Management of hepatitis C

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Hepatitis C virus (HCV) infection is a common cause of chronic liver disease and hepatocellular carcinoma. It is estimated that 15–20% of those infected will develop cirrhosis after 20 years of infection. It is transmitted parenterally, and HCV antibody and HCV RNA tests diagnose infection with a high degree of accuracy. Currently, a combination of peginterferon and ribavirin is the most efficacious treatment, with sustained viral response rates of 45% for genotype 1 and 80% for genotypes 2 and 3. There is some evidence that treatment with interferon-based regimens can improve the natural history of this infection. The side effects of treatment are well recognized and include leucopenia, thrombocytopenia, haemolytic anaemia and depression. Patients with HCV-related decompensated cirrhosis and/or hepatocellular carcinoma should be considered for liver transplantation. The management of special groups, including those with acute HCV infection, co-infected with hepatitis B (HBV) or human immunodeficiency virus (HIV), continues to be defined.

Introduction

Approximately 170 million people worldwide are infected with the hepatitis C virus (HCV). HCV infection is a common cause of cirrhosis and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in Europe and the USA. HCV is transmitted by blood-to-blood contact, and currently intravenous drug use is the most important risk factor for transmission in developed countries. Transmission by blood transfusions in most developed countries has been almost eliminated since the advent of screening for HCV antibody in 1991; however, transmission by unsafe medical practices and blood transfusion still occurs in developing countries. Other less common modes of infection include perinatal transmission and sexual contact.
Natural history

Understanding the natural history of HCV infection is crucial in guiding, monitoring and treating infected persons. Of those with acute HCV, 54–86% will progress to chronic infection. However, owing to the lack of long-term prospective studies, the natural history of chronic infection is not completely clear. Based on retrospective and combined retrospective–prospective studies, it is estimated that 15–20% of infected patients will develop cirrhosis after 20 years of chronic HCV infection. This progression to cirrhosis depends on several host and external factors. Female sex and younger age at infection are associated with lower rates of progression to cirrhosis. Two studies describe women who were infected in the 1970s with infected anti–D immune globulin, of whom only 2% were found to be cirrhotic after 17–20 years. However, the time to progression to cirrhosis for those with unfavourable factors, including male sex, age >40 years at infection, alcohol intake >50 g/day, and co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), may be <20 years. More recent prospective data suggest that an alcohol intake >30g/day is associated with more rapid progression towards cirrhosis. Obesity and diabetes are also emerging as unfavourable risk factors. There are limited data for cirrhosis rates beyond 20 years of infection, and it is unclear whether the progression rate is linear after 20 years, reaches a plateau or accelerates. Once cirrhosis develops, hepatocellular carcinoma occurs at an annual rate of 1–4%.

Clinical features

Acute HCV infection is usually asymptomatic, although a minority present with jaundice, nausea or malaise. For the majority who progress to chronic infection, common symptoms include fatigue, arthralgia, paraesthesia, myalgia, pruritus and sicca syndrome. Increased rates of depression and other psychiatric disorders have also been reported. Mixed essential cryoglobulinaemia is present in up to 40% of infected patients, of whom 30% may be symptomatic with cutaneous vasculitis, renal disease (most commonly membranoproliferative glomerulonephritis) or neuropathy. Severe systemic vasculitis is rare, occurring in 1% of patients.

Diagnosis

Hepatitis C virus antibody

Currently, third-generation enzyme-linked immunoassay (ELISA) for HCV antibody is the first-line diagnostic test. Seroconversion occurs
Management of hepatitis C

after 7–8 weeks of infection and antibodies can be detected with a specificity and sensitivity of 99%.13

**Hepatitis C virus RNA**

Confirmation of active infection is made by a qualitative HCV RNA test with a low limit of detection of 50 IU/ml (100 viral particles/ml).1,13 HCV RNA can be detected after 1–2 weeks of infection by commercially available assays which are 98% specific.13 Patients with a positive HCV antibody test but two negative HCV RNA tests 6 months apart can be reassured that they have previously been infected but have cleared the virus spontaneously, or the antibody result may have been a false positive.13 A negative HCV antibody test effectively excludes any current or previous infection except in those who are immunocompromised or on haemodialysis. In these situations HCV RNA should also be tested to exclude or diagnose infection.1,13 Patients with acute hepatitis C would typically also have a negative antibody test but be positive for HCV RNA, as the RNA is detectable within 1–2 weeks of infection whilst HCV antibody may not appear for 7–8 weeks after infection.13 Quantitative measurement of HCV RNA has been reported as being useful in predicting response to treatment, both pretreatment and during treatment.14–19 The discriminatory level separating high from low viral loads in the initial studies with standard interferon and ribavirin was $2 \times 10^6$ copies/ml in a non-commercial assay.14,15 This has recently been standardized to 800 000 IU/ml for commercial assays.20 There is evidence that a sustained viral response (SVR), defined as an undetectable HCV RNA 24 weeks after the end of treatment, is a valid marker of durable loss of HCV.21

