VIRAL HEPATITIS

Outcomes of interferon α and ribavirin treatment for chronic hepatitis C in patients with normal serum aminotransaminases

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Introduction: Information on treatment outcomes with interferon plus ribavirin combination therapy in chronic hepatitis C patients with normal alanine aminotransaminase (ALT) levels is limited.
Aim: The aims of this study were to assess outcomes of treatment with interferon plus ribavirin in patients with normal ALT levels (normal ALT group, n = 52) compared with those with elevated ALT levels (raised ALT group, n = 53), and to document the rate at which patients with normal ALT levels have an apparent worsening of disease, as shown by increases in ALT levels.
Results: At the end of treatment (week 48), 31 patients (59.6%) in the normal ALT group and 30 patients (56.6%) in the raised ALT group had undetectable hepatitis C virus (HCV) RNA (p = 0.75). A sustained virological response (SVR) was achieved in 20 patients (38.5%) in the normal ALT group and in 21 patients (39.6%) in the raised ALT group (p = 0.90). Patients were subsequently followed up for a median of 29.8 (interquartile range 25th–75th percentile (IQR) 20.8–36.2) months in the normal ALT group and for a median of 26.1 (IQR 17.7–36.3) months in the raised group (p = 0.20) after week 72 of treatment. Among patients without SVR in the normal ALT group, only three patients (9.4%) developed persistently raised ALT levels following therapy.
Conclusions: Combination therapy with interferon plus ribavirin is associated with a similar SVR in patients with normal ALT levels compared with those with elevated ALT levels. In patients with normal ALT levels, virological non-response to therapy results in new elevations in serum ALT levels in a small minority only.

Infection with the hepatitis C virus (HCV) affects an estimated 2.7 million people in the USA.[1] Clinical manifestations and spectrum of disease in those with chronic infections are broad and diverse. Approximately 20% of those with chronic infection progress to life threatening complications of hepatitis C, such as cirrhosis, liver failure, or hepatocellular carcinoma.[2 3] The remainder of patients manifest varying degrees of symptoms, viraemia, abnormalities in serum aminotransaminase levels, and histological activity on liver biopsy.

Before the identification of HCV, the diagnosis of non-A, non-B hepatitis was based on documentation of persistently elevated serum alanine aminotransaminase (ALT) values.[4] It was only after the widespread use of molecular based assays for HCV RNA that it became apparent that viraemia was frequent among individuals with persistently normal ALT. It has been estimated that 30% of patients with chronic hepatitis C have persistently normal ALT.[5] The natural history of these patients is still uncertain. Histological examination of the liver has shown mild to moderate chronic hepatitis in most cases,[6–15] and cirrhosis in some,[6 14 15] thus indicating that the presence of bridging fibrosis, or even cirrhosis, cannot be ruled out in patients with persistently normal ALT levels and detectable HCV RNA.

A major concern regarding the treatment of patients with normal ALT levels was the finding that a large proportion of patients (58%) had elevated ALT levels following treatment,[5 16] raising the possibility that treatment may result in actual worsening of disease in those who failed to achieve viral clearance. All of these studies however involved the use of interferon α monotherapy. It is uncertain if treatment with combination interferon and ribavirin in patients with persistently normal ALT levels results in rates of viral clearance comparable with those with elevated ALT.

Therefore, we have undertaken a retrospective study to determine the outcome of interferon α and ribavirin combination therapy in patients with normal ALT levels compared with those with elevated ALT levels.

PATIENTS AND METHODS

This was a retrospective study on all patients treated with combination interferon α and ribavirin at the Liver Clinic, Veterans Affairs Medical Center, San Francisco and the University of California, San Francisco, USA, between July 1998 and February 2001. All patients fulfilled the following criteria: (1) positive for anti-HCV by second generation enzyme linked immunosorbent assay (Ortho Diagnostics System, Raritan, New Jersey, USA); (2) detectable serum HCV RNA; (3) hepatitis B surface antigen negative; (4) absence of antihuman immunodeficiency virus antibodies; (5) no other chronic liver disease (alcoholic liver disease, hepatotoxic drugs, autoimmune chronic hepatitis, haemochromatosis); (6) treatment or interferon naïve; and (7) absence of decompensated liver disease.

