Treatment of chronic hepatitis C

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Introduction

Hepatitis C virus (HCV) infection is a major worldwide health problem. Indeed, although precise figures are not yet available in several geographical areas, the prevalence of infected subjects among the general population averages 1 to 2%. This prevalence is even higher in areas such as Southern Europe (3-4%) and in some parts of central Africa, South-East Asia and the Middle-East where up to 10% of the general population is chronically infected. Globally, the number of HCV infected subjects is likely to approximate 170 millions. The major feature of HCV infection is the very high rate (60-80%) of chronic infection, with the risk of chronic active hepatitis, cirrhosis and hepatocellular carcinoma (Figure 1 and reviews in : (1-5)). There are still several uncertainties regarding the natural history and course of the viral infection. In particular, at the acute stage of the infection, there is no strong evidence for a role of HCV in fulminant hepatitis in Western countries in the absence of HBV/HCV coinfection (6-8). This contrasts with reports from Asia which have implicated HCV in several cases in the absence of a detectable HBV infection (9-10). It is also unclear whether an "asymptomatic carrier state", as defined by a strictly normal liver histology despite ongoing viral multiplication, actually exists. If so, however, it is a rare condition as most chronically infected subjects show chronic active hepatitis of varying severity.

The aim of this work was to provide an update of the rapidly growing results on antiviral strategies in HCV infection. Treatments may be offered at the acute and at the chronic stage of the infection, whatever the liver histopathology (cirrhosis or not) and it has been suggested that α-Interferon may prevent the occurrence of complications of cirrhosis (variceal hemorrhage, ascites, but also hepatocellular carcinoma) even in the absence of viral eradication.

1. "Historical" Interferon therapy in chronic hepatitis C

1.1. *Responses*

Interferon was the only available and effective treatment for Hepatitis C virus infection until recently. In addition to interferon alpha, which has been widely used, alternate forms exist, including lymphoblastoid, consensus interferon, and interferon beta : there is no evidence that these molecules differ in efficacy but this has not been thoroughly evaluated. Controlled trials from the USA and Europe have shown that alpha interferon was significantly more effective when compared to placebo (11-14). Standard treatments have been mainly based on three weekly subcutaneous injections of 3 millions units (MU) interferon for 6 months and led to an approximate 50% rate of aminotransferase activity normalization, defining the primary biochemical response (Figure 2). In contrast, 50% of the patients (the so-called non responders) never normalized aminotransferase levels nor showed disappearance of serum

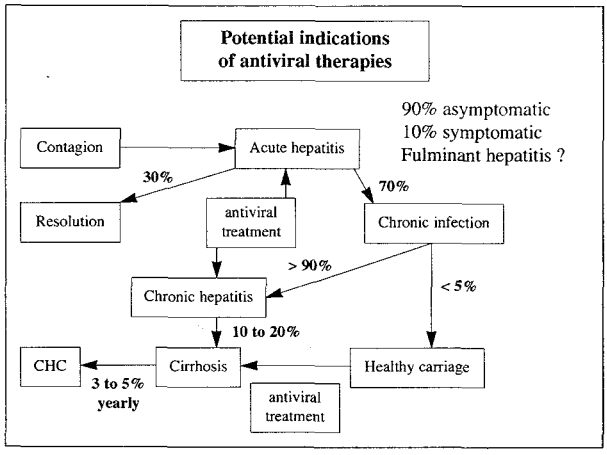

Fig. 1. — Natural history of HCV infection. This figure illustrates the clinical profile of HCV infection and the different time points of therapeutic interventions.

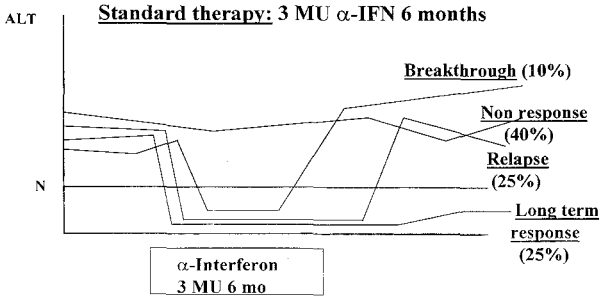

Fig. 2. — Schematic representation of the various profiles of response to interferon therapy.

