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Review

Chronic hepatitis C and no response to antiviral therapy: A perpetual problem

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SUMMARY

No-response to antiviral therapy was observed in the majority of chronic hepatitis C patients treated with interferon alpha (IFN-a) monotherapy, but continues to represent a frequent problem even after treatment with newer, more potent, combination regimens. Non-responding patients represent a fairly heterogeneous group. Subgroups of non-responders with biochemical but without virological response, or with breakthrough phenomena during therapy probably have a relatively more favorable prognosis. Re-treatment with consensus IFN may be relatively effective, while the combination of IFN-a in usual dosage and ribavirin (RIB) achieves sustained virological response in 13% and 21% of such patients treated for 6 and 12 months, respectively. Induction courses of IFN-a in combination with RIB have been found to achieve initial virological response in 36-40% and sustained virological response in 17-26%. Triple antiviral therapy with IFN-a, RIB and amantadine has also been used, but more trials are needed for firm conclusions. Recently, the combination of pegylated IFN-a plus ribavirin was reported to achieve initial virological response in 36-40% of patients non-responding to IFN-a monotherapy or to a combination of IFN-a plus ribavirin. Extensive data suggest that therapy with IFN-a may delay the progression of fibrosis and decrease the incidence of hepatocellular carcinoma even in non-responding chronic hepatitis C patients. Thus, the decision whether or not to discontinue the antiviral therapy in non-responders is related to whether therapy aims the clearance of the virus or just a histological benefit.

Key words: Chronic hepatitis C, no-response, Interferon, Ribavirin, Amantadine, Induction therapy

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1. INTRODUCTION

Interferon-alpha (IFN-a) is a drug of choice for chronic hepatitis C, but IFN-a monotherapy in usual dosage achieves biochemical and virological initial response in less than 50% and sustained response in 5-20% of cases[1]. Recent data suggest that the combination of INF-a and ribavirin is more effective in achieving initial response in 50-60% and sustained response in 30-40% of naove patients with chronic hepatitis C.[2,3] Patients who eventually do not response to IFN-a can be classified into those without initial response (non-responders) and those with initial response but relapse after the end of therapy (relapsers). Although the long-term course of relapsers and non-responders may not differ significantly, these two groups are studied separately, because of the better response rate of relapsers to re-treatment with IFN-a and mostly to re-treatment with combination of IFN-a plus ribavirin.[4,5]

Data from the initial clinical trials in chronic hepatitis C therapy showed that about 50-60% of naive patients were non-responders to IFN-a monotherapy.[1] Subsequently, the use of more sensitive assays for the detection of HCV viremia raised this rate to 67-76%,[2,3] whereas no-response to the combination of IFN-a and ribavirin was found to be between 40-50%.[2,3] No-response rate remains above 30% even after treatment with the most potent available combination of pegylated-IFN-a plus ribavirin[6,7] (Table 1). All previously mentioned no-response rates referred to naive patients with chronic hep-

Table 1. Biochemical and virological no-response rates in chronic hepatitis C patients treated with various regimens of antiviral therapy

Regimen of antibiral therapy	References	Patient no.	No-response rate	
			Biochemical*	Virological**
IFN-a_{2b} (3Mux3/week)	Poynard et al, 1998[2] McHutchison et al, 1998[3]	734	67%	71%
IFN-a_{2b}+RIB (3Mux3/week+1-1.2gr/day)	Poynard et al, 1998[2] McHutchison et al, 1998[3]	1010	34%	47%
PEG-IFN-a_{2b}+RIB (1.5μg/Kg/week+0.8g/day)	Manns et al, 2001[6]	183	36%	36%
PEG-IFN-a_{2a}+RIB (180μg/week+1-1.2g/day)	Fried et al, 2001[7]	453	N.A.	31%

IFN-a: interferon-alpha, RIB: ribavirin, PEG: pegylated, N.A.: not available

*Biochemical no-response: abnormal ALT levels at the end of therapy

**Virological no-response: detectable serum HCV RNA (>100 copies/mL) at the end of therapy

atitis C without any coexisting disease. Thus, the actual no-response rate may be even higher if a) special groups of patients with relative low probability of response, such as patients with co-infection with HBV and/or HIV, thalassaemia, haemophilia, or transplant patients[8,9] and b) patients with decompensated HCV cirrhosis or those with several contraindications to IFN-a and/or ribavirin would be included in the overall chronic hepatitis C patient population. This review focuses on the efficacy of various regimens of antiviral therapy in non-responding chronic hepatitis C patients as well as on the outcome and potential therapeutic options of patients who are non-responding to re-treatment.

