates of SVR. However, other studies have not demonstrated such benefit [14].

Iron supplementation

Iron supplementation in the presence of HCV infection may have harmful effects on hepatic fibrosis [15]. Early studies have even used iron reduction successfully as an adjuvant therapy in the treatment of chronic hepatitis [16]. There are currently no data to support or refute the use of iron supplementation in patients with ribavirin-mediated anaemia who are treated with epoetin alfa. Given its potentially deleterious effects on the course of chronic liver disease, iron supplementation is not recommended.

Recommendations

Currently, recombinant erythropoietin is not approved by the Food and Drug Administration to treat interferon- and ribavirin-mediated anaemia. Clinical trials suggest that the use of erythrocyte colony-stimulating growth factors is efficacious in raising haemoglobin concentrations, maintaining ribavirin doses and improving quality of life. We recommend initiation of epoetin alfa (40 000 units/week) or darbepoetin (3 μg/kg every other week) when haemoglobin levels fall to less than 10 g/dL. If they are used, the goal of erythropoietin therapy should be to maintain haemoglobin in the range 11–12 g/dL. In an effort to maintain these levels, the growth factors should be titrated accordingly.

Neutropenia

The neutropenia that accompanies combination therapy with peginterferon and ribavirin is thought to be due to interferon-related bone marrow toxicity. In the initial trials that established the efficacy of combination therapy, up to 19% of subjects underwent dose reductions of peginterferon for neutropenia [1,2]. Typically, neutropenia occurs within the first 3–4 months of therapy. The perceived concern of neutropenia is the development of infection. In an effort to evaluate the relationship between neutropenia and risk of infection during peginterferon and ribavirin treatment, Antonini *et al.* [17] found that the incidence of infection was 41 per 100 patient-years and the development of infection had a greater association with age than with severity of neutropenia. These findings suggest that interferon-mediated neutropenia does not confer increased risk of sepsis events. Despite our seeming lack of evidence for infection risk in the presence of interferon-mediated neutropenia, the manufacturers of both peginterferon alfa-2a and alfa-2b recommend dose reductions when the ANC falls below 750×10^6/L and discontinuation when it falls below 500×10^6/L [18,19]. In clinical practice, however, the threshold is 500×10^6/L and this serves as a balance between the maintenance of adequate doses of peginterferon and an acceptable risk of infection.

Filgrastim

Filgrastim (recombinant G-CSF) is indicated in the treatment of neutropenia for those with cancer receiving myelosuppressive chemotherapy or bone marrow transplants, those undergoing peripheral progenitor cell collection and those with severe chronic neutropenia. G-CSF has been studied in patients undergoing therapy for HCV infection in an effort to maintain peginterferon therapy.

Koirala *et al.* [20] examined a group of 60 patients being treated for HCV infection with peginterferon and ribavirin to determine the appropriate dose of G-CSF and timing of administration. In this observational study, 30 of 60 subjects developed neutropenia (ANC $< 1000 \times 10^6$/L) and were started on weekly G-CSF. While G-CSF improved neutrophil counts in those who received it, there was no difference in SVR rates between those who were treated and those who were not. An important finding of the study was that most patients who developed neutropenia were successfully maintained on a filgrastim dose of 300 μg per week, although a few patients received higher or lower doses as needed. The only adverse effect reported was bone pain, which was reduced when filgrastim was given 2 days apart from interferon.

Koskinas *et al.* [21] performed a retrospective study to examine the safety and efficacy of G-CSF in patients undergoing combination therapy and the virological outcomes. They found that adherence to antiviral therapy was 95% in the group treated with G-CSF as compared with 73.1% in the group who underwent standard dose reductions for neutropenia (ANC $< 800 \times 10^6$/L). Furthermore, none in the G-CSF group required dose reductions. There was no difference in SVR between the group receiving G-CSF and the group that did not. The authors concluded that G-CSF therapy represented an important agent in the maintenance of antiviral dose and has promise in showing improvement in virological outcomes in a randomized controlled trial.

Recommendations

The data regarding the use of G-CSF is limited by the fact that these are observational studies. G-CSF has been shown to be successful at maintaining neutrophil counts and avoiding dose reduction of peginterferon. Given the importance of therapy adherence for maximal virological response, it is appropriate to use G-CSF as adjuvant therapy in order to allow the continuation of antiviral therapy. Likewise, an association between the development of significant infection and level or duration of neutropenia has not been observed in clinical trials [17]. We recommend initiating adjuvant therapy with G-CSF 300 μg weekly when ANC falls below 500×10^6/L. The dose and frequency of G-CSF administration should be tailored to the patient's ANC response.

Thrombocytopenia

Thrombocytopenia is a common complication of chronic HCV infection and is multifactorial in nature. Direct virus-mediated bone marrow inhibition, splenic sequestration of platelets and decreased hepatic production of thrombopoietin are all contributors. Approximately 13% of patients with cirrhosis have moderate thrombocytopenia (platelet count $50–75 \times 10^9$/L) [22]. Many patients with HCV infection and concurrent thrombocytopenia are excluded from treatment consideration due to the presence of thrombocytopenia, since it can be exacerbated by interferon-related marrow suppression. Typically, thrombocytopenia occurs within the first 8 weeks of therapy and is managed by peginterferon dose reduction or discontinuation depending on the severity of thrombocytopenia. The manufacturers of peginterferon alfa-2a and alfa-2b have recommended dose reduction for platelet counts less than 50×10^9/L and discontinuation for platelet counts less than 25×10^9/L [18,19].

Interleukin-11

Oprelvekin is a recombinant human interleukin-11 that is approved for the prevention of thrombocytopenia in patients receiving chemotherapy. Oprelvekin was evaluated in 13 patients with platelet counts of less than 100×10^9/L undergoing therapy with standard interferon and ribavirin [23]. Although platelet counts improved in those who received oprelvekin, the major side effect of water retention resulted in diuretic use in most patients. Given the serious side-effect profile, the use of oprelvekin is limited.

Eltrombopag

Eltrombopag is an oral thrombopoietin receptor agonist approved for use in refractory idiopathic thrombocytopenic pupura. Given the potential of other haematological growth factors in the management of treatment-related cytopenias, it has been considered in the management of patient with HCV infection. Recently, McHutchison *et al.* [24] evaluated the efficacy of eltrombopag in patients with HCV-related cirrhosis and platelet counts between 20 and 70×10^9/L [24]; 74 patients were randomized to receive placebo or three graduated doses of eltrombopag. At 4 weeks of treatment, 95% of those receiving the highest dose of eltrombopag (75 mg) had platelet counts of 100×10^9/L or greater, while none of the patients in the placebo arm had platelet counts greater than 100×10^9/L. Antiviral combination therapy was then commenced for 12 weeks in those with platelet counts greater than 70×10^9/L. Although platelet counts were found to decrease during antiviral therapy, those receiving concurrent eltrombopag maintained higher platelet counts than those in the placebo group. The authors concluded that therapy with eltrompobag increased platelet counts sufficiently to allow the initiation of combination therapy for HCV infection.

Recommendations

We recommend that thrombocytopenia that is exacerbated by interferon therapy should be managed by dose reduction or discontinuation of interferon. Thrombopoietin receptor agonists may provide an alternative to medication reduction or cessation but are currently under investigational use only.

Summary

Table 15.1 shows the recommended course of action when cytopenias occur during the treatment of HCV infection.

TABLE 15.1 Summary of recommendations.

Anaemia	
Haemoglobin ≤ 10 g/dL	Initiate therapy with epoetin alfa 40 000 units/week or darbepoetin 3 μg/kg biweekly Goal: haemoglobin 11–12 g/dL. Titrate growth factors as necessary
Neutropenia	
ANC ≤ 500×10^6/L	Initiate therapy with G-CSF 300 μg weekly Goal: ANC > 1500×10^6/L
Thrombocytopenia	
Platelet count ≤ 50×10^9/L	Dose reduction of peginterferon. Some clinicians may not reduce at this dose and continue off-label full dose until platelet count ≤ 25×10^9/L
Platelet count ≤ 25×10^9/L	Discontinuation of peginterferon

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16 Management of patients with multiple HCV genotypes

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LEARNING POINTS

- Infection with multiple HCV genotypes may occur in up to 10% of infected patients.
- The optimal assay system for identifying multiple genotypes is unclear and current assays may underestimate the prevalence of this disorder.
- The pathological and clinical relevance of infection with multiple genotypes is unclear but there may be compartmentalization of the different strains and a dominant strain may emerge.
- Therapy for patients with multiple genotypes should probably involve a treatment duration dictated by the most treatment-insensitive strain.

Introduction

Hepatitis C virus (HCV) may be divided into at least six major genotypes and more than 30 subtypes according to the phylogenies of available HCV sequences [1]. Moreover, even in patients infected with a single HCV subtype, HCV circulates as a group of variants with up to 10% nucleotide sequence difference, termed quasi-species. Perhaps due to the lack of protective immunity, superinfection by different HCV isolates in patients with chronic HCV is clinically observed, particularly in individuals at very high risk for infection, such as injection drug users, patients on haemodialysis and patients who received multiple blood transfusions in the era before HCV screening of blood donors was introduced. Multiple infection by different HCV genotypes may be of great clinicopathological interest.

Extent of the problem

The extent of infection with multiple different subtypes/genotypes of HCV simultaneously in a given individual is controversial. Basically there are two different scenarios that may result in the presence of more than one genotype: superinfection by another genotype of a patient already infected with a single genotype [2] or co-infection with multiple genotypes.

The results of studies about frequency and clinical implications of co-infections are conflicting, possibly due to problems associated with testing for HCV genotype and subtypes. Using serological methods it has been shown that patients infected with a single genotype of HCV may experience transient or occult superinfection with different genotypes of HCV [3]. Today, the most commonly used genotyping test is the line probe assay, which explores changes in the 5′ untranslated region (5′-UTR). Using this testing methodology, multiple HCV genotypes were detected in 10.8% of HCV monoinfected patients [4] and in 5% of HCV/HIV co-infected patients [5]. In the latter group, the presence of multiple HCV genotypes was associated with faster HIV progression. However, it should be noted that the 5′-UTR genotyping approach is not necessarily the most appropriate way to identify infection with multiple genotypes. One consistent error in conventional 5′-UTR-based assays is between subtypes 1a and 1b; about 20% of subtype 1a isolates may be misclassified as subtype 1b due to differences in only a single nucleotide [6,7]. Thus more accurate tests have to be used to ensure that multiple infections with different viral strains are detected.

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One attractive explanation for the persistence of multiple different genotypes of HCV is that the different genotypes may persist in different viral reservoirs. Extensive distribution of HCV genomes throughout non-hepatic reservoirs has been described, and some evidence supports the hypothesis that different HCV variants may acquire specific tropism for hepatic versus non-hepatic reservoirs. However, the issue remains controversial, and one of the major limitations in reaching consensus about this aspect of HCV virology is that there are many technical approaches described for assessing HCV genotype [8].

Clinical implications of infection with multiple genotypes

The clinical implications of infection with multiple HCV genotypes are unknown and the clinical trials completed so far have almost invariably excluded such patients, leading to difficulties in assessing the impact of infection with multiple genotypes on treatment response. The setting of liver transplantation where both recipient and donor are infected with different HCV strains provides an interesting scenario for studying host–virus and virus–virus interactions, although the immunosuppression used to prevent rejection of the transplanted liver may modify the nature of the interactions. In six HCV-positive liver donor–recipient pairs, serial serum samples were collected at multiple time points. At each time point, HCV genotype was determined by restriction fragment length polymorphism analysis and phylogenetic analysis. Furthermore, three full-length HCV isolates at the earliest time points after liver transplantation were selectively sequenced, including both 5′ and 3′ ends. Detailed genetic analyses showed that only one strain of HCV could be identified at each time point in all six cases. Recipient HCV strains took over in three cases, whereas donor HCV strains dominated after liver transplantation in the remaining patients. In all six cases studied, no genetic recombination was detected among HCV quasi-species or between donor and recipient HCV strains [9]. Similar observations have been made by others [10] and these suggest that in multiply infected patients one viral sequence will dominate.

A French study [11] investigated 119 patients with previously untreated chronic HCV infection. The internal ribosomal entry site (IRES) of HCV RNA was amplified and compared between plasma and peripheral blood mononuclear cells (PBMCs) by means of single-strand conformational polymorphism (SSCP) analysis, line-probe assay and cloning sequencing. The IRES SSCP patterns differed between plasma and PBMCs in 54 (48%) of 113 assessable patients; 24% of these patients were co-infected by two HCV types or subtypes, only one of which was detectable in PBMCs ($N = 25$) or in plasma ($N = 2$). SSCP-defined compartmentalization was more frequent in former drug users than in others, and less frequent in patients with genotype 1 HCV in plasma. Patients co-infected by two or more HCV variants were more likely to experience a sustained virological response to peginterferon/ribavirin combination therapy. In contrast, a large study in HCV patients from Alaska did not confirm the presence of compartmentalization. A large proportion of mixed-genotype and switching-genotype patterns generated by 5′-UTR analysis were not reproducible using the heteroduplex mobility analysis approach [8].

Summary

Infections with multiple HCV genotypes may occur in some patients, but technical issues regarding optimal test procedures have to be resolved before the clinical implications of this condition can be assessed. Some studies indicate that the presence of multiple genotypes has important implications for choosing therapeutic regimens but this has not been universally accepted. In clinical practice the dominance of one viral genotype will usually ensure that only one viral strain is detected but it is prudent to ensure that a recent genotyping result is used to determine treatment duration as reinfection (or reactivation) of other strains may lead to a change in the dominant genotype over time. In patients who relapse following therapy, many clinicians repeat the viral genotyping assessment to ensure that activation is with the dominant pretreatment strain.

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17 HCV and injecting drug users: how do we approach them?

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LEARNING POINTS

- Chronic infection with HCV is common in those who use illicit drugs.
- Illicit drug users may be categorized as regular users, those who are stable on opiate replacement therapy, or as past injectors. Each phase of activity is unstable and many drug users oscillate between the different stages.
- Uptake of antiviral therapy is low in active injectors and in those who are stable on opiate replacement therapy. However, successful therapy has been achieved, particularly in the latter group, and case-by-case assessment is required.
- Treatment in past injectors is common and usually associated with excellent compliance and success rates.

Introduction

Hepatitis C virus (HCV) infection is hyperendemic among injecting drug users. Within a few years of starting drugs, the majority will be exposed to the virus and approximately 50% will develop chronic HCV infection sooner or later [1]. The main route of transmission is obviously sharing of needles but HCV is probably also transmitted within the drug-user community by other routes including sharing of cookers (used to heat the drugs and dissolve them) and cotton filters (used for filtration to remove contaminating material from the drugs) [2].

Chronic HCV infection is a slowly progressive disease and few develop symptoms before they are in their sixth decade [2]. Considering the difficulties in delivering HCV treatment, it seems reasonable to ask whether injecting drug users be offered this? In my view the answer is yes. The natural history of injecting drug use frequently manifests as a lifelong history of dependency, with individuals moving between active drug use, maintenance treatment and abstinence of variable duration [3]. In other words, in a great numbers of HCV patients the drug dependency will always be there and HCV infection will have to be dealt with within this frame. It is also important to note that the response to HCV treatment is strongly associated with the age of the patient. In fact for every decade treatment is postponed, the chance of obtaining a sustained virological response (SVR) will decrease by approximately 10% [4]. Therefore, in injecting drug users with an indication for HCV therapy, treatment should be delivered as soon as possible and during any phase of drug addiction.

This chapter reviews some of the experience gathered so far on providing HCV care to injecting drug users.

The problems

There are several challenges that have to be understood and dealt with before effective HCV care can be provided to this patient group.

1 Treatment uptake: even though there are numerous drug users in need of HCV therapy, only a minority are treated. Why this is the case and how we should reach the unreachable is unclear.
2 Adherence: it is still unclear whether drug users who start HCV treatment are less likely to adhere to treatment. If so, we need to develop strategies that allow us to help drug users to adhere to therapy.
3 Side effects of HCV treatment are numerous and sometimes even dangerous. It is unclear how best these can be safely managed within the context of drug dependency.
4 Relapse to drug use: it is unknown whether there is an increased risk of relapse to drug use in patients who are

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currently abstinent or on maintenance therapy when HCV treatment is delivered.

5 Reinfection: even though HCV may be successfully treated in drug use, it may be futile due to a high risk of reinfection.

Approaches to therapy during different phases of addiction

Phase 1: active drug use

Active injecting drug users are difficult to reach. In Oslo we performed an epidemiological study among users of the needle exchange programme within the city [5]. Drug users willingly took part in the study and 420 were tested for anti-HCV and HCV RNA in serum. HCV RNA was detectable in 200 and these received a letter with information about the disease they had contracted and an invitation to come to the outpatient clinic at a local hospital for further diagnostics and eventually treatment. Only four of the 200 showed up: two were treated and one achieved SVR. In Amsterdam a stronger effort has been made to reach this patient group [6]. A project has been developed with a committed nurse, a hepatologist and a specialist on maintenance treatment in the team. The cohort of active drug users in this study comprise 466 persons, among whom 125 have been diagnosed with chronic HCV infection. In the last report from this project 13 have started treatment. This study illustrates that even with major efforts only 10% of injectors access HCV treatment in this population. Better results were recently reported from London. In this study a community-based treatment programme was established and antiviral therapy was offered to all drug users who wanted it [7]. Of the 441 patients who were known to be HCV RNA positive and who attended the specialist addiction services in the area, 58 started treatment and 50% achieved SVR. Neither active drug use nor homelessness was associated with low adherence. In Seattle, a cohort of active drug users were followed regularly with HCV testing. Those who became HCV RNA positive were offered HCV treatment in the acute phase. In 21 patients such treatment was started but only four completed therapy. SVR was obtained in three patients. Unfortunately, two of these were soon reinfected (Wang AASLD 2005).

