The question ‘why treat chronic hepatitis C?’ usually arises in mild, self-limited diseases with little or no impact on the health and quality of life of affected individuals. It is also pertinent in the case of severe disease when the efficacy of existing therapies is questionable, side effects are frequent and/or severe, and therapy is consequently adding to the disease cost and toxicity. In the case of chronic hepatitis C (CHC), the decision to treat is sometimes viewed with
skepticism because of a rather limited therapeutic efficacy of interferon alpha (IFN) monotherapies, several and sometimes severe side effects of these agents and the high cost (1,2). In addition, some data on the natural course of hepatitis C virus (HCV) infection (3,4) suggest that the incidence of life-threatening complications may be rather low, particularly if HCV infection has been acquired in early life and histological abnormalities of the liver are mild (1,4). In view of these uncertainties, before any discussion on the efficacy of current and developing forms of therapy in CHC, a critical account of the rationale for treatment is in order.

THE RATIONALE FOR THERAPY

HCV infection is a major health problem worldwide with more than 200 million people chronically infected (1,5). (Some epidemiological data are compatible with an even larger pool of chronic HCV infection) in certain African and Asiatic countries, and in some regions of European countries, the prevalence of chronic HCV infection in the general population has been found to exceed 15% (2,5). The majority of newly acquired infections, probably more than 80%, result in chronic infection (6-8). This unfavourable outcome is independent of the age at acquisition of HCV infection.

Although the rate of liver disease progression may differ significantly from patient to patient, the majority of chronically infected individuals deteriorate progressively over several years, and one-third of patients eventually develop end-stage liver disease. Also, 1% to 2% of HCV patients each year develop hepatocellular carcinoma (HCC). Thus, chronic HCV infection seems to account worldwide for the etiology of one-third of cirrhosis cases requiring liver transplantation and of 70% of those developing HCC (9).

Moreover, in view of the relatively high prevalence of HCV infection in most parts of the world in those aged 35 to 50 years old, even if the incidence of new HCV infection is decreasing, the health care burden of HCV infection is expected to increase in the next decades (2). Davis et al (9), projecting the future health care burden from hepatitis C in the United States, estimated that, in the absence of effective therapeutic intervention, the number of patients with decompensated cirrhosis in that country will increase by the year 2000 to 279%, liver-related deaths to 223% and the need for liver transplantation to more than five times the current rate. In view of these data on the survival of HCV-infected individuals and of the extent of this health problem, the need for effective therapy cannot be disputed.

EFFICACY OF EXISTING THERAPIES

The aim of therapy in CHC is to eradicate HCV infection and consequently to cure or halt progression of liver disease. If therapy does not prove curative, then the aim is to change at least the unfavourable course of chronic HCV infection, reducing its morbidity and mortality (10-12).

To what extent, then, and at what cost are available and licensed forms of therapy – consisting of IFN alone or in combination with ribavirin – able to achieve these goals?

In clinical practice, the efficacy of IFN therapy in HCV infection is measured mainly by serum alanine aminotransferase (ALT) levels and the presence of HCV RNA in serum. Independent of other response variables, treatment with IFN is associated with various changes in these two parameters.

Responses to therapy have been grouped into four main response profiles: sustained response (SR), relapsing response (RR), biochemical response (BR) and no response (NR). In SR, HCV RNA is cleared from serum and ALT returns to normal levels. In RR, viremia is not cleared, but in some patients can be sustained (13). Finally, in NR there is no response either at the virological or the biochemical level. On the other hand, clearance of HCV RNA is almost always accompanied by BR if sustained, is considered to be practically equivalent to cure of HCV infection and liver disease (13-15).

Sustained virological response accompanied by sustained liver disease remission may be achieved by IFN therapy. This goal depends on the doses and duration of IFN treatment, as well as on several variables related to the virus or the host, for example, age at acquisition of infection, stage of liver disease, viral load, HCV genotypes and sex. In certain patient subsets, particularly those with HCV genotype other than 1 and those with low viral load, the rate of SR can exceed 60% and 70%, respectively. However, the overall efficacy of the initially approved IFN schemes of IFN 3 MU three times per week (TIW) for six to 12 months has proven rather limited (2,10).

Several large series (13,16) and meta-analysis reviews (17,18) have shown that, even with 12 months of therapy with IFN 3 to 5 MU TIW, the overall rate of SR cannot exceed 20% to 30%. Moreover, when the infecting HCV genotype is genotype 1, then the SR rate may fall to less than 10%.

Also, approximately half of the patients initially exhibiting complete response and maintaining that status to the end of treatment, may relapse soon after therapy is stopped. Such relapsed responders may eventually respond again, at least to some extent, to a second IFN regimen with 3 MU TIW preferably for 12 months. This is particularly effective if the RR had been associated with a short duration of six or fewer months of IFN treatment.

