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Combined antiviral options for the treatment of chronic hepatitis C

Jesús Medina, Luisa García-Buey, José A. Moreno-Monteagudo, María Trapero-Marugán, Ricardo Moreno-Otero*

Unidad de Hepatología (planta 3), Hospital Universitario de la Princesa, Universidad Autónoma, Diego de León 62, E-28006-Madrid, Spain

Abstract

In the absence of antiviral treatment, chronic hepatitis C virus (HCV) infection is a liver disease characterized by the development of necroinflammatory changes and progressive liver fibrosis, leading to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). The approval of ribavirin in combination therapy regimens with interferon (IFN) dramatically improved therapy. Another advance was the introduction of pegylated IFNs, which allow a once-weekly subcutaneous administration and show more favorable pharmacokinetics and greater efficacy. Two forms are available: pegylated IFN alpha-2b (12 kDa) (1.5 μg/kg) and pegylated IFN alpha-2a (40 kDa) (fixed dosage of 180 μg). Ribavirin is administered orally, at doses ≥10.6 mg/kg, resulting in higher sustained virological responses (SVR) than IFN monotherapy. The highest SVR rates are attained with pegylated IFNs in combination with ribavirin. Factors associated with treatment outcome include HCV genotype, viral load, body weight, age, cirrhosis or bridging fibrosis, coinfection with HIV or hepatitis B virus, and treatment adherence and tolerance. Currently, the main therapeutic challenges ahead are: (a) the dosage optimization of pegylated IFNs and ribavirin according to the patients' characteristics; and (b) to evaluate the efficacy and safety of this combination therapy for difficult-to-treat patients, such as nonresponders, cirrhotics, transplant recipients, renal disease patients or those coinfected with HIV.

Keywords: Hepatitis C; Interferon; Ribavirin; Pegylated interferon; Combination therapy; Antiviral therapy

1. Introduction

The World Health Organization estimates that 170–200 million people are infected with hepatitis C virus (HCV) globally (Anonymous, 1999), despite the substantial decline in the incidence of acute HCV infection since the development of assays to detect antibodies against the virus. Chronic hepatitis C (CHC) typically follows an indolent course, with 80% of patients being asymptomatic and 30–40% having serum concentrations of alanine aminotransferase (ALT) within normal limits (CDC, 1998; NIH, 2002). The adverse consequences of CHC are usually not evident for at least 20 years following infection (Poynard et al., 1997), leaving a large number of patients at particularly high risk for the life-threatening disease sequelae. The natural history of untreated CHC infection is characterized by necroinflammatory changes and progressive liver fibrosis leading to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC) (Takano et al., 1995). Without effective antiviral treatment, HCV-related mortality is expected to triple in the next 10 years (NIH, 2002).

The HCV is a small RNA virus of the flaviviridae family, with a 9.6 single-stranded RNA encoding a single polyprotein of about 3000 amino acids. After cleavage, a number of structural and nonstructural proteins are produced, including two envelope glycoproteins (E1 and E2), the nucleopeptide protein (core-C) and several nonstructural (from NS2 to NS5) proteins (Major and Feinstone, 1997). Functional studies suggest that these proteins may be involved in the pathogenesis of CHC: NS3 has helicase and protease activities while NS5 contains the RNA dependent RNA polymerase activity, both of crucial importance for HCV replication. The HCV core proteins regulate apoptosis of infected cells (Ruggieri et al., 1997). NS5A and the core proteins interfere with intracellular metabolism of lipids and of lipoproteins with a direct effect on the development of steatosis (Perlemuter et al., 2002). NS5A may contain a sequence domain able to regulate the cellular response to IFN (Tan and Katze, 2001).

Overall, the pathogenesis of CHC liver damage is most likely due to a combination of direct cytopathic effects of viral proteins and of immune mediated mechanisms including cytolytic and noncytolytic reactions mediated by cytotoxic T lymphocytes and inflammatory cytokines (Cerny and Chisari, 1999; Moreno-Otero et al., 1996). The main factors contributing to disease chronicity are the rapid production

* Corresponding author. Tel.: +34-913093911; fax: +34-914022299.
E-mail address: rmoreno.hlpr@salud.madrid.org (R. Moreno-Otero).