2. DEFINITIONS OF RESPONSE

Both the consensus meetings of the American National Institute of Health (NIH)[10] and the European Association for the Study of the Liver (EASL)[11] have defined the criteria of treatment-response in patients with chronic hepatitis C on the basis of alanine aminotransferase (ALT) levels (biochemical response) and the detection of serum HCV RNA by a polymerase chain reaction (PCR) assay (virological response). Thus, end of therapy response (or initial response) is defined as the presence of normal ALT (biochemical) or the absence of serum HCV RNA (virological) at the end of the treatment (normal ALT one month before the end of treatment is also required for initial biochemical response). Sustained response is defined as the maintenance of normal ALT levels (biochemical) or undetectable serum HCV RNA (virological) for 6 months following the end of therapy. Finally, no-response is defined as the maintenance of abnormal ALT (biochemical) or detectable serum HCV RNA (virological) during therapy.

It is obvious that the achievement of virological response depends on the sensitivity of the method used for the detection of serum HCV-RNA.[12] The application of more sensitive virological methods is expected to raise the percentage of non-responders with the conversion of at least some of relapsers to non-responders. Recent data suggest that the Transcription Mediated Amplification (TMA) assay may detect serum HCV RNA at the end of treatment in up to 64% and 36% of the patients who were classified as initially responders-relapsers by the Amplicor PCR 1.0 and the Amplicor PCR 2.0 respectively.[13] The sensitivity of the above methods does not seem to differ significantly, being 1000 cp/mL for Amplicor 1.0,[14,15] 100 cp/mL for Amplicor 2.0[15] and 50 cp/mL for TMA.[13,16] However, such small differences, which may not be important for the evaluation of untreated patients with chronic hepatitis C, seem to be extremely important for the evaluation of the presence of residual viremia during therapy.[13]

The separation into biochemical and virological response may create problems in the classification of treated patients into responders or not. Biochemical response is usually achieved more frequently than virological response, but a few cases with virological but without simultaneous biochemical response have also been reported. In a recent analysis of 26 prospective studies, Craxi et al showed that, in patients with initial biochemical response, the maintenance of residual viremia is usually, but not always (79%), followed by a biochemical breakthrough.[11] Thus, 20% of the patients with biochemical,

but without virological response, remain in biochemical remission for at least 6 months after the end of therapy and 78% of them will remain in such remission for many years despite persistent viremia.[11] Another subgroup of non-responder patients consists of those who have an initial normalization of ALT and disappearance of viremia during therapy, but subsequently experience virological and/or biochemical breakthrough despite continuation of therapy. This subgroup of patients may have a favorable response to the re-administration of a stronger antiviral regimen.[17,18]

3. THERAPEUTIC APPROACHES FOR NON-RESPONDER PATIENTS

3.1. IFN-a monotherapy

3.1.1. IFN-a in usual dosage

IFN-a in a dose of 3-6 million units (MU) thrice weekly has been found to be ineffective in patients who did not respond to a previous treatment with IFN-a.[17,19] Thus, it is recommended that re-treatment with IFN-a in usual dosage should be avoided in non-responding chronic hepatitis C patients.[20]

3.1.2. Consensus IFN (CIFN)

CIFN is a genetically engineered molecule, which consists of the most commonly observed amino acids of several natural INF-a subtypes.[21] Administration of 15 μg CIFN thrice weekly for 24 or 48 weeks was found to achieve initial response in 18% of patients who had not responded to a previous treatment with 9 μg CIFN or 3 MU IFN-a;[22] long-term virological response was observed in 13% (9/69) of patients who received CIFN for 48 weeks and in only 5% who received CIFN for 24 weeks.[22] Treatment with 15 μg CIFN was found to be more effective in patients with breakthrough phenomena (temporary normalization of ALT and/or clearance of serum HCV-RNA) during the initial therapy.[18] In particular, long-term virological response was observed in 28% (5/18) of patients with breakthrough and in 8% of patients without breakthrough during the initial therapy (P=0.048).[18]

