Treatment choices for people infected with HCV

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Hepatitis C virus (HCV) infection is one of the leading causes of liver disease in the world. It is a common cause of cirrhosis and hepatocellular carcinoma (HCC), as well as the most common reason for liver transplantation. Thus, appropriate therapeutic approaches have a strong clinical impact on the morbidity and mortality of HCV-infected patients. In this review we outline the most recent results in the therapy of HCV chronic hepatitis. Patients with the best prognostic factors treated with combination therapy (peginterferon and ribavirin) obtained a sustained response rate of 80–95%. We also provide some hints on the most promising results of the newest therapeutic options, which include molecules that inhibit specific enzymes, such as inhibitors of serine proteases, which are now in preclinical or early phase human trials. Host factors influencing the rate of response are also outlined.

Keywords: chronic hepatitis C, hepatitis C virus, interferon, ribavirin, anti-serine

Introduction

Hepatitis C virus (HCV) has an estimated prevalence of 3% in the general population all over the world. Epidemiological studies have shown that 80–90% of these subjects are asymptomatic; nevertheless, they can have significant histological lesions at liver biopsy. In Europe and the USA, HCV infection accounts for 15–20% of all cases of acute hepatitis, 70% of chronic hepatitis, 40% of decompensated cirrhosis, 25–60% of hepatocellular carcinoma (HCC) and 30–40% of all liver transplantations.

The primary goal of treatment in patients with chronic hepatitis C is long-lasting HCV eradication. Those who remain HCV-RNA-negative for 24 weeks after the completion of therapy are defined as having achieved a sustained virological response (SVR). More than 95% of these subjects will have a permanent virological response. Successful therapy prevents the development of cirrhosis and HCC.

The use of interferon (IFN) in the treatment of chronic hepatitis C represents a milestone in the therapy of this disease. Alpha-IFNs are a family of small proteins with pleiotropic antiviral, antiproliferative and immunomodulatory effects. Their subcutaneous injection is followed by rapid absorption and high serum concentrations, but also by fast metabolism and clearance of the drug. Unfortunately, the short duration of the action facilitates replication of the virus and the development of resistance. With standard IFN monotherapy consisting of 3 MU three times a week, only 10–25% of patients achieved SVR.

The advent of ribavirin in the therapy of chronic hepatitis C markedly improved the responses to therapy. Ribavirin is a synthetic purine nucleoside analogue that may involve a combination of direct inhibition of the HCV NS5B polymerase, immunomodulation and promotion of the host immune response. Ribavirin, which exhibits activity against some DNA and RNA viruses, when used alone at the dose of 1000–1200 mg/day, has been demonstrated to reduce alanine aminotransferase (ALT) levels, but not to have an effect on the HCV-RNA concentration. The use of combination therapy with IFN and ribavirin increased the overall (independent of virus genotype) SVR rate from 10–25% to 38–43%. Patients with high HCV viraemia and genotype 1 had a three-fold increased SVR.

Recently, the attachment of inert polyethylene glycol (PEG) polymers to IFN resulted in a larger sized molecule and in a longer half-life due to a reduction in the clearance. Thus, these new preparations started the era of weekly injections of IFN. Pegylation modifies the immunological, pharmacokinetic and pharmacodynamic properties of the protein, extending serum half-life and providing constant viral suppression. At the moment, two peginterferon preparations are available: peginterferon-α-2b, which is a 12 kDa linear polyethylene glycol moiety; and peginterferon-α-2a, comprising two identical 20 kDa chains linked to form a large 40 kDa branched chain. In controlled clinical trials, treatments with these two types of pegylated IFN have been followed by a better response compared with standard IFN. Although there are some differences in the structural and pharmacokinetic profiles of the two peginterferons, both agents show a significant advantage in terms of SVR, which in naive patients with chronic hepatitis C has been reported to be ~35%, while combination therapy of peginterferon injection plus ribavirin leads to sustained viral eradication in more than 50% of patients, increasing to 85–90% in patients with favourable genotypes.

