Peer reviewed article

Twenty-four vs. forty-eight weeks of re-therapy with interferon alpha 2b and ribavirin in interferon alpha monotherapy relapsers with chronic hepatitis C

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Summary

Background/aim: Roughly 50% of patients with chronic hepatitis C, who relapsed after a previous monotherapy with interferon alpha, will respond in a sustained fashion to 24 weeks of re-therapy with the combination of interferon alpha plus ribavirin. Whether prolonging treatment duration to 48 weeks will further increase sustained response rates remains ill defined. In this randomised controlled pilot trial we compared the efficacy and tolerability of a 24 week with that of a 48 week course of combination therapy with interferon alpha and ribavirin in interferon monotherapy relapsers with chronic hepatitis C.

Methods: Interferon alpha monotherapy relapsers with chronic hepatitis C were randomised to receive interferon alpha 2b (3 × 3 MIU sc weekly) and oral ribavirin (1000/1200 mg po daily) for either 24 weeks or 48 weeks. Virological response was evaluated by HCV RNA PCR at week 10 (initial response), at the end of treatment (end-of-treatment response) and at the end of 24 weeks follow-up (sustained response). Only patients with negative HCV RNA at week 10 continued treatment. Adverse events were recorded at regular intervals.

Results: Thirty-seven patients were enrolled, 19 (6 females, median age 43) in the 24 week and 18 (5 females, median age 40) in the 48 week treatment arm. Baseline characteristics were similar in both groups. At treatment week 10, 12/19 (63%) in the 24 week group and 14/18 (78%) patients in the 48 week group had lost HCV RNA in serum ($p = 0.33$). All initial responders remained HCV RNA negative throughout the treatment period. Sustained response rates were 10/19 (53%) in the 24 week group and 13/18 (72%) in the 48 week group ($p = 0.31$). Three patients discontinued treatment early (two due to moderate adverse events, one due to non-compliance). Dose modifications were necessary in 9 patients, 4 in the 24 week and 5 in the 48 week group for anaemia, neutropenia, nausea and depression, respectively.

Conclusion: Prolonging interferon / ribavirin combination therapy in interferon alpha monotherapy relapsers with chronic hepatitis C from 24 to 48 weeks may increase sustained response rates. Larger controlled trials using pegylated interferon alpha and ribavirin in relapsers with chronic hepatitis C seem warranted.

Key words: hepatitis C; relapse; combination therapy; interferon alpha; ribavirin; SASL

The preliminary data of this trial were presented as a poster (P43) at the 66th annual meeting of the Swiss Society for Gastroenterology and Hepatology and the Swiss Society for visceral Surgery in Interlaken (Swiss Medical Forum 2001; 41(Suppl 4):18S).

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Introduction

Chronic hepatitis C is associated with progressive liver disease in a considerable proportion of patients. 10–20% of patients with chronic hepatitis C will develop cirrhosis within 20 years and are at risk for complications. Annually ~5% will decompensate and ~2–4% will develop hepatocellular carcinoma, leading to a 5-year mortality rate of ~20% [1–3]. Concomitant daily alcohol consumption (>25–50 g/d), older age at infection (>40 years), co-infection with HBV or HIV, and male gender are known to speed up progression to cirrhosis [4–8].

Monotherapy with interferon alpha was the first treatment of proven efficacy for chronic hepatitis C. About 20% of patients achieved a sustained response rate, i.e. long-term HCV clearance [9–11]. Monotherapy with ribavirin – a synthetic nucleoside analogue – led to a reduction of alanine aminotransferase, but not to clearance of serum HCV RNA [12–15]. More recently, large controlled trials demonstrated that combining interferon alpha and ribavirin increases antiviral efficacy, i.e. sustained response rates to 36–46% in previously untreated patients [6, 7, 16–18]. A 24 week course of re-treatment of relapsers to interferon alpha monotherapy with interferon alpha and ribavirin leads to sustained HCV clearance in approximately 50% of patients [19]. Whether this encouraging response rate can be further improved by prolonging treatment to 48 weeks is unknown.

The aim of this pilot study was, therefore, to compare the efficacy and tolerability of 24 versus 48 weeks of combination therapy with interferon alpha and ribavirin in interferon alpha monotherapy relapsers with chronic hepatitis C.

Methods

Patients

Eligible for the study were adult patients, aged between 18 and 65 years, with biopsy proven chronic hepatitis C who had relapsed, i.e. were HCV RNA negative in serum at the end of a previous treatment with interferon alpha alone (≥3 × 3 MIU sc weekly for ≥24 weeks), but became HCV RNA positive again within 24 weeks of follow-up after cessation of treatment. Biopsies must have been performed within the last 5 years and METAVIR [20, 21] scored for degree of inflammation and fibrosis. HCV genotype was determined by the GeneBank database when not provided by local investigators.