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of virus and a lack of vigorous T-cell immune response to HCV with emergence of HCV variants which are prone to escape immune control (Farci et al., 2000). The recent development of subgenomic replicons of HCV, able to support efficient HCV RNA replication and synthesis of all viral proteins (but not complete virus particles production), has provided a promising functional and pathogenic research tool (Blight et al., 2000; Lohmann et al., 1999).

According to the latest NIH Consensus Development Statement for the management of CHC, all patients with CHC are potential candidates for antiviral therapy (NIH, 2002). The therapeutic strategy to be followed is currently well defined, mainly due to the significant progress that has occurred since the initial availability of IFNs. The main advances derive from (a) the introduction of antiviral ribavirin in combination with IFN; (b) the development of pegylated forms of IFN, with an increased and sustained duration of activity, as a result of the longer serum half-lives and decreased renal clearance. However, the decision to treat infected patients depends on multiple factors. These include: (1) accurate diagnosis of the disease and its risk for progression; (2) the patient and/or virological characteristics, as several factors have been identified as predictors of poor response to therapy, including infection with HCV genotype 1, age above 40 years, high viral load ($\geq 1 \times 10^6$ HCV genome copies/ml) or advanced liver disease (e.g. cirrhosis).

The present article sets out to briefly review (a) the latest advances in the treatment of CHC and the currently accepted combined antiviral options and (b) those groups of patients whose characteristics determine a need for different treatment strategies and therefore represent a therapeutic challenge.

2. Treatment options

The current guidelines recommend combination therapy with pegylated IFN and ribavirin as the standard treatment (NIH, 2002). However, a number of factors influence treatment decisions. The best indicator of effective treatment is a sustained virological response (SVR), defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with a lower detection limit of 50 IU/ml or less at 24 weeks after the end of treatment. Antiviral therapy of CHC has continuously improved since the approval of IFN monotherapy and SVR rates have increased significantly with the use of ribavirin in combination regimens, first with IFN and more recently with pegylated IFNs.

2.1. Interferon

Monotherapy with IFN was approved for use in CHC patients before the introduction of ribavirin. It was shown to induce loss of detectable serum HCV RNA and normalization of serum ALT in 40–60% of patients, although most of them relapsed once treatment was discontinued. After 24–48 weeks of monotherapy, SVR rates were lower than 20% (Hoofnagle and Bisceglie, 1997; NIH, 2002). In general, when viremia (HCV RNA) was still evident after 12 weeks of therapy, the patient was unlikely to respond to further IFN therapy. The recommended IFN dose of 3 million international units (MU) or higher given subcutaneously thrice weekly for 48 weeks led to transient virological effects, which did not prevent the later appearance of relapses after therapy was stopped (Marcellin et al., 1995; Poynard et al., 1996; Liang et al., 2000).

2.2. Interferon plus ribavirin

Ribavirin is a synthetic nucleoside analog with in vitro activity against several viruses. Ribavirin may exert its antiviral activity indirectly by stimulating IFN gamma (T-cell-derived IFN) production and associated TH1 antiviral functions. Treatment with ribavirin alone reduces serum ALT concentrations, but not serum HCV RNA levels, in CHC patients. However, in three large, placebo-controlled trials of 1844 IFN-naïve subjects, IFN plus ribavirin therapy was superior to IFN alone in terms of SVR achieved, with rates in the range of 35–45%, thus leading to its replacement (McHutchison et al., 1998; Poynard et al., 1998; Reichard et al., 1998).