Phase 2: maintenance treatment

HCV treatment uptake among methadone users has not been well documented, but in this phase of drug dependency it also appears to be low. For example, in Oslo all methadone users with an indication for HCV treatment were offered treatment if HCV RNA was detectable and alanine aminotransferase was elevated and no contraindication was evident [8]. An indication for treatment was found in 180 patients but only 18 started treatment. However, when treatment is started, methadone users seem to adhere well to HCV treatment. In a German trial that included 50 patients stable on methadone and 50 controls infected through drug use but abstinent and without maintenance treatment for 5 years, it was found that 75% of methadone users adhered to therapy with peginterferon alfa and ribavirin compared with 85% of controls [9]. In both methadone users and controls, those who did not comply with treatment almost always stopped treatment within the first 4 weeks of treatment. The SVR rates were 21% in cases and 28% in controls ($P = 0.16$).

Side effects are common during treatment with interferon and ribavirin. Psychiatric side effects including psychosis and serious depression may be induced and suicides have occurred. Drug addiction and psychiatric diseases often coexist and it is therefore a concern that pre-existing psychiatric disease may be seriously exacerbated during interferon treatment. In the German trial, 15 of 50 treated methadone users and 10 of 50 controls started treatment with antidepressive drugs during HCV treatment [9]. Thus, the incidence of depression was high and awareness of the problem is mandatory. Patients with ongoing moderate or grave depression should not start interferon treatment and close contact should be maintained during HCV treatment for patients belonging to this vulnerable group. In several centres, directly observed therapy is administered to injecting drug users by weekly injection of peginterferon, enabling the necessary contact between health provider and patient.

It is conceivable that the side effects and perhaps even the exposure to needles increases the risk of patients on maintenance treatment relapsing to injecting drug use. However, in the German trial no case of relapse during treatment or during the 6-month follow-up period was recorded [9]. In another German study at a detox center, HCV treatment was introduced immediately after methadone [10]. Among the 50 enrolled unstable methadone users, 25 soon relapsed to drug use and three later stated that the relapse was connected to the HCV treatment. SVR had been obtained in 18 patients, and at follow-up 33 months later two were most probably reinfected. The incidence of reinfection was 0–4 per 100 person-years of follow-up [11].

Phase 3: abstinence

It is probably during abstinence that most drug dependents seek HCV treatment. Treatment uptake in these patients is difficult to estimate but is probably not very different from that for HCV patients in general. It was recently calculated that treatment uptake in most of Europe ranged from 5 to 15% [11].

In a Scandinavian treatment trial, 432 patients with genotype 2 or 3 infection were included [12]. Previous frequent drug use was reported by half of the patients included in the study. Approximately 80% took more than 80% of both drugs more than 80% of the prescribed time. The rate of adherence was independent of whether the patient was a former regular drug user or not. Relapse to drug use was observed in 15 of 186 former regular users and death due to overdose occurred in two of these. In another study by our group we performed a follow-up 5 years after HCV treatment to abstinent drug users [13]. We found that 9 of 27 sustained responders had relapsed to drug use and that one had been reinfected with HCV.

Conclusion

HCV is endemic among injecting drug users. When HCV treatment is indicated, treatment should be provided as soon as possible. Drug dependency often oscillates between three phases: active drug use, maintenance treatment, and abstinence. Treatment uptake is low among active drug users and reinfection may occur. Active drug users who seek treatment for HCV should be considered for therapy on an individual basis. Treatment uptake is probably also low among those on maintenance treatment. These are patients who may be reached and efforts should be made to increase HCV treatment uptake in this group. HCV treatment should preferably be postponed until the patient is stabilized on maintenance treatment. This phase often provides the opportunity to deliver directly observed therapy. Treatment to abstinent drug users is as effective as in non-drug users. Relapse to drug use may occur, but reinfection is a rare event. Psychatric illnesses are common among the drug dependent and high awareness of psychiatric side effects during HCV treatment is important.

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18 HCV with and without autoimmune features: how do you sort them out and manage?

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LEARNING POINTS

- Antiviral therapy for HCV comprises peginterferon alfa and ribavirin, which are thought to have immunostimulatory activities.
- Medical therapy of autoimmune hepatitis is with immunosuppressive medications.
- Autoantibody positivity (ANA, SMA, anti-LKM1), which is central to the diagnosis of autoimmune hepatitis, is also common in the setting of chronic HCV.
- In general, ANA or SMA positivity in the setting of HCV does not affect disease progression or response to antiviral therapy.
- Occasionally, chronic HCV with autoimmune features may be present. Since antiviral therapy with immunostimulatory medications can exacerbate underlying immune processes, it is important to identify these patients. High-titre ANA or SMA positivity, unusually highly elevated liver enzymes and liver biopsy suggestive of autoimmune hepatitis should heighten suspicion of chronic HCV with autoimmune features.
- In general, antiviral therapy of HCV should proceed in the usual fashion in the setting of ANA or SMA positivity; however, if HCV with autoimmune features is suspected, antiviral therapy with interferon alfa-based medical regimens should be deferred.

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Introduction

Hepatitis C virus (HCV) is a linear single-stranded RNA virus of the *Flaviviridae* family that was first identified in 1980 as the major causal agent of non-A, non-B hepatitis. It is estimated that there are 170 million people infected worldwide with HCV, with a global prevalence of 3% [1]. Approximately 30% of patients with chronic disease will develop cirrhosis over an estimated 20-year period. Almost all afflicted patients have histological hepatitis, although there are no pathognomonic features for HCV. Findings include focal areas of necrosis, periportal necrosis, chronic inflammation and fibrosis. Steatosis is also common. Peginterferon alfa-2a or alfa-2b in combination with ribavirin comprise the standard treatment regimen for HCV. Although the precise mechanisms of action are unclear, peginterferon is thought to have immunostimulatory activities.

Conversely, autoimmune hepatitis (AIH) is a progressive chronic inflammatory hepatitis of uncertain aetiology. It has been identified throughout the world. The clinical presentation is wide, ranging from asymptomatic disease to chronic non-specific symptoms such as fatigue. Patients may present with complications of cirrhosis. Alternatively, severe acute hepatitis may be observed. There is no single definitive diagnostic test that confirms the diagnosis; however, serological tests are important including antinuclear antibody (ANA), smooth muscle antibody (SMA) and anti-LKM1. Liver biopsy is vital to the diagnosis. Findings may include periportal necrosis, periportal plasma cell infiltration and fibrosis. It is important to accurately diagnose this condition as it is responsive to immunosuppressive therapy.

Chronic HCV infection is associated with several immunological abnormalities, such as production of autoantibodies and cryoglobulins [2]. Although some of the immunological disorders, such as mixed cryoglobulinaemia or membranoproliferative glomerulonephritis, may affect clinical outcome the presence of non-organ-specific antibodies (i.e. ANA, SMA) is of uncertain clinical relevance [3]. When detection of anti-HCV antibodies and HCV RNA became available, the first autoantibodies to be associated with HCV were those recognized as markers of AIH including SMA, ANA and anti-LKM1 [4]. Since then, other autoantibodies including anti-neutrophil cytoplasmic antibody (ANCA), anti-parietal cell antibody, anti-thyroid antibodies and rheumatoid factor have been associated with chronic HCV, although the clinical significance remains unclear [5].

In this chapter, the roles of ANA, SMA and anti-LKM1 are discussed with regard to chronic HCV infection and its link to autoimmune phenomena. Further, the evaluation and management of patients with HCV and autoimmune features are discussed.

Prevalence

There is wide variability in the reported prevalence of autoantibodies in chronic HCV (Table 18.1). This is likely related to the different laboratory techniques used to detect autoantibodies, the titres at which positive results are reported, and geographical and ethnic variations in the populations examined [6]. Studies show that SMA is the most frequently detected autoantibody in HCV, identified in 10–66% of cases. ANA occurs in 7–63% of chronic HCV patients in comparison with 5% of healthy controls [6]. Treatment of HCV with autoimmune features may exacerbate underlying AIH, so resolving the dilemma of whether or not autoantibody positivity has clinical relevance is important [7].

Prevalence of ANA

ANA is an autoantibody directed against various nuclear antigens including DNA, RNA, histones, acidic nuclear proteins, or complexes of these molecular elements. In a cross-sectional study of adult naive patients with biopsy-proven chronic HCV from South America, the incidence of ANA positivity was 9.4% when an ANA titre of 1 : 80 was considered positive [2]. A similar study from the UK documented an incidence of 5.6% when an ANA titre of either 1 : 32 or 1 : 40 was considered positive [6]. Furthermore, the presence of ANA was associated with increasing age (45 vs. 39 years; $P < 0.001$). In an Italian cohort the incidence of ANA positivity was 7.7% when a titre of 1 : 40 was considered positive [8]. Once again, an association between increasing age and presence of ANA positivity was documented. It is possible that the relationship between age and presence of ANA could represent an ageing immune system that is more prone to developing autoantibodies.

Prevalence of SMA

Much like ANA, the variability of SMA positivity is likely multifactorial. SMA tends to be the most common autoantibody encountered in chronic HCV infection. In a cohort from the UK, the documented incidence of SMA was 10.8%, whereas it was 12.7–20% in two Italian cohorts [4,6].

Prevalence of ANA and SMA

Whereas the prevalence of autoantibody positivity in the setting of chronic HCV was 23.5% and 17.9% in Italian and British cohorts, respectively, the presence of concomitant

TABLE 18.1 Prevalence of autoantibodies in chronic HCV infection.

Autoantibodies	Prevalence	Comment
ANA	9–38%	Does not alter clinical course or predict response to treatment
Anti-SMA	5–91%	Does not alter clinical course or predict response to treatment
Anti-LKM1	0–10%	Presence of anti-LKM1 may lead to marked elevation in liver function tests in patients with HCV on interferon-based therapy
Rheumatoid factor	8–76%	Significance unclear
Anti-thyroid antibodies	9–20%	May be at increased risk for thyroid dysfunction following interferon-based therapy

antibody positivity was 2.1% in the Italian study and 1.5% in the British study [6,8].

Prevalence of LKM1 antibody

The target of anti-LKM1 is the isoform 2D6 of the cytochrome P450 family, located in the microsomal fraction of the hepatocyte. However, it may also be exposed on the plasma membrane, thus allowing accessibility to immune system effectors [9]. In patients with chronic HCV infection, the overall prevalence of anti-LKM1 in adult populations tends to be low, ranging from 0 to 10% [3,10–12].

Pathophysiology

There is increasing evidence that autoantibody production appears to be due to non-specific activation of the immune system during the course of chronic HCV infection. HCV is capable of infecting lymph nodes, which can then serve as haematopoietic reservoirs [13]. These reservoirs can potentially play a role in viral persistence through mechanisms such as immune escape and viral modulation of the immune system. In fact, the infected phenotypes in lymph nodes are primarily CD20 B cells, which can be responsible for antibody production [13]. It is possible that B cells and other lymphocytes circulating in blood through the liver may become infected. Local infection within the perihepatic lymph nodes may then be established. Alternatively, HCV infection might spread locally through the lymphatics to perihepatic lymph nodes where B cells and other lymphocytes become infected.

It is possible that the interaction between B lymphocytes and HCV leads to B-lymphocyte proliferative disorders, ranging from autoantibody production to lymphoma. In fact, an *in vitro* recombinant form of the major HCV envelope protein E2 binds with high affinity to the CD81 molecule, which is present on not only hepatocytes but also B lymphocytes [14]. On B lymphocytes, CD81 associates with CD21 and CD19, forming a complex that when appropriately engaged can lower the B-cell activation threshold [15]. HCV targets this complex via E2 and perhaps delivers a costimulatory signal to B cells, leading to activation and production of autoantibodies *in vivo*.

Finally, there is an additional hypothesis that molecular mimicry might play an important role in the production of LKM1 autoantibodies. LKM1 autoantibodies specifically target cytochrome P450IID6 (CYP2D6), a protein located on the cytoplasmic side of the endoplasmic reticulum of hepatocytes. It appears that circulating autoantibodies in patients with HCV who are also LKM1 positive are directed against conformational epitopes of CYP2D6, while autoantibodies in type 2 AIH recognize linear epitopes on CYP2D6 [16]. Using immunoprecipitation and absorption with CYP2D6-absorbing resin, molecular mimicry at the B-cell level between CYP2D6 and HCV NS3 and NS5a proteins has been confirmed [16]. This suggests that the antibodies that recognize CYP2D6 also recognize NS3, NS5a, or NS3 and NS5a, leading in some cases to anti-LKM1 positivity. The putative regions of NS3 and NS5a that cross-react with CYP2D6 are highly conserved in HCV genotypes 1a, 1b, 2, 3, 4, 5 and 6, elucidating the possible presence of anti-LKM1 in all genotypes.

Clinical significance of presence of autoantibodies

There is ongoing debate about the clinical significance of autoantibodies in patients with chronic HCV infection. After the identification of HCV as the aetiology of non-A, non-B hepatitis, the first-generation diagnostic antibody tests were insensitive. In fact, the first-generation enzyme immunoassays (EIA-1) were positive in only 80% of patients infected with chronic HCV [17]. This was primarily due to the fact that EIA-1 only used a single target antigen. Not only was EIA-1 insensitive, false-positive results were common. In particular, patients with AIH occasionally had HCV EIA-1 positivity. Unfortunately, some chronic HCV patients with negative EIA-1 but positive autoantibodies were misidentified as having AIH and were erroneously treated with immunosuppressive medications. Alternatively, some AIH patients with false-positive HCV EIA-1 and positive autoantibodies were misidentified and treated with antiviral therapy.

The first-generation HCV EIA-1 test subsequently evolved into a multi-antigen test (EIA-2 and later EIA-3) that not only improved the sensitivity to 97% but also allowed earlier identification of acute infection and fewer false-positive results [18]. This led to the appropriate diagnosis and treatment of chronic HCV and AIH. However, the question of whether the presence of autoantibodies alters disease course or response to treatment of HCV was unresolved.

Multiple epidemiological studies have evaluated this issue, and it appears that the presence of ANA or SMA does not affect disease progression or response to therapy. In a cross-sectional study of 234 patients with biopsy-proven chronic HCV and

ANA positivity, the prevalence of ANA was not associated with fibrosis stage or portal/periportal and lobular necroinflammatory changes [2]. Furthermore, histological features of AIH such as lymphoplasmacytic infiltration and hepatocyte rosettes were not found in ANA-positive patients. The presence of ANA did not influence response to antiviral therapy. The incidence of on-treatment flares in alanine aminotransferase (ALT) was 12%, and the ALT elevations were mild (about two to three times the upper limit of normal). There was no correlation between ALT flares on treatment and ANA positivity [2]. Similarly, in a British cohort of 927 patients, there was no association between total Ishak score, necroinflammatory grade, fibrosis, viral genotype, or liver panel values in patients with chronic HCV infection who were ANA positive, SMA positive, or both [6].

Although the presence of ANA and SMA might reflect epiphenomena, the presence of anti-LKM1 may indicate a propensity towards worsening liver enzyme elevations with interferon-based therapy. In a retrospective study in which 60 patients with chronic HCV infection and anti-LKM1 positivity were compared with age- and sex-matched patients with chronic HCV infection and anti-LKM1 negativity, there was a 7% likelihood of developing severe liver enzyme elevations (10 times the upper limit of normal) on interferon therapy [9]. Interestingly, two patients developed *de novo* anti-LKM1 positivity during a hepatitis flare in the group with anti-LKM1 negativity. Furthermore, of the 22 patients with chronic HCV and anti-LKM1 positivity, anti-LKM1 disappeared in 11 of 12 patients achieving a sustained virological response (SVR) but in only 4 of 10 in non-responders or relapsers. One patient treated with peginterferon did not develop a marked elevation of liver enzymes. It is possible that the pharmacokinetics of different interferon formulations could influence the development of autoimmune phenomena. Continuous stimulation of the immune system with peginterferon could avoid the 'bolus' stimulation of the immune system observed with the non-pegylated formulation, thereby preventing the formation of anti-LKM1. Treatment with proinflammatory interferon may unmask latent type 2 AIH. Of note, none of the patients in these studies had histological, clinical or biochemical features consistent with AIH. Furthermore, treatment of HCV infection led to clinical improvement, and SVR was usually associated with clearance of autoantibodies. This would not be the case if there were an underlying autonomous autoimmune process.

Although ANA or SMA positivity in the setting of confirmed HCV infection usually has no clinical implications, occasionally patients with HCV have high-titre autoantibody positivity. There is little literature regarding this issue and much of the experience is anecdotal. In some of these cases, ANA is elevated for unclear reasons. In other patients, ANA is elevated for other reasons such as lupus erythematosus. Finally, a small number of patients have HCV with an autoimmune component. Such patients tend to have higher liver enzyme elevations than normally encountered with chronic HCV infection. Biopsy may reveal an aggressive histological picture with periportal and lobular inflammation and increased plasma cells. If antiviral therapy is instituted, liver enzymes should be followed closely early in therapy. If liver enzymes rise markedly, it would suggest a possible exacerbation of an autoimmune component of chronic liver disease, and antiviral therapy should be discontinued.

Summary and recommendations

Autoantibody positivity in the setting of chronic HCV infection is common. Alternatively, HCV EIA positivity may be observed as a false-positive result in the setting of AIH. ANA and SMA positivity does not impact on the natural history of HCV, nor does it affect response to antiviral therapy. However, in the setting of high-titre ANA or SMA positivity, an autoimmune component of chronic liver disease must be contemplated. It is important to distinguish these issues prior to commencing medical therapy. Treatment of confirmed HCV with an autoimmune component or AIH with false-positive HCV EIA testing with immunomodulatory interferon alfa-based medical regimens exacerbates the underlying autoimmune process.

