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Interferon therapy for hepatitis C[1]

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Abstract

Initial trials indicated that around 50% of patients respond to recombinant alpha interferon by normalizing alanine aminotransferase (ALT) at the end of therapy and that half of these relapsed within 6 months following cessation of treatment. Both dose and duration of treatment are critical in the response to therapy. Higher doses and longer duration have been suggested to be more effective than the current recommendations of 3 MUI thrice weekly for 6 months based on results of these initial studies which used ALT and histological scores to evaluate the efficacy of interferon therapy. Following studies using virological markers have shown that improvments in clinical features of disease are associated with decrease or loss of hepatitis C virus (HCV) from serum and liver. The heterogeneity of the response rates between clinical centers using identical protocole emphasizes that the selection of the patients treated was as important for the outcome than the therapy regimen itself with better responses in cases without cirrhosis and with low levels of HCV RNA. Furthermore, the genotype of HCV seems to be also critical for the response rate. Virological evaluations appears therefore crucial to assess not only HCV infection but also for the indication and monitoring of therapy.

Key words: Interferon; Hepatitis C; Chronic hepatitis

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1. Reassessement of the definition of therapy response

The natural history of chronic hepatitis C leads to progressive inflammation of the liver with development of cirrhosis and its complications including hepatocellular carcinoma (Alter et al., 1989). There is an extreme variability in the proportion of cases with progressive liver disease and in the pace of that evolution. Most studies indicate that 20% of chronic hepatitis C cases do develop liver cirrhosis. However in a long term follow up study carried out by Seef et al., in patients who had suffered from acute hepatitis C no significant mortality excess was demonstrated over a 18 year period (Seef et al., 1992). Liver-related mortality was increased only in the subgroup in which alcoholism was not ruled out.

This extreme heterogeneity calls for a careful definition of end points in all the trials devoted to the therapy of chronic hepatitis C. Ideally, the true end-points of therapy should be to abolish the cause of the disease, i.e., eradicate HCV infection and suppress its consequences, liver necrosis and inflammation and its sequelae, fibrosis and cirrhosis. After many years, this outcome may be associated with different symptoms due to impairment of liver function as well as extrahepatic manifestations.

Reduction of morbidity and mortality are the objectives of therapy. Because of the long duration of the disease they cannot be chosen as end-points of prospective studies since those would require several decades. Moreover, as suggested from the retrospective studies, they may lead to nonsignificant results and therefore will most probably never be carried out.

All the studies published so far have only used readily available markers such as alanine aminotransferase (ALT) and histological scores, usually the Knodell score (Knodell et al., 1981). It should be emphasized that these only have to be considered as convenient markers.

Since true end-points, i.e., morbidity and mortality, cannot be used. It is critically important to select which end-points may be the most relevant as surrogate markers for therapeutical trials. We should select them by taking into consideration the suppression of both the cause and the consequences of the disease. The ultimate markers therefore should be those that allow direct appraisal of viral replication in qualitative and quantitative terms, i.e., a quantitative estimation of HCV RNA in serum and liver for each of the genotypes. As far as the consequences of viral infection of the liver are concerned, ALT may be both convenient and misleading since HCV is probably not directly cytopathic as indicated by many recent studies. Necrosis and inflammation of the liver are relevant parameters and the Knodell score is aiming at their quantification. Unfortunately, this score has many limits and flaws, especially in chronic hepatitis C. Cirrhosis is of critical importance but it is a very late marker and it is crippled, as all histological parameters, by the frequency of sampling errors in liver biopsies. Fibrosis is most crucial but it is most difficult to assess and it is certainly the least used of all histological parameters.

These conceptual considerations are of utmost importance for the interpretation of all the clinical trials. These have been carried out so far which have mainly focused on ALT as a basis for definition of response which may infact be hazardous

and potentially misleading (Lau et al., 1993). A response was considered complete if ALT normalised within a few weeks to 6 months of therapy. It was called sustained whether maintained for more than 6 months after cessation of treatment. Remarkably, this definition did not take into account either the elimination of HCV RNA or the liver histological benefit. Partial response was used for cases with reduction of 50% of base line ALT values. However, this was a loose definition since ALT are highly fluctuating and base line are too often short and poorly defined. An other trend has also been to coin the term "near complete response" for cases with ALT less than 1.5 the upper limit of normal. Lack of response was characterised by persistency of ALT at a similar level regardless of histological or virological changes.

Proper definition of response should in fact focus on clearance of HCV RNA normalisation of ALT. Such a response will then invariably be associated with improved histology.

2. Correlations of interferon dosage with responses to therapy

The main factors which determine the response rate are certainly the modalities of interferon therapy. Initial open studies have been followed by controlled, randomized studies with or without placebo. Using different regimen in different situations, the complete response rate varies from 23 to 87% with a relapse rate of 25 to 75% in such responders. A meta-analysis involving 916 patients, enrolled in 17 studies (Tins et al., 1991), indicated that around 50% of patients respond to interferon recombinant alpha by normalizing ALT at the end of therapy. Half of these will relapse within the 6 months following cessation of treatment. Histological improvement is present in over 60% of complete responders with significant decrease of inflammation and necrosis (Tins et al., 1991; Di Bisceglie et al., 1990). Quite remarkably this histological improvement is not strictly correlated with the ALT response and in fact histological benefit has been found to be similar in cases which normalized ALT and in those with near complete response (Manabe et al., 1993). Although the many studies published provide very different results, both dose and duration of treatment are critical in the response to therapy.