2.3. Pegylated interferons

A second major breakthrough in the treatment of CHC was the development of two pegylated forms of IFN alpha: branched pegylated IFN alpha-2a (40 kDa), and pegylated IFN alpha-2b (12 kDa). In an attempt to prolong the systemic half-life of standard IFN alpha, a polyethylene glycol (PEG) molecule was covalently attached to it, allowing for sustained concentrations of IFN to be maintained over longer periods of time (Glue et al., 2000; Algranati et al., 1999). Both pegylated IFNs possess an increased and sustained duration of activity derived from the longer serum half-lives and decreased renal clearance; pegylated IFN alpha-2a is metabolized primarily in the liver (Modi et al., 2000). These optimized pharmacokinetic properties of the two pegylated IFNs allow reduction of administration to once-weekly dosing, thus yielding enhanced efficacy against chronic HCV infection (Wills, 1990; Nieforth et al., 1996; Xu et al., 1998). The efficacy of both pegylated IFNs used as monotherapy or in combination with ribavirin to induce SVR is similar, although no comparative randomized clinical trials have been carried out.

The results of the randomized control trials performed with pegylated IFNs in monotherapy (Zeuzem et al., 2000; Reddy et al., 2001; Heathcote et al., 2000; Lindsay et al., 2001) showed an improvement in efficacy with respect to standard IFN, with a maximum SVR of 39% in the case of treatment of CHC noncirrhotic patients for 48 weeks.

2.4. Pegylated interferons plus ribavirin

Subsequently, combination therapies with pegylated IFN and ribavirin were investigated in clinical trials, leading to the achievement of significantly improved SVR rates in CHC patients.

In a randomized trial of 1530 patients with CHC, pegylated IFN alpha-2b plus ribavirin was compared with IFN alpha-2b plus ribavirin (Manns et al., 2001). The patients were randomized into one of the following 48-week therapy regimens: IFN alpha-2b (3 MU thrice weekly) plus ribavirin (1000–1200 mg per day orally); 1.5 μg/kg once weekly pegylated IFN alpha-2b plus 800 mg per day ribavirin (high-dose pegylated IFN group); or 1.5 μg/kg of pegylated IFN alpha-2b plus ribavirin (1000–1200 mg per day orally) for 4 weeks—then 0.5 μg/kg pegylated IFN alpha-2b per week plus daily ribavirin for an additional 44 weeks (low-dose pegylated IFN group). The SVR was significantly higher in the high-dose pegylated IFN group (54%) than in the low-dose pegylated IFN (47%) or standard IFN (47%) groups ($P = 0.01$ for both comparisons). Pre-treatment variables that correlated with SVR were HCV genotype 2 and 3, low HCV-RNA levels, lower body weight, young age and absence of cirrhosis. Additionally, it was found that SVR was dependent on the ribavirin dose expressed as mg/kg body weight with a threshold value of 10.6 mg/kg below which rates of SVR became unsatisfactory.

A key comparative study evaluated the efficacy of pegylated IFN alpha-2a (180 μg per week) combined with ribavirin (1000–1200 mg per day), compared to pegylated IFN alpha-2a alone and IFN alpha-2b plus ribavirin. SVRs (72 weeks) were significantly increased with the use of pegylated IFN alpha-2a (40 kDa) plus ribavirin (56%) or pegylated IFN alpha-2a (40 kDa) alone (44%), versus standard IFN (29%) (Fried et al., 2002). A strong influence of genotype was observed in patients receiving the combination of pegylated IFN alpha-2a plus ribavirin, as the SVR was 46% in patients with genotype 1 and 76% in those with genotypes 2 and 3. Importantly, the absence of a 12-week virological response (undetectable or 2-log10 drop in HCV RNA titer) in patients treated with pegylated IFN alpha-2a plus ribavirin was highly predictive of a nonresponse (negative predictive value) in 97% of patients at follow-up. This finding is important because treatment can be stopped earlier (12 weeks) in patients without initial virological response (Fried et al., 2002; Cornberg et al., 2001). Another important finding in this study was that a high proportion (41%) of patients considered to have the most treatment-resistant disease (that is, those with both HCV genotype 1 and high baseline viral levels) achieved an SVR with pegylated IFN alpha-2a plus ribavirin, as compared with those treated with standard IFN alpha-2b in combination with ribavirin (33%) or with pegylated IFN alpha-2a in monotherapy (13%). The tolerability profile was also improved using pegylated IFN alpha-2a, both with and without adjunctive ribavirin; patients receiving these therapies experienced less of the influenza-like symptoms (10% reduction of symptoms experienced in the IFN/ribavirin group) characteristic of IFN therapy. These patients also presented 8–10% less myalgia or depression-related events than patients receiving IFN alpha-2b plus ribavirin (Fried et al., 2002).