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HCV.RNA. Within 6 months following discontinuation of interferon, half of the so-called responders (i.e, 25% of treated patients) relapsed. Fewer than 2% of controls showed spontaneous responses. Non-responders to interferon also included 5 to 15% of patients (so-called "breakthrough") who normalized aminotransferase activities within the first 3 months of therapy but relapsed despite continuation of treatement. Thus, long term normalisation of aminotransferases was obtained in only 15-25% of the treated patients. Interruption of HCV replication, as shown by loss of detectable serum HCV RNA, has been observed in one half to two thirds of these cases, late relapses (at least one year after treatment) were rare (15). At least some of these subjects showed negative tests for liver and peripheral blood mononuclear cells HCV RNA, consistent with viral eradication, but the frequency of this event is unclear (16). Finally, some histological improvement was observed in about 60% of treated patients as compared to 15% of controls, thus further supporting the potential of this therapeutical approach.

1.2. *Predictive factors of response to alpha-Interferon*

In spite of these encouraging results, limitations in the efficacy of interferon therapy, its side effects, and cost, emphasize the need to delineate those patients who will benefit from the treatment. This can be achieved through use of a combination of clinical, biological, and virological variables. Young age, recent infection, and low levels of GGT have been validated as positive predictive factors (17). However, most of these variables which are most strongly established from several multivariate analyses are negative predictive factors of long term response to interferon. Thus, cirrhosis and hyperferritinemia have been clearly identified as negative predictive factors of primary and long term biological and virological responses. Cirrhosis decreases by about half the rate of biochemical long term response (19% in cirrhotics, compared to 39% in non-cirrhotics in our experience). Other variables also have been reported, such as obesity or alcohol consumption which have a negative impact on treatment efficacy (17).

Despite the importance of these clinical and histological factors, the major impact on response of virological parameters has been recognised in virtually all studies on this topic. There is indeed a general agreement that the response to interferon therapy depends on the infecting HCV type. The particular profile of response to interferon of genotype 1b was first suggested from studies in Japan. Thus, in univariate analyses, the relative prevalence of type 1b was significantly higher among nonresponders than among responders (5,18-21). However, several potential biases must be considered before concluding that a given genotype is a predictive factor for poor response to treatment. In particular, the correlation between genotype and other previously established host factors, such as duration of infection, cirrhosis, etc., has to be considered, as well as the HCV viremia level. We and others have provided evidence based on multivariate analysis of these various parameters in different geographical areas showing that both infection by genotype 1b and high levels of HCV viremia were independent predictive factors of poor response to IFN (5,22) (Table I). Further studies have now shown that HCV 1a shares a low response rate to interferon with 1b. This issue can also be adressed by analysing the genotype distribution among long term responders (LTR) where types 2 and 3 predominate. Similar results have been obtained with NS4 based serotyping assays (20,22-24). Thus, in our experience, treatment of infections by HCV 1b, 1a, 2 or 3 result in a biological long term response in 18.0, 27.9, 54.1 and 43.1%, respectively, regardless of the therapeutic schedule. In these conditions, the probability of obtaining a long term response in a patient infected by HCV 1b who shows a high level of viremia is extremely low.