3.1.3. Induction therapy with IFN-a

Induction therapy with IFN-a, which includes any course starting with initial administration of daily doses of IFN-a, has been tried in patients with chronic hepatitis C in the late nineties. According to pooled data from 3 initial studies, induction therapy with 10 or 5 MU IFN-a for 4-12 weeks achieved initial virological response in 17 (23%) of 75 non-responders to usual dosage of IFN-a.[23-25] In particular, initial response was observed in 12 (22%) of 55 patients treated with 10 MU[23,24] and in 5 (25%) of 20 patients treated with 5 MU IFN-a daily.[25] The administration of induction doses of IFN-a for a longer period might improve the therapeutic efficacy, as was suggested by a more recent trial which lasted 48 weeks and reported a response rate of 74%.[26] Such an encouraging result, however, was not confirmed by another trial, in which initial response was 27% at 45 weeks of therapy regardless of the induction IFN-a dose (9 MU or 6 MU).[27] The induction courses with IFN-a monotherapy had limited use and were soon withdrawn in favour of the potentially more effective combination therapy of IFN-a plus ribavirin. Although data for sustained response after induction IFN-a courses in previously non-responders have not been reported yet, the sustained response rate was expected to be low based on the experience on the efficacy of such regimens in naove chronic hepatitis C patients.[28,29]

3.2. Combination of IFN-a with ribavirin

3.2.1. Usual dosage of IFN-a plus ribavirin

The combination of usual doses of IFN-a (3-5 MU thrice weekly) with ribavirin (daily dose: 1-1.2 gr for body weight < or ≥75 Kg, respectively) gave encouraging initial results for patients without sustained response to IFN-a.[30,31] The encouraging initial results have been confirmed in relapsers by a large controlled clinical trial, in which the combination of IFN-a and ribavirin given for 6 months achieved sustained virological response in 49% compared with only 5% after IFN-a monotherapy.[5] In contrast, the results of combination therapy in non-responder patients were not so impressive. In a recent meta-analysis, the combination of IFN-a plus ribavirin was found to be significantly better than IFN-a monotherapy for retreatment of non-responders, but it achieved sustained virological response in only 13,2% of cases treated with 6-month courses and 21,3% of those treated with 12-month courses.[32]

3.2.2. Induction therapy with IFN-a plus ribavirin

The daily administration of IFN-a in relatively high doses (5-10 MU) in combination with ribavirin has only recently been tried and therefore most of the available data come from abstracts mainly with initial results. Pooled data from 14 studies show that induction IFN-a courses in combination with ribavirin achieve a relatively high initial virological response of 36% (39/108)[33,34] and 40% (175/438)[26,27,33,35-41] after 6 and 12 months of therapy, respectively. Data for sustained virological response to such regimens is quite limited, coming from only three small studies. The sustained virological response rate was 26% (44/

165)[34,42] in two of these studies with treatment duration of 6 months and 17% (12/70)[43] in one study in which treatment was given for 12 months. Additional results are certainly needed before any conclusion can be drawn.

3.3. Combination of IFN-a with amantadine

3.3.1. IFN-a plus amantadine

Amantadine, a drug with antiviral activity against influenza virus, gave some encouraging initial results in patients with chronic hepatitis C without sustained response to previous IFN-a monotherapy,[44] but the efficacy of such a combination was subsequently found to be completely ineffective in non-responders to IFN-a[45,46] and certainly inferior to the combination of IFN-a and ribavirin.[47-49]

3.3.2. IFN-a with ribavirin plus amantadine

Triple combination of IFN-a, ribavirin and amantadine gave promising initial results as re-treatment in non-responding chronic hepatitis C patients.[50] In a recently published randomized trial from the same group, such a triple antiviral therapy given for one year was found to be significantly superior to the double combination of IFN-a and ribavirin, achieving sustained virological response in almost 50% of previously non-responders[51] Unfortunately, such an impressive efficacy was not confirmed in two subsequent studies, in which triple combination therapy achieved sustained remission in 23.5% and 0% of cases.[52,53]