Patients were prescribed subcutaneous recombinant interferon α-2b 3 mU (Schering-Plough, Kenilworth, New Jersey, USA) three times weekly and oral ribavirin 1000 or 1200 mg daily (1000 mg for those less than 75 kg body weight and 1200 mg for those more than 75 kg) (Schering-Plough) for 48 weeks. Patients were followed up at monthly intervals while on treatment, every three months during the first year post treatment, and approximately half yearly thereafter until

Abbreviations: HCV, hepatitis C virus; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; SVR, sustained virological response; ULN, upper limit of normal; IQR, interquartile range; OR, odds ratio

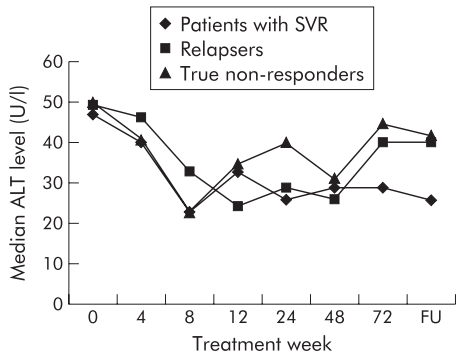

Figure 1 Median alanine aminotransaminase (ALT) levels in patients with a sustained virological response (SVR), in relapsers, and in true non-responders in the normal ALT group during and after treatment. FU, median ALT levels at the end of follow up.

the time of analysis (December 2002). During each assessment, complete blood counts and liver biochemistry were checked. HCV genotype (Inno-LIPA; Innogenetics NV, Ghent, Belgium) was measured prior to therapy. HCV RNA (Amplicor HCV Monitor Test 2.0; Roche Diagnostics, New Jersey, USA) was determined prior to treatment, at week 48, at week 72, and at the end of follow up in all patients.

A percutaneous liver biopsy was performed prior to therapy in all patients. Liver biopsies were paraffin embedded and stained with haematoxylin-eosin safran and Masson's trichrome. Histological features were scored for stage of fibrosis (no fibrosis (F0), portal fibrosis (F1), periportal fibrosis (F2), septal fibrosis (F3), and cirrhosis (F4)) and grade of inflammatory activity (portal inflammation only with no activity (A1), minimal activity (A1), mild activity (A2), moderate activity (A3), and severe activity (A4)).[17]

Patients with persistently undetectable HCV RNA six months after completion of treatment (week 72) were considered as having achieved a sustained virological response (SVR).

The primary aim of this study was to compare the response rates to interferon plus ribavirin combination therapy in patients with normal ALT levels and elevated ALT levels. The secondary aim of this study was to document the rate at which patients with normal ALT levels who were treated have an apparent worsening of disease, as shown by an increase in ALT levels. For those with normal ALT levels, an increase in ALT levels was defined as a rise in ALT by $\geqslant$1.3 times the upper limit of normal (ULN) on three different occasions in a six month period.

This study was approved by the local institutional review board and all patients provided written informed consent for chart review and data collection.

Statistical analysis

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 10.0 for windows; SPSS Inc., Chicago, Illinois, USA). The Mann-Whitney U test was used for continuous variables with skewed distribution and the χ^2 with Yates' correction for continuity, or Fischer's exact test for categorical variables. Continuous variables are expressed as median (interquartile range 25th–75th percentile (IQR)). All statistical analyses were performed on an intention to treat population. Statistical significance was defined as $p<0.05$ (two tailed).

