Treatment of Chronic Hepatitis C in Non-Responders

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INTRODUCTION

The treatment of chronic hepatitis C has evolved markedly over the past 10 to 15 years [1]. With the initially approved regimens of standard interferon-alpha given alone for 24 weeks, sustained virological response (SVR) rates were only 6 to 12% [1, 2]. These rates were increased by prolonging therapy to 48 weeks, but the response rates were only 12 to 18% [2, 3]. A major improvement in response rates to interferon therapy came with the addition of ribavirin. Combination therapy for 48 weeks yielded sustained response rates of 38 to 47%, more than twice that of interferon alone [3, 4]. The introduction of pegylated interferons [5, 6] provided further increases in response rates, and combination therapy with ribavirin yielded SVR rates in the range of 54 to 56% [7-9]. Retrospective analyses and subsequent prospective controlled trials demonstrated that response rates and optimal dose-regimens varied with different genotypes of HCV. In patients with genotype 1 infection, the optimal regimen was full doses of pegylated interferon (180ug/week of alpha-2a or 1.5ug/kg/week of alpha-2b) combined with ribavirin (1000 to 1200mg/day) for 48 weeks to achieve response rates of 41 to 52% [1, 9]. In patients with non-1 genotypes (particularly genotypes 2 & 3), the optimal response rates (75 to 81%) could be achieved with a 24-

week course of full doses of pegylated interferon and reduced doses of ribavirin (800mg/day).

With each improvement in treatment regimen, the issue arises of whether patients who fail to respond to a previous course of therapy should be retreated with the more effective regimen [10]. Although early studies demonstrated that retreatment with the same regimen was associated with poor response rates, a proportion of non-responder patients responded to the more effective regimen [11, 12]. Unfortunately, response rates to retreatment are often low, and retreatment exposes patients to the added side-effects and expense of another course of therapy. Furthermore, if retreatment is attempted after each advance in therapy, many patients would undergo repeated courses of treatment without a sustained benefit. Clearly, the potential for efficacy and relative risks of retreatment regimens require careful assessment.

In discussing treatment of non-responders, two major issues must be analyzed separately: first, retreatment of patients who have failed to respond to a previous, non-optimal course of therapy; second, retreatment of patients who have failed to respond to the current optimal regimen. Furthermore, it is also important to consider the type of previous non-response for each category, whether it is a virological response and relapse or a documented virological non-response [10].

RETREATMENT OF NON-RESPONDERS TO STANDARD INTERFERON WITH OR WITHOUT RIBAVIRIN

Response rates with pegylated interferon have been consistently higher than those with standard interferon with or without ribavirin [1, 5-9]. Results of the major registration trials of standard interferon with and without ribavirin and of pegylated interferon with and without ribavirin are given in Table 1 for patients with genotype 1 and in Table 2 for patients with genotypes 2 and 3 (or in some instances "non-1"). When analyzed by genotype, SVR rates to pegylated interferon and ribavirin were 17 to 25% higher than those to standard interferon and ribavirin and 35 to 48% higher than those to standard interferon alone. From these results one can calculate a hypothetical response rate to retreatment:

$$\text{Expected rate} = [(\text{SVR of current regimen}) - (\text{SVR to previous regimen})] / (1 - \text{SVR to previous regimen}).$$

Author (yr)	**IFNα type**	**IFNα**	**IFNα**	**IFNα & RBV**	**IFNα & RBV**	**Peg IFN**	**Peg IFN & RBV**	**Peg IFN & RBV**
		24 wks	**48 wks**	**24 wks**	**48 wks**	**48 wks**	**24 wks**	**48 wks**
McHutchison (1998)	alpha-2b	1.8%	6.8%	15.9%	27.7%	-	-	-
Poynard (1998)	alpha-2b	-	11.2%	18.1%	31.1%	-	-	-
Lindsay (2001)	alpha-2b	-	6.5%	-	-	14.0%	-	-
Heathcote (2000)	alpha-2a	-	2.1%	-	-	12.5%	-	-
Manns (2001)	alpha-2b	-	-	-	33.2%	-	-	41.7%
Fried (2002)	alpha-2a	-	-	-	36.1%	20.7%	-	46.3%
Hadziyannis (2004)	alpha-2a	-	-	-	-	-	42.4%	52.0%
Average		**1.8%**	**7.6%**	**17%**	**32.8%**	**15.4%**	**42.4%**	**49.2%**

Table 1: Sustained virological response rates in large trials in chronic hepatitis C, genotype 1.
IFNα = interferon-alpha, RBV = ribavirin.