3.4. Combination of Pegylated IFN-a (Peg-IFN-a) with ribavirin

Pegylated IFNs have been found to be more effective than usual IFNs in naove chronic hepatitis C patients given as monotherapy or in combination with ribavirin.[54] The efficacy of pegylated IFN-a plus ribavirin in non-responders to previous IFN-a monotherapy or IFN-a plus ribavirin combination therapy has not been adequately evaluated, since only preliminary relevant studies have been reported to date. According to these preliminary data, the initial virological response rate was reported to be 36% (114/313) in non-responders treated with PEG-IFNa_{2b} given in a dose of 1-1.5 μg/Kg/week plus ribavirin (800-1200 mg daily)[55-58] and 40% (68/168) in non-responders treated with PEG-IFNa_{2a} given in a dose of 180μg/week plus ribavirin 1000-1200mg daily.[59,60] In addition, the triple combination of PEG-IFNa_{2a} with amantadine plus ribavirin was found to achieve initial virological response in 38% of 31 non-responder patients.[59] It should be noted, however, that the above mentioned response rates represent findings under treatment and are expected to decrease after discontinuation of antiviral therapy. Final results of these studies are expected in the near future.

4. OUTCOME OF NON-RESPONDERS

The definitions of response to treatment rely on surrogate markers (ALT, serum HCV RNA) and not on clinically important parameters (such as the development of cirrhosis, HCC or death), which are difficult to evaluate in clinical trials of relative short duration. The long-term disappearance of serum HCV RNA (sustained virological response) comprise the ideal therapeutic end point in patients with chronic hepatitis C, since it has been shown to be followed by continuing improvement of hepatic histology and usually by disappearance of HCV even from the liver.[61,62] In addition, the outcome of patients with sustained biochemical response is considered to be favorable regardless of virological response.[63,64] Thus, the small percentage of patients with sustained biochemical but without virological response seem to benefit from antiviral therapy. However, the effect of antiviral therapy on the long-term outcome of non-responding patients remains unclear.

Data relating to the histological progression of non-responders are rather conflicting. It should be kept in mind that liver biopsy shows the histological lesions at a certain time-point and usually the estimation of changes is attempted for an interval of less than 2 years, which is quite short for a slowly progressive disease, like chronic hepatitis C.[65] The timing of post-treatment liver biopsy is also very important, since histological changes usually develop several months after the virological and biochemical changes. In a recent analysis of 10 studies with IFN-a therapy in chronic hepatitis C, biochemical non-response was found to be followed by some, but not significant, improvement in the necroinflammatory activity and by no change in the extent of fibrosis.[11] In another study with IFN-a monotherapy, the extent of fibrosis was found to worsen in 22% of the patients with or without biochemical response compared with 56% of controls ($P<0.001$).[66] The combination of IFN-a plus ribavirin (almost exclusively due to IFN-a activity) has been found to improve fibrosis in 66% and worsen fibrosis in only 15% of non-responder patients.[67] It should be noted, however, that, in all trials, the effects of IFN-a on the histological lesions of non-responding patients have been evaluated within 6-12 months after the end of therapy and thus there are no data for the actual long-term outcome of this subgroup of chronic hepatitis C patients.

Another target of antiviral therapy is the reduction of HCC incidence. In our recent meta-analysis including patients with HCV cirrhosis, we showed that 6-12 months

of IFN-a therapy almost eliminate the risk of HCC for 4 years in patients with a sustained response (<1%), and significantly reduce the risk of HCC in patients without sustained response (9%) as compared to untreated patients (21.5%) (OR:2.7, 95% CI:1.9-3.9).[68] However, it is difficult to evaluate the results of therapy in non-responders, since in most studies there is no distinction between relapsers and non-responders. The effect of IFN-a therapy on overall survival is difficult to evaluate, since there is no appropriate data.

5. EARLY PROGNOSIS OF NO-RESPONSE

The possibility of an accurate early prognosis of no-response would allow the early discontinuation or modification of a useless therapy, the reduction of cost of treatment, and the avoidance of adverse events in patients without any therapeutic benefit. Pre-treatment viral or patient characteristics (HCV genotype, serum HCV RNA levels, extent of fibrosis, race, age, gender) have been associated with the possibility of response and affect the therapeutic scheme, but they cannot be used to exclude patients from treatment, since there is no subgroup of patients no probability of response.[2,3,69] The choice of prognostic markers of response, or not, to therapy depends on the type and targets of therapy.