**Genotype**

HCV can be divided into six genotypes, numbered 1–6.13 Genotype plays a significant role in predicting response to treatment and can help to guide length of treatment.14–19 Genotypes 1, 2 and 3 make up most (>90%) of the infected population in Europe and the USA.1,22 Genotype 1 is the most common, followed by genotypes 2 and 3. Genotype 4 is common in Africa and the Middle East. Genotypes 5 and 6 are the least common and are found in South Africa and Southeast Asia, respectively.22 Most studies have found no association between genotype and severity of disease.9,23
Treatment

Standard interferon-based regimens

The arrival of combination therapy with interferon-α and ribavirin, as described in two pivotal studies, superseded interferon monotherapy with SVR rates of 38–43%.\textsuperscript{14,15} The SVR rate with 48 weeks of combination therapy was 30% for genotypes 1, 4, 5 and 6 and 65% for genotypes 2 and 3.\textsuperscript{16} There was also evidence that patients with genotype 1 and those with histological evidence of cirrhosis/bridging fibrosis had significantly higher SVR rates with 48 weeks rather than 24 weeks of combination treatment.\textsuperscript{14} Those with genotype 2 or 3 and no evidence of cirrhosis/bridging fibrosis obtained no additional benefit from 48 weeks compared with 24 weeks of combination treatment.\textsuperscript{14} In these studies, factors associated with higher SVR were genotype 2 or 3, viral load \textless{}2 \times 10^6 \text{ copies/ml}, age \textless{}40 years, female sex and no or minimal fibrosis on biopsy.\textsuperscript{14,15}

Pegylated interferon regimens

Currently, the most efficacious treatment is combination therapy with pegylated interferon-α (peginterferon-α) and ribavirin. Peginterferon is interferon with a polyethylene glycol moiety attached. This results in a longer half-life and improved pharmacokinetics which allows once-weekly subcutaneous injection instead of three times a week as is required with non-pegylated interferons.\textsuperscript{19} Peginterferon monotherapy produces significantly higher SVR rates than standard interferon: 30–39\% versus 8–19\%.\textsuperscript{24,25} There have been two large randomized studies comparing interferon with ribavirin and peginterferon with ribavirin.\textsuperscript{17,18} One study used peginterferon-α2a, while the other used peginterferon-α2b. The two types of peginterferon have not been compared directly, but appear to have similar efficacies and side-effect profiles. The peginterferon-α2a dose is 180 μg once weekly, whereas the peginterferon-α2b dose is weight based at 1.5 μg/kg weekly.

The SVR rates with combination ribavirin and peginterferon are significantly higher than with standard interferon and ribavirin (Table 1), with SVR rates for peginterferon and ribavirin of around 45\% for genotype 1 and 80\% for genotypes 2 and 3.\textsuperscript{17,18} An early viral response with reduction of HCV viral load by \textgreater{}2 log or to undetectable levels at 12 weeks into treatment appears to be predictive of SVR. When the data from both these trials were analysed, only 1.6\% of patients without this early viral response at 12 weeks obtained an SVR.\textsuperscript{26} The variables associated with the likelihood of obtaining an SVR in these two studies were genotype other than 1, lower body weight, viral load \textless{}2 \times 10^6 \text{ copies/ml} and
The peginterferon-α2b trial used a lower ribavirin dose (800 mg). In logistic regression analysis, it was felt that the SVR rate was higher in patients with lower body weight who had, in effect, a higher effective ribavirin dose.18