Author (yr)	IFNα type	IFNα	IFNα	IFNα & RBV	IFNα & RBV	Peg IFN	Peg. IFN & RBV	Peg. IFN & RBV
		24 wks	48 wks	24 wks	48 wks	48 wks	24 wks	48 wks
McHutchison [a] (1998)	alpha -2b	15.6%	28.6%	68.8%	67.2%	-	-	-
Poynard [b] (1998)	alpha -2b	-	33.3%	64.0%	63.9%	-	-	-
Lindsay [b] (2001)	alpha -2b	-	28.4%	-	-	48.1%	-	-
Heathcote [a] (2000)	alpha -2a	-	14.6%	-	-	51.3%	-	-
Manns [b] (2001)	alpha -2b	-	-	-	78.8%	-	-	81.0%
Fried [b] (2002)	alpha -2a	-	-	-	60.7%	44.9%	-	75.7%
Hadziyannis [b] (2004)	alpha -2a	-	-	-	-	-	82.5%	79.4%
Average		15.6%	28.2%	65.9%	68.2%	47.7%	82.5%	79.3%

Table 2: Sustained virological response rates in large trials in chronic hepatitis C, genotype 2 & 3 or non-1.
[a] Non-1 genotype (thus genotypes 2, 3, 4, 5 and 6), [b] Genotypes 2 and 3
IFNα = interferon-alpha, RBV = ribavirin.

Thus, for a patient with genotype 1 who previously received a 48-week course of interferon alone (SVR=7.6%) and is retreated with pegylated interferon and ribavirin for 48 weeks (SVR=49.2%), the expected response rate would be [(0.492-0.076)/(0.924)=45%]. Similarly for patients with genotype 1 who previously received a 48-week course of combination therapy (SVR=33%), the expected response rate to retreatment with 48 weeks of pegylated interferon and ribavirin would be [(0.492-0.328)/(0.672)=24%]. For genotype 2 and 3 infected patients, the expected response rates to retreatment with pegylated interferon and ribavirin would be 71% in patients who had received monotherapy and 35% in those who had received combination therapy using standard interferon. This analysis is clearly

oversimplified and requires prospective assessment. It is based on several assumptions: a lack of bias in patients selected for retreatment, an expected clinical and virologic profile and response rate that is similar to patients in the published registration studies, and a lack of change in the likelihood of response with time or with previous treatment. Thus, patients willing to undergo retreatment are likely to have tolerated therapy well during the first course and had at least a partial response to treatment or even a virological response and relapse. Patients who have had poor tolerance to interferon therapy are unlikely to accept retreatment. Perhaps even more important, there are specific clinical factors associated with response and an overall average response rate may not apply to the individual patient being retreated.

Although there have been many studies of retreatment, few have used the current recommended regimen of therapy for hepatitis C. The largest study to date was recently published based upon the lead-in phase of the HALT-C trial (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) in which patients with advanced fibrosis or cirrhosis who were non-responders (remaining HCV RNA-positive on therapy) to a previous course of standard interferon with or without ribavirin were retreated with pegylated interferon and ribavirin for at least 24 weeks [13]. The overall SVR was 18% and further analyses showed that SVR rates were 12% in patients who had previously received combination therapy and 28% in those who had received interferon alone (P<0.0001). Furthermore, SVR rates varied by genotype, and were 14% with genotype 1, 65% with genotype 2, and 54% with genotype 3 (P<0.0001). Thus, response rates were generally lower than the estimated rates based on the calculations given above. It is important to note that patients retreated in the HALT-C trial all had advanced fibrosis or cirrhosis, which has been shown to be associated with lower response rates. Furthermore, all were non-responders to a previous course of therapy, and relapse patients were not enrolled. Finally, the HALT-C trial was conducted in the United States and had a high proportion of older, overweight or obese, African-American patients, all factors that have been consistently associated with lower rates of response to interferon- based therapy of hepatitis C [1, 13].

