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Research Article

A Belgian Randomized Trial in Hepatitis C Virus-Infected Patients with Persistently Normal Alanine Aminotransferase

Abstract

Persistently normal alanine aminotransferase (PNALT) is present in 30 to 40% of chronic hepatitis patients and it is generally accepted that they have no liver damage. However, some studies suggest that there are some degrees of mild to moderate histological liver damage. We evaluated the fibrosis stage and the virological outcome in treated patients with PNALT.

We collected HCV-positive patients with normal liver enzymes in a Belgian multicenter prospective randomized study between 2002 and 2006. They had fibrosis with at least F1 in Metavir score. Patients were followed for two years. They were divided in two groups. Group 1 (n=17) were patients treated by Pegylated Interferon alfa-2b (Pegintron) plus ribavirin (Rebetol). Group 2 (n=18) received no treatment and were used as a control group for 48 weeks.

The sustained virological response (SVR) was 41% (7/17). The SVR in our study is equivalent for patients with elevated ALT levels.

We also evaluated the evolution of the transaminases during treatment in group 1 patients. We observed a diminution of the already normal ALT and AST values, in patients who were treated. In our opinion there is no other publication that showed this evolution of the transaminases during treatment of HCV. With the knowledge that in our study, the patients showed a minimal degree of fibrosis even with normal liver enzymes, we agree with the findings of some authors who suggest to lower normal limit of the transaminases.

Background

Persistently normal alanine aminotransferase (PNALT) is present in 30 to 40% of chronic hepatitis C patients [1,2] and it is generally accepted that they have no liver damage [3]. However, some studies suggest that there are some degrees of mild to moderate histological liver damage [1,4-6]. We evaluated the fibrosis stage and the virological outcome in treated patients with PNALT.

We collected HCV-positive patients with normal liver enzymes in a Belgian multicenter prospective randomized study between 2002 and 2006. They had fibrosis with at least F1 in Metavir score. Patients were followed for two years. They were divided in two groups. Group 1 were patients treated by Pegylated Interferon alfa-2b (Pegintron) plus ribavirin (Rebetol). Group 2 received no treatment and was used as a control group for 48 weeks.

The objective of this study was primarily to determine the proportion of virological response at the end of treatment and 6 months after treatment with pegylated interferon alfa-2b administered sub cutaneous once per week plus ribavirin given twice daily during 48 weeks in comparison with no treatment, in patients with chronic hepatitis C and persistently normal transaminase levels with fibrosis.

The second objective was to assess the stage of fibrosis in these patients.

Materials and Methods

Study population

Naïve adult patients with chronic hepatitis C and persistently normal ALT levels were selected for this study. The patients were randomized between treatment and observation (control group). PNALT was defined as the presence of 3 consecutive measurements within the normal range over a 6-month period [7].

Inclusion criteria

All adult male or female patients (age 18-65) with positive anti-HCV antibodies and serum HCV-RNA by RT-PCR and repeatedly normal ALT activity without any abnormal value (at least three assays over a minimum of 6 months) were included.

Patients had to be serum hepatitis B surface antigen (HBsAg) negative and HIV negative (ELISA positive results were confirmed by Western blot).

Liver biopsy was performed in all cases within a year prior to the entry in this protocol with a pathology report confirming that the histological diagnosis was consistent with chronic hepatitis.

On liver biopsy, at least slight fibrosis classified in the METAVIR scoring system as F1 was needed for patients to be randomized between treatment and observation. Patients without fibrosis F0 were not randomized.

Statistical analysis

SPSS v23 was used for all statistical analyses. The Mann-Whitney U-test was used to compare the continuous variables. A two-tailed *P* value of <0.05 was considered significant.

Ethical considerations

The ethical committee of C.HU BRUGMANN, in Brussels granted ethical approval. All participants gave written informed consent.

Results

Initially forty-seven patients were screened. The informed consent of seven patients was not found on site. All data related to these patients have been removed from the database. Two patients had elevated transaminases and one patient was 74 years old on the randomization date, which were deviations to the inclusion criteria and so they were removed from the database. Two patients had no fibrosis and thus they were not randomized. So at the end, we selected 35 patients; 17 males and 18 females. They were randomised in Group 1 (treatment group) and Group 2 (control group). Group 1 consist 17 patients (9 males and 8 females), Group 2 consist 18 patients (8 males and 10 females).