RESULTS

During this period, there were 105 chronic HCV patients treated with interferon α and ribavirin for 48 weeks, 52 patients (49.5%) in the normal ALT group and 53 patients (50.5%) in the raised ALT group. Baseline characteristics of the two groups are shown in table 1, and were comparable except for baseline ALT and aspartate aminotransaminase (AST) levels ($p<0.0001$ and $p<0.0001$, respectively) (table 1). Patients in the normal ALT group also had a significantly lower fibrosis stage compared with patients in the raised ALT group ($p = 0.04$). No significant difference was detected in HCV RNA level or infecting genotype between the two groups (all NS). During this period, there were 108 patients with normal ALT levels who did not receive antiviral therapy.

Virological response

Eight patients (15.4%) in the normal ALT group required dose reduction. The reasons for dose reduction were fatigue (n = 4), anaemia (n = 3), and thrombocytopenia (n = 1). In the raised ALT group, 10 patients (18.9%) required dose reduction. The reasons for dose reduction were anaemia (n = 5), fatigue (n = 3), and thrombocytopenia (n = 2). There was no significant difference in the number of patients requiring dose reduction between the two groups ($p = 0.64$; odds ratio (OR) 0.78 (95% confidence interval (CI) 0.28–2.17)).

At the end of treatment, 31 patients (59.6%) in the normal ALT group and 30 patients (56.6%) in the raised ALT group had undetectable HCV RNA ($p = 0.75$; OR 1.13 (95% CI 0.52–2.46)). SVR was present in 20 patients (38.5%) in the normal ALT group and in 21 patients (39.6%) in the raised ALT group ($p = 0.90$; OR 0.95 (95% CI 0.44–2.09)). In the normal ALT group, nine patients (27.3%) with genotype 1 had SVR while 11 patients (57.9%) with non-genotype 1 had SVR ($p = 0.03$; OR 0.27 (95% CI 0.08–0.90)).

There were no significant differences in baseline characteristics of patients with SVR and those without SVR in the normal ALT group (table 2) (all NS).

Treatment was discontinued in six patients (11.5%) from the normal ALT group. The reasons for discontinuation of treatment in the normal ALT group were anaemia (n = 3), depression (n = 2), and thyrotoxicosis (n = 1). Six patients (11.3%) from the raised ALT group were discontinued from treatment for anaemia (n = 3), depression (n = 2), and fatigue despite dose reduction (n = 1). There was no significant difference in the number of patients requiring discontinuation of treatment between the two groups ($p = 0.97$; OR 1.02 (95% CI 0.31–3.40)). At week 48 and week 72, no patient in either group defaulted follow up. At the end of follow up, seven patients (13.5%) in the normal ALT group defaulted follow up while in the raised ALT group, five patients (9.4%) defaulted follow up ($p = 0.56$; OR 1.49 (95% CI 0.44–5.05)).

ALT levels in the normal ALT group

Patients were followed up further (end of follow up) for a median of 29.8 (IQR 20.8–36.2) months in the normal ALT group and for a median of 26.1 (IQR 17.7–36.3) months in the raised ALT group ($p = 0.20$) after week 72.

Median ALT levels in patients in the normal ALT group with SVR, those without SVR but with undetectable HCV RNA at the end of treatment (relapsers), and those with detectable HCV RNA at the end of treatment and at six months after completion of treatment (true non-responders) are shown in table 3 and fig 1. There was no significant difference in median ALT levels between relapsers and true non-responders at week 48, week 72, or at the end of follow up ($p = 0.07$, $p = 0.61$, and $p = 0.26$, respectively).

When median ALT levels at week 48, week 72, and at the end of follow up between relapsers and those with SVR were

Table 1 Baseline characteristics of the normal ALT group and the raised ALT group