A recently published study using peginterferon-α2a compared 24- and 48-week regimens with standard-dose ribavirin (1000 mg for weight <75 kg and 1200 mg/day for weight >75 kg) and low-dose ribavirin (800 mg) (Table 2).19 For genotypes 2 or 3, a reduced dose of ribavirin (800 mg) and 24 weeks of treatment was just as efficacious as higher doses of ribavirin and longer treatment.19 Patients with genotypes 2 or 3 with significant fibrosis/cirrhosis did not appear to benefit any more from 48 weeks of treatment than from 24 weeks.19 Patients with genotype 1 treated for 48 weeks with standard-dose ribavirin had significantly higher SVR rates than those treated with low-dose ribavirin or 24-week regimens (Table 2). In these studies, 96–97% of the patients were of genotypes 1, 2 or 3.17–19 The less common genotypes 4, 5 and 6 are thought to have a less favourable response to treatment than genotypes 2 or 3 and to behave more like genotype 1, but patients have been studied to make meaningful comparisons with the more common genotypes.17–19

<table>
<thead>
<tr>
<th>Table 1 SVR rates with peginterferon-α-ribavirin combination</th>
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<tr>
<td><strong>SVR rate overall (%)</strong></td>
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<tr>
<td>Fried *et al.*17</td>
</tr>
<tr>
<td>Interferon-α2b + ribavirin SD 48 weeks 44</td>
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<tr>
<td>Manns *et al.*18</td>
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<tr>
<td>Peginterferon 1.5 μg/kg 4 weeks, 0.5 mg/kg 44 weeks, 48 weeks ribavirin SD 48 weeks 47§</td>
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<tr>
<td>Interferon-α2b + ribavirin SD 48 weeks 47</td>
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SD (standard dose) ribavirin was 1000 mg/day in two divided doses for weight <75 kg and 1200 mg/day for weight >75 kg. The dose of interferon-α2b was 3 MU three times per week.

P value for comparison with standard interferon and ribavirin: *P = 0.01; †P = 0.02; ‡P = 0.46; §P > 0.73; ††P < 0.001; **P = 0.01; ††P = 0.005.

<table>
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<tr>
<th>Table 2 SVR with different doses of ribavirin and lengths of treatment19</th>
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<tr>
<td><strong>SVR genotype1 (%)</strong></td>
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<tr>
<td>Peginterferon-α2a 180 μg + ribavirin SD 48 weeks 52</td>
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<tr>
<td>Peginterferon-α2a 180 μg + ribavirin SD 24 weeks 42</td>
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<tr>
<td>Peginterferon-α2a 180 μg + ribavirin 800 mg 48 weeks 41</td>
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<tr>
<td>Peginterferon-α2a 180 μg + ribavirin 800 mg 24 weeks 29</td>
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</table>

SD (standard dose) of ribavirin was 1000 mg/day for weight <75 kg, and 1200 mg/day for weight >75 kg.
On current evidence, first-line treatment should be combination peginterferon-α and ribavirin. Patients with genotype 1 should be treated for 48 weeks with standard-dose ribavirin (1000 or 1200 mg). Patients with genotypes 4 and 5 should probably be treated using the same regimen as for genotype 1. Treatment duration for genotypes 2 and 3 should be 24 weeks with the reduced dose of ribavirin (800 mg). Patients with genotype 1 who do not have an early viral response at 12 weeks should be considered for early cessation of treatment. In patients in whom ribavirin is contraindicated, peginterferon monotherapy would be the treatment of choice.

Initiation and follow-up of treatment

Detailed discussion and education about the natural history of HCV infection, treatment efficacies and side effects of treatment are essential before initiation of treatment. Based on current evidence, we adopt the following clinical practice in treating HCV (HCV Clinic, Royal Infirmary of Edinburgh). Treatment is on an outpatient basis with visits at week 2 and then every 4 weeks. Full blood counts are checked at these visits and liver function tests, including a prothrombin time, are performed every 12 weeks. Dose adjustments are made according to the blood counts. Side effects, including psychological symptoms, are actively looked for at each visit. A quantitative viral load is checked at 12 weeks into treatment for genotype 1, and treatment is stopped if there has not been at least a 2 log fall in viral load. A qualitative HCV viral load is checked at the end of treatment and 6 months later to see whether an SVR has occurred.