Initial randomized trials compared doses of 1 MU thrice weekly for 6 months (Davis et al., 1989; Causse et al., 1991; Marcellin et al., 1991; Sarraco et al., 1990). More recent studies (Iino et al., 1992) have showed that higher doses of up to 10 MU may provide more effective response than those obtained with lower doses thrice weekly. The same, as well as other authors (Lindsay et al., 1993) insist that the daily dosage at the induction phase, followed later by usual thrice weekly schedule was superior to other therapy modalities.

This, however, awaits further confirmation. Although higher doses have been suggested to be more active, escalating doses have only been permitted to obtain a small proportion of additional complete responders (Brouwer et al., 1992).

Duration of therapy has also been proven to be important for achieving sustained response. Several authors have failed to show a beneficial response of 12 versus 6

months if they were pooling all the cases together (Métreau and the French Group of NANB/C Chronic Hepatitis Treatment, 1992; Craxi et al., 1992). However if patients without cirrhosis were singled out, a significant benefit was obtained in those treated for 12 versus 6 months. 43.2% of complete durable responders versus 16.7% in the cirrhotic group (Jouet et al., 1992). A similar trend was confirmed by others (Saracco et al., 1993).

Whether an induction therapy and a maintenance regimen should be distinguished has been the topic of several studies. Higher initial doses may be followed by lower relapse rates. Again Iino et al. have showed that a 2 month course at 10 MU was able to induce long term remission in up to 31.3% of cases. Although a 1 MU dose was initially suggested by some authors to be able to maintain normal ALT follow up, this did not hold true. Recent studies do suggest that a 3 MU maintenance dose is better than 1 MU between the 6th and 12th months (Jouet et al., 1992; Saracco et al., 1993; Poynard et al., 1993; Carrero et al., 1992; Piazza et al., 1992). Among the best results reported so far are those obtained by Alberti et al. (1993) using an induction dose of 6 MU × 6 months + 3 MU × 6 months. 76% of complete response and 51% retaining normal ALT at 12 months.

Titrating the maintenance dose on ALT levels turned out to be deceitful. This is not surprising and emphasizes once more that ALT is a poor surrogate marker for HCV replication. It has been shown that a maintenance therapy at 3 MU was more efficacious than discontinuation and retreatment at 3 MU to obtain complete ALT normalisation and sustained remissions (Poynard et al., 1993).

3. Selection of the best candidates for therapy

In the early randomized studies 4 groups in Europe and the US used an identical protocol with α-2b. They obtained different results emphasizing a surprising heterogeneity of responses between clinical centers using identical protocols and the same α-2b recombinant interferon product. While in two studies 3 MU were better than 1 MU (Davis et al., 1989; Causse et al., 1991), this was not found in the two others (Marcellin et al., 1991; Saracco et al., 1990). Response rates varied from 23 to 50% between Lyons and Paris for example. This emphasizes that the category of patients treated was certainly as important for the outcome than the therapy regimen itself and prompted the search for predictive factors of response.

An intensive search for such factors was conducted by several groups. Initially in our first controlled study, we had been able to demonstrate that cirrhosis was a crucial factor in the response to therapy (Causse et al., 1991). Although initially a source of controversy, that was further confirmed by all recent investigations. A multiple step logistic regression analysis was carried out between Lyons and Paris. Absence of cirrhosis, young age, female sex and presence of lobular hepatitis were all associated with better response to interferon (Degott et al., 1991).

The problem of sex remains a questionable issue since females have a lower mean body weight and this may be in part an indirect consequence of higher dosage. It can also (as for HBV) translate a genuine biological phenomenon.

In two studies using multivariate analysis, young age and absence of cirrhosis were consistently found to predict long term response to interferon (Alberti et al., 1993; Degott et al., 1991). The similar finding on the impact of severity of liver disease is again reported by Iino et al. (Japan, 1991) and from Davis et al. (USA, 1989). Whether age and progression of liver disease may be completely separated remains to be critically evaluated.

The role of duration of disease prior therapy as a predictive factor of response is most difficult to assess since it can only be known in post-transfusion cases, in this mostly asymptomatic condition. Very early therapy for acute HCV infection does suggest that response to interferon at this early stage is mostly beneficial (Omata et al., 1991; Esteban, 1992; Colombo, 1992; Viladomiu et al., 1992).

As far as chronic hepatitis C is concerned, two studies may indicate that in fact duration of disease may be important. In an early report from Japan, this appears to be the case with better response in patients treated within a mean duration of 3.5 years (Iino et al., 1992; Lino, 1993). Another therapy study, carried out in France, in which patients were treated within an average of 18 months after onset, has shown an amazing proportion of sustained remission 2 years after a 1 year course of interferon at moderate dose. The analysis of that trial indeed suggested that the most unique factor possibly accounting for this exceptional response rate could be the early therapy (Poynard et al., 1991).