In all patients with presumed chronic HCV infection as identified by EIA positivity, HCV must be confirmed by HCV RNA testing prior to commencing antiviral therapy. For patients with confirmed HCV and autoantibody positivity, an autoimmune component must be considered. Since there is little literature on this issue, recommendations are based on experience (Figure 18.1). If autoantibody titre is high (ANA > 1 : 160 or SMA > 1 : 80), especially if liver enzyme elevations are higher than usual (ALT more than eight times upper limit of normal), suspicion of an autoimmune component should be heightened. Liver biopsy should be performed prior to commencing antiviral therapy of HCV. If the biopsy is not suggestive of HCV with autoimmune features, plans for antiviral therapy of HCV should

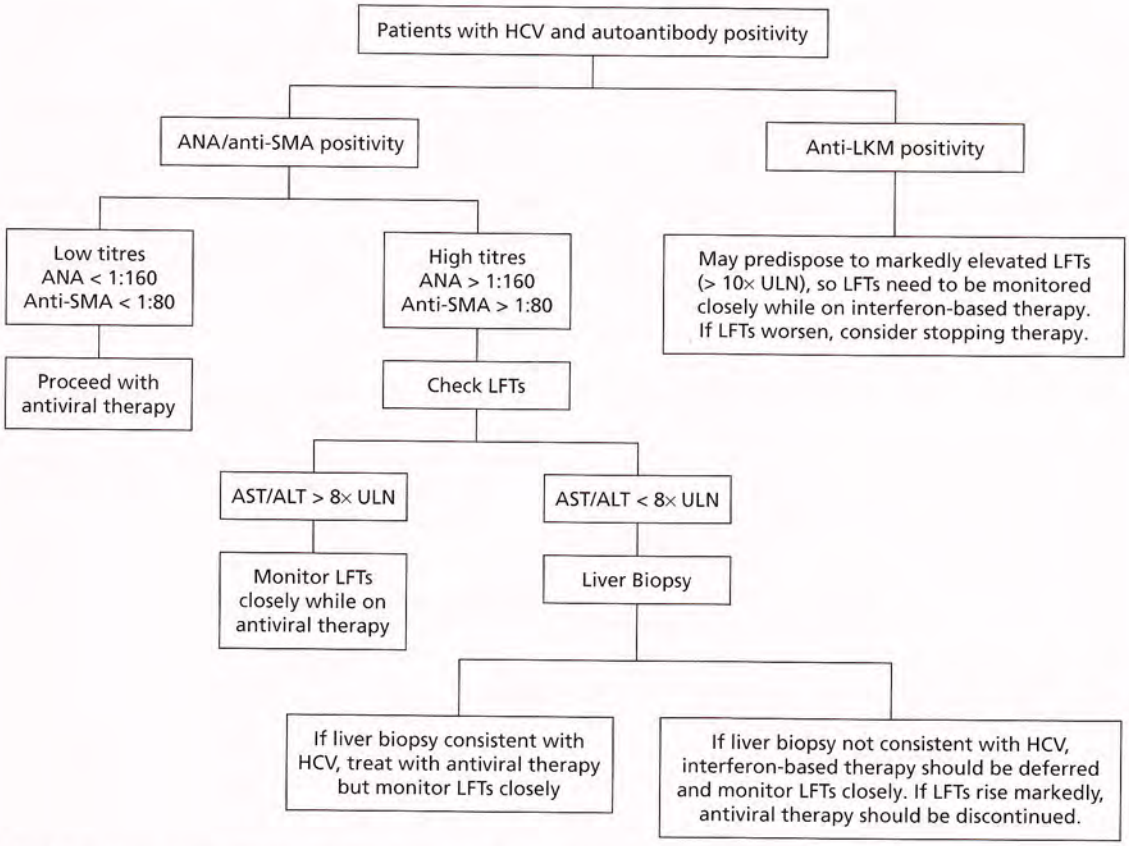

FIG. 18.1 Algorithm for patients with HCV infection and autoantibody positivity. AST/ALT, aspartate aminotransferase/alanine aminotransferase; LFTs, liver function tests; ULN, upper limit of normal.

proceed. However, if the biopsy is suggestive of HCV with autoimmune features, interferon alfa-based medical regimens should be deferred. If HCV therapy is administered, liver enzymes should be followed closely throughout the early weeks of therapy, and if liver enzymes rise markedly antiviral therapy should be discontinued.

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19 HCV and iron excess: the interaction and how to handle it

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LEARNING POINTS

- On the first visit, measure iron parameters in all patients (serum iron, ferritin, and transferrin-iron saturation) to establish a baseline and determine if iron overload is present.
- Perform *HFE* genotyping in all patients who have transferrin-iron saturation above 45% and/or ferritin greater than 500 ng/mL.
- Iron depletion via phlebotomy is appropriate if hepatic iron stores are increased (> 2+) and if the patient is not a candidate for interferon/ribavirin combination therapy.
- Consider phlebotomy in cirrhotics with increased iron stores to reduce progression and to possibly reduce the risk of hepatocellular carcinoma.
- Iron depletion before the initial round of treatment with interferon/ribavirin combination therapy is not indicated unless the patient has concomitant hereditary haemochromatosis.

Since the initial description in 1992 by Di Bisceglie *et al.* [1], many studies have confirmed that hepatitis C virus (HCV) infection is associated with elevation in serum iron parameters (iron, ferritin, transferrin-iron saturation) compared with non-HCV-infected control subjects. Di Bisceglie *et al.* reported that 36% of patients with chronic HCV infection had elevated serum iron values and increased stainable iron in Kupffer cells and hepatocytes [1]. Similar staining patterns have been noted in subsequent studies and further support the assertion that HCV is associated with hepatic iron accumulation in a mixed pattern of deposition [2,3]. Furthermore, patients with chronic HCV infection have markedly raised levels of iron compared to those with cholestatic or autoimmune liver disease [4]. Ferrara *et al.* [5] recently suggested that serum ferritin, an easily measured parameter, might predict therapeutic response at different points during antiviral treatment and may be a marker for disease progression.

Although there are data supporting the premise that hepatic iron deposition may be caused by HCV, it is also possible that increased iron deposition in these patients may be due to coexisting factors such as age, race, gender, body mass index (BMI), HCV genotype, viral load, insulin resistance and alcohol use [6,7]. In particular, African-American race has been found to be a unique contributor to elevated iron indices in the context of HCV infection. A standardized analysis showed that HCV-infected African-Americans with elevated liver enzymes were much more prone to have increased iron stores (odds ratio 17.8) [8]. Although some have proposed that hepatic iron deposition may result from damaged hepatocytes, the overall mechanism of iron accumulation remains uncertain [9]. Regardless of the cause of increased hepatic iron, once present this metal may exacerbate liver injury and hepatic fibrosis via the Fenton reaction, leading to generation of hydroxyl radicals that act on structural macromolecules and DNA [10]. In one study, 8-hydroxy-2′-deoxyguanosine, a marker for DNA damage in the liver, was shown to increase in parallel with hepatic iron stores in HCV-infected patients, suggesting that iron may be implicated in oxidative stress and progression of fibrosis [11].

There are conflicting data regarding the relationship between *HFE* mutations, hepatic iron accumulation and

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disease severity in chronic HCV infection. Several studies have found a positive relationship between *HFE* mutations and increased liver iron storage [12–17]. However, the relationship between increased hepatic iron and advanced fibrosis has been less clear, with a direct relationship in some studies [13,14,18–20] but not in others [2,21–25]. Some studies have found that both the C282Y and H63D mutations are associated with increased inflammation and fibrosis, whereas others have found a much weaker association with the H63D mutation than the C282Y mutation [13,14,18–20]. We previously found both H63D and C282Y mutations to be associated with more rapid progression of chronic HCV infection after adjustment for duration of disease [13]. Both the H63D and C282Y mutations were strongly associated with advanced fibrosis, with odds ratios of 22 and 30, respectively [13].

It has been well established that iron overload is associated with lower rates of sustained virological response (SVR) to interferon monotherapy [3,26,27]. Following this discovery, studies were conducted to test the effect of pretreatment phlebotomy on SVR in treatment-naive patients [28–32]. Most have shown a trend towards increased SVR [28–31] and improved iron indices and aminotransferase levels [28–32]. A recent meta-analysis of six randomized controlled studies showed a significant difference between the phlebotomy and control groups, with SVR of 27% and 12%, respectively ($P < 0.0001$) [33].

Similar phlebotomy studies were performed in groups of patients who had previously not responded to interferon monotherapy [34–38]. The largest trial, performed by Di Bisceglie *et al.* [34], did not show increased SVR in iron-depleted patients but did show decreased levels of liver injury and improved aminotransferase levels. Many other studies have shown improved aminotransferase levels as well [35–38], but only two studies showed significance for improved SVR [37,38]. Overall, iron depletion prior to interferon monotherapy has been shown to be effective in lowering aminotransferase levels and iron indices, but is inconclusive with regard to change in SVR. Furthermore, the results of these studies is becoming less relevant in current practice as monotherapy has been replaced with interferon/ribavirin combination therapy, which has been shown to have much higher response rates [39].

While pretreatment liver iron concentration can be a predictor of non-response in monotherapy, SVR is generally found to be independent of iron parameters with combination interferon and ribavirin therapy [40–42]. The exception is a study by Fujita *et al.* [43]. These authors measured total iron liver score in 103 HCV-infected patients before and after 24 weeks of combination therapy and found that this variable was the only factor independently associated with non-response to combination therapy ($P = 0.0277$). Most other studies have shown no association between hepatic iron concentration and response to combination therapy [40–42]; two studies suggested that high serum ferritin levels at baseline were associated with non-response [40,44]. In summary, the bulk of the evidence suggests that iron studies and hepatic iron concentration are not likely to predict response to combination therapy; the role of serum ferritin as a predictor of response remains unclear.

Recent work has also examined the relationship between *HFE* mutations and response to combination therapy. Bonkovsky *et al.* [12] recently found in a study of 363 patients that H63D mutations actually predicted a higher rate of SVR ($P = 0.009$). There was an inverse relationship between SVR and stainable iron in portal triads and endothelial cells, suggesting that location of hepatic iron may be more important than concentration [12]. In contrast, a smaller study with 34 patients showed that patients with any *HFE* mutations were much less likely to achieve SVR [45]. Based on the data discussed previously on *HFE* mutations, it is clear that combination therapy is still the best choice for antiviral treatment as its effectiveness is widely considered independent of iron status.

Combination therapy is clearly proven to be the most effective therapy in most HCV-infected patients; however, there are situations where alternative therapies may be recommended, such as for non-responders and patients who cannot tolerate antiviral therapy. In these situations, it is reasonable to recommend iron reduction with phlebotomy because has been shown to significantly reduce alanine aminotransferase (ALT) levels in both treatment-naive and non-responder patients [28–32,34–38,46–48]. This significant improvement in biochemical response highlights the possibility that if iron depletion is maintained, it may help to reduce hepatic necroinflammation and fibrosis in HCV-infected patients. It may also be worthwhile for patients to consider an iron-restricted diet as Tandon *et al.* [49] have shown that treatment with a 50% reduced iron rice/casein-based diet was associated with significant improvement serum iron, transferrin-iron saturation, and serum ALT levels.

It is possible that iron depletion via phlebotomy has the potential to prevent DNA damage and development of

hepatocellular carcinoma (HCC). Several studies have demonstrated that hepatic iron concentration is a relevant factor in the development of HCC [50]. Cirrhosis associated with HCV infection is accompanied by increased hepatic iron concentration [51]. Markers of iron-related damage such as 8-hydroxy-2′-deoxyguanosine are commonly found to be elevated in patients with HCC, especially those with increased hepatic iron, and are thought to indicate a hepatic microenvironment prone to cancerous mutations [52]. Chapoutot *et al.* [50] compared patients with chronic HCV infection, cirrhosis and HCC with non-cancer patients and found that iron deposits were much more common in the HCC group than in controls ($P = 0.0056$). *HFE* mutations have been examined in patients with chronic HCV infection and HCC, with some studies showing positive correlations [53,54] and others negative correlations [55,56]. It is possible that iron may be the more pertinent risk factor for HCC in chronic HCV infection rather than *HFE* mutations.

TABLE 19.1 Summary of studies examining iron depletion therapy for treatment-naive patients and prior non-responders.

Reference	No. of patients		IFN treatment	SVR		End biochemical response/sustained biochemical response	
	IFN	Iron reduction + IFN		IFN	Iron reduction + IFN	IFN	Iron reduction + IFN
Treatment-naive patients							
Carlo *et al.* [31]	40	43	6 MU IFN alfa-2b or alfa-2a q.o.d. for 6 months; then 3 MU q.o.d. for 6 months	6 (15%)	12 (28%)	18 (45%)/ 8 (20%)	24 (56%)/ 16 (37%)
Fargion *et al.* [29]	57	57	6 MU IFN alfa-2b t.i.w. for 4 months; then 3 MU t.i.w. for 8 months	9 (15.8%)	16 (28.1%)	18 (32%)/ 15 (26%)	24 (42%)/ 19 (33%)
Fong *et al.* [30]	21	17	3 MU IFN alfa-2b t.i.w. for 6 months	1 (4.8%)	5 (29.4%)	6 (29%)/ 1 (4.8%)	9 (53%)/ 6 (35%)
Fontana *et al.* [28]	42	40	3 MU IFN alfa-2b t.i.w. for 6 months	3 (7%)	7 (17%)	20 (48%)/ 6 (14%)	25 (63%)/ 11 (28%)
Piperno *et al.* [32]	61	20	3 MU IFN alfa-2b t.i.w. for 12 months	NR	0 (0%)	21 (34%)/ 13 (21%)	1 (5%)/ 1 (5%)
Non-responders							
Alexander *et al.* [36]	18	N/A	NR	NR	N/A	4 (22%)	N/A
Di Bisceglie *et al.* [34]	32*	32	Not known	0 (0%)	0 (0%)	ALT (×ULN) 2.9 to 1.9†	ALT (×ULN) 3.2 to 1.6†
Guyader *et al.* [35]	No control	Pilot study $N = 15$	Min. 3 MU IFN t.i.w. for 3 months	N/A	0 (0%)	N/A	2 (13%)/0
Tsai *et al.* [37]	No control	20	3 MU IFN alfa-2b t.i.w. for 6 months	N/A	3/20 (15%)	N/A	11 (55%)/ 10 (50%)
Van Thiel	15	15	5 MU IFN daily for 6 months	2 (13%)	9 (60%)	2 (13%)	7 (47%)

* Iron reduction only (not IFN alone).
† 24 weeks after treatment.
ALT, alanine aminotransferase; IFN, interferon; NR, not reported; t.i.w., three times weekly; ULN upper limit of normal.

Studies investigating iron depletion therapy to prevent HCC have shown some promising results. Kato *et al.* [57] performed iron depletion therapy in 35 patients with moderate to severe liver fibrosis who were likely to progress to HCC and who could not tolerate, or previously failed to respond to, antiviral therapy. Treatment was associated with significantly decreased ALT levels and was independently associated with a lowered risk of HCC ($P = 0.0337$) compared with controls. Additional studies are needed to further explore the effect of iron depletion for this indication.

In summary, increased serum and hepatic iron levels are relatively common in patients with chronic HCV infection. We postulate that the combined action of HCV and the generation of free radicals by iron may increase the rate at which liver damage occurs, especially in patients with cirrhosis when iron accumulation may occur at a faster rate. *HFE* mutations are associated with increased hepatic iron concentration. Although hepatic iron content predicts a negative response to interferon monotherapy, the SVR with interferon/ribavirin combination therapy is independent of iron markers. Treatment with iron depletion is associated with the prevention of hepatic complications in patients with hereditary haemochromatosis but has not been shown to clearly improve prognosis in chronic HCV infection except in pilot studies (Table 19.1). Phlebotomy may be considered for patients with advanced fibrosis and increased iron stores (> 2+ stainable iron on biopsy with or without serum ferritin > 500 ng/mL) who are either not candidates for combination therapy or have been previously treated without success; in such patients, iron depletion is associated with improved serum liver biochemical tests and may slow progression of liver disease and reduce the risk of HCC.

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20 Management of patients with genotype 3 chronic hepatitis C: can we change the duration of therapy?

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LEARNING POINTS

- Patients infected with genotype 2 and 3 HCV have traditionally been regarded as easy to treat. However, patients with genotype 3 HCV have significantly lower response rates than those with genotype 2 infection.
- The on-treatment virological response is increasingly being used to determine the duration of therapy in patients with chronic HCV infection and a rapid virological response (i.e. undetectable HCV RNA after 4 weeks of therapy) is increasingly used as an indication that a shortened duration of therapy may be effective.
- In the absence of a rapid virological response, patients with genotype 3 HCV respond less well than genotype 2 HCV patients, even after 24 weeks of treatment.
- In patients with genotype 3 HCV, advanced liver damage is the most important adverse factor associated with the absence of a rapid virological response and/or of a poor response after an early response and the reduced response occurs in patients treated with either a short or a standard courses of antiviral therapy.

Introduction

Hepatitis C virus (HCV) is an RNA virus that belongs to the family *Flaviviridae*. Six HCV genotypes exist, of which genotypes 1, 2, 3 and 4 are most prevalent worldwide. While the evaluation of HCV genotypes bears no relevance to the natural history of the liver disease, they impact substantially on both duration and outcome of antiviral therapy. Compared with genotype 1, genotype 2 and 3 infections are consistently associated with significantly higher rates of sustained virological response (SVR) [1]. When genotypes 2 and 3 are considered as a homogeneous group, combination therapy with peginterferon and ribavirin for 24 weeks achieves SVR in over 70–80% of individuals, whereas no more than 40% of patients harbouring genotype 1 infection will clear the virus after a 48 week-course of treatment [1–3]. It has become common to label the former patients 'easy to treat' and the latter 'difficult to treat'. The difference in SVR rates between these two categories of patients is most likely a reflection of viral kinetics in response to interferon therapy, as viral decline among genotype 2 and 3 infections is up to eight times faster than that of genotype 1 [4].

In this chapter we discuss the emerging data on virological response in patients with genotype 3 HCV infection as reported in different studies of either standard or abbreviated courses of treatment, and discuss the most appropriate course of therapy and investigate whether host-related factors play a role in the response rate to antiviral therapy in patients with this viral genotype.

Genotype 3 infections are not easy to treat

It has been ascertained only recently that even among easy-to-treat patients, there are differences in SVR rates that can be achieved after the standard course of 24 weeks of combination therapy (Table 20.1). The original observation of a lower rate of SVR in patients harbouring genotype 3

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TABLE 20.1 Sustained virological response rates in patients infected with HCV genotype 3 and genotype 2 after 24 weeks of therapy with peginterferon and ribavirin.