	Normal ALT group (n = 52)	Raised ALT group (n = 53)	p Value
Age (y)	47.5 (43.3–52)	49 (43–51.5)	0.90
Sex (M:F)	46:6	47:6	1.00
Genotype			0.55
1	33	33	
2	9	6	
3	6	9	
Indeterminate	4	5	
BMI (kg/m^2)	28.2 (25.4–29.2)	25.5 (21.4–31.7)	0.35
ALB (g/l)	4 (3.8–4.2)	4 (3.8–4.1)	0.46
BIL (mg/dl)	0.8 (0.5–0.9)	0.7 (0.6–0.9)	0.60
ALT (U/l)	45 (32.5–53)	132.5 (109–179.8)	<0.0001
AST (U/l)	46 (37–52)	92.5 (73.5–139)	<0.0001
ALP (U/l)	69 (57.3–87.3)	68 (54–87)	0.47
HCV RNA (IU/ml)	420 000 (83 000–>850 000)	530 000 (50 570–>850 000)	0.60
Race			0.16
Caucasian	16	20	
African American	5	1	
Other	1	4	
Decline to answer	30	28	
Education			0.63
College	17	18	
High school	5	6	
Elementary school	0	1	
Decline to answer	30	28	
Annual income			0.07
>$50 000	1	4	
$25 000–$50 000	4	7	
$10 000–$25 000	9	2	
<$10 000	7	7	
Decline to answer	31	33	
Risk for infection			0.10
Transfusion	15	26	
IV drug abuse	20	14	
Unknown	17	13	
Stage of fibrosis			0.04
F0–F1	24	14	
F2–F3	28	39	
Necroinflammatory grade			0.17
A0–1	11	6	
A2–3	41	47	

BMI, body mass index; ALB, albumin; BIL, bilirubin; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; ALP, alkaline phosphatase; HCV, hepatitis C virus; IV, intravenous.
Values are median (interquartile range 25th–75th percentile) or number.

compared, no significant differences were detected ($p = 0.54$, $p = 0.08$, and $p = 0.15$, respectively). There was also no significant difference in median ALT levels at week 48, week 72, and at the end of follow up between true non-responders and those with SVR ($p = 0.07$, $p = 0.09$, and $p = 0.10$, respectively).

Table 2 Baseline characteristics of patients with SVR and those without SVR in the normal ALT group

	Patients without SVR (n = 32)	Patients with SVR (n = 20)	p Value
Age (y)	47.5 (44–53)	47.5 (43–51)	0.90
Sex (M:F)	29:3	17:3	0.66
Genotype			0.03
1	24	9	
Non-1	8	11	
(2)	(4)	(5)	
(3)	(2)	(4)	
(Indeterminate)	(2)	(2)	
BMI (kg/m^2)	27.4 (24.4–29.2)	26.6 (22.4–34.2)	0.24
ALB (g/l)	4 (4–4.2)	3.8 (3.8–4.1)	0.08
BIL (mg/dl)	0.8 (0.6–1.0)	0.7 (0.5–0.8)	0.09
ALT (U/l)	47 (40–53)	50 (41–55)	0.49
AST (U/l)	46 (32–54)	47 (39–51)	0.85
ALP (U/l)	70 (57–90)	67 (57–87)	0.98
HCV RNA (IU/ml)	450 000 (83 000–>850 000)	420 000 (75 020–>850 000)	0.94
Stage of fibrosis			0.66
F0–F1	14	10	
F2–F3	18	10	

SVR, sustained virological response; BMI, body mass index; ALB, albumin; BIL, bilirubin; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; ALP, alkaline phosphatase; HCV, hepatitis C virus.
Values are median (interquartile range 25th–75th percentile) or number.

Table 3 Median alanine aminotransaminase in patients with SVR, relapsers, and true non-responders in the normal ALT group

	Patients with SVR (n = 20)	Relapsers (n = 11)	True non-responders (n = 21)
ALT at week 48 (U/l)	29 (25–39)	26 (18–39)	31 (23–56)
ALT at week 72 (U/l)	29 (18–39)	40 (20–55)	45 (29–54)
ALT at follow up (U/l)	26 (20–31)	40 (27–54)	42 (25–57)

SVR, sustained virological response; ALT, alanine aminotransaminase.
Values are median (interquartile range 25th–75th percentile).

At the end of follow up, three patients (9.4%) in the normal ALT group developed persistent elevation in ALT levels. The elevation in ALT levels occurred more than six months after completion of treatment. These three patients were true non-responders. None of the relapsers developed transient rises in ALT levels.