Effect of treatment

Fibrosis

There is good evidence that the combination of interferon/peginterferon and ribavirin significantly reduces the rate of fibrosis progression in patients with chronic hepatitis C, and in some cases it can reverse the degree of fibrosis. One study pooled the data from four randomized controlled trials consisting of peginterferon-α2b alone or in combination with ribavirin, and two trials of interferon and ribavirin. They found that in all treatment groups fibrosis progression rates after treatment were lower than those before treatment. Also, the degree of histological improvement or lack of progression correlated with the efficacy of the treatment regimens. Sustained responders were less likely to progress than relapsers and non-responders, with 7%, 17% and 21% (P < 0.001)
of patients, respectively, having worsening fibrosis. Strikingly, 49% of patients with cirrhosis treated with interferon and ribavirin for 48 weeks had evidence of fibrosis improvement, which in effect was a reversal of cirrhosis (33% of those with fibrosis improvement were sustained responders).

**Development of hepatocellular carcinoma**

There is retrospective evidence that interferon treatment reduces the incidence of HCC in treated patients, particularly those who showed an SVR. Two separate meta-analyses have also described significant reduction in the incidence of HCC in patients treated with interferon compared with untreated patients. This effect was seen in those with a sustained viral response, but also to a lesser degree in non-sustained responders.

**Mortality**

Two retrospective cohort studies on Japanese populations revealed that patients treated with interferon had a reduced risk of death from liver-related causes than untreated patients, with risk ratios of 0.208 [confidence interval (CI), 0.088–0.495] in one study and 0.284 (CI, 0.164–0.494) in the other. These effects were more impressive in those with SVRs. This survival benefit has not been found in other studies with Western patients. Two likely reasons for these differences include a higher incidence of HCC and better SVR in the Japanese studies. Hence the Western studies may not have benefited as much from reduction in HCCs, as well as having overall reduced treatment efficacy. Long-term follow-up of these patients is needed.

**Side effects of treatment**

The side effects of interferon and ribavirin are well described (Table 3). In general, peginterferon–ribavirin produce similar side-effect profiles to interferon–ribavirin. The frequencies of premature discontinuation for peginterferon–ribavirin and interferon–ribavirin combinations are also similar, ranging from 10% to 14%. Neutropenia occurs more commonly with peginterferon–ribavirin than with interferon–ribavirin, with dose reductions needed in 18–20% and 5–10% of patients, respectively. Neutrophil counts usually fall ~2 weeks from start of treatment, and generally stabilize by 4 weeks. Thrombocytopenia is also more severe with peginterferon–ribavirin.
combinations, with a median platelet count reduction of $60 \times 10^9$/litre at 4 weeks compared with $10 \times 10^9$/litre with interferon–ribavirin.\textsuperscript{34} However, this rarely necessitates a peginterferon dose reduction (4% of patients).\textsuperscript{17} Ribavirin-induced haemolysis occurs in all patients to varying degrees, usually within 2–4 weeks of initiation of treatment, with a mean maximum haemoglobin decrease of 3 g/dl.\textsuperscript{34} Full blood counts should be checked at weeks 2 and 4 (as a minimum) and then every 4 weeks thereafter.\textsuperscript{2} The mainstay of treatment of significant neutropenia and ribavirin-induced anaemia is dose reduction of interferon and ribavirin, respectively. There is limited evidence for the use of erythropoietin and cytokines, such as granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor for anaemia and neutropenia.\textsuperscript{34} Further studies are needed to define the exact roles of these potential supportive measures. Pretreatment neutropenia, thrombocytopenia or anaemia are contraindications to treatment.\textsuperscript{1} Owing to potential teratogenicity, ribavirin is also contraindicated in pregnancy, 6 months before planned conception and in patients with lack of effective contraception.\textsuperscript{1}

Depression is a common and potentially serious complication of interferon treatment and should be identified early by specific questioning at each review.\textsuperscript{34} Management with antidepressants, particularly selective serotonergic reuptake inhibitors, is appropriate for mild to moderate depression. Immediate cessation of treatment with psychiatric referral is indicated for severe depression including presence of suicidal ideation.\textsuperscript{34} Active severe depression and current or past history of psychosis are