Reference	Year	HCV-3		HCV-2	
		No. of patients	SVR (%)	No. of patients	SVR (%)
Zeuzem *et al.* [5]	2004	183	79	42	93
Mangia *et al.* [23]	2005	17	76	53	76
Shiffman *et al.* [13]	2007	369	66	356	75
Powis *et al.* [21]	2008	81	75	276	85
Jacobson *et al.* [18]	2006	251	60	298	71
Bailey *et al.* [19]	2007	389	72	276	79
Aghemo *et al.* [20]	2008	71	75	136	78
Lagging *et al.* [29]	2008	139	78	49	82

HCV in comparison with those with genotype 2 infection [5] has been substantially corroborated by the finding of a recent meta-analysis: after pooling the results from eight studies that enrolled 2275 patients treated for 24 weeks with peginterferon and ribavirin, the SVR rate among genotype 3 infections was 74% (95% CI 71.8–77.1) compared with 68% (95% CI 66.0–71.2) among those patients with genotype 2, and the pooled estimate of the difference was 8.7% (95% CI 5.1–12.3) [6].

Unfavourable predictors of SVR in genotype 3 infection

A clear biological explanation for the difference in SVR rates between genotype 2 and genotype 3 infection is not obvious. There are several conceivable claims for the reduced response in genotype 3 infection, including higher amount of liver steatosis, insulin resistance, advanced fibrosis and cirrhosis, and high viral load.

Liver steatosis

The 2.5-fold increased prevalence of steatosis in patients with HCV infection suggests that the virus *per se* promotes the accumulation of fat into the hepatocyte [7]. The association seems to prevail in patients infected with genotype 3. Studies *in vitro* and in experimental animals indicate the existence of 'steatogenic' sequences in the core region of the HCV genome. Of note, the core protein from HCV genotype 3 isolates is about threefold more efficient than the corresponding protein from genotype 1 isolates in reducing lipid export from the hepatocyte and inducing lipid accumulation in the liver [8]. The degree of hepatic fat accumulation correlates with levels of HCV replication and the condition may be reversed by inducing a sustained viral clearance with a course of antiviral therapy [9]. Given the documented impact of steatosis on the development of liver fibrosis [10], it may be hypothesized that the poorer outcome of antiviral therapy in genotype 3-infected patients may, at least in part, be explained by a higher frequency of patients with steatosis [10,11]. A complementary explanation would refer to experimental data showing that liver steatosis increases hepatic expression of factors that inhibit interferon signalling, such as SOCS-3, a mechanism that, at least in patients with genotype 1 infection, would reduce the likelihood of achieving SVR with appropriate therapy [12]. However, the association between liver steatosis and poor outcome of therapy among genotype 3-infected patients has not been uniformly reported [13].

Insulin resistance and obesity

Liver steatosis has been recently outlined as a further component of the metabolic syndrome [14]. As it may aggravate liver disease in patients with genotype 3 and those with other genotypes, it is still uncertain whether hepatic fibrosis is a secondary effect of steatosis or a direct consequence of insulin resistance. Recent investigation would indicate that virus-induced steatosis as seen in genotype 3-infected patients did not appear to directly promote hepatic fibrogenesis, a condition that was primarily correlated with insulin resistance [15].

Insulin resistance may also explain the lower rates of SVR observed in obese patients. Patients with a body mass index (BMI) above 30 kg/m^2 constitute one of the most difficult-to-treat groups, independently of the infecting genotype, as shown in several studies [16]. In African-Americans, BMI, diabetes and hypertension are all associated with the lower response rate to antiviral therapy [17]. In HCV genotype 3 patients, SVR rates were lower and declined with increasing weight when a flat dose of 800 mg ribavirin daily was used in combination with peginterferon [18].

Advanced fibrosis/cirrhosis

One of the most consistently reported observations when treating patients with chronic HCV infection is the hypo-responsiveness that characterizes patients with cirrhosis compared with those who do not have cirrhosis after completion of the standard 24 weeks of treatment.

Among 241 HCV genotype 3 patients enrolled in the 24-week treatment arm of the Accelerate study, SVR was observed in 49% of cirrhotic patients and in 70% of those without cirrhosis [13]. An inverse correlation between stage of fibrosis and SVR in genotype 3 infection was also reported in the observational POWeR study, where SVR rates were 47% and 68% in patients with or without liver cirrhosis, respectively [19]. In an Italian retrospective observational study including patients treated with peginterferon and ribavirin combination, only 6 of 17 (35%) patients with genotype 3 and cirrhosis were responders after 24 weeks of therapy compared with 62 of 74 (84%) non-cirrhotic patients. These disappointing results were attributed to the high rate of relapse in cirrhotic patients (57% vs. only 9% in non-cirrhotic patients) [20]. Similar results were reported in a Canadian study, where only 2 of 12 (37%) genotype 3-infected patients with advanced fibrosis were responders, as opposed to 7 of 9 (79%) equally staged patients with genotype 2 [21]. Although the validity of the conclusions reached in some of these studies is limited by the small number of patients with cirrhosis enrolled, overall these results confirm that in patients with genotype 3 treated with the standard 24-week course the presence of cirrhosis reduces the likelihood of attaining SVR.

Viral load

The other factor associated with a lower SVR rate in patients with genotype 3 in comparison with genotype 2 is viral load at baseline evaluation. In 185 patients infected with genotype 3, after a standard course of peginterferon alfa-2b and ribavirin, the occurrence of relapse was associated with both HCV RNA levels at baseline and amount of steatosis [5]. In patients with HCV RNA levels above 600 000 IU/mL enrolled in the large community-based Win-R study, the relapse rate was up to 16%, whereas it was only 6% in patients with HCV RNA levels below this cut-off [18]. However, discordant data were provided in subsequent studies [20,22]. In particular, in 374 patients enrolled in the registration studies of peginterferon alfa-2a and ribavirin, high baseline levels were not associated with lower SVR [22]. After reviewing this issue with a meta-analytical approach, we have found that among high-viraemic patients SVR rate in genotype 2-infected patients was 24.9% higher than the rate in genotype 3-infected patients, while among low-viraemic patients the difference amounted to 7.1%.

Variations on the standard schedule of antiviral therapy: the role of rapid virological response

Treatment guidelines for chronic HCV infection recommend treating patients with genotype 2 and 3 with either of the two peginterferons commercially available in combination with low-dose ribavirin (800 mg daily) for a duration of 24 weeks. Several attempts to further simplify treatment have focused on decreasing the recommended dosages of either peginterferon or ribavirin, and on shortening the duration to 12 or 16 weeks [23–26].

As reported in recent studies, in patients with genotype 2 and 3 who clear the virus by 4 weeks, i.e. who achieve a rapid virological response (RVR), length of treatment might be safely reduced to 16, 14 or even 12 weeks of therapy without compromising SVR rates [23–26]. RVR is now considered as the most valuable tool predicting ultimate SVR in all HCV-infected patients, not only among those with the easy-to-treat genotype. The question whether patients with genotype 3 and RVR respond equally well as those with genotype 2 to an abbreviated course of therapy remains unanswered.

Only a few studies on short courses of antiviral therapy have separately evaluated RVR in patients with genotype 2 and 3; the respective data are reported in Table 20.2. It is of note that after RVR, SVR rates in genotype 2- and 3-infected patients were not different. Of 632 genotype 3 patients, globally evaluated in five studies [13,25–27,29], SVR was observed in 480 (76%) individuals; of 490 genotype 2 patients, SVR was reported in 402 (82%).

TABLE 20.2 Sustained virological response rates in patients with viral clearance at week 4 after starting antiviral therapy: comparison of outcome after a short (12–16 week) course of therapy in HCV genotype 3 and 2.

Reference	Year	HCV-3		HCV-2	
		No. of patients	SVR (%)	No. of patients	SVR (%)
Andriulli *et al.* [26]	2005	104	91	157	88
von Wagner *et al.* [25]	2005	51	76	19	79
Shiffman *et al.* [13]	2007	230	80	230	86
Dalgard *et al.* [27]	2008	110	75	29	93
Lagging *et al.* [29]	2008	137	58	55	56

In contrast, in patients without RVR the difference in SVR rates between the two genotypes is much more pronounced. In the combined analysis of Norwegian and Italian patients, only 46% of 50 genotype 3 patients without RVR attained SVR after the standard 24 weeks of therapy, while 73% of 79 genotype 2 patients were long-term responders [26]. Similar figures were also reported in the Accelerate study where only 30 of 109 genotype 3 patients without RVR eventually cleared the virus after 24 weeks (27%) [13]. Together these results suggest that treatment longer than the recommended 24 weeks may be needed in genotype 3 patients in the absence of RVR.

Cirrhosis and RVR in patients treated with a short course of antiviral therapy

In genotype 3 patients with cirrhosis, the results of the clinical trials are concordant in showing reduced rates after an abbreviated course of therapy. This low response rate may be due to a reduced number of patients achieving RVR due to the advanced liver fibrosis. In our studies, only 48% (13 of 27) of patients with severe fibrosis achieved an RVR as compared with 76% (71 of 94) of those with a lower fibrotic score [26]. Our data are in keeping with those attained by von Wagner *et al.* [25] in a limited number of HCV genotype 3 patients. In contrast, in the recently published North C Trial, high aspartate aminotransferase to platelet ratio index (APRI) score was used as an non-invasive tool to estimate the severity of liver damage; a high APRI score did not predict RVR, as 21% of patients with RVR and 20% of those without had APRI scores above 2 [27]. Therefore, whether genotype 3 patients with advanced liver damage experience RVR less often than patients with lesser degrees of liver damage requires further clarification in future studies.

A related question in patients with advanced liver fibrosis receiving shortened courses of antiviral therapy is whether, once they achieve RVR, genotype 3-infected patients maintain this response. Of 718 patients treated for 12 weeks on the basis of achievement of RVR in a large Italian cohort, 108 were infected with genotype 3 and 19% had advanced liver damage. A platelet count lower than 140×10^9/L, considered a surrogate marker of advanced liver damage, was an independent predictor of relapse [28], suggesting that in patients with genotype 3 chronic HCV relapse is common in those with advanced fibrosis who achieve RVR.

Conclusions

In conclusion, not all patients with genotype 3 are easy to treat. In patients receiving the recommended 24 weeks of therapy with peginterferon and ribavirin, non-responder patients had significantly more fibrosis and higher BMI. Both these conditions might be consequent on insulin resistance that may be higher in non-responders than in responders, and insulin resistance may be responsible for the reduced SVR rates seen in these patients. Still a matter of debate is the impact of baseline viraemia on the therapeutic outcome. Studies evaluating the early (week 4) RVR have consistently shown that patients failing to achieve RVR status are poor responders to therapy and might need longer than the currently recommended 24 weeks of antiviral treatment. Patients with genotype 3 and rapid viral clearance may be easily treated with shorter courses of treatment, especially those with less advanced fibrosis and

normal BMI. It is unknown whether patients with advanced fibrosis and abnormal BMI can respond to a shortened course of therapy and further studies are needed to determine which patients with genotype 3 can safely be treated with shortened courses of antiviral medication.

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21 Management of hepatitis C in children

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LEARNING POINTS

- Only a minority of individuals with chronic HCV are children, and liver disease is generally mild and slowly progressive in this population. However, some children have advanced liver disease, and others are at risk for future complications such as cirrhosis and hepatocellular carcinoma.
- The majority of new cases of HCV infection in children are due to perinatal transmission. The likelihood of perinatal transmission is about 5% with each pregnancy.
- Children as young as 3 years of age with chronic HCV may be candidates for treatment. The recommended therapy is the combination of peginterferon and ribavirin.
- The success of treatment for chronic HCV in children and adolescents depends on multiple factors such as genotype, viral level, side effects, adherence, close monitoring, and the availability of a supportive and involved family.

Acute hepatitis C virus (HCV) infection is rarely detected in children, and fulminant HCV is rare. Accordingly, there are few data regarding treatment of acute HCV in the paediatric age group. Also, children are only a small proportion of the HCV-infected population, but there are a significant number of children with chronic HCV. Chronic infection is generally asymptomatic during childhood, but long-term infection can lead to significant morbidity and mortality, such as cirrhosis and hepatocellular carcinoma, later in life. The proportion of HCV-infected children who will suffer these serious consequences in unknown, but several paediatric studies have demonstrated that the degree of hepatic fibrosis generally correlates with age and duration of infection, although progression seems to be slower than observed in those infected later in life. Understanding that HCV in children has different modes of acquisition, complications and natural history will influence management and treatment decisions.

The groups of children at risk for HCV infection are listed in Table 21.1. After 1992 and universal testing of blood products, vertical transmission has become the leading source of infection for children. The rate of vertical transmission averages about 5% from most studies. Universal screening of pregnant women is not cost-effective or useful at the present time. The American Academy of Pediatrics (AAP) Committee on Infectious Disease does not recommend testing of pregnant women for HCV unless they have an identifiable risk factor. Vertical transmission is associated with a high incidence of viraemia and abnormal aminotransferases during the first 12 months. Of 70 prospectively followed infants in five European centres during 1990–1999, 93% had abnormal alanine aminotransferase (ALT) during the first 12 months, and only 19% cleared HCV RNA with normal ALT by 30 months of age [1]. Clearance

TABLE 21.1 Children who should be tested for HCV infection.

Children born to mothers with HCV*
International adoptees
Children who received blood or blood products prior to 1992
Adolescents with parenteral exposures
Intravenous drug use
Non-professional tattoos or body piercings

* Testing for anti-HCV should be done after 15 months of age, since younger infants may be seropositive from passively transferred maternal antibody.

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of viraemia was independent of sex and maternal HIV co-infection. Peak ALT greater than five times normal during the first 18 months and genotype 3 were more common in the patients in whom viraemia resolved spontaneously.

The largest paediatric natural history study to date describes a cohort of 200 HCV-infected children in Europe [2]. The majority had genotype 1b, 45% from vertical transmission and 39% from transfusion. Of these patients 15% had normal ALT and none had jaundice or extrahepatic manifestations. After follow-up of 1–17.5 years (mean 6.2), only 6% achieved sustained virological clearance and normalization of ALT. Liver biopsies were performed in 118 of these patients at various times during follow-up; the majority (76%) had mild hepatitis and low fibrosis scores. One patient (1%) had cirrhosis and one (1%) had severe hepatitis. Greater degrees of fibrosis were seen in children older than 15 years, suggesting long-term effects of chronic HCV infection.

There have been only a few case reports of hepatocellular carcinoma associated with HCV during childhood [3–5]. Liver transplantation for complications of chronic HCV infection during childhood is uncommon. According to the Study of Pediatric Liver Transplantation (SPLIT) Registry that collects data from 37 North American paediatric liver transplant centres, chronic HCV with cirrhosis or 'subacute hepatitis C' was the reason for transplant in 13 of 1378 children (1%) from 1995 through June 2003. For these reasons, the primary indications for treatment of paediatric patients with HCV infection are prevention of future complications and the psychosocial benefits of eradication in this young and vulnerable population.

In 2003 the Food and Drug Administration (FDA) in the USA approved the combination of interferon and ribavirin for the treatment of chronic HCV infection in children aged 3–17 years. Until very recently, this was the only licensed treatment for children with HCV. Studies had demonstrated that response rates depended on genotype and viral load, as in adults. This was illustrated in a study of 118 children [6] who had a 46% overall sustained virological response (SVR) rate. Among children with genotype 1, the SVR rate was 48% in children who had viral levels of 2 million copies/mL or less compared with 26% in those with more than 2 million copies/mL. Children with genotype 2 or 3 HCV had 84% SVR, and younger children had higher SVR rates than adolescents (57% vs. 26 %). Similar findings had been described in an earlier smaller study [7].

There are limited data regarding the use of peginterferon monotherapy or in combination with ribavirin in children. In an open-label uncontrolled pilot study, 62 children and adolescents, aged 2–17 years (mean 10.6 years), were treated with peginterferon alfa-2b and ribavirin for 48 weeks [3]. The SVR rate was 59%. In 2008, the FDA approved combination therapy with peginterferon alfa-2b and ribavirin for use in children with HCV 3 years and older with compensated liver disease. This decision was supported by the results of a trial [8]. In this study, children with genotype 1 or 4, or genotype 3 with greater than 600 000 IU/mL, were treated for 48 weeks, while those with genotype 2, or genotype 3 with less than 600 000 IU/mL, were treated for 24 weeks. The SVR rate was 55% in the first group and 96% in the second.

A randomized trial of peginterferon alfa-2a with or without ribavirin in children aged 5–17 years was recently reported in abstract form [9]. This study demonstrated the superiority of combination therapy in children, with SVR of 53% in children who received combination therapy compared with 21% in those who received monotherapy. The difference was significant for both genotype 1 and non-genotype 1 infections. Analysis of the pretreatment liver biopsies in this cohort had reaffirmed the generally mild histological disease during childhood, but cases of marked fibrosis and even cirrhosis were observed [10].

In both of these trials, peginterferon and ribavirin were generally well tolerated in these young subjects. Side effects were generally those observed in adults, although weight loss and changes in linear growth velocity are of particular importance in paediatrics (Table 21.2). In the peginterferon alfa-2b trial, weight loss and growth inhibition were common. In addition, 3% were treated for clinical hypothyroidism. In the peginterferon alfa-2a trial, dose reductions and early discontinuation were needed in 51% and 4%, respectively, of those receiving combination therapy, primarily for neutropenia.

Given these considerations and the superior results in adults with peginterferon versus standard interferon, it

TABLE 21.2 Interferon side effects in children and adolescents.

Flu-like symptoms, especially in first few weeks
Weight loss (reversible)
Decreased growth velocity
Neutropenia
Thyroid dysfunction
Depression, behavioural changes (uncommon)

is reasonable to infer that peginterferon, in combination with ribavirin, is the treatment of choice for children with chronic HCV infection who are considered to be appropriate candidates for therapy. There are no published consensus statements or guidelines for treatment of HCV-infected children, and treatment decisions may vary with the child's age and individual disease characteristics. Examination of a liver biopsy may not be a prerequisite for treatment; it is rare to find advanced histology in young children, and the response rates of children with genotype 2 or 3 HCV are so high that baseline biopsies may provide little information regarding either likelihood of response or long-term prognosis. Exceptions are children whose parents want to know the stage of disease in considering treatment, and those with comorbid diseases in whom the results of a biopsy might influence the decision to treat. In genotype 1 infections, especially in older children, biopsy information might be useful, since the SVR rate is not as high, and those with mild histological changes may choose to wait for the availability of newer more effective therapies (Figure 21.1).