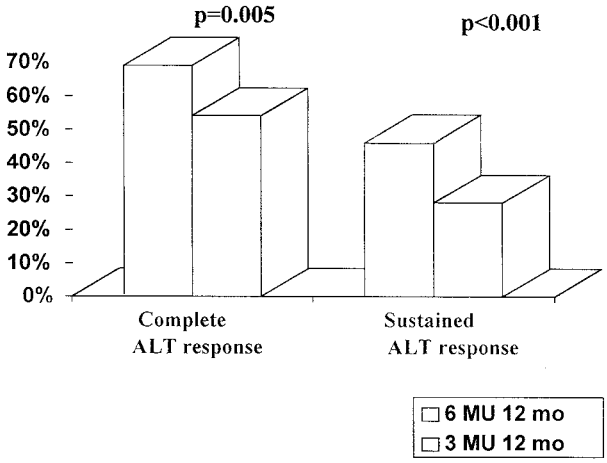

Fig. 3. — Dose-effect of alpha Interferon (according to the meta-analysis of Poynard *et al.* Ref 31).

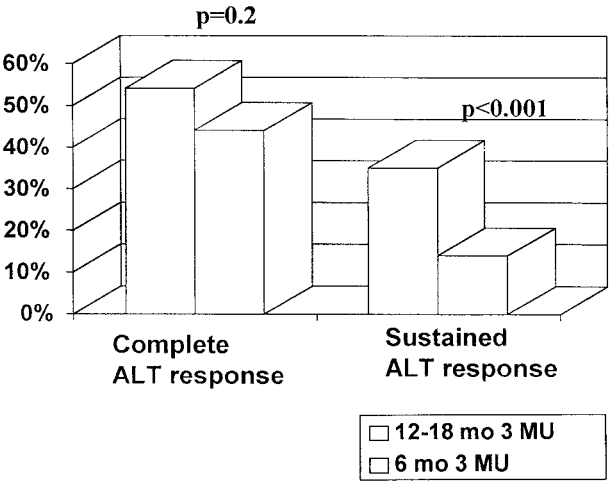

Fig. 4. — Dose-effect and duration-effect of alpha Interferon (according to the meta-analysis of Poynard *et al.* Ref 31).

The extent of HCV genome complexity (quasi-species) is another important variable. It has been suggested that in Japanese patients detection of a highly heterogeneous population of HCV RNA sequences before treatment correlates with a lower rate of response to interferon (25-26). Our recent results also support this possibility in European patients infected by types 1 or 3 (27). Here, using a PCR test followed by Single-Strand Conformation Polymorphism (SSCP), we showed in a multivariate analysis that the degree of HCV genome complexity is, together with HCV type 1b and a high viral load, an important and independent risk factor for a nonresponse to treatment. Clearly, large scale evaluation of patients with PCR-SSCP is not feasible at present. Such observations, however, support the current hypotheses that resistant HCV RNA molecules are selected during therapy.

These data have important implications for the treatment of HCV infection : 1. the major impact of virological parameters must be considered when designing a therapeutical protocol. Clearly cirrhosis, HCV type, viral load, and HCV genome complexity are the variables with an independent impact in most of the multivariate analyses. However, it is important to emphasize that these parameters should not be used to decide whether to treat, but rather they should be used to develop a specifically designed therapy.

2. Improvement of results in alpha interferon therapy (Table II)

Optimization of the treatment to counteract the mechanisms of virological non response, breakthrough or relapse should be based both on different schedules for interferon treatment and on its combination with other molecules to minimize the risk of selecting "resistant" HCV molecules.

2.1. *"Early" treatment of HCV infection*

Early treatment is logical, before development of fixed severe liver lesions and generation of highly complex populations of HCV genomes. Therefore treatment of acute and chronic HCV infections may be cost effective by decreasing the prevalence of HCV related cirrhosis and HCC.