Response to therapy is influenced by different factors related to virus or host characteristics.

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Viral factors

Viral genotypes and viral load are considered the most important predictors of response. Genotypes 2–3 are the most responsive to therapy, while genotypes 1 and 4 are the least likely to respond. The high replication rate of HCV is one of the factors that interferes with the probability of response. Based on viral kinetic studies in chronically infected individuals, the virus has a half-life of 2.7–7.2 h with an estimated production of $10^{11}–10^{12}$ virions daily. Because of this rapid replication, HCV spontaneously mutates within infected individuals, resulting in related quasispecies. In the majority of patients the virus escapes the immune response, probably as a result of mutations in the envelope genes. 10, 11 Many lines of evidence suggest that HCV-encoded proteins interfere directly with IFN signalling and expression of IFN-stimulated genes, the protein products of which mediate the antiviral immunomodulatory, antiproliferative and pro-differentiative effects of IFN. Both transformed and virally infected cells have evolved mechanisms to resist the biological activities of IFN and its direct inhibition of antiviral functions. 12, 13

Host factors

Male gender, more advanced fibrosis/cirrhosis and older age are the factors associated with a less favourable response to antiviral therapy. 7, 14 Habitual alcohol consumption is known to aggravate the clinical outcome of HCV-related chronic liver disease, to increase the risk of HCC and to reduce the chance of response to therapy. 15 The enhanced quasispecies complexity in the hypervariable region of HCV in alcoholics may be the main cause of more progressive HCV-related disease and may explain the resistance to therapy. 16

Genetic factors

Race has repeatedly been considered one of the factors influencing the response rate to therapy. It has been reported that African-American men appear to be least likely to spontaneously clear the virus and to respond to IFN therapy. A recent study on viral kinetics in African-American patients infected with genotype 1 (90–95% of African-Americans are infected with this subtype) and treated with IFN plus ribavirin showed that the failure of response to IFN was due in part to an impaired ability to inhibit viral production, with a consequent impaired viral decline and viral negative rate. New drugs with higher degrees of effectiveness are needed to treat these patients. 17

Polymorphisms in the MHC class II loci may influence the outcome of HCV infection. Self-limiting HCV infection was found to be associated with HLA-DRB1*1101 and HLA-DRB1*0101, 18 but no significant association was found between MHC II class alleles and response to IFN therapy. Outside the MHC the most investigated regions are the cytokine and chemokine genes. There are a number of polymorphisms in the regulatory region of interleukin-10 that appear to influence the level of secretion of this cytokine. It has also been reported that there is an association between persistent infection and polymorphisms of the tumour necrosis factor-α gene.

Weight and steatosis. Obesity was found to be associated with more severe liver disease. 19 Recently, Bressler et al. 20 demonstrated that obesity (body mass index >30 kg/m²) is an independent negative predictor of response to treatment. The effect of weight was particularly evident in patients who received a fixed dose of drug (IFN or ribavirin), and the percentage of SVR decreased to about half in patients weighting >90 kg. In the last few years steatosis has been identified as a risk factor for progression of disease and for non-response to therapy.

Iron overload. Several findings indicated a relationship between iron and response to IFN. In a recent multicentre, randomized, controlled trial we observed that iron removal by phlebotomy is able to improve the rate of response to IFN, suggesting that phlebotomy could be useful as adjuvant therapy. 21

Indications for antiviral therapy

Naive patients

Treatment is recommended for patients who are most likely to have progressive liver disease, such as those with persistent elevation of ALT levels, detectable serum HCV-RNA and portal fibrosis with moderate inflammation on liver biopsy. Accepted criteria for treatment are as follows: (i) persistent elevation in serum ALT for at least 6 months; (ii) detectable serum HCV-RNA; (iii) portal or bridging fibrosis and/or moderate liver inflammation; (iv) compensated liver disease; (v) compliance and acceptance of treatment; (vi) abstinence from alcohol and/or illegal drugs >6 months; and (vii) no contraindications to therapy. Young age of the patient is one of the variables in favour of treatment. Host and viral variables predictive for an SVR are genotype other than 1, low viral load (<2 million copies), smaller body surface area (<2 m²), age <40 years and lack of bridging fibrosis/cirrhosis. 7