In one study using PEG-IFN alpha-2a in combination with ribavirin for 24 or 48 weeks (Hadziyannis et al., 2002), the highest SVR rates (51%) were achieved in HCV genotype 1 patients when treated for longer (48 h) and with high doses of ribavirin, independently of pretreatment viral load. In patients with genotypes 2 and 3 the SVR rates ranged from 73 to 78%, regardless of duration of treatment of ribavirin dosage (800 mg versus 1000–1200 mg). These results indicate that HCV genotype 1 patients required a high dose of ribavirin (1000–1200 mg per day) and 48 weeks of therapy to achieve optimal SVR, whereas those with genotype 2 or 3 were adequately treated with a 24-week combination regimen administration and responded sufficiently to a fixed dose of 800 mg of ribavirin.

In summary, the current recommendation is to use combination therapy with pegylated IFNs and ribavirin as the standard of treatment for all cases of CHC, except in the case of contraindications to ribavirin (NIH, 2002). The recommended dose of pegylated IFN alpha-2a is 180 μg per week, independent of body weight, while that of pegylated IFN alpha-2b is weight adjusted at 1.5 μg/kg per week. The dose of ribavirin and the duration of therapy should be decided according to the HCV genotype. Patients with HCV genotypes 2 and 3 should be given a fixed dose of 800 mg daily of ribavirin and should be treated for 24 weeks, while those with genotypes 1 and, possibly, 4, should be given a full dose of ribavirin (1000–1200 mg daily, based on body weight less than or greater than 75 kg) and treated for 48 weeks.

3. Challenging patient groups

As stated above, combination therapy with pegylated IFN and ribavirin is the treatment of choice for most HCV-infected patients. However, in a number of situations, either a different approach may be required, based on the particular characteristics of the patients, or not sufficient data exist indicating which therapeutic strategy is the most appropriate. We summarize below the subpopulations of CHC patients that represent a challenge for treatment and outline some therapeutic options that might prove useful.

3.1. Nonresponders and relapsers

Despite the great advances in the therapy of CHC, a high proportion of treated patients do not achieve an SVR and re-treatment needs to be considered. The available preliminary information indicates that the option of pegylated IFNs,

normally in combination with ribavirin, may be the most convenient. Before taking decisions regarding re-treatment, it must be taken into account (a) the type and duration of the first treatment; (b) the previous type of response (including efficacy, tolerability and patient adherence); and (c) certain factors such as HCV genotype infection and absence or presence of cirrhosis, which may condition the future response.

There is evidence that IFN plus ribavirin may be of use in relapsers and nonresponders initially treated with IFN alone. In a placebo-controlled study with CHC patients who had relapsed after therapy with standard IFN, treatment with IFN plus ribavirin was shown to be more effective in obtaining an SVR (as well as biochemical, and histological responses) than retreatment with IFN alone (Davis et al., 1998). IFN plus ribavirin produced an SVR in 49% of these patients, compared with 5% of those patients treated with IFN alone. A meta-analysis of 941 patients with CHC who had not responded to previous therapy with IFN involved in 12 randomized controlled studies revealed that administration of IFN and ribavirin (1000–1200 mg per day) for at least 24 weeks, resulted in greater levels of SVR than those obtained with IFN alone (Cummings et al., 2001). However, these virological responses remained low, with less than 20% of patients achieving SVR with IFN plus ribavirin, even in the most responsive subgroups.