In addition, the following criteria had to be fulfilled: (1) Elevation of alanine aminotransferase (ALT) above normal value on three occasions within 24 weeks; (2) detection of HVC RNA by PCR in serum (Cobas Amplicor® HCV Monitor™ v2.0, Roche Diagnostics, Switzerland); (3) the following minimal haematological, biochemical and serological criteria: Haemoglobin concentration >12 g/100 ml in women and >13 g/100 ml in men; white-cell count of >3.0 G/l, neutrophil count of >1.5 G/l; platelet count of >100 G/l, bilirubin, prothrombin time, serum albumin, uric acid, serum creatinin, fasting blood glucose, TSH, alpha-1-antitrypsin, caeruloplasmin and alpha-fetoprotein within normal range, ferritin less than 1000 µg/l, antinuclear antibodies (ANA) <1:160, anti-smooth-muscle antibodies and anti-mitochondrial antibodies negative. Additional exclusion criteria were: HbsAg positivity, HIV infection, alcohol consumption ≥50 g weekly; illicit drug use within the last 12 months, severe cardiovascular disease, severe psychiatric conditions, a seizure disorder, prior organ transplantation, immunosuppression, and pregnancy or lactation. All women in the study were required to practice adequate contraception.

Study design and treatment regimens

This is a prospective, randomised, controlled, multicentre, parallel group pilot trial conducted on behalf of the Swiss Association for the Study of the Liver (SASL). Recruitment in 15 Swiss centres started in February 1999 and continued until February 2000. Patients were randomised in blocks of 10 to receive interferon alpha-2b 3 MIU sc TIW and ribavirin (b.w. <75 kg: 1000 mg po daily; b.w. ≥75 kg: 1200 mg po daily; in two divided doses) either for 24 or 48 weeks, respectively. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of all participating centres and the Swiss federal regulatory authorities (Interkantonale Kontrollstelle für Heilmittel/SwissMedic). During treatment patients were followed twice monthly until week 10 and monthly thereafter. At each visit, blood samples were gathered and concomitant medication and adverse events recorded according to the protocol.

Biochemical (ALT) and virological (HCV RNA) response was assessed at the end of treatment week 10 (if HCV RNA remained positive, treatment was stopped), at the end of treatment week 24 or 48 respectively (end-of-treatment response) and 24 weeks after cessation of treatment, where sustained response was determined.

End points

Primary end point was a sustained biochemical and virological response, i.e. normal ALT and undetectable HCV RNA in serum 24 weeks after completion of the treatment course.

Secondary end points were initial (at the end of treatment week 10) and end-of-treatment virological responses (HCV RNA in serum undetectable). In addition, tolerability (adverse events) was recorded and factors potentially associated with virological response explored.

Statistical analysis

Data were analysed with an intention to treat perspective, i.e. including all patients who received at least one dose of study drug. Data collection was fairly complete. Missing variables were not imputed. The final model contained no missing variables. If normality of numeric data was not rejected by the Wilk-Shapiro test, baseline-variables were compared by t-tests. If normality was questionable, a Wilcoxon rank-sum test was performed. Categorical variables were analysed by Fisher's exact test or the Mantel-Haenszel Chi-Square test for trend, as appropriate. No correction for multiple testing was used because the main outcome was not statistically significant. Finally the variables treatment group, viral genotype (1 vs. other than 1), gender, age, viral load, degree of histological inflammation, and fibrosis were included in a stepwise logistic regression model. These variables were selected according to previous descriptions in the literature.

Statistical analysis was performed using the statistical package SAS version 8 e (SAS Institute, Cary, North Carolina, USA).

Results

Characteristics of patients

Baseline characteristics are detailed in table 1. Demographics, mode of HCV transmission, genotype distribution and viraemia, histological grading and staging, and previous interferon alpha therapy (dose, duration) were similar in both groups.