In the last 5 years a major advance in the treatment of chronic hepatitis C has occurred. The addition of ribavirin to IFN-α-2b resulted in a two- to three-fold higher SVR compared with IFN-α-2b monotherapy. The recent availability of pegylated molecules, which are larger, with a longer half-life and longer biological activity which allows more convenient once-weekly dosing, has further enhanced the SVR rate. A significantly better SVR was observed in previously untreated patients with chronic hepatitis C who received peginterferon-α-2a plus ribavirin versus patients who received IFN-α-2b plus ribavirin or peginterferon alone (56, 44 and 29%, respectively). 14 Patients with the worst prognostic factors (genotype 1 and higher baseline viral RNA levels (>2 millions copies/mL)] had 41% SVR when treated with peginterferon plus ribavirin and 33% when treated with IFN-α-2b plus ribavirin. It is worth noting that there is a mild increase of ALT during treatment with peginterferon, even after HCV-RNA becomes negative.

Recently, SVR was observed in 56% of previously untreated patients in therapy with peginterferon 2b plus ribavirin, and the SVR reached 88% in patients with genotypes other than 1. 14 A better response was also observed using a weight-based dose compared with standard therapy. Manns et al. 6 demonstrated that weight is a significant predictive factor for response when therapy is delivered as a fixed-dose regimen. The results reported in the recent trials suggested that weight-adjusted therapy with both peginterferon and ribavirin increases the chance of SVR.

Furthermore, in a recent multicentre, randomized, international trial using a validated model to project lifelong clinical outcome, treatment with peginterferon-α-2b plus ribavirin was reported to reduce incidence of liver complications, to prolong and improve quality of life, and to be cost-effective for the initial treatment of chronic hepatitis C. 22

Dose adherence. In a large-scale analysis of IFN-α-2b plus ribavirin and peginterferon-α-2b plus ribavirin, McHutchison & Fried 23 assessed the effect of dose reduction on SVR. They observed a 72% SVR in patients who received >80% of the IFN and ribavirin dose for
a period >80% of the expected duration of therapy. The impact of adherence to therapy was more apparent for genotype 1. The most common types of events leading to discontinuation therapy were psychiatric disorders and anaemia. The reported incidence of discon-
tinuation of therapy was 22% in patients treated with peginterferon-α-2a plus ribavirin, 32% in those given IFN-α-2b plus ribavirin and 32% in peginterferon-α-2a plus placebo.14 Peginterferon-α-2a required a dose modification in 11% of cases, ribavirin in 21% and IFN-α-2b in 11%. In general, among the main side effects of combination therapy are that the absolute neutrophil and platelet counts decrease by 25–40% in the first 2–3 weeks of treatment. In addition, besides a very common haemoglobin fall (<2 g), 10% of patients receiving ribavirin will develop a dose-dependent, reversible, intravascular haemolytic anaemia in the first 4–8 weeks of therapy. The co-administration of antidepressants and growth factors to stimulate the production of red and white blood cells is under investigation.

Several studies have shown that the first phase of viral decay after a dose of therapy occurs within 24–48 h. Phase I decay represents direct inhibition of intracellular production and release of HCV by the drug. The rate is dependent on the dose of IFN and viral genotype, but sustained response correlates with the subsequent slow, pro-
longed and more variable period of viral decline (phase II). Some non-responders show nearly constant viraemia and some even have a rebound throughout phase II. Early identification of patients who will not respond allows treatment to be stopped, and thus reduces the cost of therapy. The best definition of early virological response (EVR) is a reduction in HCV-RNA by at least 2 logs after the first 12 weeks of treatment compared with baseline. In a recent study, 60–76% of patients achieved this threshold, and SVR occurred in 60–80% of them.15 In contrast, patients who did not reach EVR did not respond to further therapy.16 Thus, EVR is predictive of SVR, and evaluation of viraemia at 12 weeks of therapy should be included in the routine follow-up of patients in order to decide whether or not to continue therapy.