Table 3 Side effects of interferon and ribavirin\textsuperscript{2,40}

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<tr>
<th>Frequency of side effect</th>
<th>Interferon-α</th>
<th>Ribavirin</th>
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<tr>
<td>Common (up to 50%)</td>
<td>Influenza-like symptoms</td>
<td>Haemolytic anaemia</td>
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<tr>
<td></td>
<td>Headaches</td>
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<td></td>
<td>Fatigue</td>
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<td></td>
<td>Fever</td>
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<td></td>
<td>Rigors</td>
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<td></td>
<td>Myalgia</td>
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<tr>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td>Less common (up to 25%)</td>
<td>Neuropsychiatric</td>
<td>Pharyngitis</td>
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<tr>
<td></td>
<td>Depression</td>
<td>Insomnia</td>
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<td></td>
<td>Insomnia</td>
<td>Dyspnoea</td>
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<td></td>
<td>Lack of motivation</td>
<td>Pruritus</td>
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<td></td>
<td>Poor concentration</td>
<td>Rash</td>
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<td></td>
<td>Neutropenia</td>
<td>Nausea</td>
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<td></td>
<td>Diarrhoea</td>
<td>Anorexia</td>
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<td></td>
<td>Anorexia</td>
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<tr>
<td></td>
<td>Induction of autoimmune disease</td>
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<td></td>
<td>Injection site erythema</td>
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<td></td>
<td>Hair loss</td>
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contraindications to initiation of treatment. Occasionally these patients may still be treated under close supervision by a psychiatrist.

**Patient selection for treatment**

In theory, anyone with hepatitis C could be a candidate for treatment. Arguments against treating everyone include the potential significant side effects, the comparatively low efficacy of treatment for genotype 1 and the cost of treatment. More importantly, it is likely that the majority of patients may not develop cirrhosis despite protracted HCV infection.

**Moderate and severe chronic hepatitis C**

One approach would be to identify and offer treatment to those more likely to progress to cirrhosis. Evidence of moderate and severe inflammation or fibrosis on histology for the individual patient is at present the most reliable predictor of future development of cirrhosis. In one series of patients with sequential liver biopsies, 30% of patients with little or no periportal fibrosis developed cirrhosis after 13 years compared with 42.9% of those with portal/periportal fibrosis at 17 years and 100% of those with septal fibrosis at 10 years. Only 30% of those with low-grade inflammation developed cirrhosis after 13 years, whereas 96–100% of patients with at least intermediate inflammation developed cirrhosis after 10–17 years. Another study suggested that the severity of inflammatory activity at initial biopsy was associated with worsening fibrosis at repeat biopsy at $3.7 \pm 2.5$ years. The recent National Institute of Health (NIH) Consensus Statement on HCV 2002 and the National Institute for Clinical Excellence (NICE) guidelines on interferon and ribavirin 2004 (Table 4) both recommend that patients with moderate to severe fibrosis and/or inflammation on histology should be treated. Patients with significant inflammation or fibrosis would be at higher risk of progression to cirrhosis and as such would make good potential candidates for treatment.

**Mild chronic hepatitis C**

Patients with normal or minimal fibrosis or inflammation are less likely to progress to cirrhosis. They are also more likely to obtain an SVR with treatment. In this group of patients, one approach would be to wait for evidence of increased activity before offering treatment. When advising an expectant approach other prognostic factors should
be taken into account. Those with other good prognostic factors (female sex, low alcohol intake, age of infection <40 years), whose rate of progression to cirrhosis may be as slow as 40–42 years, may feel more reassured about taking an expectant approach. However, this approach entails repeated liver biopsies at periodic intervals, which would entail significant risks. Biopsies every 3 years have been recommended previously; however, the efficacy of this is not validated. The decision to treat or not to treat will have to be made on an individual basis, with the patient’s wishes a central consideration. When contemplating treatment, it is important to note that NICE has suggested that the presence of extrahepatic manifestations sufficient to impair quality of life is appropriate indication on its own for treatment.

The changing role of liver biopsy

The prognostic information obtained by liver biopsy has to be weighed against the potential complications of this invasive procedure. This is especially pertinent in light of the recent advances in the efficacy of HCV treatment. A benign histology conveys, but cannot guarantee, a benign outcome for the individual patient. In a recent prospective study with patients with no or mild (stage1 Ishak score) fibrosis, 33% showed evidence of progression by at least one Ishak stage score after a median of 2.5 years. The natural history of HCV infection after 20 years is also unclear. For the individual patient faced with this uncertainty, treatment no matter what the histology may be the preferred option. This is especially pertinent for younger patients facing 30–40 years of infection. Treatment could also offered, irrespective of the presence or absence of liver disease, to patients who want it for psychological reasons, such as fear of transmission of the virus to family members or feeling ‘unclean’, or with extrahepatic manifestations of HCV. In these situations, liver histology may not alter the decision to offer treatment. On the other hand, histological risk stratification may be important for patients in whom the risks of treatment are high (e.g. past history of depression) or who