As indicated in the introduction, virological factors must not be considered as surrogate marker but as potential true end point. They deserved therefore maximum attention. Levels of different anti-HCV antibodies have been found to decline somewhat with therapy but those changes appeared to be slow and could not be correlated with response by using Elisa test. When turning to quantification of Western blots based assays, a more significant trend could be observed, especially with C100 and C33 antibodies (Saracco et al., 1993). Such trends should be, however, improved when correlated with more acurate markers than ALT normalization. It is remarkable that in the study of Omata et al. (1991) in acute infection all patients who cleared HCV RNA subsequently cleared anti-NS4, NS3 antibodies. New tests including IgM anti-capsid antibodies or IgM anti-envelope or anti-NS5 proteins may turn out to be much more useful in the future (Hellstrom et al., 1993; Brillanti et al., 1992). In long term responders anti-E2 NS 1 antibodies were found in 88.2% but in only 14.3% of the non responders (Saracco et al., 1993).

Far more important is the impact of HCV genotype on the interferon response. Many studies have recently focused on this and they do suggest that genotype is of utmost importance in the response to interferon. Using the Okamoto classification (Okamoto et al., 1992), which has been widely used so far, chronic hepatitis associated with genotype type II was found by several groups to be the most resistant to interferon (Okamoto et al., 1992; Kanai et al., 1992). In our own study we did find a dramatic difference between the interferon responses to genotype I and the most prevalent ones in France. That difference did remain significant after multiple variable analysis together with age and severity of liver disease (Qu et al., unpublished data).

Japanese workers have found that genotype 4 responded similarly to type I, while

type III was the most responsive genotype to interferon therapy (Okamoto et al., 1992; Kanai et al., 1992; Yoshioka et al., 1992).

The pretreatment level of HCV RNA, when carefully quantified, appears to be also correlated to interferon response, especially if replaced within the frame of a specific genotype. In a recent study (Lau et al., 1993), which re-analysed sera from the early multicenter US trial (Davis et al., 1989), it appeared that patients with a sustained complete response to interferon alpha therapy had lower pretreatment viremia levels than complete responders who relapsed after the drug was stopped ($P<0.001$) or non responders. High viremia levels were not related to the histological diagnosis but were associated with specific features of HCV infection including lobular inflammation, lymphoid agregates and bile duct lesions (Lau et al., 1993). In another study from Japan (Hagiwara et al., 1993) multivariate logistic regression indicated that HCV RNA titer before therapy was the strongest independant factor of sustained response to interferon.

Although titration of HCV RNA is the most important issue, a merely qualitative determination will also be useful. In most of the complete responders HCV RNA is cleared soon after ALT normalized. It has been documented that in some patients, viremia can still be detected by PCR, although ALT may remain normal for some time. Prospective studies have, however, shown that a secondary increase in ALT is common in that situation. By contrast, less than 10% of complete responders are prone to late reactivation of hepatitis if HCV RNA remains negative for 6 months after cessation of therapy. While negativation of HCV RNA in serum and in liver at the end of treatment may not always be predictive of sustained remission, it becomes so after 6 months. According to another study, absence of both HCV RNA positive and negative strands in liver serum and mononuclear cells at the end of therapy, may be predictive of sustained remission (Gil et al., 1993).

Finally, demonstration of HCV antigen in the liver by immunostaining has been found to be positive in more than 80% of liver biopsies from patients who have chronic hepatitis C. Pretreatment levels of HCV antigen appear to be lower in patients responsive to interferon therapy (Krawczynski et al., 1992; Di Bisceglie et al., 1993) and expression of HCV antigen decreases in the liver of patients responding to therapy. It is in the cases in which HCV antigen cannot be detected prior therapy that the best response and longest sustained remission were observed (Di Bisceglie et al., 1993).

5. Responses to other interferons and antiviral agents

It has been suggested that differences in responses may exist between different types of alpha interferons either recombinant or not. So far, evidence for that remains scanty. It is known that natural human interferon is not a single entity and is composed of a family of proteins. Lymphoblastoid interferon alpha does contain different molecules. Whether this could turn out to be important in the response is the subject of prospective comparative randomized studies. Whether the response to interferon beta (Kakumu et al., 1993) will be identical to alpha and whether some

failures with interferon alpha may be rescued by interferon beta has been suggested in anecdotal cases but this remains to be further substantiated.

It has also been suggested that the emergence of neutralising anti-interferon antibodies may account for some breakthroughs. On theoretical ground it is conceivable that multivalent interferon preparation may overcome some of the neutralizing effects of anti-alpha 2a or alpha 2b antibodies.

The response to ribavirin appears different to that of interferon. Indeed several investigators have noticed that patients that did not respond to interferon alpha recombinant may well respond to ribavirin. Factors of predictive response to ribavirin remain to be substantiated. Preliminary results do indicate that association of interferon alpha or beta with ribavirin may be of benifit (Di Bisceglie et al., 1993; Kakumu et al., 1993) and definitely warrant further studies.

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