Several trials have emphasized the increased response rate to interferon alpha when treatment was initiated in patients with chronic hepatitis before fibrosis became extensive. The low rate of spontaneous resolution of an acute HCV infection (around 20-30%) has even led to deciding to treat such patients. Most controlled trials compared a 3 MU-regimen for 3 months with no therapy (28-30). This data has been analyzed recently in a metaanalysis (31). Sixty nine per cent of treated patients vs. 29% in the control groups showed complete biochemical response at the end of treatment, with a mean difference of 40% ($p < 0.001$). Furthermore, the rate of sustained biochemical response 12 months after stopping treatment was 53% vs. 32% in controls ($p = 0.02$). Serum HCV RNA disappeared in 41% of treated patients as compared to 4% in controls with a mean difference of 34% ($p < 0.01$). In fact the percentages might be even higher since one cannot exclude that patients with recent chronic hepatitis were included in these trials. These very encouraging results should further stimulate : 1. early screening for acute hepatitis by repeated HCV RNA tests in subjects who have been accidentally exposed to HCV (nurses, surgeons, health care workers, hemodialyzed patients) before biological evidence of hepatitis or anti-HCV seroconversion and 2. early treatment of acute HCV infection. With this view, one might envisage treating an acute HCV infection, as defined by a positive serum HCV RNA test, despite absence of clinical and biological signs of hepatitis. It would also be interesting to evaluate

Table I. — **Predictive factors of response to α-INF (according to references 5 and 27)**

Genotype	1a	1b	3	Odd ratio
Biochemical response				
Non Response	58.5%	56.2%	17.8%	
Long term response	24.4%	14.1%	40.0%	8
Quantitative viremia : negative branched DNA assay				19
Genetic heterogeneity : SSCP bands > 3				19
Liver histology	Long term response			
Cirrhosis	14.3%			
No cirrhosis	27.8%			

Table II. — **Theorical strategies for improvement of α-IFN therapy results**

Modulation of α-IFN regimen :
- dose-effect (increase in doses)
- duration-effect (increase in duration)
- both dose- and duration-effect

New Interferon : Consensus/Pegylated/Natural

Combined therapies :
- Ribavirin
- UCDA, N-acetyl-cystein, Non steroidal anti-inflammatory drugs, Iron depletion } Inefficient
- Amantadin ?
- Growth factors ?

Table III. — **Unanswered questions in therapy of chronic hepatitis C**

When to treat ?	Acute hepatitis Chronic hepatitis
Who to treat ?	Minimal lesions Cirrhosis Immunocompromised patients
How to treat ?	Primary combination Early switch if inefficiency of α-IFN (ALT, PCR) Doses and duration of both drugs
How to be costs saving ?	Kinetics of HCV RNA

whether longer duration of therapy (4 or 6 months ?) might increase therapeutic efficacy.

2.2. *The potential of modifying interferon schedules*

The mechanisms used by the virus to persist in a chronically infected patient suggest that several complementary strategies need to be envisaged. Results of new INFs (consensus, pegylated, natural) should not be detailed since they are mainly preliminary. Increasing the dosage of interferon might lower selection of some HCV RNA molecules. In addition, increasing the duration of therapy might prevent relapse of viral multiplication (31). Therefore these two approaches have been extensively tested, alone or in association, some with promising results, still, definitive conclusions are difficult to draw. Increasing the alpha interferon dosage from 3 to 6 MU or using escalating doses in non responders does not appear to be effective (32). Trials using increased doses of interferon alpha for treating naive HCV infected patients have led to controversial results (15,33-40). Several studies and two independent metaanalyses of interferon alpha treatment in chronic hepatitis C have concluded that there is a greater benefit from longer treatment (Fig. 3). In a recent metaanalysis (31), a sustained biochemical response was obtained in 28% of the 6 MU group vs. 18% in the 3 MU group ($p = 0.13$) among patients treated for 6 months and in 46% vs. 28% ($p < 0.001$), respectively, in patients treated for 12 months. However, a benefit from higher doses was only suggested in those patients treated for 12 months (Fig. 4). Thus it was difficult to distinguish between the effects of dose and duration. In the various meta-analyses, a significant duration effect (12 vs. 6 months) on sustained response has been reported at 3 MU with a mean increase from 9 to 23% ($p < 0.001$) and for the 6 MU regimen with a mean sustained response rate of 49% in the 12 month-group as compared to 29% in the 6 month-group. In contrast there was no evidence that therapy of longer duration influenced the primary biochemical response (66 vs. 65%). Thus, prolonging therapy does not enhance the rate of response but appears to decrease the rate of relapse. This benefit, shown by meta-analysis, was observed for a 3 MU regimen (with a sustained response of 35% in a 12 to 18-month group as compared to 14% in a 6-month regimen, $p < 0.001$) and for the 6 MU regimen (49 vs 29%, respectively, $p < 0.001$) (31).