<table>
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<tr>
<th>National Institute of Clinical Excellence 2004 recommendations on patient selection for treatment with peginterferon and ribavirin for chronic hepatitis C</th>
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<tr>
<td>Patients ≥18 years in the following groups should be treated</td>
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<tr>
<td>1. Moderate to severe chronic hepatitis C, defined as those with evidence of significant fibrosis and/or significant necrotic inflammation on histology OR 2. Those with extrahepatic manifestations sufficient to impair quality of life</td>
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<td>prior histological classification not necessary</td>
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are wary of the potential side effects. In this situation, a benign liver biopsy may be sufficient to reassure the patient that treatment could be deferred until better-tolerated and more efficacious treatments (particularly for genotype 1) are available.

The NIH Consensus Statement 2002 suggested that a pretreatment liver biopsy is probably not warranted in patients with genotypes 2 and 3 where the SVR rates are 80%. This distinction has not been made by the NICE guidelines, which currently still recommend liver biopsy regardless of genotype to select those with significant histological changes for treatment. However, a recent Royal College of Physicians HCV Consensus Conference concluded that liver biopsy was no longer essential before treatment. Pretreatment liver biopsy still has an important role in the evaluation of the individual patient, however, its role is changing and it may not be necessary in all patients.

Special groups

Persistently normal alanine aminotransferase

Patients with persistently normal alanine aminotransferase (ALT) make up 30% of the HCV-infected population. The incidence of significant fibrosis in this group has varied widely from 1% to 29% in various case series. This probably reflects the heterogeneous nature of this group of patients and the varying strictness in definition in different studies. When tight criteria are used, the overall incidence of significant histological disease is low. In one large cohort of nearly 800 patients with persistently normal ALT measured every 3 months for 1 year, with no other evidence to indicate significant disease (including normal liver function tests, haematology, ferritin and absence of excess alcohol), 5% had either severe chronic hepatitis or cirrhosis on biopsy. It was noted that 78% had either minimal or mild hepatitis, with only 17% having normal histology. Disease progression after 5 years of follow-up is also slow in this group. Although these patients have been previously excluded from large treatment trials, there is recent evidence that they respond just as well to the interferon–ribavirin combination as the group with raised ALT. The initial fears about safety, with persistently elevated ALT post-treatment reported with initial interferon monotherapy studies, have not been seen with the more recent combination studies. In light of current evidence, treatment of these patients would, on the whole, be comparatively less urgent; however, it is clear that they should not be routinely excluded from treatment. The decision to treat these patients will have to be made on a case by case basis, taking into account host factors, genotype and the patient's wishes. In particular,
the presence of significant histological features in this group would indicate that treatment should be offered.

**Re-treatment of non-responders and relapers**

Non-responders are patients who do not become HCV RNA positive during therapy, and relapers are those who are HCV RNA negative during therapy but become HCV RNA positive after treatment is stopped. Of those with non-response to interferon monotherapy, 25–40% achieve an SVR when re-treated with the peginterferon–ribavirin combination. However, only 12% with non-response to interferon–ribavirin achieve an SVR with peginterferon–ribavirin. Of those who relapse after interferon monotherapy, 47–56% have been reported to achieve an SVR with standard interferon–ribavirin. One current study is treating those who relapsed with standard interferon–ribavirin with peginterferon–ribavirin. Initial results are promising with 60% of the 15 patients reported so far achieving SVR.

Relapers to interferon monotherapy or combined interferon and ribavirin, as well as non-responders to interferon monotherapy should probably be re-treated with peginterferon–ribavirin. Based on current evidence, non-responders to standard interferon–ribavirin are unlikely to attain an SVR with peginterferon–ribavirin.

**Cirrhosis**

Patients with compensated cirrhosis/bridging fibrosis have similar SVR rates of 41–43% and 33–41% for peginterferon–ribavirin and standard interferon–ribavirin, respectively. Neutropenia and thrombocytopenia are more common than in non-cirrhotic patients, particularly with the peginterferon regimens, necessitating greater dose reductions. Therefore these patients require close haematological monitoring. Patients with genotypes 2 and 3 attain similar SVRs with 24 weeks of peginterferon plus 800 mg ribavirin (SVR 75%) and 48 weeks of treatment with the higher ribavirin dose (SVR 73%), whereas those with genotype 1 require 48 weeks with 1000–1200 mg ribavirin. Patients with cirrhosis treated with standard interferon and ribavirin should be treated for 24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1.

