Why and how to treat chronic hepatitis C

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SJ Hadziyannis. Why and how to treat chronic hepatitis C. *Can J Gastroenterol* 2000;14(Suppl B):45B-48B. Chronic hepatitis C (CHC) is a major health problem worldwide, with approximately 200 million affected individuals and a significant rate of progression to end-stage cirrhosis and hepatocellular carcinoma (HCC). If hepatitis C virus (HCV) infection is left untreated in the population, then the number of liver-related deaths will soon double and the need for liver transplantation may increase to five times that seen today. Available therapies for CHC are restricted to interferon alpha (IFN) monotherapy and to the combination of IFN and ribavirin. Despite their high cost and side effects, both of these therapies have proved to be cost effective, particularly combination therapy. IFN monotherapy for one year can induce sustained response (SR) rates of approximately 10% in native patients infected with HCV genotype 1, and above 50% in those infected with other genotypes. Combination therapy can double or even triple the rate of SR in genotype 1 infections and may further increase the SR rate in the other HCV genotypes. Combination therapy has also been proven to be effective in approximately 50% of relapsed responders to IFN monotherapy. In clinical practice, the decision to treat should be individualized and tailored on the basis of several virus- and host-related factors, particularly the grade and stage of liver disease, HCV genotype and levels of viremia. Appropriate monitoring of therapy by careful clinical evaluation, liver biochemistry and serum HCV RNA testing is mandatory. IFN therapy may also prove to be effective in reducing the rate of HCC development in CHC regardless of whether a virological response is achieved, but this remains to be established.

Key Words: Chronic hepatitis C; Hepatitis C virus; Hepatocellular carcinoma; Interferon

Pourquoi et comment traiter l'hépatite C chronique?

RÉSUMÉ : L'hépatite C chronique (HCC) constitue un problème de santé important dans le monde : environ 200 millions de personnes sont porteuses de la maladie et le taux d'évolution vers la cirrhose terminale et le carcinome hépatocellulaire (CHC) est élevé. Si rien n'est fait pour traiter le virus de l'hépatite C (VHC), il est à prévoir que le nombre de morts associées aux maladies du foie doublera bientôt et que le nombre de greffes du foie quintuplera. Les traitements offerts se limitent à la monothérapie à l'interféron alpha (IFN) et à la bithérapie IFN-ribavirine. Malgré leurs coûts élevés et leurs effets secondaires, les deux traitements sont avérés rentables, en particulier le deuxième. La monothérapie à l'IFN d'une durée d'un an peut produire une réaction soutenue (RS) chez environ 10 % des patients naïfs, infectés par le VHC de génotype I et plus de 50 % des patients infectés par d'autres génotypes. Le traitement associé peut doubler ou même tripler le taux de RS dans les cas d'infection à VHC de génotype I et peut accroître le taux de RS dans les cas d'infection à VHC d'autres génotypes. En outre, la bithérapie s'est également révélée efficace chez environ 50 % des sujets répondants qui avaient fait une rechute après une période de traitement à l'IFN seul. En clinique, la décision de traiter devrait être individualisée et adaptée aux besoins des patients, compte tenu de plusieurs facteurs liés aux virus et à l'hôte, notamment la gravité et le stade de la maladie du foie, le génotype du VHC et les taux de virémie. Un suivi approprié du traitement comprenant une évaluation clinique minutieuse, des épreuves biochimiques du foie et des examens sanguins à la recherche de l'ARN du VHC s'impose. La monothérapie à l'IFN pourrait également diminuer le taux d'évolution de l'HCC vers le CHC indépendamment du fait qu'il y ait eu ou non une réaction virologique, mais cela reste à prouver.

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 effi-

cacy 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

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skepticism because of a rather limited therapeutic efficacy of interferon alpha (IFN α) 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 α alone or in combination with ribavirin – able to achieve these goals?

In clinical practice, the efficacy of IFN α 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 α 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 SR this effect is maintained after stopping therapy, while in RR, viremia and ALT activity soon reappear after treatment discontinuation. BR signifies normalization of ALT levels, which are usually transient if 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 and, 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 α therapy. This goal depends on the doses and duration of IFN α 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 α schemes of IFN α 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 α 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 α 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 α treatment.

COMBINATION AND OTHER THERAPIES FOR RELAPSED AND NAIVE PATIENTS

If retreatment of relapsed responders is not restricted to a course of IFN α monotherapy but IFN α 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 α and ribavirin) are similar to those of naive patients undergoing IFN α 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 (20,21). 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 regimens, 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 even 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 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 retesting 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.

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