These data suggest that combining higher doses of interferon (6 MU) with longer duration (12 to 18 months) would be beneficial (Figures 3 and 4). However, it should be stressed that, to date, it is still difficult to confidently conclude that there is real benefit from such strategies. Indeed some results (36, 40), including those from a large retrospective analysis of our patients (S. Pol *et al.* unpublished observations), do not support these conclusions. The issue of long term therapy should therefore take into account additional costs and a potentially higher risk of breakthrough. One should also consider the possible use of combined antiviral therapy in relapsers and non responders (see below). These discrepancies may reflect differences, especially geographical, between the patient populations who have been studied. It might also point to methodological differences since most studies which reported dose and duration effect were based on an "intention to treat" analysis ; however this approach does not take into account reduction or withdrawal of therapy, a major drawback in reinforced interferon regimens.

3. Combined antiviral therapies : the cornerstone of the Ribavirin/Interferon combination

Limitations in the efficacy of interferon monotherapy as well as the trend to combine several antivirals to prevent emergence of resistant isolates, led to "combination therapies". This attitude was reinforced by the disappointing results obtained when evaluating alternative strategies such as the use of corticosteroids, iron depletion before interferon or the association of interferon with ursodeoxycholic acid. To date, evaluations of non steroidal antiinflammatory drugs, antibiotics such as quinolones, or growth factors like GM-GSF have also produced inconclusive results.

In contrast, Ribavirin shows promising results. Ribavirin is a nucleoside (Guanosine) analogue which exhibits *in vitro* activity against several DNA and RNA viruses, including Flaviviridae to which HCV belongs. Ribavirin may exert its *in vitro* antiviral activity by interference with nucleotide synthesis, inhibition of 5'-cap structure of the mRNA methyltransferase and inhibition of the viral RNA dependent-RNA polymerase encoded by NS5B (41-42). However, at least some of these antiviral effects may not be relevant *in vivo*. Indeed, the present evidence points to a limited antiviral activity of Ribavirin when given alone for HCV infection (43) despite the biochemical efficacy of Ribavirin was suggested by frequent normalization of aminotransferases (which was not maintained after Ribavirin withdrawal) in pilot studies and controlled studies. In contrast, histological activity diminished, especially intralobular inflammation (43). Thus, monotherapy by Ribavirin appears to be poorly effective, but may be proposed for patients with severe disease and contraindications to Interferon. Yet, despite absence of antiviral activity, Ribavirin may provide some benefit by its antiinflammatory activities. Ribavirin modulates the cytokine response profile *in vitro*, inhibiting in particular the Th2 response at the transcriptional level while the Th1 pathway is unaffected (44-45). These observations provide some rationale for the combination of Ribavirin and Interferon.

In naive HCV patients, the combination has been evaluated in 3 randomized trials ; all three indicated that combined treatment with Ribavirin and Interferon for 24 weeks is more effective than alphainterferon

alone or Ribavirin alone. Sustained biochemical and virological responses were significantly increased in the combination group (around 45%) compared to placebo (0%) or alpha interferon alone (around 25%) groups. Importantly, this 2-3 fold enhancement of efficacy was observed for all included genotypes (46-48). Usual predictive virological factors are also determinant in the response to the combination ; unpublished data suggest that a 24-week combination will be proposed in those patients with non-1 genotype infection and low viremia while a 48-week combination appears to be more efficient than a 24-week course in patients infected by type 1 and high viremia.