However, several studies have shown a reduction in median fibro-
sis progression rates, even in patients who did not eradicate HCV infection.16 By comparing the fibrosis progression rate of virologi-
ical non-responders after IFN with their estimated progression before treatment and with non-randomized untreated patients, Shiffman et al.26 observed that IFN slowed the fibrosis progression and improved the necrosis and inflammation. Currently, several large-scale multi-centre trials are evaluating the role of maintenance therapy with pegylated IFN in monotherapy in preventing further progression of cirrhosis, clinical decompensation and development of HCC [National Institutes of Health (NIH) Consensus Development Conference Statement Management of Hepatitis C, 2002].

**Patients with normal ALT levels**

Approximately 30% of patients with chronic HCV hepatitis have normal ALT levels. Treatment decisions need to be individualized in these patients, and should take into account factors such as age, liver histology, extra hepatic manifestations of hepatitis C, co-morbid states and patient motivation. Patients with HCV genotype 2 or 3 have excellent response rates and should be treated even with normal ALT levels.

**Cirrhotic patients**

Response to treatment of chronic hepatitis C is lower when cirrhosis has already developed. This could be due to intrinsic viral factors or be related to the low amount of IFN given in the presence of leucopenia and thrombocytopenia. Peginterferon has been shown to be effective either alone or in combination with ribavirin, and to be safe in these patients.7 One small study of decompensated patients awaiting ortho-
topic liver transplant (OLT) showed an on-treatment viral response rate in 33% of patients.27 An ongoing study of a cohort of 51 patients with advanced, non-compensated cirrhosis showed that ~50% of subjects have cleared HCV-RNA, and this is maintained up to the sixth month of treatment. The guidelines (February 2002) of the Consensus Conference on the Treatment of Hepatitis C of the Euro-
pean Association for the Study of Liver Disease indicated that patients with chronic hepatitis C with fibrosis F2 or F3 need to be treated, and that patients with cirrhosis (stage F4) should be treated not only to reach SVR, but also to stabilize the disease, and possibly to reduce the risk of HCC.

**Co-infected patients**

In the last few years treatment with antiretroviral therapy has modi-
fied the prognosis and life expectancy of patients with HIV. Thus the HCV–HIV co-infection, usually characterized by more severe disease and increased risk of HCC development, requires treatment. The indication to treat patients with HCV–HIV co-infection is related to the number of T4 lymphocytes (>350/mm³) and HIV viraemia (<30 000 copies/mL).28,29 The tolerance and efficacy of combination IFN plus ribavirin in patients with good conserved immunological response are similar to those of patients with only HCV infection. Preliminary data on AIDS Clinical Trials NIH group on PEG 180 µg + ribavirin indicate a virological response at 24 weeks of 44%. Careful monitoring for potential adverse events is strongly recommended.

**Treatment of HCV in active injection drug users**

In many countries, injection drug use is the most common risk factor for new HCV infections. Despite the limited experience and the absence of controlled trials, recent experience has demonstrated the feasibility and effectiveness of treatment of chronic hepatitis C in people who use illicit injection drugs. Treatment is motivated by the fact that HCV eradication reduces transmission. Efforts should be made to promote collaboration between experts in HCV and healthcare providers specializing in substance abuse treatment.

**Treatment schedules**

The best treatment is the combination therapy peginterferon-α-2a (180 µg/week) or peginterferon-α-2b (1.5 µg/kg/week in genotypes 1 and 4 and 1 µg/kg/week in genotypes 2 and 3) plus ribavirin (800 mg/day for weight <65 kg, 1000 mg/day for 65–85 kg, and 1200 mg/day for >85 kg). Recent NIH guidelines (2002) suggest a 800 mg/day ribavirin dose for genotypes 2 and 3 and 1000–1200 mg/ day for the other genotypes.