Mean characteristics of the study population is listed in the following **Table 1**.

Mean age of the patient is 44.1 years in Group 1 and 43.6 years in Group 2.

All patients had a positive RNA, but due to lack of absolute values of the viral load, if HCV RNA was more than 500000 UI/ml, an average could not be calculated.

All the 17 patients in Group 1 were treated with Pegylated Interferon alfa-2b (Pegintron) plus ribavirin (Rebetol) for 48 weeks. 7 patients were non responders (positive PCR at week 24) and their treatment was stopped. 10 patients had a negative PCR at week 24 of treatment. Of the 10 patients who responded at week 24, 7 remained negative PCR at week 72, 1 patient presented a breakthrough between week 24 and 48 of treatment, 1 patients relapsed after treatment and 1 patient was lost to follow up.

So overall, sustained virological response (SVR) was 41% (7/17) and 59% (10/17) were non responders. One patient had responded on the end of the treatment but was lost of follow-up and was considered as positive at week 72. Results are shown in the following **Table 2** (**Figure 1**).

We also evaluated the evolution of the transaminases during treatment in Group 1 patients. We observed a diminution of the values of the transaminases, ALT and AST, in patients who were treated. This diminution was more pronounced and also maintained in responders.

The diminution of the transaminases was statistically significant between different groups for ALT and AST. Using the Mann-Whitney U-test we noted a *P*-value of $0.001<0.05$ for ALT and $0.0001<0.05$ for AST in group 1 (patients treated) and group 2 (control group). There was also a statically significant difference between group 1 and in the

group with response to the treatment, *P*-value was $0.001<0.05$ for ALT and $0.042<0.05$ for AST (**Figures 2,3**).

Conclusions

Persistently normal alanine aminotransferase (PNALT) is present in 30 to 40% in chronic hepatitis patients [1,2] and it is generally accepted that those patients have no or minimal liver damage[3].

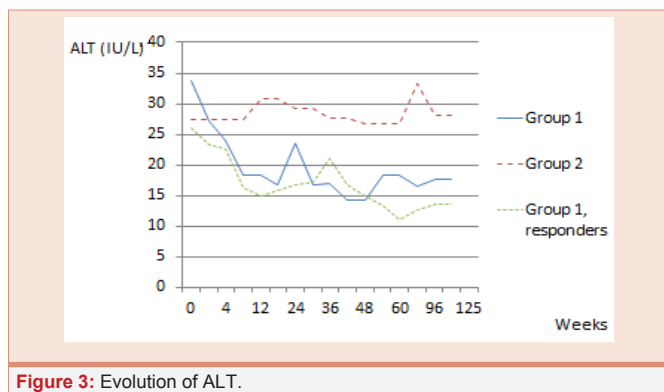
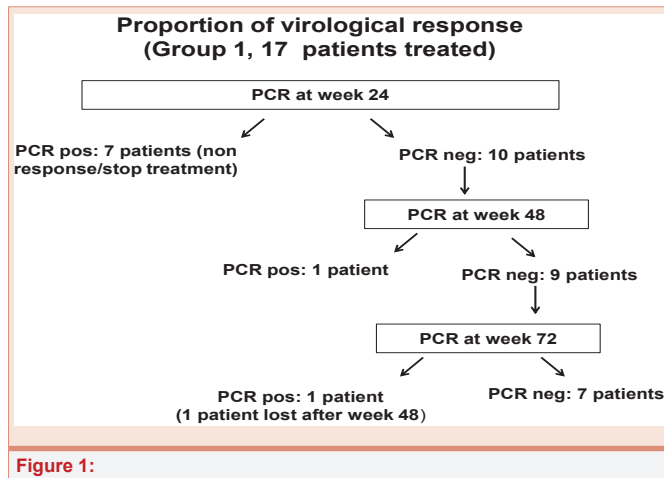
Table 1: Baseline clinical, virological, biochemical and histological characteristics of the study population.