Thus, the recommendation of retreatment for non-responders to a previous less-than-optimal course of therapy, resulted in SVR rates that are generally lower than predicted. Favorable clinical,

biochemical, histological and virological factors should be considered in the decision to retreat patients. Thus, retreatment might be recommended with some optimism for a young patient with genotype 2 or 3 who previously received a short course of interferon monotherapy. In contrast, retreatment may not be appropriate for the older, overweight patient with genotype 1 who previously had a virological nonresponse to the combination of standard interferon and ribavirin. Patients who relapse after an initial course of standard interferon with or without ribavirin are probably good candidates for retreatment with pegylated interferon and ribavirin. In this situation, longer courses of therapy might be considered as the duration of treatment is correlated strongly with a relapse [3, 9, 11]. Clearly, more studies of retreatment using pegylated interferon and ribavirin for different periods of time are needed to provide more reliable recommendations on retreatment.

RETREATMENT OF NON-RESPONDERS TO AN OPTIMAL REGIMEN OF THERAPY

Patients who have already received pegylated interferon and ribavirin and who have not had a virological response to therapy should not be retreated with the same regimen. Previous studies with standard interferon have demonstrated that retreatment with the same regimen usually results in the same non-response, unless there was a major lack of compliance or another unrelated adverse event during the initial therapy [10-12].

An alternative approach, however, is to retreat, not for virus eradication, but to ameliorate disease activity and prevent disease progression. This approach is based on long-term, maintenance therapy with either interferon (or pegylated interferon) or ribavirin or the combination. An important factor to mention when discussing these studies is that prevention of disease progression is a less well defined endpoint for antiviral therapy of hepatitis C than sustained virus eradication. The criteria for documentation of prevention of progression have not been clearly established, and results of studies of maintenance therapy must be viewed with caution. Disease progression in chronic hepatitis C is slow, variable and difficult to document. The proof that maintenance therapy can delay progression of hepatitis C requires large, randomized, controlled trials with well characterized cohorts of patients followed for several years with

careful documentation of disease activity and stage. Endpoints in these studies need to be carefully selected and focus on the prevention of fibrosis and cirrhosis and ultimately clinical decompensation. These requirements have not yet been met by any of the published studies on long-term maintenance therapy of chronic hepatitis C with interferon, ribavirin or both.

Maintenance therapy with interferon

Maintenance therapy with standard interferon alpha was evaluated by Shiffman and coworkers in a preliminary study of patients who had histological improvement without a complete virological response (remaining HCV RNA-positive) during 24 weeks of interferon monotherapy [14]. Patients underwent liver biopsy at the end of interferon treatment and 65 of 167 non-responder patients were found to have had a 50% decline in hepatic inflammatory scores compared to baseline. These patients were considered to be eligible for the study, and 53 agreed to be enrolled: 26 were assigned to stop interferon therapy and be followed on no treatment and 27 were continued on maintenance interferon at doses of 3 million units thrice weekly for an additional 2 years, with follow-up liver biopsies at 12 and 24 months. Thus, only virological non-responders who appeared to have had histological improvement during therapy were enrolled in this study. Eligible patients constituted approximately 39% of all non-responders who were evaluated for inclusion and only 32% agreed to enroll in the study and be treated for an additional 2 years.

The results of this trial showed that continuing interferon therapy maintained improvements in serum aminotransferase levels, HCV RNA titers and histological necroinflammatory scores in most patients. In contrast, discontinuation of treatment was followed by a shift of the serum biochemical, virological and histological improvements towards baseline. Thus, the biochemical and histological improvements that occur in approximately one-third of virological non-responders can be maintained by continuous interferon therapy. Of course, the major issue is whether these maintained responses result in reversal or retardation of disease progression. In this study fibrosis scores were improved by maintenance therapy but the differences between treated and untreated patients were not statistically significant. Thus, mean fibrosis scores increased in the control patients from 2.2 $\pm$ 0.3 to 2.4 $\pm$ 0.4 (P=0.11) and declined in

the patients on maintenance interferon from 2.5 $\pm$ 0.3 to 1.7 $\pm$ 0.4 (P=0.07). This study provided valuable preliminary results which supported the need for larger and more ambitious studies on maintenance interferon therapy.