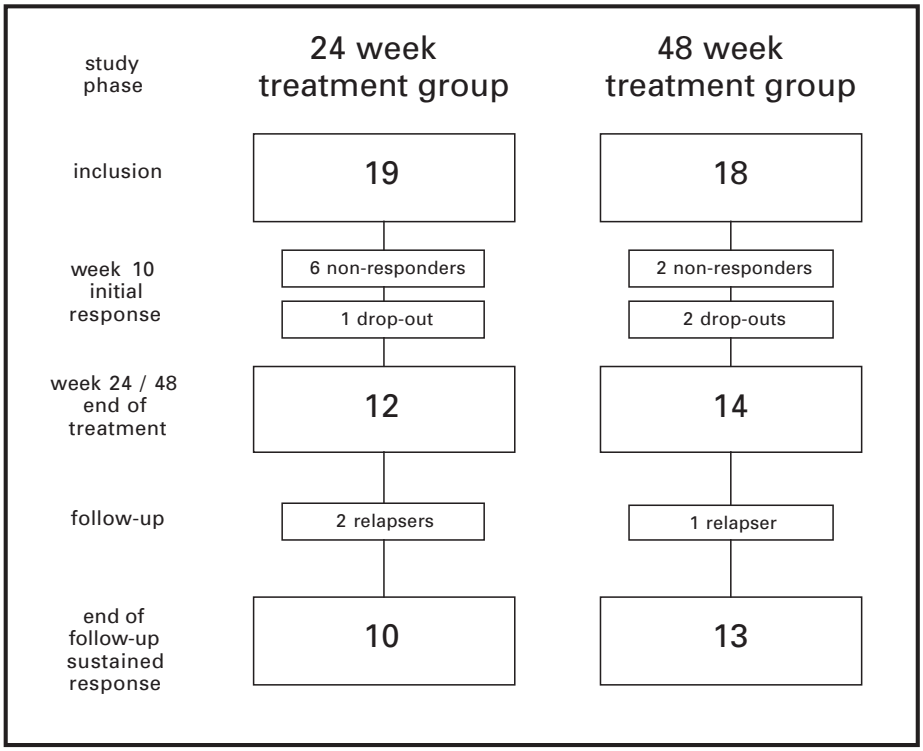
Table 1

Comparison of baseline characteristics.

Characteristics	24 week treatment group	48 week treatment group
no. and sex (m/f) of patients	19 (13/6)	18 (13/5)
median age (range)	43.0 (32–60)	39.5 (30–65)
median weight in kg (range)	74.0 (56–104)	78.0 (60–121)
median BMI (range)	23.2 (19.1–32.1)	26.2 (21.3–41.9)
source of infection		
parenteral	14	9
sporadic	5	9
histology		
inflammation		
none / mild	11	12
moderate / severe	8	5
fibrosis		
none / mild	9	8
moderate / severe / cirrhosis	9	9
ALT level	150.8 ± 80.8	167.3 ± 91.0
HCV genotype		
1	4	5
non-1	15	13
serum HCV RNA		
$>2 \times 10^6$ copies/ml	5	7
$<2 \times 10^6$ copies/ml	14	11
previous IFN treatment		
median duration (weeks)	45.2	45.6
median total IFN dose (MU)	524.5	448.3

Figure 1

Flow chart of the results of 37 included patients in the 24 week and 48 week treatment groups.



Virological and biochemical response

The detailed treatment course is shown in figure 1. The treatment phase was successfully completed by all patients who had responded at week 10: 12 in the 24 week group (63%) and 14 in the 48 week group (78%). At the end of follow-up, two patients in the 24 week and one patient in the 48 week treatment regimen had suffered a relapse. After adjustment for viral genotype, the odds ratio for sustained virological response at the end of follow-up was 3.1 (95% CI 0.7–14.4, p = 0.14).

The response rates at crucial points are displayed in figure 2.

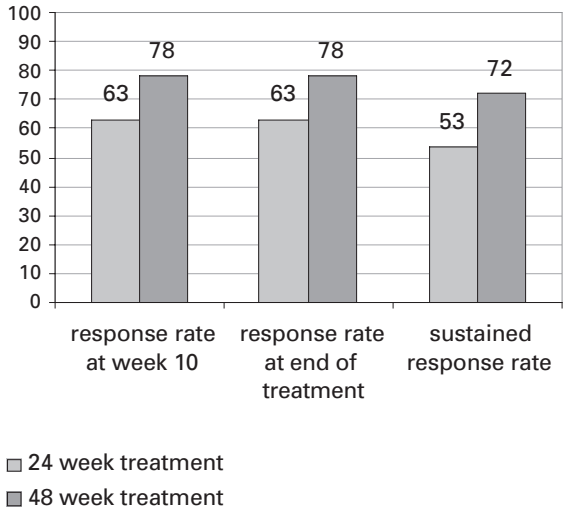
Factors associated with a response

Significantly higher response rates could only be observed in carriers of a genotype other than 1 compared to those with genotype 1 irrespective of the groups at all time points with an odds ratio of 6.3 (95% CI 1.1–35.6, p = 0.037) for sustained virological and biochemical response at the end of follow-up.

Differences in histological inflammation, fibrosis score, serum HCV RNA and ferritin levels did not predict sustained virological response. The subgroups were too small to allow for statistical testing (table 2).

Figure 2

Response rates in percent at week 10, at end of treatment, and at end of follow-up (sustained response).



Tolerability

Subjectively perceived adverse events, well known for ribavirin and interferon alpha, were recorded in 1 patient in the 24 week and 2 patients in the 48 week treatment arm, respectively.