** Decompensated cirrhosis**

Decompensated cirrhosis is defined by the presence of one or more of the following complications of chronic liver disease: ascites, encephalopathy,
variceal bleeding and/or impaired hepatic synthetic function.\textsuperscript{50} There are no randomized controlled trials of treatment with interferon-based regimens in patients with decompensated cirrhosis. Also, combination interferon and ribavirin is not licensed for this group of patients. There are case series which describe poor tolerance to interferon and ribavirin, with profound neutropenia, thrombocytopenia and severe infections commonly occurring.\textsuperscript{49} There is some non-controlled data showing mildly decompensated patients [mean Child–Turcotte–Pugh (CTP) scores of 7.1 ± 2.0] who were on a liver transplant waiting list achieving SVRs of 50\% for genotypes 2 and 3, but only 11\% for genotype 1.\textsuperscript{51} A recent expert panel consensus report suggested that patients with a CTP score of ≤7 should be strongly considered for treatment, those with scores of 8–11 should be considered for possible treatment and those with scores >11 should not be treated.\textsuperscript{52} In principle, patients with decompensated cirrhosis should be referred for liver transplantation assessment. Antiviral treatment in this group should only be considered by experienced liver units in liaison with liver transplant units, and ideally in the setting of a randomized clinical trial.\textsuperscript{49,51}

Liver transplantation

Patients transplanted for HCV have survival rates of 80\% and 70\% at 1 and 5 years, respectively.\textsuperscript{49} Reinfection in the graft occurs in nearly all patients. Progressive HCV hepatitis leads to cirrhosis in 25–33\% of patients in 5 years,\textsuperscript{53} and 1–5\% develop rapidly progressive fibrosing cholestatic hepatitis leading to hepatic failure in 1–2 years.\textsuperscript{53} The management of post-transplantation HCV infection is controversial with no clear evidence at present to advise on whom to treat, the dose or the timing of treatment.\textsuperscript{49,53}

Co-infection with hepatitis B virus

Patients co-infected with HCV and HBV carry a much higher risk of developing cirrhosis and hepatocellular carcinoma than if infected with either virus alone.\textsuperscript{10} Data for this group are lacking, as co-infected patients have previously been excluded from large clinical treatment trials.\textsuperscript{14,15,17–19} There is some evidence that interferon [9 million units (MU) three times per week for 6 months] could clear HCV in 31\% of patients.\textsuperscript{10} One small trial with standard interferon–ribavirin produced promising results with similar efficacies in HBV and HCV co-infected patients compared with HCV mono-infected patients, with SVR rates of 43\% and 60\% respectively ($P = 0.63$).\textsuperscript{10} Interestingly, in this study suppression of HCV was associated with increased activity of HBV. One
strategy in approaching these patients is to treat the dominant virus first (e.g. lamivudine if HBV is dominant, followed by HCV treatment, or vice versa). Although logical, this has not been tested in clinical trials. Based on current evidence, combination therapy may be the best option although more trials are needed.

**Co-infection with HIV**

Patients co-infected with HIV and HCV have a more rapid progression to cirrhosis than if infected with HCV alone. As survival of patients with HIV is now improved with the highly active antiretroviral therapies, HCV liver disease is emerging as an important cause of morbidity and mortality in these patients. In a recent study with HCV and HIV co-infected patients, SVR with interferon and ribavirin was a disappointing 11% (2.5% for genotype 1, 41.7% for genotypes 2, 3 and 4). This may in part be explained by the high premature discontinuation rate of 51% compared with 19–21% in trials with HCV mono-infection. Common reasons for discontinuation were treatment-related depression, anxiety, anaemia and fatigue. This group of patients represent a challenging cohort who are at risk of progression to cirrhosis, with limited data at present to guide treatment. Initial results suggest poor efficacy and tolerability with standard interferon–ribavirin. Results from current ongoing trials of peginterferon–ribavirin are urgently awaited.