Maintenance therapy with pegylated interferon

The possibility that maintenance therapy with standard or pegylated interferon will result in long-term improvement of hepatitis C despite lack of virus eradication is the focus of several ongoing trials, including the National Institutes of Health-supported trial entitled HALT-C. In that study, over 1500 patients with chronic hepatitis C and advanced fibrosis or cirrhosis (Ishak fibrosis scores 3-4 and 5-6) who previously failed to respond to a course of standard interferon with or without ribavirin were retreated with pegylated interferon and ribavirin for 24 weeks [13]. Patients who remained HCV RNA-positive despite therapy with this optimal regimen were then randomized to be treated with low doses of pegylated interferon alpha-2a (90mg/week) or to be followed on no specific therapy. Treatment was scheduled to last for 4 years with repeat liver biopsies at 2 and 4 years. The endpoints in this trial are progression to liver-biopsy determined cirrhosis (in patients with bridging fibrosis initially) and/or the clinical endpoints of death, liver transplantation, clinical decompensation or hepatocellular carcinoma. This trial is in its fifth year and most patients have completed the first two years of treatment and follow-up evaluation.

Maintenance therapy with ribavirin

The use of ribavirin alone is another approach to maintenance therapy to improve disease and prevent progression. Ribavirin monotherapy has been shown to improve serum aminotransferases and liver histology in approximately one-third of patients [15-18]. Patients treated with ribavirin for one to two years have shown improvements in necroinflammatory activity on liver biopsy [15, 18]. The question is whether these biochemical and histological improvements are also associated with prevention of disease progression whose major surrogate marker is hepatic fibrosis.

Recently, a randomized controlled trial evaluated the benefits of continuing ribavirin monotherapy when there was no virological response to a 24-week course of standard interferon and ribavirin [18].

In this study 108 patients with chronic hepatitis C were treated with a standard regimen of interferon alpha-2b and ribavirin for 24 weeks. Patients who did not become HCV RNA-negative on therapy were randomized to continue placebo or ribavirin alone (1000 to 1200mg/da**y**) without interferon. Fifty patients were non-responders at 24 weeks, and 34 agreed to be enrolled into the double-blind part of the study. The results showed that serum aminotransferase levels returned to baseline in most of the 17 patients randomized to receive placebo, but remained normal or near normal in most of the 17 patients randomized to continue ribavirin. After a year of placebo or ribavirin therapy, repeat liver biopsies showed improvements in histological activity among ribavirin- in comparison to placebo-recipients. The degree of histological improvement on ribavirin monotherapy was not as great as that in sustained virological responders. Furthermore, fibrosis scores improved significantly among the virological responders but did not change in the ribavirin recipients. Thus, ribavirin was able to maintain biochemical and histological responses in patients who continued to be viremic (at least in a proportion of patients) but did not appear to improve fibrosis. Patients with marked improvement in histological scores had normal or nearly normal serum aminotransferases levels after therapy.

Thus, maintenance therapy with ribavirin or interferon or both is an attractive approach to treat virological nonresponders but has yet to be shown to have a significant effect on the course of chronic hepatitis C. While both approaches appear to induce or maintain biochemical and histological responses, neither has been shown to delay the progression of disease or reverse fibrosis.

Maintenance therapy with ribavirin and pegylated interferon must be considered experimental and of unproven benefit at present. If this therapy is to be used outside of controlled trials, it should be limited to patients who tolerate maintenance therapy well and who exhibit and maintain a biochemical response while on treatment. Better definition of patients who may benefit from maintenance therapy and optimal means of monitoring and directing therapy is likely to arise from the ongoing trials of this approach in the near future.

Future therapies of hepatitis C

The importance of hepatitis C as a liver disease and the limited efficacy of current therapeutic regimens have led to a search for more effective and better tolerated therapies. These approaches have included non-specific therapies and recommendations; immune modulatory agents and cytokines, and specific antiviral drugs. These approaches are particularly appropriate for patients who have failed to respond to the optimal current regimen of pegylated interferon and ribavirin or who have specific contraindications to this therapy. The recent description of marked inhibitory effects of a HCV-specific serine protease inhibitor provides great promise that safe and effective small molecule therapies for hepatitis C will eventually be developed [19]. Furthermore, multiple alternative and innovative approaches to the treatment of hepatitis C are under active investigation and are likely to bear fruit [20]. At present these therapies remain experimental [21]. A patient who has failed to respond to optimal current therapy of hepatitis C is a prime target for new therapies of this important disease.

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