The treatment duration varies between (i) 24 weeks for patients with genotype 2 or 3; and (ii) 48 weeks for patients with genotype 1, 4, 5 or 6. Continuation of therapy after 12 weeks of treatment should be based on the concentration of HCV-RNA. If HCV-RNA is still present at week 12 or reduction of viraemia is <2 log, therapy should be stopped.

**Relapsers**

Patients who achieve end of treatment virological response but recurrence of HCV-RNA viraemia after stopping therapy are defined as
relapsers. Relapse usually occurs in 10–15% of patients after 48 weeks of therapy with standard IFN. Re-treatment of these patients with combined IFN plus ribavirin for 24 weeks gives an SVR rate of 49%. The extension of therapy to 48 weeks further enhances SVR to 72%. Ongoing trials with peginterferon-α-2b plus ribavirin indicate that >80% of these patients achieve viral clearance at 24 weeks of therapy.

Non-responders

A large proportion of patients fail to eradicate HCV-RNA even after 1 year of the best-choice therapy. Decisions regarding re-treatment should be based on previous therapy and the difference in potency of the new therapy, severity of the liver disease, prognostic variables associated with response, and tolerance and adherence to previous treatment. Meta-analysis reported that re-treatment of IFN monotherapy non-responders with combination therapy for at least 24 weeks resulted in an SVR rate of ∼13%. It has been suggested that an induction period with a high IFN dose may improve response rate. Recently, in a controlled multicentre study in which non-responders to high-dose IFN monotherapy were enrolled, we observed a 20% SVR using combination therapy of IFN-α-5 MU plus ribavirin. No difference in SVR was observed between patients treated with or without 1 month of a daily dose of IFN. The SVR was more frequent in younger patients (43.5%) with genotype non-1 (44%).

Two studies reported contrasting results on the addition of amantadine sulphate to IFN plus ribavirin: in one open pilot, triple antiviral therapy was considered not to be useful, and in the second (multicentre, controlled) the addition of amantadine was well tolerated and led to an improvement of SVR compared with retreatment with IFN-α/ribavirin alone, in particular in patients with low baseline viraemia.

Preliminary data from our group indicate that triple therapy consisting of peginterferon plus ribavirin and amantadine in patients who failed to respond to the standard IFN/ribavirin combination leads to SVR in 24%. Patients with genotype 2 or 3 do better than those with genotype 1, as well as those aged <40 years.

Acute hepatitis

The diagnosis of acute hepatitis C is made by chance in most cases because of the mild, non-specific symptoms (only 20–30% may have jaundice) and the relative low prevalence of anti-HCV antibodies in the early phase of infection. Current evidence recommends IFN treatment of patients with acute hepatitis C in order to reduce the very high rate of chronicity of untreated patients (ranging from 85% in controlled and 65% in uncontrolled studies). A recent meta-analysis suggests treating patients 60 days from the onset of symptoms, and provides evidence that treatment with a daily induction dose during the first month of IFN monotherapy is the best option for SVR.

Future treatment options

The new therapies under development are based on inhibition of viral enzymes such as polymerase, protease and helicase of HCV. Experimental data from in vitro studies indicate that small interfering RNA (siRNA) against the full-length HCV genome (1a strain) inhibits virus expression and replication. Antiviral activity of SCH6, an inhibitor of hepatitis C virus NS3 serine protease, has also been described. Two studies have already been performed in vivo. The first study, in mice, indicated a good antiviral inhibitory activity of BC2125, an oral drug HCV polymerase inhibitor; the second, performed as an experimental trial in man, using BILN 2061 a novel serine protease inhibitor, demonstrated antiviral activity in non-genotype 1 patients.

Acknowledgements

This paper was partially supported by Progetto a Concorso IRCCS 2003, FIRST 2002, 2003, FIRB 2001 and COFIN 2002.

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