The maintenance of detectable serum HCV RNA at 4 weeks after IFN-a monotherapy has been associated with absence of sustained virological response in more than 95% of cases and may be used as an early marker of no-response and for discontinuation of therapy.[70,71] Recently, the reduction of viremia within the first 4 weeks of therapy was suggested to be the strongest prognostic marker of response to pegylated IFN-2a monotherapy.[72] In contrast, in the case of IFN-a plus ribavirin combination therapy, it has been suggested that a relatively accurate prognosis of response, or not, may be made only after six months, since a 12-month course achieves sustained virological response in 10% of patients with detectable serum HCV RNA at 3 months and in only 2% of patients with detectable serum HCV RNA at 6 months.[73] It should be noted, however, that a more sensitive assay for serum HCV RNA detection was used in the last trial[73] compared with those used in the earlier trials of IFN-a monotherapy[74,75] and this might have influenced the positive predictive value of viremia in relation to no-response. In addition, the therapeutic benefit of 8% should be balanced against the increase both cost and side effects by the prolongation of therapy.

The clinical significance of any predictive marker of no-response is directly related to the target of therapy. Thus, if the only target is the clearance of HCV, then the detection of serum HCV RNA after 4 weeks of IFN-a monotherapy or at 6 months of combination therapy must be followed by discontinuation of the therapy. However, if the therapeutic target is the delay of histological progression or the reduction of HCC incidence, then the detection of HCV RNA in the first months of therapy may be of no clinical relevance, since therapy may have a beneficial effect on histological lesions or on HCC incidence even in non-responder patients.[76] In particular, in the group of virological non-responders, the histological liver lesions have been shown to improve after 2.5 years of therapy in case of continuous IFN-a administration and to worsen in case of stopping IFN-a at 6 months of therapy.[77] Thus, the evaluation of virological non-responders might rely on liver histology at 6-12 months of therapy, which should be followed by maintenance of IFN-a therapy in case of early histological improvement. The administration of IFN-a may also continue for a long period in patients with partial biochemical and/or virological response, since such patients usually benefit at the histological level.[76] Such therapeutic strategy may only be limited in patients with pretreatment severe histological lesions. However, the duration of such IFN-a administration and its possible effect on the long-term outcome of such patients remain unclear.

6. CONCLUSIONS

Unfortunately, non-responders still represent a large percentage of chronic hepatitis C patients despite the improvements in the efficacy of antiviral therapy. Since there is no approved antiviral regimen for the treatment of non-responding chronic hepatitis C patients, they should be treated only within clinical trials. Given the limited efficacy and the high cost of current antiviral regimens, well-designed trials are certainly needed in order to evaluate the actual benefit from treatment in several subgroups of chronic hepatitis C patients. The relatively slow progression rate of patients with mild histological lesions suggest that such non-responding patients may not benefit from retreatment, particularly when they are old and have a relative short expected life span.

All patients with chronic hepatitis C who do not respond to antiviral therapy as well as those who cannot tolerate or have contraindications to therapy must try to slow down the progression of their liver disease. Patients, alcohol consumption must certainly beavoided and normal body weight should be preserved. They should be advised to be vaccinated against HBV and HAV, if at risk, particularly those with cirrhosis. Patients with cir-

rhosis are usually followed by regular ultrasounds and measurements of a-fetoprotein levels because of the risk of HCC development, although the benefit of such a strategy remains unproven. On the other hand, non-cirrhotic patients have to be reassured that their life span could be normal, similar to that of the general population.[78]

Finally, particular attention should be paid to the type of non-responding chronic hepatitis C patients that the newer antiviral therapeutic regimens create. Almost all reported studies have included patients with chronic hepatitis C who did not respond to a previous course of IFN-a monotherapy. However, such patients have almost disappeared in clinical practice, since the combination of IFN-a and ribavirin is the standard antiviral therapy for naove or relapsing patients and pegylated IFN-a with or without ribavirin have invaded this setting. Whether non-responders to more potent combination therapies will respond to retreatment as non-responders to IFN-a monotherapy is currently unknown. In the new era of the more potent pegylated IFN-a, the management of these patients who are so difficult to treat successfully represents the most challenging therapeutic task in chronic hepatitis C.

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