Preliminary data from several ongoing studies predict that pegylated IFNs plus ribavirin will be of benefit to 15–20% of patients who have not achieved SVR with standard IFN plus ribavirin, with patients with HCV genotypes 2 or 3 achieving better responses than those with HCV genotype 1 (Shiffman, 2001; Shiffman, 2002; Jacobsen, 2002; NIH, 2002). For patients who have not responded to previous therapy, the probability of achieving a virological response has been greater in patients who were previously treated with standard IFN alone rather than standard combination therapy with IFN plus ribavirin (Shiffman, 2001; Jacobsen, 2002).

The dose of ribavirin may be a determining factor for successful therapy with combined IFN and ribavirin. Theoretically, it may be individualized as a function of the type of patient (i.e. relapsers, nonresponders, those with cirrhosis, or patients coinfected with HIV). In all studies using ribavirin at 1000–1200 mg per day, the combined IFN plus ribavirin therapy was more efficacious than IFN alone (Barbaro et al., 1999; Barbaro et al., 1998; Bell et al., 1999; Bellobuono et al., 1997; Milella et al., 1999; Sostegni et al., 1998). However, in studies using lower-dose ribavirin (800 mg per day) mixed results were obtained, with some investigators reporting no differences in SVR between IFN alone and combined IFN/ribavirin-treated groups (Andreone et al., 1999; Brillanti et al., 1994; Brillanti et al., 1995). One study demonstrated greater SVR with the use of only 600 mg per day ribavirin (versus 1000–1200 mg per day dosage) plus standard IFN in relapsers or nonresponders to prior IFN treatment (Bonkovsky et al., 1999). Yet, given their risk for treatment resistance, nonresponder patients may initiate therapy with higher doses of ribavirin to achieve its synergistic effects with IFN. An additional factor to consider is the period of treatment: nonresponders showing short-term benefits after 24 weeks treatment with combined IFN plus ribavirin did not achieve SVR in the long term. Therefore, longer treatment periods may be indicated (Pol et al., 1999; Scotto et al., 1996). For CHC relapsers to IFN, the combination therapy with IFN plus ribavirin for 12 months also yields higher SVR rates (Moreno-Monteagudo et al., 2002).

Finally, failure to respond to optimal therapy with pegylated IFN and ribavirin presents a significant problem, particularly in the presence of advanced fibrosis or cirrhosis. The role of long-term, maintenance therapy with PEG-IFN and ribavirin, as well as new therapeutic strategies are currently being investigated (NIH, 2002).

3.2. HCV genotypes

The major pretreatment determinant of favorable response in CHC patients undergoing therapy with any type of IFN is HCV genotype, with SVR rates consistently higher for patients with genotypes 2 and 3 than for those with the commonly occurring HCV genotype 1. In one clinical trial, 28% of patients with HCV genotype 1 infection had an SVR to monotherapy with pegylated IFN alpha-2a, whereas in previous studies, standard IFN therapy resulted in an SVR of less than 10% in such patients (Zeuzem et al., 2000). In a trial investigating pegylated IFN alpha-2b, the SVR rates ranged from 10 to 14% in patients with HCV genotype 1 infection treated with this drug, compared to 6% in patients who received IFN on its own (Lindsay et al., 2001). In a small study involving patients with another relatively unresponsive HCV genotype (genotype 4) the SVR was higher in patients treated with pegylated IFN alpha-2a compared to those receiving standard IFN (Sherman et al., 2001). The combination regimen of pegylated IFNs plus ribavirin significantly increased efficacy, yielding global SVR rates of 54–56% (Fried et al., 2002; Manns et al., 2001). HCV genotype correlated with response, increasing the SVR rates from 42 to 46% for genotype 1 patients to 76–82% for those with genotypes 2 and 3.