Children as young as 3 years may be considered candidates for combination therapy. Decisions regarding timing of therapy are influenced by disease factors, such as degree of hepatic inflammation and fibrosis, the presence of comorbid diseases, and psychosocial factors such as school and athletic activities, family stability and availability for support, and participation in high-risk behaviours such as intravenous drug use. Treatment might be more strongly

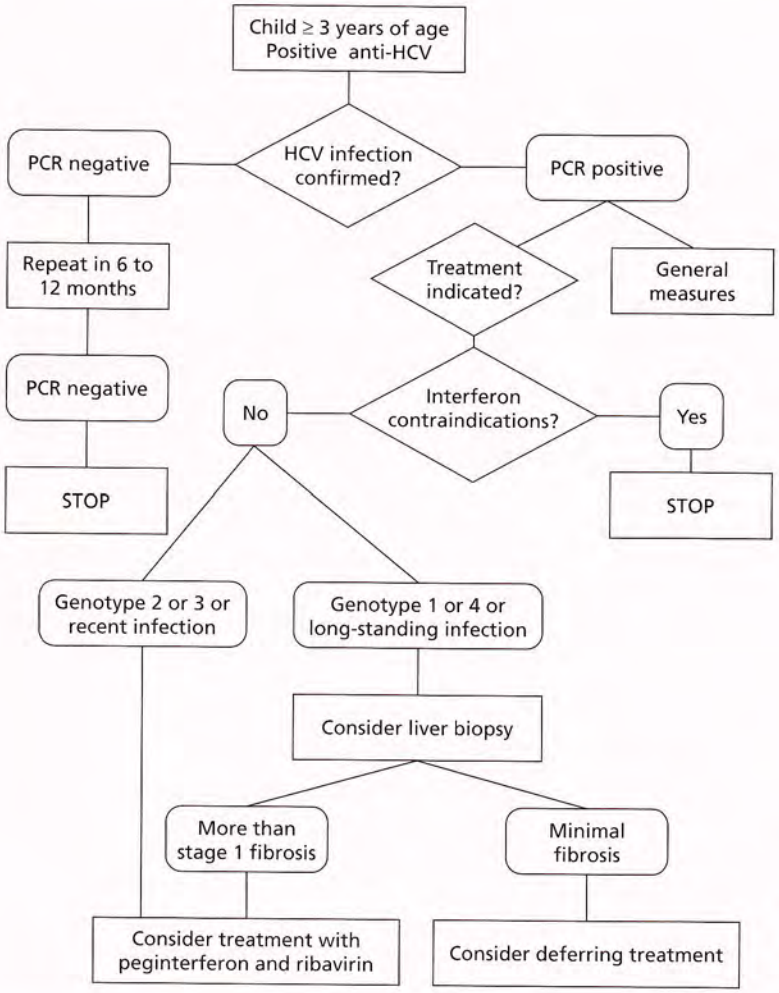

FIG. 21.1 Selection of paediatric patients with chronic HCV for treatment. PCR, polymerase chain reaction.

advocated for children with perinatally acquired HCV who are older than 10 years, those with at least moderate hepatic fibrosis, and in those with a comorbid disease or other features that raise concern for rapid progression. Just as in adults, obesity and insulin resistance might need to be addressed prior to HCV treatment in children, since these factors are likely to decrease the likelihood of SVR in children.

Peginterferon alfa-2b (60 μg/m^2 once weekly) has been approved by the FDA for use in children 3 years and older, in combination with ribavirin (15 mg/kg daily in two divided doses). Although peginterferon alfa-2b is most commonly available in standardized doses in a multidose injection device (PegIntron RediPen, Schering Plough), this approach may not be feasible in the smallest children; doses may be individualized using more typical vials of the drug. Ribavirin is available as an oral suspension at a concentration of 40 mg/mL (Rebetol, Schering Plough) to allow accurate dosing and adjustments. Peginterferon alfa-2a (180 μg/1.73 m^2 weekly) can also be used in combination with ribavirin, although this type of interferon is not yet approved for use in this age group, and pharmacokinetic data are only available for children aged 5 years and older. Peginterferon and ribavirin should be given for 24 weeks for genotype 2 and 3, and for 48 weeks for genotype 1 infections. There are insufficient data regarding other genotypes, although the longer course of therapy could be considered for genotype 4 infections, extrapolating from adult data. There are no data using slow early virological response (reduction of at least 2 log IU/mL from baseline but not to undetectable at week 12) to substantiate the provision of 72 weeks of treatment in children with genotype 1 HCV but, once again, a case could be made for extrapolating from these recommendations in adults.

It has been well demonstrated in adults that medication dose reductions and interruptions resulting in less than 80% of recommended doses are clearly associated with suboptimal responses. The success of treatment for chronic HCV infection in children and adolescents depends not only on viral factors such as genotype and viral level, host factors such as age and histological stage, but also on careful medical and psychosocial monitoring by the provider and medical support staff, and the availability of a supportive engaged family. Anticipation and early intervention for side effects such as weight loss, fatigue and behavioural changes can help to promote completion of recommended doses of these medications and ensure the highest likelihood of achieving SVR. There are no data regarding the use of haematopoietic growth factors in children receiving HCV treatment, but most children tolerate some degree of anaemia quite well; although neutropenia was common in the clinical trials, significant infections were not observed. Interferon-associated thyroid dysfunction has been demonstrated in children, just as in adults. In one recent retrospective review, thyroid dysfunction was detected in 17% of children with HCV treated with either standard or pegylated interferon [11]. It would be prudent to monitor thyroid-stimulating hormone and promptly refer children who develop abnormalities for consideration of treatment, although it is transient in most instances.

The general management of children and adolescents with HCV infection includes more than just antiviral therapy. Education about the infection, its natural history and modes of transmission, and risk factors for progression such as alcohol use, obesity and other infections is critical to ensure optimal outcomes. In addition, the clinician can be of importance in dissipation of parental guilt regarding vertical transmission, and destigmatization in school and other social settings, as well as provision of other health measures such as hepatitis A and B immunization, and pregnancy prevention counselling and measures. It is also important to emphasize that children and adolescents with HCV can participate fully in school and extracurricular activities including sports without any more than the standard universal precautions already advocated for these settings.

In summary, the minority of individuals with chronic HCV infection are children, and most children and adolescents with this infection have clinically unapparent and histologically mild liver disease. However, some children have more advanced liver fibrosis, and it has been demonstrated that this is a progressive, albeit slow, disease. Children as young as 3 years of age with chronic HCV infection are candidates for treatment. The recommended treatment is the combination of peginterferon alfa and ribavirin for 24–48 weeks, depending on genotype. In general, children tolerate this therapy well. Consideration of age, family and social factors, and anticipatory management of side effects are important in achieving optimal therapeutic responses.

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22 Controlling symptoms in chronic HCV on and off treatment: does anything work?

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LEARNING POINTS

- Individuals chronically infected with HCV demonstrate decreased quality-of-life scores in comparison with healthy controls.
- Patients may have physical, psychosomatic or emotional complaints as a result of their viral hepatitis or as a direct result of side effects related to HCV therapy.
- Almost all patients on HCV therapy experience one or more symptoms. The most common symptoms related to chronic HCV infection include constitutional complaints such as fatigue and malaise, neuropsychiatric symptoms, and associated complaints related to anaemia and dermopathies that may evolve or be exacerbated by HCV treatment.
- The control of symptoms in chronic HCV infection both on and off therapy is clinically challenging and largely supportive in nature.

Introduction

Systematic clinical research describing the signs and symptoms of chronic hepatitis C virus (HCV) infection are limited and therefore begets controversy regarding effective symptom control. The majority of chronically infected individuals are asymptomatic and progression to cirrhosis is typically silent. However, once cirrhosis is established, the rate at which decompensated liver disease develops is about 4% per year in the HCV-infected patient. The diagnosis of *chronic HCV infection is often an incidental finding during* the comprehensive evaluation of patients with abnormal transaminases or of at-risk populations such as intravenous drug users or those who received blood products prior to 1992.

While clinically there is a perception that chronic HCV infection is asymptomatic, there is a significant amount of information reflecting a negative impact on patient quality of life. Thus, health-related quality of life (HRQL) assessments are widely adopted in the approach to the chronic HCV-infected individual in conjunction with routine objective laboratory, radiographic and histological assessments. HRQL assessments aim to assess the effects of health on well-being and incorporate extrinsic factors as well, including economic and environmental variables. A number of HCV-specific quality-of-life assessments have been developed, such as SF-36, a self-assessment that incorporates both a physical and mental component (Figure 22.1) [1]. Lower quality-of-life scores have been appreciated in patients who are aware of their diagnosis compared with those who are infected yet unaware of their chronic HCV infection status. Moreover, compensated HCV patients demonstrated diminished quality of life in comparison with healthy controls as a whole. Most notably, chronic HCV-infected patients scored categorically worse in the physical and emotional roles and attributed poor quality of life to extrahepatic complaints of fatigue, malaise, athralgias, depression and poor cognition [1,2].

Symptom control in chronic HCV infection is a clinical challenge, partly due to the subjective symptoms believed to be associated with the disease at baseline, compounded by the well-described adverse effects associated with therapy and psychosocial factors such as drug and alcohol use. The mainstay of chronic HCV therapy comprises once-weekly injections of peginterferon alfa in combination with ribavirin

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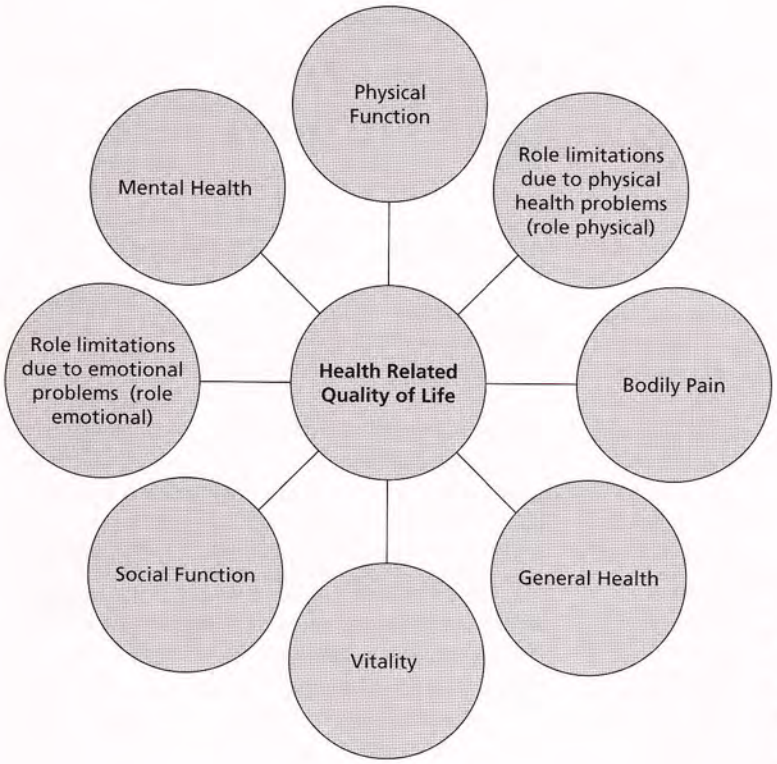

FIG. 22.1 Quality-of-life assessment tools may be generic or specific instruments: the SF-36 (short form questionnaire) is a health survey consisting of 36 questions which target eight domains.

orally. Treatment side effects are often predictable, yet there is some heterogeneity in how best to treat side effects given the lack of double-blind placebo-controlled studies in this area and increasing healthcare costs.

Baseline patient education from the physician and nurse specialist prior to treatment initiation cannot be overestimated and plays a major role in setting a patient's perception about the potential for HCV treatment-induced side effects and the subsequent ability to cope with them. Moreover, it fosters necessary patient–provider trust and continued communication that in turn enables the treating provider to establish individual thresholds for applying side-effect management techniques. Finally, prior to treatment initiation and as part of the initial assessment of a patient pursuing HCV therapy, identification of a social support network (e.g. family, friends, church) will help to improve patient motivation and adherence to therapy and perhaps even to avoid drug and alcohol relapse. It is highly recommended that a patient support person be identified beforehand and be present for patient counselling at baseline.

Flu-like syndrome

Flu-like syndrome is common and often one of the first side effects induced by HCV therapy a patient may experience. Often the symptoms noted include general malaise, fever, anorexia, nausea, vomiting, diarrhoea and body aches. This constellation of symptoms is related to cytokine reactions induced by interferon products as a whole. However, with the advent of once-weekly injections, patients and providers have noted a decrease in frequency of symptoms compared with traditional thrice-weekly preparations. Patients should be educated about these potential side effects, particularly within the first 12 weeks of interferon exposure. Pre-emptive supportive therapy is helpful and includes premedication with paracetamol prior to the interferon injection and continuation of paracetamol dosing as needed over the subsequent 24–48 hours after the interferon injection. Paracetamol doses up to 2 g per 24 hours is acceptable. Additionally, antiemetic and antidiarrhoeal drugs may be employed (Table 22.1).

TABLE 22.1 Commonly encountered side effects related to HCV therapy and suggested adjunctive therapy.

HCV therapy-induced side effects	Suggested adjunctive therapy
Flu-like syndrome Malaise Fever Gastrointestinal upset Anorexia Body aches	Paracetamol (2 g/day maximum) NSAIDs (limit use in cirrhotics, previous gastrointestinal bleed) Proton pump inhibitors/antiemetics (e.g. ondansetron) Antidiarrhoeals (loperamide, Lomotil) Drobinal, megestrol Tramadol, oxycodone (consider APAP max) Increased hydration, exercise
Fatigue	Modafinil (non-sleep-deprived patients) Bupropion
Insomnia	Zolpidem, mirtazapine, trazodone
Mood changes, depression, anxiety	Citalopram, escitalopram, bupropion Benzodiazepines (limit use of alprazolam) Presence of mania: low threshold for psychiatry consultation
Cough	Antitussives (guaifenesin, hydrocodone bitartrate) Survey for pulmonary infiltrates (ribavirin related)
Rash	Topical steroids, Benadryl, hydroxyzine
Neutropenia	Filgrastim 300 μg weekly versus as-needed Start: ANC < 500×10^6/L (non-cirrhotic) Start: ANC > 750×10^6/L (cirrhotic)
Anaemia	Epogen 40 000 units or more weekly as needed Start: haemoglobin < 10 g/dL if asymptomatic Start if decline in haemoglobin is > 3 g/dL ± symptoms Stop/modify dose if haemoglobin > 12.5 g/dL
Thrombocytopenia	No adjunctive therapy available to date Consider low-dose interferon if baseline platelet count < 70×10^9/L at baseline Modify/stop therapy if platelet count < 20×10^9/L; monitor for bleeding

ANC, absolute neutrophil count; NSAIDs, non-steroidal anti-inflammatory drugs.

Fatigue

Fatigue is the most common patient complaint both on and off treatment with interferon monotherapy or interferon/ribavirin combination. The aetiology of treatment-induced fatigue is likely multifactorial given the known neuropsychiatric and endocrine disturbances related to interferon products, and the anaemia related to bone marrow suppression (interferons) and haemolysis (ribavirin). With that said, optimizing fatigue levels on treatment is multifaceted.

Anecdotal evidence suggests that conservative measures such as good sleep hygiene, avoidance of caffeine and nicotine, and increased hydration and exercise, to avoid muscle atrophy, are beneficial. Care must be taken to identify if fatigue both on and off therapy is related to depression, in which case antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or bupropion is favoured. Correction of anaemia, albeit with the use of erythropoietin or dose reductions of ribavirin (less favoured), may help to decrease fatigue levels as well.

Finally, modafinil and methylphenidate have been used for off-label treatment of fatigue in the setting of interferon usage and this has achieved modest improvements [4]. Otherwise, limited data exist to support the use of methylphenidate and modafinil for the treatment of fatigue associated with HCV infection both on and off therapy. Information has been largely borrowed to support their clinical use from response rates in patients suffering from

profound fatigue related to multiple sclerosis and primary biliary cirrhosis [5,6]. The physiological effects of modafinil differ from those of methylphenidate in that the former shows greater inhibition of observed and reported sleep, less facilitation of orthostatic tachycardia and less reduction of caloric intake. These findings are consistent with pharmacological data suggesting that modafinil has wake-promoting actions similar to sympathomimetic agents such as amphetamine and methylphenidate, although the pharmacological profile is not identical [7]. Thus modafinil may arguably be a less addictive and more attractive agent for treatment of fatigue in patients with a history of substance abuse, which is commonly encountered in the HCV-infected population or those afflicted with weight loss and anorexia associated with interferon usage. However, modafinil has been associated cutaneous reactions including drug rash with eosinophilia.

Neuropsychiatric symptoms

Neuropsychiatric complaints are associated with chronic HCV infection *per se*. It is estimated that nearly 30% of patients infected with HCV who are new to interferon treatment suffer from neuropsychiatric problems [6]. Moreover, the rate of depressive disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV ranges from 25 to 70%, in contrast to 6–10% in the general population. *De novo* complaints such as depressed mood, fatigue, sleep changes, anorexia, anhedonia, anxiety, irritability, suicidal/homicidal ideation and in rare cases psychosis are also well described in patients receiving interferon-based therapies [8,9]. Major registration treatment trials investigating peginterferon alfa plus ribavirin in the treatment of chronic HCV infection have reported neuropsychiatric changes in upwards of 35% of patients receiving treatment [10,11].

Identifying and optimizing baseline depression is vital to the control of depressive symptomatology on and off therapy. DSM-IV, along with depression screening tools such as Beck's Depression Inventory and the Hamilton Depression Rating Scale, may be helpful diagnostic tools (particularly in clinical research trials) but often pragmatic and interactive discussions between the treating clinician, the patient and the patient's support systems will suffice. Pharmacological therapy is often tailored to the patient's most dominant neuropsychiatric complaints related to interferon. Despite the numerous antidepressant and anxiolytic agents available on the market, SSRIs are deemed the most appropriate choice for interferon-induced depressive symptoms given their ability to modulate the serotonergic system. Citalopram, escitalopram and sertraline all appear to be the most suitable agents given their accepted efficacy, minimal to no hepatic toxicity and limited drug–drug interactions. An improvement in depression scores was noted as early as week 2 on peginterferon therapy in a prospective trial investigating the efficacy of citalopram versus placebo [12]. Pre-emptive treatment of depression with paroxetine has also been examined; however, no significant difference was noted compared with the control group yet the study appeared to be limited by population size and drop-out rates [13]. Finally, mirtazapine and trazodone appear to be accepted for the treatment of interferon-induced depression and have added benefits of sedation for insomnia-related complaints and, in the case of mirtazapine, increased appetite, which may be an added advantage for those patients suffering from anorexia induced by interferon. Psychiatric consultation is recommended if the severity of symptoms is outside the treating clinician's scope of practice and highly recommended at baseline for those patients with a history of bipolar disease, schizophrenia or schizoaffective disorder. Patients who develop *de novo* mania on HCV therapy warrant treatment discontinuation and referral to psychiatry thereafter for close monitoring and/or treatment.