DISCUSSION

Van Thiel *et al* and Rossini *et al* demonstrated in 1997 that the virological response to interferon therapy in patients with normal ALT levels was similar to patients with elevated ALT.[15 18] Gordon *et al*, in their analysis of the subgroup of patients with slightly elevated ALT levels (defined as 1–1.3 times the ULN) from a multicentre interferon plus ribavirin trial, found that the 71 patients in this subgroup who received the combination had similar response rates to the 939 patients with elevated ALT levels (defined as >1.3 times the ULN) (30% *v* 37%, respectively).[19] The results of these two studies suggest that virological responses to interferon plus ribavirin are independent of ALT levels.

In a pilot study by Lee and Sherman on the outcome of combination interferon plus ribavirin therapy in patients with normal ALT levels, the SVR achieved in patients with normal ALT levels was 47%.[20] This was similar to the SVR of 36–41% achieved in patients with elevated ALT levels in the two landmark studies of combination therapy.[21 22] However, Lee and Sherman used an induction regimen in their study, as at that time it was believed that patients with normal ALT levels were more resistant to standard treatments compared with patients with elevated ALT levels.[20] Moreover, Lee and Sherman did not include patients with abnormal ALT levels for comparison.

The SVR rate of 38.5% achieved in patients with normal ALT levels was similar to that achieved in patients with elevated ALT levels. This is comparable with responses in the current literature,[21–24] thus suggesting that patients with normal ALT levels are not more resistant to combination therapy than those with elevated ALT levels, and deleterious effects of treatment were not observed. Since we undertook this retrospective study, recommendations regarding the treatment of patients with normal ALT levels have been liberalised in the National Institute of Health Consensus Statement 2002 as the natural history of disease in this population is poorly defined and some may show disease progression.[25] Our data would support the validity of these new recommendations.

A total of three patients from the normal ALT group developed persistently raised ALT levels at the end of follow up. Persistently raised ALT in these three patients may be part of the natural history of patients with normal ALT levels, as identified in a study by Persico and colleagues[26] and Martinot-Peignoux and colleagues[27] in which 23% and 21% of their patients with normal ALT levels developed elevated ALT levels on follow up. If the relative frequency of patients with normal ALT levels developing persistently raised ALT levels is indeed approximately 20%, then the finding of 9.4% in our series is low. Perhaps even in patients with normal ALT levels, combination interferon plus ribavirin therapy can decrease the incidence of developing elevated ALT levels in those without SVR instead of worsening their ALT levels, as was initially feared.[28] Furthermore, there were no significant differences in median ALT levels at week 48, week 72, or at the end of follow up between patients with SVR, relapsers, and true non-responders.

The results of this study must be interpreted with care because of several limitations. Firstly, there was no randomised control group of patients with normal ALT levels who did not receive treatment. Secondly, as with all other studies on patients with normal ALT levels, we do not know historically whether patients in the normal ALT group had normal ALT levels before they presented to our clinic or if they were in a stage of transient although prolonged biochemical remission before commencement of treatment. Thirdly, as this was not a prospective study, follow up liver biopsies to demonstrate whether ALT levels in those without SVR reflected worsening or improvement in disease were not available. Fourthly, this retrospective study did not allow us to calculate the cumulative doses of interferon and ribavirin or to determine the indication for liver biopsy or treatment of patients with normal ALT levels. Finally, the possibility of a type II error cannot be excluded due to the small number of patients.

In conclusion, this study showed that interferon and ribavirin combination therapy for chronic hepatitis C in patients with normal ALT levels caused comparable SVR rates to those with elevated ALT levels. Combination therapy did not lead to an increased risk of persistently increased ALT levels in patients without SVR. Therefore, patients with normal ALT levels should be evaluated for stage of liver disease as a treatment option is now available. However, the majority of patients with normal ALT levels do not show significant fibrosis and thus do not require treatment.

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