Duration of therapy and ribavirin dosage do affect response to treatment in patients with HCV genotype 1 (Hadziyannis et al., 2002). In this multicenter, controlled trial 1284 CHC patients were stratified according to their HCV genotype (1 or non-1) and randomized to pegylated IFN alpha-2a plus ribavirin 1000 or 1200 mg per day for 24 or 48 weeks, or pegylated IFN alpha-2a plus ribavirin 800 mg per day for 24 or 48 weeks. There was a 51% SVR in HCV genotype 1 patients receiving ribavirin 1000 or 1200 mg per day for 48 weeks compared with 29% in patients treated for 24 weeks with the lower dose of ribavirin, 40% in the 48-week low-dose ribavirin treatment group and 41% in the 24-week standard ribavirin dosage treatment group. In contrast, reducing ribavirin dosage and/or halving treatment duration did not compromise SVR in

patients with HCV genotype non-1 (73–78%). In summary, patients with genotype 1 respond better to longer treatment (48 weeks) and higher ribavirin dosages, while for genotype 2 and 3 patients, 24 weeks duration and a fixed dose of ribavirin (800 mg daily) are adequate to maximize SVR rates.

3.3. Normal ALT serum levels

Up to 30–40% of patients with CHC have normal or minimally elevated long-term serum ALT-levels. In these cases, virological or biochemical testing cannot predict the presence of significant liver disease or the risk of future ALT reactivation. When biopsied, most of them show only mild liver disease, but the possibility of progression to advanced fibrosis and cirrhosis exists (CDC, 1998; NIH, 2002). After reviewing a number of published studies, Alberti and Benvegnù (2003) conclude that 22% of HCV carriers with normal ALT levels show significant fibrosis on biopsy. Treatment of these patients with monotherapy or IFN plus ribavirin combination yielded rates of SVR similar to those achieved in patients with high ALT levels (Bacon, 2002).

Although studies with pegylated IFNs have not been completed, patients with normal ALT levels should not be excluded from treatment and decision must be based on favorable factors such as genotype, stage of fibrosis, patient's age and motivation, and presence of co-morbidities (NIH, 2002).

3.4. Cirrhosis

Chronic hepatitis C becomes more difficult to treat when the liver disease has advanced to stages characterized by the presence of bridging fibrosis or cirrhosis. In a trial of 271 patients with advanced fibrosis or compensated cirrhoris (stages 3 and 4), pegylated IFN alpha-2a improved SVR rates as compared with standard IFN therapy (30% versus 8%) (Heathcote et al., 2000). Promising data on the efficacy and safety of pegylated IFNs in combination with ribavirin in these patients have been mostly derived from subgroup analysis of larger trials (Fried et al., 2002; Manns et al., 2001). Additional studies are currently in progress to evaluate efficacy and tolerance of long-term combined antiviral therapy in patients with cirrhosis.

3.5. Human immunodeficiency virus coinfection

HCV may be regarded as a frequent opportunistic infection in HIV infected patients, with a higher incidence than in the normal population. Since the course of CHC is accelerated in these patients, screening for HCV is strongly recommended in all of them. Patients with CHC and concurrent HIV infection have a greater risk of periportal necrosis, portal inflammation, and fibrosis compared with those not coinfected with HIV (Eyster et al., 1993; Garcia-Samaniego et al., 1997). Moreover, these patients may be at risk of developing cirrhosis in a shorter period of time. In one study, 25% of HIV/HCV-coinfected patients presented with cirrhosis 15 years after the estimated date of HCV infection, compared with only 6.5% of patients with HCV infection alone (Sanchez-Quijano et al., 1995).

According to the National Institutes of Health, HCV/HIV-coinfected persons should be considered for HCV treatment (NIH, 2002). At present, treatment is recommended for patients who are at greatest risk for progression to cirrhosis—characterized mainly by persistently elevated ALT levels, detectable HCV RNA, and histological findings of portal or bridging fibrosis, or at least moderate degrees of inflammation or necrosis.