Anaemia

Apart from side effects related to interferon, ribavirin is also a significant contributor to on-treatment symptoms in chronic HCV infection given its ability to induce haemolytic anaemia. Approximately 25% of patients receiving weight-based ribavirin dosing in the registration trial investigating peginterferon alfa-2a in combination with ribavirin 1000–1200 g daily experienced clinically significant anaemia [9]. Clinically, patients will often complain of worsening fatigue levels, exertional dyspnoea and chest tightness. The off-label use of subcutaneous injections of recombinant epoetin alfa 20 000–40 000 units weekly or darbepoetin 200–300 µg every other week is widely accepted by clinicians in the field as improving haematocrit levels, quality of life and symptoms while on HCV therapy. While the use of growth factors for symptom relief is not generally recommended, a reasonable approach would be to treat anaemia when haemoglobin is below 10 g/dL. Also, it is important that the dose and frequency be titrated to improve haemoglobin to around 12 g/dL, as a significant increase above this might potentially

increase the risk of thromboembolic phenomena. There are no convincing results to suggest that the use of growth factors increases sustained virological response (SVR) on therapy; however, an impressive amount of data demonstrates improved SVR rates with adherence to ribavirin and increased rates of relapse with dose reductions of ribavirin [14].

Skin manifestations

Dermatopathic findings and associated symptoms of pruritus are also associated with chronic HCV infection. Lichen planus is a violaceous plague-like eruption often found on extensor surfaces, genitalia and occasionally mucous membranes. Although not specific to HCV infection, it is often associated with the disease [15]. Treatment is often supportive with topical corticosteroids and, for severe cases, treatment with calcineurin inhibitors or psoralen with UV-A (PUVA) may be considered. Ribavirin may induce a maculopapular rash with pruritus or sensations of burning. Anecdotally, this rash subsides with the use of topical steroids in combination with oral antihistamines such as Benadryl or hydroxyzine 25 mg four times daily. There is little evidence to support the view that dose reduction improves rash given its often transient nature and lack of dose dependence correlation. Likewise, interferon-induced rash is often appreciated and resembles psoriatic plagues which may be optimized with topicals as well. Further interferon therapy almost invariably worsens pre-existing psoriasis and certainly deserves discussion with the patient prior to initiation of interferon-based therapy.

Other

A broad spectrum of additional physical, psychosomatic and emotional symptoms may be encountered clinically in chronic HCV infection. Symptoms encountered on interferon and ribavirin-based therapy may include gastrointestinal complaints, upper respiratory complaints, migraine headaches, alopecia, visual disturbances and manifestations of thyroid dysfunction. Treatment is often supportive in nature (antiemetics, antidiarrhoeals, analgesics, antitussives) and are anecdotal at best. Correction of underlying thyroid dysregulation at baseline or experienced on chronic HCV therapy are standard of care (i.e. levothyroxine). Upper respiratory complaints should be evaluated thoroughly to rule out concomitant sinus infection or, in rare cases, pulmonary infiltrates/interstitial pneumonitis associated with ribavirin or interferon use, which would prompt therapy discontinuation in the case of the latter.

Summary

A number of physical and psychosomatic side effects can be encountered in the chronically infected patient on or off treatment. A thorough baseline assessment comprising history and physical and laboratory work-up is recommended to identify static versus dynamic patient predictors that will impact treatment success. This, combined with patient counselling about the potential for side effects and identification of a patient support network, is essential. Typically, clinicians will need two or more consultations with the patient to adequately achieve this prior to therapy initiation. Ongoing monthly to bimonthly in-office assessments with frequent laboratory surveillance are needed to effectively impact patient motivation and implement reasonable adjuvant therapy. Finally, and to paraphrase Theophrastus, an ancient Greek philosopher, regardless of the clinician's ability to absolve patients of their HCV symptoms, treatment-induced side effects or achieve SVR with HCV therapy, time spent with the patient and the support network both on and off therapy is invaluable.

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23 Complementary therapies in chronic HCV: exploitation or something to offer?

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LEARNING POINTS

- Many complementary and alternative therapies are currently used worldwide to treat HCV infection with potential but unproven benefits.
- Oral silymarin, glycyrrhizin, HM861, TJ-9 and various other compounds are commonly used for their touted benefit as antioxidants. Intravenous silymarin has been observed in a preliminary study to have antiviral effect.
- There is a specific need to develop methods of standardization in the production of these preparations.
- Once appropriate regulations regarding the production of these preparations have been developed, further randomized clinical trials are necessary in order to better assess their safety and efficacy.
- At this time, complementary and alternative therapies cannot be firmly recommended for the treatment of HCV.

Hepatitis C virus (HCV) is a major cause of mortality and morbidity worldwide. Globally, an estimated 170 million people have HCV infection and the majority of these will go onto develop chronic hepatitis C [1]. Standard treatment of HCV infection includes combination standard interferon or peginterferon plus ribavirin therapy, which are costly, limited in their efficacy and carry the risk of adverse events. Consequently, patients with HCV infection often seek alternative treatments to either complement or replace standard therapy. Some of the more common alternative therapies used in the treatment of HCV include silymarin (milk thistle), antioxidants such as *N*-acetylcysteine (NAC) and vitamin E, glycyrrhizin (liquorice root), Chinese traditional medicine, Japanese Kampo medicine, and thymic extracts. Given the extent of patients' utilization of these complementary treatments, it is important to determine their efficacy, if any, and also understand their mechanisms of action in the treatment of chronic liver disease secondary to HCV via their potential antioxidant, antifibrotic or immunomodulatory activities (Table 23.1).

Silymarin, an extract of *Silybum marianum* (milk thistle), is the most commonly used alternative treatment of HCV infection in the USA. It is found commonly throughout Europe, Asia and North America and has been available in the form of highly purified extracts since the 1960s [2]. Silymarin contains multiple biologically active compounds, including the flavonoid silibinin which accounts for 90% of the herb's components in most preparations [2]. It has been used as therapy for liver disease and jaundice since the sixteenth century and more recently in the treatment of *Amanita phalloides* poisoning [2]. In the laboratory, silymarin has been shown to have antifibrotic effects. Specifically, it interferes with leukotriene formation in Kupffer cell cultures and may thereby inhibit hepatic stellate cell activation, a crucial event in fibrogenesis [3]. Moreover, it has been demonstrated to block the proliferation of hepatic stellate cells and their transformation to myofibroblasts [4].

A 2007 study evaluated the anti-inflammatory and antiviral effects of a highly standardized silymarin extract (MK-001) in human cells. Specifically, human peripheral blood mononuclear cells obtained from two healthy donors were stimulated with plate-bound anti-CD3 in the presence and absence of MK-001. The secretion of tumour necrosis factor (TNF)-α, an inflammatory cytokine, was markedly reduced in the presence of MK-001, while the silymarin extract had no effect when tested in the absence of anti-CD3

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TABLE 23.1 Summary of mechanisms of action and side effects of various complementary therapies used in the treatment of hepatitis C.

Alternative therapy	Mechanism of action	Side effects
Antioxidants	Inhibits the production of inflammatory cytokines	Well tolerated
Silymarin (milk thistle)	Antifibrotic effects via inhibition of leukotriene formation in Kupffer cells, hepatic stellate cell activation, and the proliferation of hepatic stellate cells; anti-inflammatory effects via inhibition of both NF-κB-induced transcription in human hepatoma cells and inflammatory cytokine induction; questionable antiviral effects	Well tolerated
Glycyrrhizin (extract of liquorice root)	Antioxidant activity via the induction of glutathione-*S*-transferase and catalase activity	Mineralocorticoid activity which causes sodium and fluid retention, elevated blood pressure, and hypokalaemia
CH-100 (blend of 19 herbs used in Chinese traditional medicine)	Unknown	Possible hepatotoxic effects of the herbal compound's active constituents
Sho-saiko-to (a form of Japanese Kampo medicine, also known as TJ-9)	Antifibrotic effects via the inhibition of action of hepatic stellate cells	Has been associated with interstitial pneumonitis in case reports
Thymic extracts	Suggested increase in Th1 response and decrease in Th2 response	Well tolerated

stimulation. Moreover, T cells obtained from four HCV-infected subjects also demonstrated pronounced decreases in secretion of TNF-α on treatment with MK-001 (mean fold change 6.5, range 1.7–11.7) [5].

Because TNF-α signals through NF-κB, the effect of MK-001 on TNF-α activation of NF-κB transcription in human hepatoma cells was also evaluated. MK-001 was found to dose-dependently inhibit TNF-α induction of NF-κB transcription [5]. To determine the effect of MK-001 on HCV infection, human hepatoma cells were treated with various doses of MK-001 and then infected with the JFH-1 virus, an infection culture system derived from a genotype 2a genome isolated from a Japanese patient with fulminant hepatitis. Pretreatment of the human hepatoma cells with MK-001 dose-dependently inhibited HCV infection, indicating a prophylactic effect of silymarin against the virus. Finally, human hepatoma cells already infected with the JFH-1 virus were subsequently treated with MK-001 or interferon for 24 hours; MK-001 demonstrated pronounced antiviral effects to an almost similar extent as interferon. When combined with interferon, HCV replication was inhibited to a greater extent than with interferon treatment alone [5]. These data confirmed the anti-inflammatory actions via the inhibition of both NF-κB-induced transcription in human hepatoma cells and inflammatory cytokine induction in human peripheral blood mononuclear cells. They also revealed both prophylactic and therapeutic effects of silymarin against HCV infection, particularly in combination with interferon treatment [5].

However, the clinical benefits of silymarin are uncertain given inconsistent results of clinical trials, most likely due to the lack of a standardized product [5]. The first long-term, double-blind, randomized controlled trial comparing silymarin with a placebo vitamin in 170 patients with cirrhosis of diverse causes was conducted in 1971. Although this study was designed before the discovery of HCV, it showed a significant difference in survival between patients treated with silymarin and those treated with placebo (77% vs. 67% at 2 years, and 58% vs. 39% at 4 years, respectively) [6]. Subgroup analysis identified patients with Child A cirrhosis and those with alcoholic cirrhosis to particularly benefit, and silymarin did not have any associated side effects. However, the study had several weaknesses: lack of reported histological data, high drop-out rate, uneven randomization showing more severe liver damage in the placebo group, and lack of control for alcohol consumption during

the trial [7]. Despite these weaknesses, the results of this trial fuelled the widespread use of silymarin by patients with chronic liver disease in Europe during the last several decades.

In a 2002 meta-analysis of nine trials that studied the use of silymarin in chronic liver disease, the overall odds ratio for mortality in the silymarin group compared with placebo was 0.9 (CI 0–1.5; $P = 0.6$). Overall no differences were observed in transaminases, serum albumin, or prothrombin time, and no improvement in histology was noted among patients assigned to the silymarin group compared with those receiving placebo [8]. More recently, a randomized, double-blind, placebo-controlled cross-over study was conducted in 24 patients with chronic hepatitis C who received 12 weeks of oral milk thistle and placebo separated by a 4-week washout interval. In the 17 patients who completed the trial, mean changes in HCV RNA titres and serum alanine aminotransferase (ALT) levels were not significantly different for those who received silymarin versus placebo [9]. These findings were confirmed in the 2008 Hepatitis C Anti-viral Long-Term Treatment Against Cirrhosis (HALT-C) Trial, in which 1145 patients with biopsy-confirmed fibrosis or cirrhosis secondary to HCV who had previously failed antiviral treatment volunteered to participate in a trial of long-term interferon-based therapy for histologically advanced hepatitis C. As part of the study these patients were questioned regarding their use of herbal supplements in the treatment of their chronic liver disease. Of the 1145 patients interviewed, 195 were actively taking silymarin. Statistical comparisons made between those who used silymarin and those who did not revealed no significant difference in HCV RNA levels; similarly, no significant difference between silymarin users and non-users was noted for mean aspartate aminotransferase (AST) or total serum bilirubin levels [10]. In contrast, the mean ALT level was significantly lower in non-users, whereas the mean serum alkaline phosphatase level was significantly lower in users. Silymarin users were found to have significantly lower levels of fatigue, nausea, pain at the site of the liver, anorexia, headaches, and muscle and joint pains [10].

The majority of published data on silymarin in the treatment of hepatitis C (although limited in their scope and quality) provide little convincing support for its efficacy. Yet a recent study conducted in patients with chronic hepatitis C who were previous non-responders to full-dose interferon/ribavirin therapy revealed that high dose *intravenous* silymarin acted as a potent antiviral agent in this setting and was well tolerated with no serious adverse effects. Intravenous administration of a standardized formulation of silymarin allowed higher doses to be given with increased bioavailability, in contrast to the oral forms of silymarin used in past studies that varied in their formulations and which had limited bioavailability secondary to their poor water solubility [11]. Several additional randomized controlled trials are currently being conducted with standardized doses, formulations and routes of administration in order to better assess whether silymarin is of benefit in patients with hepatitis C, either by itself or in conjunction with standard antiviral treatment [10,11].

Complex immune mechanisms are involved in the response to HCV infection. Although the mechanisms of liver damage by HCV are not completely understood, it is thought that the immune response to the infection contributes to the inflammatory infiltration seen on liver biopsy, which then leads to fibrosis and chronic liver disease [1,12]. In healthy individuals, the T helper 2 (Th2) component of the immune system is responsible for cell-mediated immunity, while T helper 1 (Th1) cells promote cell-mediated defence. These two systems are mutually inhibitory and act to balance cell-mediated and humoral immunity [1]. However, in the setting of HCV infection, the Th2 system dominates, leading to the overproduction of TNF-α and other proinflammatory cytokines. In this setting, the Th1 system is suppressed, resulting in decreased natural killer cell activity (cells that directly inactivate the virus) [1]. Antioxidants such as NAC and vitamin E inhibit cytokine production and may be useful in preventing or delaying the inflammation that leads to hepatocyte necrosis and subsequent fibrosis observed in HCV infection.

Several randomized clinical trials have assessed the efficacy of antioxidant therapy with NAC and/or vitamin E in combination with interferon alfa in patients with hepatitis C [13]. A systematic review of six such trials, which included a total of 463 patients, revealed no significant differences in virological response between treatment regimens [13]. In a separate randomized double-blind trial studying the effect of 800 IU of vitamin E daily in 23 patients with hepatitis C who had failed interferon therapy, significant reductions in ALT and AST were noted in 48% of subjects, although HCV RNA remained detectable in the serum of all patients at the conclusion of the trial and transaminases returned to near pretreatment values after cessation of vitamin E treatment [14]. Although antioxidants are generally well tolerated, at present there is insufficient evidence to support their use in the treatment of hepatitis C [13].

Glycyrrhizin is an aqueous extract of liquorice root, which has been used for centuries in traditional medicines to treat

cough, bronchitis, gastritis and liver inflammation [7]. In Japan it has been developed into a standardized extract called Stronger Neominophagen C (SNMC) which has been used for over 20 years in the treatment of chronic hepatitis. In animal models, glycyrrhizin has been shown to modify arachidonic acid metabolism and inhibit the activity of 11β-hydroxysteroid dehydrogenase and PGE_2 production by macrophages [15]. It also has antioxidant activity via the induction of glutathionine-*S*-transferase and catalase activity and has been shown to blunt ALT elevations and impede fibrosis in animals [15,16]. In a Japanese study of SNMC in patients with hepatitis C, cirrhosis developed after 15 years in 21% of treated patients compared with 37% of untreated controls; hepatocellular carcinoma arose in 12% of those treated versus 25% of controls [2,17]. However, this trial was neither prospective nor randomized; varying doses of SNMC were used; HCV RNA levels, biochemical tests and liver histology were not reported; and some patients simultaneously received other unknown herbal therapies [2].

To date, four randomized trials of glycyrrhizin (all administered as SNMC) have been identified. In two of these trials, there was no significant difference in the biochemical or virological response of patients who received SNMC in combination with interferon therapy versus those who had received interferon alone [13]. In the third trial, reductions in ALT levels were seen in patients who received SNMC versus placebo, but this was not sustained after the cessation of treatments and there were no significant effects on HCV RNA levels. In the final trial, significant differences existed in transaminase levels between treatment groups, although these were not sustained at follow-up and there were no virological effects observed [13]. Given the mineralocorticoid activity of glycyrrhizin, treatment with it is also not without side effects: patients can experience worsening complications of cirrhosis, including sodium and fluid retention, elevated blood pressure and hypokalaemia [2,13].

Chinese traditional medicine has been practised for roughly two millennia and comprises multiple forms of ritualistic healing practices, including acupuncture, herbal therapy, massage, and exercise therapy [2]. *Plantago asiatica* is one of the more common Chinese herbal remedies used in the treatment of chronic liver disease, although its use has been studied mainly in the context of hepatitis B. A second combination of 10 herbs known as Compound 861 has been shown *in vitro* (using human stellate cells) and *in vivo* (using animal models of fibrosis) to block cyclin/cyclin-dependent kinase activity in the cell cycle, thereby inhibiting stellate cell activation and even reversing early stages of cirrhosis via the reduction of collagen and transforming growth factor (TGF)-β transcripts while increasing that of matrix metalloproteinase I [2,18]. However, neither *Plantago asiatica* or Compound 861 have been evaluated in the treatment of hepatitis C.

CH-100, another form of Chinese traditional medicine, is a combination of 19 herbs that has been used to treat chronic hepatitis C. In a double-blind placebo-controlled trial involving patients with the virus, treatment with CH-100 was associated with a significant reduction in ALT levels, although no person treated cleared the virus [19]. Several other formulations of Chinese traditional medicine also exist that may be useful in the treatment of hepatitis C, either as alternatives or supplements to standard treatments, or to ameloriate side effects of traditional therapy. However, further studies are necessary since pharmacologically active constituents of these herbal compounds are ill-defined, interactions between multiple compounds may occur, and many of these compounds may in themselves be hepatotoxic [7].