COMBINATION AND OTHER THERAPIES FOR RELAPSED AND NAIVE PATIENTS

If retreatment of relapsed responders is not restricted to a course of IFN monotherapy but IFN is combined with ribavirin, then approximately 50% of relapsed responders appear to achieve a SR (19). The SR rates in patients retreated with combination therapy (IFN and ribavirin) are similar to those of naive patients undergoing IFN monotherapy, and both are related to HCV genotypes as well as to pretreatment HCV RNA levels (19).
Combination treatment with IFN and ribavirin has also been evaluated in naive patients (20-23). The results of large multicentre, randomized trials have been communicated in several liver meetings and have been recently published (22,23). Combination therapy has been licensed in United States and Europe, both for relapsed responders to IFN monotherapy and for naive patients. Consensus IFN has also been successfully tried in the retreatment of patients with CHC who have relapsed or not responded to an initial course of IFN (24).

The new question arises, “what can one make out of these new data?”

Licensed IFN regimens for naive patients are restricted to 3 to 5 MU IFN TIW for 12 months. With such therapy, a 20% to 30% SR rate and a 20% to 30% RR rate are expected (13,17). For RR, the approved regimen is a six-month combination of IFN and ribavirin therapy which yields an efficiency (SR) of approximately 50% (19) and can add 12.5% to 15% more SRs, reaching an overall level of SR of between 30% and 45%.

The actual SR rates observed in the recently published multicentre trial and other trials of combination therapy among naive patients (20-23) are indeed similar to the above anticipation. In the American multicentre study, the rate of sustained virological response was 31% and 38% among patients treated for 24 and 48 weeks, respectively, compared with 6% and 13% in 24- or 48-week, respectively, therapy with IFN alone (22). In the international study, 35% and 43% of the naive patients had an SR when treated with the combination scheme for 24 or 48 weeks, respectively, compared with 19% in patients given IFN alone for 48 weeks (23).

These results are much better than the SR rates reported in the early days of IFN monotherapy. Nevertheless, the results are still not satisfactory because the proportion of non-responders is still higher than that of responders. This is particularly true for patients with cirrhosis, HCV genotype 1 and most probably genotype 4, high viral loads, older age and male sex. Moreover, combination therapy has a number of side effects that can become clinically significant with long duration of treatment (22). In one study, 21% of the patients assigned to combination therapy for 48 weeks discontinued treatment because of severe side effects (25). In view of these observations, more efficacious modes of therapy with fewer side effects are highly desirable.

Monotherapy with consensus IFN seems to be quite effective in relapsed responders (24), as does induction doses of IFN with daily administration for several weeks. Continuation of therapy with IFN alone TIW for 11 months after the initial reduction appears to be effective in maintaining these good results up to the end of treatment. However, after therapy stops, a large number of patients relapse and the SR rate dips rather low (26). Induction schemes with IFN combined with ribavirin may further increase the SR rates to levels higher than 50%. A similar effect may also be achieved by PEGylated IFN compounds, probably enhanced when combined with ribavirin.

Figure 1) Virological responses at the end of a four-week daily administration of interferon alpha (IFN-a) (induction therapy) followed by 11 months of maintenance IFN monotherapy three times per week

OTHER POTENTIAL BENEFITS OF THERAPY AND CONSENSUS PRACTICES

Benefits from IFN therapy are generally viewed to be restricted mainly to patients who achieve sustained clearance of HCV, ie, the sustained virological responders. However, benefits can also be expected in initial responders who relapse after stopping therapy and in nonresponders. Such beneficial effects are increasingly reported and documented in the literature in relation to liver necroinflammation and fibrosis, as well as to progression to cirrhosis and to HCC development (27,28). Thus, the previous 1997 consensus “to assess ALT and HCV RNA at 3 months and to stop therapy if HCV RNA is still detectable and ALT is increased” has now become outdated (25).

Emerging and evolving strategies in the treatment of CHC are now directed toward intensified IFN schemes, daily administration and/or PEGylated compounds, and combination treatment with IFN along with ribavirin or other compounds. The aim of these strategies is to enhance viral clearance and to achieve sustained viral suppression. Figure 1 shows the early impressive results of an ongoing study on the efficacy of induction doses of IFN given daily over four weeks, followed by 11 months of IFN monotherapy TIW (26).

In addition to these goals, continuation of IFN therapy in nonresponders is gaining popularity as a preventive strategy aimed at decreasing the progression of liver fibrosis to cirrhosis and at reducing the risk of HCC development. However, in the recent EASL International Consensus Conference on Hepatitis C (2), it was agreed that IFN monotherapy should be assessed by detecting HCV RNA after three months of treatment, and that treatment should be interrupted if HCV RNA is positive. For combination therapy with IFN and ribavirin, it has been agreed that its duration should be limited to six months. The presence of HCV RNA should be tested after six months, and if it is undetected, then therapy should be continued for an additional six-month period only in patients with genotype 1 and high pre-
treatment viremia levels. In all other cases, treatment should be stopped.

At the same consensus conference (2), it was also agreed that other potential benefits of therapy, such as prevention of HCC and progression of cirrhosis to decompensation, are not yet proven and should be assessed in future controlled studies. However, therapeutic concepts and strategies are continuously changing and new approaches to treatment are burgeoning. Hopefully, the benefits of treatment in CHC will soon increase significantly and physicians will be in a position to handle and monitor therapeutic modalities more efficiently than we can today.

REFERENCES
Submit your manuscripts at
http://www.hindawi.com