Characteristics	Group 1	Group 2
Patients enrolled (n:35)	17	18
Age (years)	44,1 ± 10,9	43,3 ± 9,9
BMI (kg/m ²)	24,99 ± 4,09	26,34 ± 3,60
Gender male/female (n)	9/8	8/10
AST (IU/L)	29,29 ± 6,50	29,78 ± 9,15
Genotype		
Genotype 1 (n)*	9	3
Genotype 2 (n)	2	1
Genotype 3 (n)	3	1
Genotype 4 (n)	3	2
Unknown	0	11
Metavir fibrosis stage		
F0 (n)	0	2
F1 (n)	7	8
F2 (n)	10	6
F3 (n)	0	0
F4 (n)	0	1
Unknown	0	1
Metavir activity grade		
A0 (n)	1	0
A1 (n)	10	11
A2 (n)	1	3
A3(n)	0	0
Unknown	5	4

Data are expressed as means ± standard deviation
ALT = alanine aminotransferase; AST= aspartate aminotransferase;
PNALT= persistently normal alanine aminotransferase; BMI= Body Mass Index.

Table 2:

Proportion of virological response Group 1: 17 patients treated	Week 24	Week 48	Week 72	Response
PCR POSITIVE	7 (patient non response)		11 patient lost who were neg at 48 weeks	SVR: 7/17 (41%) Non responder: 10/17 (59%)
PCR NEGATIVE	10	9	7	(1 PCR negative at 24 & 48 but lost and considered as positive)



However, some studies suggest that there are some degrees of mild to moderate histological liver damage [1,4-6].

In this Belgian multicenter prospective randomized study, we included 35 HCV-positive patients with normal liver enzymes between 2002 and 2006 to evaluate the histological stage and the proportion of virological outcome. Patients were divided in a group treated with PegIFN/ribavirine (group1, 17 patients) and a group without a treatment (group 2, 18 patients). Patients were followed for two years.

The antiviral effect of pegylated interferon plus ribavirin combination therapy in chronic hepatitis C (CHC) patients with

normal alanine aminotransferase levels has been reported to be equivalent to the effect for patients with elevated ALT levels [8].

In our study 10 patients out of 17 (59%) had a virological response after 24 weeks and 9 out of 17 (53%) after 48 weeks of treatment.

Six month after treatment 1 patient relapsed and one patient was lost to follow-up. Therefore, the overall sustained response rate to treatment was 41 % (7 patients of 17). These results confirm SVR in previous studies with PNALT.

Some authors suggest that the natural history of PNALT in chronic hepatitis C patients in terms of fibrosis and clinical complications shows no or slow evolution [3].

Unfortunately because the lack of liver biopsies in most patients during the follow-up period, 6 months after treatment, we were not able to evaluate the histological evolution in patients with and without treatment.

Liver enzymes in HCV patients are fluctuating. The Trent Hepatitis C Study Group showed that most patients with a PNALT will ultimately have an elevated ALT [9]. In the same study, they demonstrated that a significant proportion of patients with elevated ALT will have a period where the ALT remains normal over a period of 6 months and so they could be wrongly labeled as PNALT.

Even more the normal value of transaminases and his consequences on the liver tissue is debatable and some authors suggest to lower normal limit of transaminases [10].

In a study of Sanai et al. all patients with PNALT had evidence of histological disease, but their necro-inflammatory activity and score did not differ significantly from patients with elevated ALT. Even in patients with ALT<30IU/L, no differences were found. They concluded that ALT is a poor surrogate marker for inflammation and fibrosis in HCV patients [11].

In another study fibrosis progression in patients with ALT <30 and ALT<40 was the same over a period of median follow up of five years [9].

In one study PNALT in HCV patients with AST/ALT ratio >1 in combination with a platelet count of <150,000/mm³ and in absence of alcohol abuse could be associated with severe fibrosis [12].

Until the beginning of 2015, the presence of elevated transaminases was an essential criteria in Belgium to get reimbursement for the available HCV treatment regimens at that moment. Our study is the only study of HCV patients with PNALT in Belgium treated with PegIFN/Ribavirine.

Because it is now very clear that transaminases should not be taken into account in the decision to treat HCV patients, fortunately this criteria of elevated transaminases was removed from the reimbursement conditions, since January 2015 with the arrival of the new treatment options with high rates of SVR [13-20].

In our study, we also observed a diminution of the values of the transaminases, ALT and AST, in patients who were treated. This diminution was even more pronounced and also maintained in patients with SVR. In our opinion there is no other publication

showing this evolution of transaminases during treatment of HCV. The definition of normal transaminases can thus be questioned given the evolution of transaminases during treatment and the clear correlation with the presence of SVR.

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