Coinfection with HCV and HIV represents a significant challenge to management of CHC. The availability of highly active antiretroviral therapy (HAART) has increased the healthy lifespan of patients with HIV to the extent that many HCV coinfected patients will face a greater threat from progressive liver disease. Although the potential for hepatotoxicity is greater in HIV/HCV-coinfected patients, only a small percentage (<12.5%) of coinfected patients were found to experience significant liver toxicity following HAART with any viral protease inhibitor, except ritonavir, and no irreversible effects were noted among those who did experience such toxicity (Sulkowski et al., 2000). Further supporting these conclusions are data from two recent studies showing that anti-HCV therapy (IFN plus ribavirin) does not alter the course of HIV infection either in the presence (Zylberberg et al., 2000) or absence (Landau et al., 2000) of HAART therapy. Preliminary results suggest better response to pegylated IFNs plus ribavirin than to other regimens in patients with HCV/HIV receiving HAART. In one study, 56% of patients who received pegylated IFN alpha-2b plus ribavirin (800 mg per day) had a virological response at 24 weeks of therapy compared with 12.5% of patients treated with pegylated IFN alpha-2b alone ($P = 0.0023$) (Soriano et al., 2002). Such results do suggest that, although on a case-by-case basis, patients with HCV/HIV should be considered for HCV therapy in conjunction with HAART. Monitoring for potential adverse effects, including lactic acidosis (a rare complication of combination therapy in patients undergoing therapy for HIV and HCV), is strongly recommended by the NIH (NIH, 2002).

3.6. Orthotopic liver transplantation

Recurrence of HCV infection occurs virtually always after liver transplantation (Samuel and Feray, 2000). Although its course is normally accelerated, the severity of the recurrence of CHC after transplant is dependent on the degree of immunosuppression in the posttransplantation period. The treatment of HCV in immunosuppressed orthotopic liver transplant recipients presents a special challenge, and studies investigating the utility of IFN plus ribavirin and pegylated IFN alpha-2a in such patients are under

way (Casanovas-Taltavull et al., 2001; Ferenci et al., 2001; Manzarbeitia et al., 2001). However, according to the recent NIH Consensus Conference on the Management of Hepatitis C (NIH, 2002), treatment of these patients should be considered experimental and carried out in the context of clinical trials.

3.7. Alcohol intake

Alcohol markedly influences the progression of liver disease in HCV-infected patients, with a rapid progression to cirrhosis and eventually to HCC. This has been clearly shown for patients with a high daily alcohol intake, but the issue requires more thorough investigations in the case of moderate consumers. The NIH Consensus Conference stated that CHC patients with a high alcohol consumption should not be excluded from treatment (NIH, 2002). However, the use of alcohol before and during treatment with antivirals should be avoided based on the evidence that the effectiveness of therapy is compromised in patients with a high daily alcohol intake (>80 g per day).

3.8. Additional groups of patients

Additional groups of patients have been identified as probably requiring modifications to standard therapeutic regimens, based on their particular characteristics. However, more research is needed in order to define the most appropriate strategies:

- Children infected with HCV generally have no symptoms. When diagnosed and treated, they normally show improved SVR rates with respect to adults. However, large scale trials are needed to define the best treatment options (Jonas, 2002; Wirth et al., 2002).
- Active injection drug users present an incidence of HCV infection higher than the normal population. Limited data show that HCV therapy may be successful even when the patients have not abstained from continued drug use or are on daily methadone. Therefore, they should not be primarily excluded from antiviral therapy (NIH, 2002).
- Although the precise mechanisms are unknown, HCV patients with a high degree of liver steatosis have been shown to undergo a markedly accelerated progression of their liver disease. Therefore, dietetic and/or therapeutic strategies able to prevent or reduce steatosis should be used side by side with combination antiviral therapies (Alberti and Benvegnù, 2003).
- *Hepatitis B virus coinfection*: In patients with both HCV and HBV infection, it may be of use to identify the dominating virus and treat the patients accordingly (i.e. therapy against the virus showing positive viremia). When a serum positivity coexists, Alberti and Benvegnù (2003) recommended first IFN plus ribavirin for HCV infection followed by HBV treatment. However, large-scale trials are clearly required in this context.