**Acute hepatitis C virus**

Most patients with acute HCV infection are asymptomatic and hence undiagnosed. Cases that are diagnosed are frequently in the context of serial HCV antibody tests in someone with known exposure (e.g. needlestick injury, exposure to infected blood products). Often the diagnosis is inferred in someone with symptomatic hepatitis and HCV antibody positivity, as well as a likely recent source of infection. The management of these patients is unclear, mainly because of the lack of large randomized trials. A meta-analysis of four small randomized controlled trials using 3 MU standard interferon three times a week for 12 weeks revealed an SVR rate of 32% compared with 4% in those who were untreated. A recent study of 44 patients treated immediately with 5 MU interferon daily for 4 weeks, followed by 5 MU interferon three times a week for 20 weeks reported an impressive 43 of 44 patients (98%) achieving SVR. This would suggest immediate treatment of all acute HCV patients. However, a more recent paper investigating 60 patients with symptomatic acute HCV hepatitis found that 52% cleared HCV spontaneously, usually within 12 weeks.
who did not clear HCV were treated with interferon, interferon–ribavirin or peginterferon–ribavirin, with an SVR rate of 80%. This resulted in an overall SVR rate of 91%. Based on current evidence, treatment of acute hepatitis with interferon is highly efficacious. The ideal timing of treatment is unclear. It may be that a period of waiting (e.g. 12 weeks) to watch for spontaneous clearance would be prudent, especially with patients with high risk of side effects of treatment. The best regimen is also unclear, extrapolating from data from chronic hepatitis C trials, peginterferon–ribavirin would probably be the most efficacious.

**Alcohol and hepatitis C virus**

There is evidence that patients with a high alcohol intake (>50 g/day) have more aggressive disease with quicker progression to cirrhosis as well as reduced response to treatment. Response rates for patients with a high alcohol intake were better if there was a period of abstinence prior to treatment. There is some evidence that lower levels of alcohol intake (30 g/day) are also detrimental for HCV. It is unclear whether alcohol consumption of 10–20 g/day affects outcome. The current NICE guidelines use a cut off of >70 g a week of alcohol as being detrimental. Patients with alcoholism should be treated for their dependence, and HCV treatment could be offered after a period of abstinence. Non-dependent patients should probably abstain from alcohol during treatment, given the current lack of knowledge regarding a safe level of intake.

**Renal disease**

There is evidence that treatment with standard interferon-based regimens in patients with cryoglobulinaemic glomerulonephritis can lead to improvement in renal disease, although relapse is common. In patients with endstage renal disease in whom treatment for coexistent chronic hepatitis C is contemplated, interferon monotherapy alone is recommended. There is some early evidence to suggest that 135 µg/week of peginterferon-α2a can be used in patients with endstage renal disease with close haematological monitoring; however, results of ongoing trials are awaited. Ribavirin is associated with a severe dose-dependent haemolytic anaemia in patients with renal impairment, and is contraindicated for creatinine clearance <50 ml/min. The use of ribavirin in milder degrees of renal impairment is at present unclear.
Other aspects of management

Minimizing transmission to others

Patients actively using intravenous drugs should be counselled about safe injecting practices to avoid transmission to others. Individuals in long-term monogamous relationships have an annual risk of sexual transmission of 0–0.6%, and currently barrier contraceptives are probably not necessary but could be used if they want to reduce their risk even more. Those with multiple partners or at risk for sexually transmitted diseases (STDs) have an annual risk of 0.4–1.8%, and barrier contraceptives should be used. Barrier contraceptives should also be used if STDs are present, or genital trauma is likely to occur. Couples should not share razors, toothbrushes and other items that could be contaminated by infected blood.

Screening for hepatocellular carcinoma

HCC in the setting of HCV occurs as a complication of cirrhosis and rarely in patients without cirrhosis. The prognosis and response to treatment for HCC, including liver transplantation, depend largely on the size and number of tumours. Although there have been no randomized trials for screening, there is some evidence from a non-randomized prospective cohort that screening with α-fetoprotein (AFP) and ultrasound every 6 months results in detection of tumours at an earlier stage. There has also been recent evidence to suggest that screening in cirrhotic patients in general may result in improved survival. Although not validated, cirrhotic patients with HCV should probably be screened for HCC every 6 months by AFP and abdominal ultrasound.

Conclusions

HCV infection is an important cause of cirrhosis and HCC. There have been advances in treatment with interferon and ribavirin, and more recently with peginterferon and ribavirin. HCV infection remains a challenging problem with improvements still needed, particularly for genotype 1. Better tolerated treatments for those unable to tolerate current treatment or those with contraindications to treatment are needed. Decisions regarding patient selection and the role of liver biopsy are likely to continue to change in light of ongoing advances.
References

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