This approach may also be beneficial to relapsers. Results of a multicenter controlled study have clearly indicated the superiority of the combination, whatever the virological factors in 350 treated patients, with a 10-fold increase in the percentage of HCV RNA disappearance in the combination group (around 49%) as compared to Interferon alone (less than 5%) after a 24-week course (49). In contrast, in non responders most pilot studies have produced negative results (50-52). However, in a recent randomized trial, we have obtained encouraging results when comparing the efficacy of alpha interferon alone or in combination with a 4 month course of Ribavirin (53).

In summary, most of the preliminary results suggest that combinations of Ribavirin with alpha interferon therapy have synergistic effects. Significant histological improvement has been obtained in naive patients, relapsers and non responders who have been treated with the combination therapy. The mechanisms accounting for this efficacy are not known but should lead to important insights into the pathogenesis of HCV infection.

Three recent controlled studies have confirmed these preliminary results, 2 in naive patients (54-55) and one in relapsers (56). Results may be summarized as follows : 1. the combination significantly increases the rate of long term response (31% and 38% for a 24-weeks and 48-weeks schedules, respectively) as compared to alpha interferon alone (6% and 13% for a 24-weeks and 48-weeks schedules, respectively) by increasing the rate of primary response and decreasing the rate of relapse ; 2. usual predictive virological factors modulate the response rate and in patients with genotype 1 and/or high viremia, a 48-weeks course is more efficient than a 24-weeks course in inducing long term response ; 3. tolerance is rather fair with a 10% rate of withdraw in the 24-weeks course of combination reaching to 20% in the 48-weeks course. In naive patients with genotype 1b, a 48-weeks combination with high doses of interferon (6 Mu for 6 months then 3 MU for 3 months) may increase the sustained response rate to 50% (57). In relapsers, a 24-weeks combination led to a 49% rate of sustained response as compared to 5% in patients treated by interferon alone (56).

In conclusion, the combination appears to be now the first line treatment of chronic hepatitis C, at least in naive patients and relapsers.

4. Improved monitoring of treated patients and definition of "end points" for therapy

The low rate of efficacy of alpha interferon in monotherapy or combination trials, their cost and side effects, raise difficult issues when considering how to treat HCV infection. Moreover, patients who are included in randomised controlled trials might not adequately reflect the actual profile of the general population infected with HCV who also seeks antiviral therapy. Therefore, at least two approaches should be explored to improve the results of antiviral therapy : first, "tailorization" of therapy according to pretherapeutic predictive factors and second, early withdrawal of inefficient therapies in order to be cost-effective.

4.1. *"Tailorization"*

Logistic regression analyses of data from more than 500 patients treated for chronic hepatitis C, led to models to predict response, non response and sustained response in individual patients (58). When treatment schedules are "tailored" to factors that predict response, the cumulated dose of interferon has emerged as a more important parameter to consider than the therapeutic schedule itself. Thus, patients with parameters that suggest low response to treatment (cirrhosis, 1b infection ...) might benefit from high cumulated doses of interferon (8 MU/Kg) while patients with good predictive parameters might receive an overall dose of 4 MU/Kg (58).

4.2. *Early modification of antiviral therapies*

Several studies have shown that an analysis of HCV RNA kinetics and determination of aminotransferase levels 3 months after the initiation of interferon are effective in determining which patients should have a long term benefit from treatment (59-60). In our experience, HCV RNA is still detectable in a significant proportion of subjects with normal ALT levels at 3 months and is associated with a high incidence of relapse (0.94) and non response (0.97) (61). However, it should be noted that the disappearance of HCV RNA has a low (0.49) positive predictive value for long term response. Such studies suggest that it is possible to avoid unnecessary prolongation of treatment by evaluating patients 3 months after initiation of treatment. However, it is debated whether histological benefit might occur with more prolonged treatment despite the absence of biochemical and virological evidence of a therapeutic response (see below). This debate really relates to the issue of which end point should be used when initiating antiviral treatment in an HCV-infected individual. It appears today to be outdated since such

kinetics analysis are poorly relevant in combination therapies since viremic patients after 3 months of therapy may hope to be long term responders at the end of followup, at least in the relapsers study.