Kampo medicine is the Japanese study and adaptation of traditional Chinese medicine. Unlike the USA, herbal medicines in Japan are regulated as pharmaceutical preparations and as such have been integrated into Japan's national medical system [2]. Hundreds of Kampo extracts are currently approved for use. Sho-saiko-to (also known as TJ-9) is one of the most common herbal medicines used in Japan to treat chronic hepatitis. It has been shown *in vitro* and in animal studies to inhibit the action of hepatitic stellate cells, thus slowing the process of fibrosis [20]. However, very few clinical data exist on the safety and efficacy of TJ-9 in the treatment of hepatitis C.

Thymic extracts have also been recognized as a potential complementary treatment of hepatitis C. A 2004 review of complementary and alternative therapies in the treatment of hepatitis C identified five trials in which thymic extracts were used. In three of these trials, synthetic thymosin alpha 1 (Tα1) was given in combination with interferon; the number of patients who experienced a complete virological or biochemical response at the end of treatment was significantly higher in the group receiving both interferon and Tα1 versus those who received either interferon alone or placebo [13]. These differences were sustained at 6 and 12 months after cessation of treatment, and thymic extracts were generally well tolerated. However, no significant difference in biochemical or virological response occurred

when patients received thymic extract alone [13]. Current data on the use of thymic extracts in the treatment of hepatitis C are limited, although further randomized trials are warranted to better assess the safety and efficacy of this alternative therapy.

In summary, numerous compounds have been used worldwide in the treatment of hepatitis C. Many of these compounds have been shown to protect against experimental liver disease *in vitro* or in animal models. None, however, have been shown to be consistently effective in ameliorating the course of hepatitis C in properly conducted randomized controlled trials [2]. Moreover, patients must be made aware that the production of herbal products is not regulated in the same manner as pharmaceuticals. Yet, as these products continue to become more mainstream, methods to test their safety and efficacy will need to be established. Only with such a system in place can randomized controlled trials be appropriately designed and conducted in order to better assess the safety and efficacy of these preparations prior to their integration into the common practice of Western medicine for the treatment of hepatitis C [2].

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24 HCV in liver transplant recipients: how do you approach them?

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LEARNING POINTS

- HCV-infected patients have lower survival rates than non-HCV-infected patients after liver transplantation.
- Pre-emptive therapy is not well tolerated in the post-liver transplant population.
- Consider treatment of recurrent HCV in patients with biopsy-proven advanced fibrosis and/or increased hepatic venous pressure gradient.
- Treatment using combination of peginterferon and ribavirin in patients with confirmed HCV recurrence can improve allograft and patient survival.
- Barriers to treatment include patient tolerance due to adverse effects of antiviral therapy, risk of cellular rejection, and risk of alloimmune hepatitis.

Introduction

Hepatitis C virus (HCV) is one of the leading indications for liver transplantation (LT) worldwide. With recurrence of HCV being universal and a significant percentage developing severe histological recurrence, recurrent HCV infection represents one of the most significant issues facing the transplant physician today. Treatment of HCV in the transplant setting is challenging given the limited applicability, reduced tolerability and lower efficacy in comparison with the non-transplant setting.

Natural history of recurrent HCV

Recurrent HCV after LT has been shown to be accelerated and more aggressive when compared with HCV infection in the non-transplant setting. Up to 40% of patients transplanted for HCV develop allograft cirrhosis in 5 years, in contrast to 5–20% at 20 years in the non-transplant setting [1,2]. Once allograft failure occurs, decompensation occurs in up to two-thirds of patients within 3 years. In addition, it has been demonstrated that 5-year survival rates after LT in HCV-positive patients are diminished compared with HCV-negative patients (56.7% vs. 65.6%; $P < 0.05$) (Figure 24.1) [3]. Factors associated with severe HCV recurrence include advanced donor age, female gender, viral load, genotype, cytomegalovirus infection and the treatment of rejection.

Treatment of recurrent HCV

Given the high prevalence of HCV recurrence, one must decide if and when to start antiviral treatment. Considerations include presence of viraemia, degree of allograft damage as well as recipients' psychosocial status. The post-LT treatment

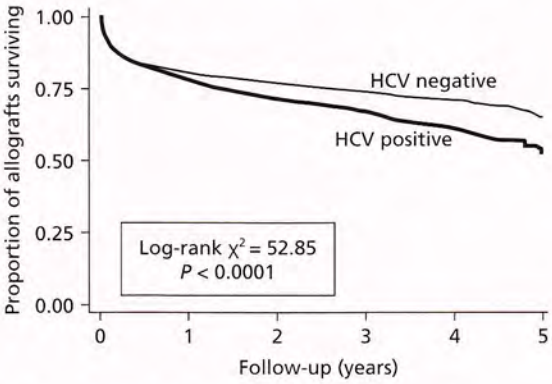

FIG. 24.1 Kaplan–Meier estimates of allograft survival according to HCV status. (From Forman *et al.* [3] with permission from Elsevier.)

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of HCV has improved over the past decade with the best results obtained using the combination of peginterferon and ribavirin [4]. However, sustained virological response (SVR) rates are much lower than those achieved in immunocompetent HCV-infected patients (on average 20–25% less). Positive predictors for SVR include early virological response (> 2 log reduction in HCV RNA at 12 weeks), non-genotype 1 virus, adherence to therapy and lower levels of baseline viraemia.

Pre-emptive antiviral treatment

Pre-emptive treatment refers to early antiviral therapy days to weeks after LT, prior to the development of histological recurrence. Several hypothesized advantages with this approach include low HCV RNA levels and the absence of histologically advanced disease. However, from a clinical standpoint, this timing of treatment is most challenging due to poor performance status, cytopenias from maximal immunosuppression, and higher rates of rejection and infection. Based on limitations due to antiviral toxicity, it has been estimated that only 60% of LT recipients are eligible for pre-emptive therapy and half will require the need for dose reduction [5]. From the only published randomized trial investigating efficacy of pre-emptive HCV therapy (Table 24.1), 41% of patients were eligible and achieved an SVR of only 9% [6]. Hence, the efficacy of pre-emptive antiviral therapy remains poorly defined. We do not favour this approach due to the lack of proven benefit. However, this approach could be considered in patients undergoing re-transplantation for rapidly progressive recurrent HCV or in patients (e.g. living donor recipients) who were transplanted with lower Model for End-stage Liver Disease (MELD) scores. Regarding the latter, these patients are relatively 'healthier' and therefore may be able to better tolerate treatment [7].

Treatment of established recurrent HCV

Given the lack of efficacy and limitations of pre-emptive therapy, most hepatologists have opted to delay treatment until patients develop significant recurrent disease. This approach selectively targets those likely to achieve most benefit with antiviral therapy and avoids unnecessary toxicity in those without significant disease recurrence.

There have been multiple published studies evaluating the efficacy of recurrent HCV therapy. However, these studies are difficult to compare as a wide variety of study designs and end-points (SVR, histological improvement, allograft and patient survival) have been used (Table 24.1). The majority of these studies have shown that SVR leads to histological improvement or reduction of fibrosis progression and improved allograft and patient survival [4,8–11].

TABLE 24.1 Published controlled trials utilizing antiviral therapy for pre-emptive treatment or for recurrent HCV.

Reference	Type of trial	No. of patients	Antiviral regimen α-2b C/R	SVR
Castells *et al.*, 2005 [10]	NRT Post-LT HCV recurrence	48	Peginterferon α-2b (1.5 μg/kg per week) + ribavirin (600–800 mg/day) for 24 weeks + 24 weeks if RNA negative	33%
			No treatment	0%
Bizollon *et al.*, 2007 [11]	NRT Post-LT HCV recurrence	48	Peginterferon α-2b (1.5 μg/kg per week) + ribavirin (800–1000 mg/day)	30%
			No treatment	0%
Carrion *et al.*, 2007 [9]	RCT Post-LT HCV recurrence	54	Peginterferon α-2b (1.5 μg/kg per week) + ribavirin (800–1200 mg/day)	48%
			No treatment	0%
Shergill *et al.*, 2005 [6]	RCT Pre-emptive	51	Interferon α-2b (3 MU three times per week) or peginterferon α-2b (1.5 μg/kg per week) or peginterferon α-2b (1.5 μg/kg per week) + ribavirin (600–1200 mg/day)	9%
			No treatment	0%

LT, liver transplantation; MU, million units; NRT, non-randomized trial; RCT, randomized controlled trial; SVR, sustained virological response.

Castells *et al.* [10] studied 24 patients receiving peginterferon alfa-2b (1.5 μg/kg per week) and ribavirin (600–800 mg/day) for 48 weeks (if HCV RNA undetectable at 24 weeks) and 24 consecutive untreated controls. Overall SVR was 33% in the treatment group and 0% in controls. On univariate analysis, SVR was associated with absence of corticosteroid administration to treat rejection ($P = 0.01$), presence of early virological response ($P = 0.002$) and absence of cytomegalovirus infection ($P = 0.001$).

Bizollon *et al.* [11] studied 27 patients with established recurrent HCV (median 10 months after LT) receiving peginterferon alfa-2b (1.5 μg/kg per week) and ribavirin (800–1000 mg/day) for 48 weeks and compared them to 21 consecutive untreated controls. SVR was 30% in the treatment group and 0% in controls. All eight patients achieving SVR had improvement in histology. Based on univariate analysis, the use of cyclosporine ($P = 0.03$) and early virological response ($P = 0.02$) were associated with SVR.

Carrion *et al.* [9] have published the only randomized study to date. In this study, 54 patients with mild HCV recurrence at least 6 months after LT were randomized to either peginterferon alfa-2b (1.5 μg/kg per week) and ribavirin (800–1200 mg/day) for 48 weeks or no treatment. Overall SVR in the treatment group was 48%. Histological response was seen in 74% of the treated compared with 30% of controls, with all patients achieving SVR having a histological response.

Given the supportive data for treatment in patients with biopsy-proven HCV recurrence, there remains the question of how to approach the timing of therapy. One approach initiates antiviral treatment at the time of initial diagnosis of acute recurrent hepatitis, utilizing liver biopsy to exclude other causes for elevated liver enzymes such as acute cellular rejection. The second approach is to initiate antiviral therapy when clinically significant fibrosis exists based on predetermined protocol liver biopsies.

The 12-month post-LT liver biopsy has the capability to stratify fibrosis progression among patients transplanted for HCV and to help determine whether to initiate antiviral therapy. Patients whose biopsies show severe disease recurrence within the first year after transplant are at a higher chance of progressing to allograft failure and should be considered for antiviral therapy [12]. Another option for monitoring post-LT patients with HCV is measurement of the hepatic venous pressure gradient (HVPG). This appears to have some benefit in the assessment of progressive fibrosis from recurrent HCV [13]. Elevated HVPG at 1 year after LT has been shown to be superior to liver biopsy in accurately predicting clinical decompensation. Similar studies have also shown strong correlation between HVPG measurements and histological response after treatment with antivirals [10].

We recommend that patients with recurrent HCV-related fibrosis (Metavir stage ≥ 2), severe inflammation (Metavir grade ≥ 3), evidence of significant hepatic dysfunction (elevated bilirubin, prolonged prothrombin time), or elevated HVPG gradients should be evaluated for antiviral therapy [7]. Overall, treatment of appropriately selected patients with HCV recurrence and confirmed progressive histological disease has been shown to reduce or possibly reverse progression of fibrosis, decrease the risk of allograft failure, and improve patient survival.

Barriers and limitations to antiviral treatment

There are several limitations or barriers to antiviral therapy in patients with recurrent HCV. SVR rates in these patients are significantly less than in non-transplant patients due to a higher percentage of genotype 1 patients, poor patient tolerability, and lower drug dosing secondary to drug toxicity and the possibility of interferon-induced acute cellular rejection.

Patient tolerance of antiviral medications is a major limitation for treatment success. Patients may not be able to tolerate the major adverse effects of peginterferon or ribavirin at therapeutic doses, especially cytopenias. During the post-LT period, immunosuppression can lead to severe reduction in bone marrow production of white blood cells as well as production of red blood cells. Antiviral therapy may further reduce these cell lines, leading to serious complications such as infection or sepsis. However, with the addition of medications that stimulate red cell and white cell production, more patients may be able to tolerate antivirals at higher doses and for longer periods of time. Another option is to use a low-accelerating dose regimen (LADR) to help increase patient tolerance and assist with improved survival after transplantation. Using LADR, Everson *et al.* [14] achieved an overall SVR rate of 24%; tolerance was much improved and patients required less dose reduction and/or discontinuation.

A potentially serious and controversial complication of antiviral therapy unique to the post-transplant population is interferon-induced rejection. Studies using peginterferon

and ribavirin have yielded conflicting results [9], but the trend for acute rejection has been observed and cannot be dismissed. Another concern is the development of chronic cellular rejection due to the patient having repeated episodes of acute cellular rejection. In addition, calcineurin inhibitor levels must be monitored during antiviral therapy; a greater proportion of antiviral responders experienced a greater reduction in immunosuppression levels than non-responders. This is presumably due to improved hepatic function leading to enhanced biotransformation and lower immunosuppression levels and may play a key role in predisposing these patients to rejection.

Another potential complication from antiviral therapy is alloimmune hepatitis, a condition characterized by biopsy findings of severe interface hepatitis with plasmacellular infiltration and rosettes [15]. A positive predictor for the occurrence of alloimmune hepatitis includes the use of anti-lymphocyte antibodies for immunosuppression induction. A protective variable is the use of granulocyte colony-stimulating factor. Unfortunately, due to a small sample size, it is difficult to determine the clinical significance of these findings, but alloimmune hepatitis as a potential complication of peginterferon-based therapy cannot be dismissed. There should be a high suspicion for either alloimmune hepatitis or acute cellular rejection in patients on antiviral therapy who have worsening liver enzymes in the setting of undetectable HCV RNA.

Liver biopsy is important for differentiating rejection, HCV recurrence or alloimmune hepatitis. This is extremely important since the treatment of rejection/alloimmune hepatitis with OKT3 and steroids can lead to rapid progression of HCV-induced allograft injury. Of course, a greater challenge for the clinician is how to treat the patient with simultaneous acute rejection and HCV recurrence. This remains a much-debated topic and thus far no conclusions can be made.

Summary

HCV recurrence is frequent and leads to a significant reduction in patient and allograft survival as well as fibrosis progression after transplantation. SVR is achievable, but challenging, with the use of combined peginterferon and ribavirin. Several obstacles remain for the transplant physician and include patient tolerance, risk of rejection and the development of alloimmune hepatitis. Moreover, during this time after transplantation, social and psychiatric factors may also add into the equation of selecting which patients would be capable of tolerating these medications.

Based on our experience, we do not endorse pre-emptive treatment due to the lack of proven efficacy. However, this approach could be used in the future for living-donor LT and other patients with 'lower' MELD scores, depending on the presence of future supportive data. We do advocate using protocol liver biopsies or biopsy when liver tests are abnormal. If these biopsies show any advanced histological changes due to HCV recurrence, we would consider using the LADR approach consisting of peginterferon and ribavirin. We would also use the trend of HCV RNA levels and liver tests to assist with efficacy of treatment as well as titration of antiviral dosing. There may be a need to re-biopsy if liver tests continue to remain elevated during treatment in order to evaluate for superimposed acute cellular rejection and/or alloimmune hepatitis. If alloimmune hepatitis or rejection develops, HCV therapy may need to be held or possible additional immunosuppression added to antiviral treatment. Treatment of recurrent HCV is challenging and remains a major clinical dilemma in LT. Future trials and protocols will need to be developed in order to improve our management of these patients.

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25 HCV in patients with advanced disease: do you treat them and do you have any caveats?

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LEARNING POINTS

- An increasing number of patients with advanced hepatitis C are presenting to clinics for treatment of chronic hepatitis C.
- The clinician must characterize the severity of the underlying liver disease before recommending or embarking on a course of antiviral therapy. In general, the Child–Turcotte–Pugh classification is useful for defining compensated (class A) and decompensated (class B or C) cirrhosis.
- Compensated patients have reasonably good chances for SVR and are less prone to severe adverse events or complications.
- Decompensated patients are difficult to treat and difficult to cure and should be managed primarily by physicians or care providers experienced in the treatment of HCV and management of cirrhosis.
- Rendering blood free of HCV RNA prior to liver transplantation reduces the rate of post-transplant recurrence of hepatitis C.
- These patients are prone to cytopenias, which worsen with treatment: growth factors such as G-CSF and erythropoietin analogue are often required.
- The clinician is required to monitor these patients carefully to detect and manage treatment-emergent adverse events or complications.

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Natural history after development of cirrhosis

Clinically, cirrhosis due to hepatitis C virus (HCV) progresses from compensation to decompensation. The term 'compensation' defines patients with Child–Turcotte–Pugh (CTP) class A or score 6 or less, low MELD (Model for End-stage Liver Disease) score, and no history of clinical complications. Despite relative clinical stability at time of presentation, patients with compensated cirrhosis are at risk for progression of disease and clinical deterioration. Estimated rates for development of clinical deterioration (decompensation), hepatoma and death from liver disease in patients with compensated cirrhosis are 3.6–6.0% per year, 1.4–3.3% per year, and 2.6–4.0% per year, respectively [1–7]. Patients with hepatitis C and cirrhosis who experience decompensation have a 5-year survival of only 50% [3].

Goals of antiviral therapy

Disease progression is driven by ongoing active viral replication. Sustained virological response (SVR) to antiviral therapy reduces the risk of progression of fibrosis to cirrhosis [8] and, in patients with compensated cirrhosis, reduces the risk of decompensation, liver-related death and hepatoma [9,10]. SVR may even improve outcomes in patients with decompensated cirrhosis [11]. Thus, the main goal of treatment of cirrhosis, compensated or decompensated, is SVR. In patients on transplant waiting lists, another goal is rendering the patient's blood negative for HCV RNA prior to transplantation to prevent post-transplant HCV recurrence and allograft hepatitis [12–14].