The mean decrease of haemoglobin concentration under therapy was slightly less pronounced in the 24 week treatment regimen with values below 110 g/l in 26% versus 39% in the 48 week group (ns).

Fatigue and headache in one patient in the 24 week group and severe dizziness and persistent concentration and sleep disturbance in one patient in the 48 week group led to premature discontinuation of treatment. The second dropout in the latter group was due to non-compliance.

Dose modifications, both temporary interruption and reduction, were necessary in five patients in the 24 week arm (26.3%) and four patients in the 48 week arm (22.2%) (ns). Reasons included anaemia, neutropenia, nausea and vomiting, depressive symptoms, allergic exanthema, severe pruritus, and severe fatigue.

Table 2

Rates of sustained response (SR) to treatment according to baseline characteristics (statistics were not performed due to small numbers).

Characteristics*		24 week treatment group		48 week treatment group	
		SR/*	%	SR/*	%
all		10/19	53	13/18	72
sex	male	8/13	62	9/13	69
	female	2/6	33	4/5	80
genotype					
	1	1/4	25	2/5	40
	other than 1	9/15	60	11/13	85
histology					
inflammation					
	none/mild	4/11	36	10/12	83
	moderate/severe	6/8	75	2/5	40
fibrosis					
	none/mild	3/9	33	8/8	100
	moderate/severe/cirrhosis	7/10	70	4/9	44
serum level HCV RNA					
	$<2\times 10^6$ copies/ml	7/14	50	9/11	82
	$>2\times 10^6$ copies/ml	3/5	60	4/7	57

Discussion

The presented comparison of 24 week versus 48 week combination treatment in chronic hepatitis C with interferon alpha 2b and ribavirin in previous interferon-monotherapy relapsers was designed on the basis of the observation, that combination therapy of interferon alpha and ribavirin on one hand [19] and prolonging interferon monotherapy on the other hand [22, 23] were proven to be more effective than interferon alone in both naive [6, 10, 24] and relapse [22, 25–27] patients.

The primary aim of any treatment regimen in chronic hepatitis C – efficacy is generally assessed by clearance of HCV RNA, ALT normalisation, and histological improvement – is the prevention of progression and its fatal complications cirrhosis and hepatocellular carcinoma.

In our study, the overall sustained response rate of 62% 24 weeks after end of treatment demonstrates the high effectiveness of this well-tolerated combination therapy and is in line with previous study results of 49% and 54% [19, 28].

Prolonging the therapy from 24 to 48 weeks resulted in a higher sustained response rate of 72% versus 53% without higher rates of adverse events. Similar data were recently published [28] with a 72% versus 36% response rate ($p = 0.01$).

Infections with a genotype other than genotype 1 responded better, confirming other studies [6, 7, 28].

Due to small numbers we could not demonstrate a statistical significance in our primary endpoint results, nor could the role of variables such as age, sex, and histological or biochemical findings be clarified. Reasons for the limited scope are the highly focused patient group, strict inclusion and exclusion criteria and the complex protocol with a 10 week stopping rule on failed HCV clearance. No further patients were included after promising data on pegylated interferon and its combination with ribavirin emerged during the course of the study. Nevertheless our results demonstrate the high sustained response rates of this combination therapy, particularly in the prolonged treatment regimen. Therefore this pilot trial encourages further studies, exploring the effectiveness of a 48 week treatment with PEG interferon combined with ribavirin in both interferon alpha mono- and combination therapy relapsers.

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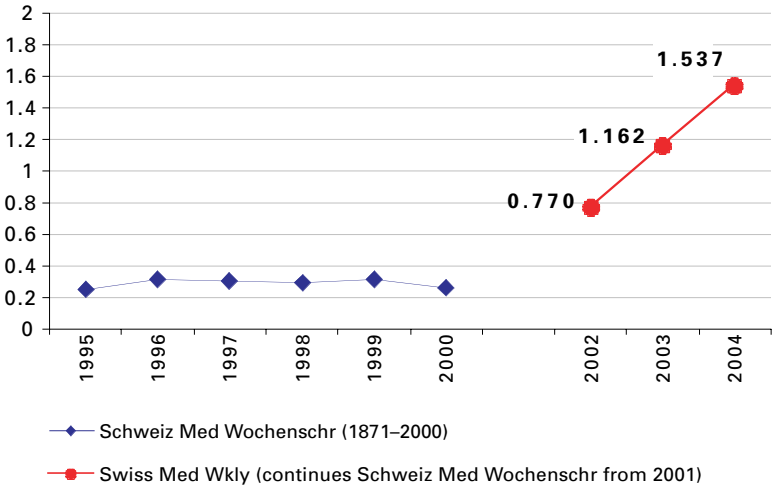

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