4.3. *The "end points" of anti-HCV treatments*

Treatment should obviously aim at eradicating the viral infection, and this is feasible, albeit in a low percentage of infected individuals. Another main goal is to improve the histological lesions, as demonstrated in long term responders to interferon (15-16,62). However, does histological improvement occur despite relapse after therapy or even in the absence of biological and virological responses to interferon alpha (59-64) ? This is a provocative and debated issue which has major clinical and economical implications. Some studies do suggest that necrotic and inflammation indexes might improve (65), and that fibrosis might be lowered (66-67). These findings are substantiated by *in vitro* tests that show an antifibrogenic activity of interferon. They lead one to envisage prolonged treatment by interferon alpha despite the absence of biological and/or virological responses. However, other studies have not confirmed this observation, and methodological issues, such as the delay between the end of treatment and liver sampling (the shorter this delay, the higher the probability of a temporary benefit from therapy) should be considered. In our experience, while significant histological improvement was noted in long term responders (Knodell score lowered by 3.2 $\pm$ 3.1 when liver biopsies were obtained before and around one year post treatment and compared), there was no clear histological benefit for relapsers or non responders (0.1 $\pm$ 2.5 and 0.31 $\pm$ 2.3, respectively). A few studies have even suggested that antiviral treatment might be cost-effective in cirrhosis by decreasing the rate of complications (portal hypertension, liver failure, and HCC), independently of an appearent antiviral effect. A prospective study and several retrospective reports (68-69) have also raised the possibility that HCV positive patients with cirrhosis treated with alpha interferon at standard doses might show a lower rate of HCC development than untreated subjects ; this effect does not appear to depend solely on a reduction of HCV multiplication since in most of these patients the antiviral effect of interferon alpha was low or absent. Retrospective French studies have suggested that the incidence of HCC (70) and other complications of cirrhosis (71) might be decreased in cirrhotic patients who were given alpha interferon, compared to non treated subjects. Although this finding would have a tremendous impact on our appraisal of HCV treatment as well as on the mechanisms of interferon action, they have not yet been confirmed (72) and potential major biases exist in such studies, such as the length of follow-up and duration of infection. Indeed, in a multivariate analysis, absence of interferon treatment was not an independent risk factor for HCC development. Larger, prospective and homogeneous trials are clearly warranted to address this question.

Conclusions

Treatment of HCV infection is an immense challenge, given the extremely high number of infected patients and low response to presently available antiviral therapy. A large body of studies, even if some raised controversial results, evidence the interest of antiviral treatment even if some unanswered questions remain (Table III). We are at a historical turn of knowledge and efficacy since the combination Ribavirin/Interferon appears to be the logical first line treatment which will not cure all the naive patients, relapsers and non responders. There is still a wide range of questions and a wide field of pharmaceutical research, especially for the development of antiprotease therapies.

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Treatment of chronic hepatitis C : Summary of the discussion

R. Brenard

After the presentation of Professor Pol concerning the treatment of chronic hepatitis C, a number of controversial questions have been discussed with the audience. After each question, the audience could answer to the question through an interactive voting system. The summary of this discussion is focused on the treatment of hepatitis C in naive patients, in relapsers and non responders and in patients with normal ALT, acute hepatitis C and compensated cirrhosis.

1. Treatment of hepatitis C in naive patients

About 90% of the audience consider that the optimal duration of interferon (IFN) therapy is *12 months* and 60% that the optimal dose is *3 MU 3 times a week.* About 50% think that *ribavirin* should always be combined with IFN in naive patients.