Antiviral therapy in naive compensated patients

The large randomized controlled trials of interferon-based therapy included a small percentage of patients with either advanced bridging fibrosis or compensated cirrhosis [15–22]. All patients with cirrhosis who enrolled into these trials had well-compensated disease, i.e. normal or nearly normal laboratory tests and absence of history of clinical decompensation. Although entry criteria allowed platelet counts as low as $90–100 \times 10^9$/L, average platelet counts were within the normal range. In all these trials SVR was 5–10% lower in patients with advanced fibrosis or cirrhosis compared to patients with lesser degrees of fibrosis. SVRs were 5–15% for interferon monotherapy, 20–30% for peginterferon monotherapy, 30–40% for interferon plus ribavirin, and 40–50% for peginterferon plus ribavirin. Response was lowest in patients with genotype 1 infection, particularly those with high viral load. In the study by Hadziyannis *et al.* [22], SVR was 41% in genotype 1 infection and 73% in genotype 2 and 3 infection with bridging fibrosis or cirrhosis. Helbling *et al.* [23] randomized 124 patients with advanced fibrosis or compensated cirrhosis to peginterferon with either standard or low-dose ribavirin. Overall SVR was 58% for patients infected with HCV genotypes 2 or 3, and 32% for patients infected with HCV genotype 1.

Antiviral therapy in treatment-experienced compensated patients

In the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial, 1145 prior non-responders to interferon or interferon/ribavirin with advanced fibrosis or cirrhosis were retreated with peginterferon/ribavirin [24,25]. The overall rate of SVR was 18% and was related to type of prior therapy: SVR was 27% when prior therapy was interferon monotherapy, 34% when peginterferon monotherapy, 13% when interferon/ribavirin, and 11% when peginterferon/ribavirin. SVR correlated with HCV genotypes 2 or 3, higher platelet count and lower fibrosis score and was compromised by dose reduction.

SVR declined from 23% in least severe disease to 9% in most severe disease independently of dose reductions [25]. Patients with least severe disease were defined by fibrosis and platelet count in excess of 125×10^9/L and patients with most severe disease as those with cirrhosis and platelet count of 125×10^9/L or less. Reduction in SVR, independent of dose reductions and other factors predicting response, indicates that patients with cirrhosis are not only difficult to treat but also relatively resistant to peginterferon/ribavirin and therefore difficult to cure.

Patients with cirrhosis infected with HCV genotypes 2 or 3 are much more likely to experience SVR than patients infected with HCV genotype 1 when retreated with peginterferon/ribavirin. In the EPIC trial [26], 2333 prior non-responders or relapsers to either interferon/ribavirin or peginterferon/ribavirin were retreated with peginterferon/ribavirin. Rates of SVR in the patients with compensated cirrhosis retreated with peginterferon/ribavirin are shown in Table 25.1. Rates of SVR were higher in relapsers compared with non-responders across all genotypes.

Outcome after SVR in compensated patients

Hepatic fibrosis reverses and clinical outcome improves after SVR. Camma *et al.* [27] performed a meta-analysis of 1013 patients enrolled in three randomized trials of interferon or peginterferon spanning the spectrum from mild fibrosis to cirrhosis who had liver biopsies at baseline and after 6 months of treatment. SVR was associated with a −0.59 reduction in fibrosis score (4-point scale). In another study, SVR was associated with a −1.0 reduction in fibrosis score and a −0.65 reduction in inflammation score [28]. In multivariate analysis, the only factors associated with histological improvement in the cohort was SVR and lower body weight.

TABLE 25.1 Rates of SVR (%) in patients with compensated cirrhosis retreated with peginterferon/ribavirin.

	Previous therapy	
	Interferon/ribavirin	Peginterferon/ribavirin
HCV genotype 1	11	9
HCV genotype 2 or 3	50	45

Veldt *et al.* [9] studied 479 patients with a median follow-up of 2.1 years (range 0.8–4.9 years); 142 patients experienced SVR and outcome was compared to the 337 without SVR. SVR was associated with reduction in a composite end-point of clinical decompensation, liver transplantation and mortality: the improvement in outcome was mainly related to decrease in risk of liver-related death. Bruno *et al.* [10] studied 883 patients with biopsy-proven cirrhosis with a mean follow-up of 96.1 months (range 6–167 months). There were no liver-related complications, and rates of hepatocellular carcinoma (HCC) and liver-related death were significantly lower in the 124 patients who experienced SVR. Thus, SVR halts or reverses fibrosis, preventing disease progression, and reduces rates of clinical outcomes in patients with advanced fibrosis or cirrhosis.

Although the patient with compensated cirrhosis may be difficult to treat and difficult to cure, achievement of SVR yields significant long-term clinical benefits that clearly warrant an attempt at antiviral therapy.

The decompensated patient: selection criteria

Treatment of patients with clinical decompensation using peginterferon/ribavirin is problematic: virological response is lower and severe complications, some life-threatening, may occur. In addition, several characteristics of these patients impair virological response (Table 25.2). Careful selection of candidates may yield greatest chance for SVR and limit risk.

TABLE 25.2 Factors impairing virological response to peginterferon/ribavirin in patients with advanced fibrosis or compensated cirrhosis.

Genotype 1 HCV (especially high viral load)
Increasing disease severity defined by increasing fibrosis (Ishak 5 or 6) and decreasing platelet count (cut-off 125 × 10^9/L)
Reduction in doses of peginterferon or ribavirin
Discontinuation of peginterferon/ribavirin
Severe hepatic impairment
Prior non-response or relapse with interferon or peginterferon plus ribavirin
Intolerant of side effects
Cytopenia

Patients experiencing decompensation are typically evaluated for liver transplantation and, if candidacy is confirmed, they may be listed. Approximately 40% of the patients listed for liver transplantation in the USA have either a primary or secondary diagnosis of hepatitis C (Organ Procurement and Transplantation Network data, http://www.OPTN.org/LatestData/rptData.asp). Because these patients may decompensate further during treatment, many centres restrict treatment of decompensated patients to those who are candidates or listed for liver transplantation [29].

The Consensus Development Conference on Liver Transplantation and Hepatitis C suggested that patients on the waiting list with MELD scores 18 or less could be considered for treatment [30]. In addition, the American Association for the Study of Liver Diseases (AASLD) practice guidelines state that patients referred for liver transplantation with a mild degree of hepatic compromise could be considered for antiviral therapy, initiated at low dose, 'as long as treatment is administered by experienced clinicians, with vigilant monitoring for adverse events' [31].

Given these guidelines, the characteristics of patients who may be potential candidates for antiviral therapy include:

- MELD score 18 or less;
- living donor recipients;
- MELD upgrade for HCC.

In the USA, the average MELD score at time of transplantation is typically greater than 25. These patients may be too sick to treat. Patients who undergo living donor liver transplantation typically have less severe disease and lower MELD score at time of transplantation, compared with patients who wait for a liver graft from a deceased donor. Also, patients who receive MELD upgrade points for early HCC can have relatively mild liver disease. MELD scores based on severity of liver disease prior to MELD upgrade for underlying HCC are typically less than 18.

Results of antiviral therapy

There are two goals in treating patients with decompensated cirrhosis. The first is to achieve SVR with the potential that SVR could stabilize or reverse disease progression and eliminate the need for transplantation. The second goal, in patients listed for transplantation, is to render the recipient's blood negative for HCV RNA prior to transplantation to prevent post-transplant recurrence of HCV infection.

TABLE 25.3 SVR in decompensated cirrhosis.

Reference	No. of patients	Treatment	RNA negative at end of treatment (%)	SVR (%)
Iacobellis *et al.* [11]	66	PEG/RBV	49	20
Forns [43]	51	PEG/RBV	29	20
Tekin *et al.* [39]	20	PEG/RBV	45	30
Annicchiarico *et al.* [38]	15	PEG/RBV	47	20
Lim/Imperiale [unpublished]	32	IFN, PEG/RBV	–	31
Everson *et al.* [32]	124	IFN/RBV	46	24
Forns *et al.* [33]	30	IFN/RBV	30	20
Thomas *et al.* [34]	20	IFN	60	20
Amarapurkar *et al.* [37]	18	IFN ± RBV	61	38
Crippin *et al.* [35]	15	IFN ± RBV	33	0
Total	391		44	23

SVR, sustained virological response (defined as HCV RNA negative 6 months or more after discontinuation of treatment); PEG, peginterferon; RBV, ribavirin; IFN, non-pegylated interferon.

Halting disease progression

The published experience with antiviral therapy of decompensated cirrhosis is given in Table 25.3. Except for the study by Iacobellis *et al.* [11], most series represented single-centre experiences, were non-randomized uncontrolled trials, and patients selected for treatment were candidates or listed for transplantation [32–39].

Iacobellis *et al.* [11] randomized 129 patients with decompensated cirrhosis due to HCV who were not candidates for liver transplantation to either peginterferon/ribavirin ($N = 66$) or no treatment ($N = 63$). The patients selected for this trial had had hospital admissions for ascites, variceal bleeding or encephalopathy, were naive to interferon/ribavirin or peginterferon/ribavirin, and lacked overt liver failure. Approximately 75% were classified as Child–Pugh class A or B and average MELD score was 14. Two-thirds were infected with HCV genotype 1 and average platelet count was 86×10^9/L. Rates of SVR were 43.5% and 7.0% for patients infected with HCV genotypes 2 or 3 and HCV genotype 1, respectively. The outcome of patients achieving SVR was favourable and included marked reduction in risk for decompensation, complications, and death related to liver disease. The results suggested that clearance of HCV with antiviral therapy may reduce disease progression and potentially be life-saving in patients with decompensated cirrhosis. However, the low response in HCV genotype 1 infection coupled with adverse and serious adverse events indicates limited application of this strategy.

Patients with cirrhosis need ongoing monitoring, even after SVR. We have examined the long-term outcome of 18 patients who experienced SVR but who did not undergo transplantation (unpublished data). These patients have experienced reduction in risk of liver-related complications and mortality, but four have expired from HCC. Despite SVR and stabilization of hepatic disease, patients with cirrhosis should continue to undergo frequent monitoring for development of HCC.

We reported our experience treating 124 patients with advanced hepatitis C with a low accelerating dose regimen (LADR) of interferon (or peginterferon) plus ribavirin [32]; 80% were classified as Child–Pugh class A or B, average CTP score was 7.4 ± 2.3 and average MELD score was 11.0 ± 3.7. SVR was 13% and relapse 65% in patients with genotype 1 HCV and 50% and 42% in patients with genotype 2 or 3 HCV. There have now been additional reports [32–39] in the literature encompassing a total of 391 patients, yielding a pooled SVR of 23% (Table 25.3).

In our experience, side effects and adverse events were common. During treatment, 56% developed anaemia (haemoglobin < 12 g/dL), 49% leucopenia (absolute neutrophil

TABLE 25.4 Prevention of post-transplant recurrence.

Reference	No. of patients	RNA negative on day of transplant (%)	Post-transplant virological response (%)*
Forns [43]	51	29	20
Everson [32]	47	32	26
Forns [33]	30	30	20
Thomas [34]	20	60	20
Crippin [35]	2	0	0
Everson (LADR-A2ALL)† [unpublished]	79	46 to 69	G1 18 G2/3 39
Total	150	34	21

* Defined as HCV RNA negative for 6 months or more after transplantation.
† Randomized controlled trial submitted to AASLD 2009. LADR-A2ALL, low accelerated dose regimen of peginterferon/ribavirin conducted as a substudy of the NIH-sponsored Adult-to-Adult Living Donor Liver Transplantation (A2ALL) study. Patients infected with genotypes 1, 4, 5 and 6 were randomized 2 : 1 treatment to control, and patients infected with genotypes 2 or 3 were treated.

count $< 1000 \times 10^6$/L) and 33% significant thrombocytopenia ($< 50 \times 10^9$/L). Of 22 serious complications, 21 occurred in 14 patients with CTP class B or C cirrhosis; complications included encephalopathy, ascites, infection, gastrointestinal bleeding, diabetes mellitus and venous thrombosis. Overall there were seven deaths, two during antiviral therapy.

Preventing post-transplant recurrence of HCV

As stated above, one of the goals of treating decompensated patients who are on the waiting list is to render their blood free of HCV RNA in order to prevent reinfection of the liver graft with HCV (Table 25.4). In our published experience, we have transplanted 47 patients, 32 of whom were HCV RNA positive and 15 who were HCV RNA negative at the time of transplantation [32]. All of the 32 who were HCV RNA positive before transplantation had recurrence of HCV after transplantation. In contrast, 12 of the 15 who were HCV RNA negative at the time of transplantation remained free of HCV after transplantatin. These results prove the concept that effective suppression of HCV RNA prior to liver transplantation can potentially eliminate post-transplant recurrence. Similar results were reported by Forns *et al.* [33], who treated 30 patients with hepatitis C and cirrhosis awaiting liver transplantation with an estimated time to transplantation of 5 months or less. Nine patients (30%) achieved on-treatment clearance of HCV RNA from blood and six (20%) remained free of HCV after transplantation. Very early virological response ($\geq 2 \log_{10}$ at week 4) was the strongest predictor of SVR. Overall, the published experience suggests that post-transplant recurrence may be prevented in 21% of patients selected for this treatment (Table 25.4).

The most recent experience from Barcelona highlights the advantages and disadvantages of pretransplant antiviral therapy [36]. On the plus side, treatment was associated with SVR of 20%, early virological response and non-genotype 1 HCV being predictive of SVR. In contrast, negative aspects of treatment included higher rates of side effects and incidence of bacterial infections compared with case-controls (17 vs. 3 episodes; $P = 0.0016$). As a result of this experience, the authors recommended antibiotic prophylaxis during antiviral therapy for this patient population.

It is currently recommended that patients with decompensated cirrhosis should only be treated with antiviral therapy by experienced clinicians or in the setting of a clinical trial [40].

Growth factors

Many patients with cirrhosis may have neutropenia, thrombocytopenia and anaemia prior to institution of treatment. Use of interferon and ribavirin in this population will tend to worsen or precipitate cytopenias. Treatment-related neutropenia and thrombocytopenia are more common and severe with peginterferon compared with non-pegylated interferon. The benefit of higher virological response rates with peginterferon may be counterbalanced by complications related to cytopenias.

Two strategies are used to control these side effects: dose reduction or use of growth factors such as granulocyte colony-stimulating factor (G-CSF) and erythropoietin analogues. The value of either G-CSF or erythropoietin in preventing complications or enhancing virological response is unknown. However, the alternative strategy, dose reduction, may compromise the primary objective of achieving the highest rate of virological response. Dietrich *et al.* [41] have demonstrated that use of erythropoietin during treatment of chronic hepatitis C with interferon plus ribavirin can increase haemoglobin concentrations and maintain higher doses of ribavirin. For these reasons, use of growth factors is favoured over dose reduction in the management of cytopenias.

Management of the patient who fails to respond

The primary goal of antiviral therapy, sustained viral clearance, can be achieved in only a minority of patients with cirrhosis, especially those with more severe disease or decompensation. In the absence of SVR, suppression of disease activity and monitoring patients for disease progression and development of HCC are secondary goals.

Maintenance therapy with low-dose peginterferon was suggested as one means of controlling disease progression. However, the recently published results of 1050 patients (622 with advanced fibrosis and 428 with cirrhosis) from the HALT-C trial indicate that this type of maintenance therapy is ineffective [42]. In HALT-C, 517 patients received low-dose peginterferon monotherapy for 3.5 years and 533 were not treated but served as controls. Although alanine aminotransferase (ALT), HCV RNA level and hepatic inflammation were significantly lower in patients receiving peginterferon, there was no difference in the rate of any clinical outcome (34.1% in the treatment group and 33.8% in the control group). Clinical outcomes included death, HCC, hepatic decompensation, or progression of fibrosis to cirrhosis. There was a trend towards higher rates of serious adverse events in the treated group ($P = 0.07$). Unpublished results from COPILOT and EPIC, other trials of maintenance low-dose peginterferon, also failed to demonstrate improvement in clinical outcome, although events related to portal hypertension, such as variceal haemorrhage, were lower in patients treated with peginterferon. The conclusion from these trials is that maintenance therapy is not likely of benefit in reducing rates of clinical outcomes.

Given the absence of effective therapy to suppress disease progression, patients with cirrhosis must be monitored for complications of liver disease and development of HCC. Screening protocols to detect and manage oesophageal varices and HCC are warranted. Although screening is particularly relevant for the patient who has failed antiviral therapy and who remains positive for HCV, patients with cirrhosis who have achieved SVR can still develop HCC and should be monitored.

Summary

Antiviral therapy for patients with chronic hepatitis C and compensated cirrhosis, decompensated cirrhosis or patients on the waiting list for liver transplantation is evolving. Current data from existing clinical trials suggest that about one-third of naive patients with genotype 1 HCV and two-thirds of naive patients with genotype 2 and 3 HCV with advanced fibrosis or early compensated cirrhosis can achieve SVR. These results have prompted many to advocate aggressive therapy in well-compensated cirrhotics (CTP Class A) who lack evidence of clinical decompensation. However, the response of cirrhotics to antiviral therapy declines with severity of liver disease and non-response to prior interferon-based treatments. The pooled experience from the published literature indicates that only 23% of patients with decompensated cirrhosis can achieve SVR with current therapies. SVR in patients with HCV genotype 1 infection range from 5 to 20%. In contrast, SVR in genotypes 2 and 3 are approximately 50%. The low rate of SVR in decompensated patients is related to high prevalence of genotype 1 HCV, inability to achieve full doses of interferon and ribavirin due to side effects and dose-limiting cytopenias, and risk of complications related to deteriorating liver function. Despite the low rates of SVR, on-treatment clearance of HCV from blood occurs in approximately 30% of genotype 1 patients and 80% of genotype 2 and 3 patients; these patients have retained some level of response to interferon/ribavirin. In addition, pretransplant clearance of HCV RNA from blood may reduce the risk of post-transplant recurrence of hepatitis C. Addition of highly active anti-HCV therapies either alone or in combination with peginterferon/ribavirin may significantly improve outcomes in cirrhosis and reduce rates of HCV recurrence after transplantation. Carefully controlled trials of current and emerging antiviral therapies are critically in need for these difficult-to-treat and difficult-to-cure patients.