4. Safety and tolerability of CHC treatments

Many studies involving IFN plus ribavirin combinations are marked by adverse reactions, the most frequent being fatigue, influenza-like symptoms, hematologic abnormalities and neuropsychiatric symptoms, that often result in discontinuation or a reduction in dose (Fried, 2002; McHutchison et al., 1998; Poynard et al., 1998; Fried et al., 2002; Manns et al., 2001) particularly in the longer treatment courses. Among patients who take ribavirin, hemolysis is the most dangerous adverse reaction. Hemolysis, which results from the accumulation of the drug in erythrocytes, necessitates a dose reduction in as many as 10% of patients (McHutchison et al., 1998). The potential for teratogenicity requires diligent contraception during therapy and for six months after discontinuation of ribavirin. For patients with potential contraindications to the use of ribavirin, or those experiencing serious adverse reactions from its use, either IFN alone or pegylated IFN-based therapy remain as the only treatment alternatives.

The adverse side effects observed with combination therapy with pegylated-IFNs plus ribavirin are similar to those described using standard IFN, although the frequency of certain adverse events may vary by preparation. However, it should be noted that no studies directly comparing the safety/tolerability profiles of pegylated IFN alpha-2b and pegylated IFN alpha-2a have, as yet, been conducted. Pegylated IFNs have been shown to induce neutropenia to a greater extent and this was the most common cause for dose reduction in clinical trials (Manns et al., 2001; Fried et al., 2002). Overall, 10–14% of patients participating in these trials withdrew due to adverse events.

In order to minimize the need for antiviral dose adjustment or discontinuation and to refine the management of side effects of therapy, several strategies may prove useful (Fried, 2002): (a) investigation of the mechanisms of IFN-induced depression and development of new therapeutic alternatives; (b) selective use of hematopoietic growth factors to ameliorate hematologic abnormalities; (c) prospective studies aimed at evaluating the impact of early versus late dose reductions and the effects on response in different genotypes.

Overall, IFN plus ribavirin combination therapy is not associated with any demonstrable treatment-related mortality, and adverse reactions are transient and resolve upon discontinuation of treatment (Cummings et al., 2001). In particular groups of patients, the safety and efficacy of IFN/ribavirin combination therapy has not been fully established: (a) in patients with HCV infection contracted prior to or resulting from organ (liver) transplants: as mentioned above, reinfection after liver transplantation is almost universal (Samuel and Feray, 2000). One small study demonstrated encouraging results with a low-accelerating dose of IFN and ribavirin administered before living-donor liver transplant (pretransplant prophylaxis) (Halprin et al., 2001). (b) In patients with decompensated hepatic disease, or coinfection with HIV or HBV the safety profile of combined IFN/ribavirin remains

unclear. Patients in these categories should be referred for treatment in the clinical trial setting (NIH, 2002).

5. Conclusion

While IFN is considered the pivotal agent in treating patients with HCV infection, room for improvement exists. The key advances during the last years have been the introduction of the combination IFN plus ribavirin, and the development of pegylated IFNs. The addition of ribavirin to standard IFN has increased SVR rates, but only by about 20%. A reason might be that whereas in clinical trials high doses of IFNs and ribavirin were used to achieve the primary clinical goal of SVR, in the "real world" clinical practice, these high doses cannot always be maintained, mainly due to the occurrence of side effects and the requirement for dose reductions, along with failures in treatment compliance. As a result, an overall lower treatment response is generally achieved. In spite of these limitations, treatment of CHC with combinations of pegylated IFNs and ribavirin represents the primary therapeutic option. Although differences in pharmacodynamic and pharmacokinetic parameters exist between the two available pegylated IFN preparations, the therapeutic superiority of one pegylated IFN needs to be evaluated in formal clinical trials focusing on efficacy and safety. Finally, further research in the form of prospective trials is strongly needed in order to explore the usefulness of combination therapy in special populations such as patients with advanced liver disease, those with normal ALT levels, those with coinfection with HIV or hepatitis B virus, children, patients with orthotopic liver transplantation, alcoholics and injected drug users.

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