Comments

Two consensus conferences (one in USA (1,2) and one in France (3)) conclude that 12 months was the optimal duration to treat naive patients, reminds Prof. M. Adler. However, Prof. S. Pol proposes to start with a 6 month period therapy and to prolong this period to 12 even 18 months in responders. Prof. F. Nevens is reluctant to this proposition ; regarding to the results of the Benelux study (4), most patients in Belgium are infected with genotype 1b and are poor responders to IFN. For this reason, he proposes to treat patients directly over 12 months. Dr. J. P. Martinet emphasizes the importance of clinical trials and encourages the audience to include patients in trials. Even if some clinical, biochemical, virological or histological factors are well known to be associated with a good response to IFN, it's always difficult for each specific patient to predict the response and the optimal duration of treatment, explains Prof. S. Pol. Moreover, if we don't treat a patient (for example because he only has minimal histological lesions), it could be interesting to perform a new liver biopsy 3 to 5 years later to evaluate the progression of the disease and the appearance of fibrosis, one of the most important prognostic factor (5), comments Dame S. Sherlock ; the appearance of bridging fibrosis leads to start therapy. Three MU, 3

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times a week seems the optimal dose in naive patients but the use of daily dose could be more interesting, specifies Dame S. Sherlock. We are waiting for the results of trials in progress. The results of the large studies concerning the efficacy of the combination IFN-Ribavirin are not yet known.

2. Relapsers

About 80% of the audience think that *ribavirin* should be associated with IFN in relapsers after monotherapy with IFN.

Comments

The benefit of the association IFN-Ribavirin seems greater in relapsers than in naive patients, comments Dame S. Sherlock.

3. Non responders

About 65% of the audience think that *ribavirin* should be associated with IFN in patients resistant to monotherapy with IFN and 35% think that the best attitude in these patients is to wait for new therapeutic agents.

Comments

No efficious therapy exist to day for non responders.

4. Patients with normal ALT and positive HCV RNA

More than 80% of the audience don't treat patients with normal ALT and positive RNA.

Comments

Prof. F. Nevens proposes to control regularly (2 or 3 times a year) transaminases levels because they can fluctuate. Nobody performs liver biopsy in patients with normal ALT and positive HCV RNA except Prof. Pol. He explains that about 25% of these patients had more agressive histological lesions than expected ; moreover, some of them had evolutive lesions. The histological examination leads to identify patients who are potential candidate to receive therapy. However, Prof. Pol reminds that IFN therapy is not indicated in the majority of these patients with normal ALT and positive RNA because they had non evolutive and mild histological lesions (75% of cases). Prof. Pol specifies that about 15% of patients with normal ALT and positive RNA show deterioration of histological lesions after IFN therapy.

5. Patients with acute hepatitis C

About 65% of the audience think that patients with acute hepatitis C must be treated as soon as possible and 35% wait 6 months and only treat patients with a chronic evolution.

6. Patients with compensated cirrhosis

About 50% of the audience don't treat patients with compensated cirrhosis. About 30% treat these patients with IFN and 20% with a combination IFN and ribavirin.

Comments

Dame S. Sherlock doesn't treat patients with cirrhosis ; moreover, she doesn't believe to the the efficacy of IFN on the prevention of hepatocellular carcinoma.

Conclusions

From this discussion between experts and the audience some conclusions could be raised. To day, the best way to treat *naive patients* with chronic hepatits C is IFN*3 MU 3 times a week* during *12 months*. The benefit of the association *IFN-Ribavirin* in naive patients remains unclear but seems greater in *relapsers*. Alternative therapies are not effective in *non responders*. It could be interesting to perform a second liver biopsy 3 to 5 years after the first one in non treated patients with mild histological lesions, in order to evaluate the progression of the disease. There is no indication to treat patients with *normal ALT and positive HCV RNA*. A liver biopsy could be performed in these patients to identify candidates to IFN therapy. Patients with acute hepatitis C must be treated as soon as possible. The indication to treat patients with compensated cirrhosis remains controversial.

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