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Research Article

Normalization of Alanine Aminotransferase Predicts Successful Antiviral Treatment in Patients with Chronic Hepatitis C

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Abstract

Introduction: Successful antiviral treatment in patients with chronic viral hepatitis C eliminates the virus from sera, preventing progression of liver disease. The aim of this study was to evaluate the incidence and predictive factors of normalization of post-treated alanine aminotransferase values in relation to viral removal.

Patients and methods: Clinical and laboratory data for 310 patients treated in the Clinic for Infectious and Tropical Diseases were analyzed. All patients had elevated alanine aminotransferase values before treatment. Biochemical and virologic analyses were performed with commercial kits routinely used in laboratories of the Clinical Centre of Serbia. Selected variables were analyzed with the SPSS Statistics software package (version 17.0).

Results: A significant correlation was found between the incidence of normal ALT values and viral negativity after treatment (70.6% and 72.6%, respectively, $p<0.001$). Biochemical response, defined as a normal ALT value after treatment, was noted as the positive predictor for sustained virologic response ($p<0.001$). Binary logistic regression analyses revealed age less than 40, viral genotype 3, intravenous drug use, and low HCV RNA as statistically significant positive variables for normalizing of ALT. Liver cirrhosis and viral genotype 1 were estimated as negative variables. Age less than 40 was the most significant positive variable in multivariate regression analyses ($p<0.00$). Pre-therapy ALT values and the incidence of normal values of ALT after therapy were not significantly related.

Conclusion: The study confirms that normalization of alanine aminotransferase activity predicts successful antiviral treatment in the majority of patients with chronic hepatitis C, particularly in younger patients.

Introduction

Chronic Hepatitis C (CHC) has different clinical outcomes. In general, the course of the disease is relatively slow in the majority of patients. Liver cirrhosis develops over 10 to 30 years in 25% to 35% of these patients leading to decompensated liver disease, hepatocellular carcinoma, and finally to liver insufficiency and death [1,2]. The primary goal of antiviral treatment is virologic cure implying eradication of viral infection and consequently prevention of disease progression with possible liver-related complications [3,4]. Until recently, "standard" antiviral therapy of CHC consisted of a combination of Pegilated Interferon Alpha (IFNα) plus Ribavirin (RBV) [5,6]. This treatment provides a Sustained Virologic Response (SVR) in approximately up to 75 % of treatment native patients six months after discontinuing the therapy. Application of the recommendations from the European Society for the Study of the Liver (EASL) with Direct-Acting Antiviral (DAA) drugs cures infection up to 100% of patients [7]. At the same time, the beneficial impact of the therapy is evident in the decrease of Asparate (AST) and Alanine Aminotransferases (ALT) levels to normal values (Biochemical Response-BR), and reduction of histological liver activity with lessening of liver fibrosis (histological response) [8].

Thus, measurement of serum aminotranseferases activity before, during and after therapy is of particular interest with regard to antiviral treatment, because these enzymes are associated with the damage to liver parenchyma characterized by the amount of hepatocyte necrosis [9- 11].

The aim of this study was to evaluate the incidence and predictive factors of normalization of serum ALT after antiviral treatment in CHC patients.

Table 1: The frequency of pre-treatment values of ALT in CHC patients.

ALT value*	Number of patients (%)
> 40-80	180 (58.1%)
> 80-200	99 (31.9%)
> 200	31 (10%)
Total:	310 (100%)

*normal value ≤40 U/l.

Patients and Methods

This retrospective study included clinical and laboratory data of 310 patients with CHC treated in the Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Belgrade, from January 1, 2008 to December 31, 2012. The mean age of the participants was 41.9 years (SD ±12.3), ranging from 18-65 years. The patients received combined antiviral therapy (pegilated IFN α2a plus RBV) for 24-48 weeks depending on virus Genotype (GT). Demographic and virologic data of the patients and pre-treatment and post-treatment of ALT values were analyzed in comparison with the virologic response. Only patients with elevated pre-treatment ALT values were included in this investigation.

The activity of ALT was determined by the spectrophotometric method routinely performed in the Centre for Medical Biochemistry, Clinical Centre of Serbia (Flex reagent cartridge, Siemens) in accordance with the manufacturer's instructions. The upper normal value for ALT was ≤40U/l. Percutaneous liver biopsy was undertaken in 294 patients to assess the extent of hepatocyte necrosis and the stage of fibrosis (using METAVIR system). Commercial enzyme immunoassay tests were used for the following analyses: detection of antibodies to Hepatitis C Virus (HCV), hepatitis B virus, and human immunodeficiency virus (Bio-Rad, Diagnosics lab, France), quantitative and qualitative load of viral RNA (COBAS® Amplicor hepatitis C virus test vs 2.0 and Amplicor HCV Monitor test, Roche Molecular Systems, Inc, Swiss) and viral genotype detection (Linear Array Hepatitis C virus genotyping tests, Roche Molecular Systems, Inc, Swiss).

Patients with co-infection with hepatitis B virus, human immune-deficiency virus, alcoholic liver disease, Wilson's disease, autoimmune hepatitis, severe cardiac diseases, thyroid dysfunction, non-regulated diabetes, etc. were excluded from the study.

The IBM SPSS software package version 17.0 (SPSS Inc, Chicago, IL, US) was used for statistical analyses of parametric and non-parametric variables. P values <0.05 and p<0.02 were considered significant for univariate and multivariate analyses, respectively with 95% Confidence Interval (CI).

Results

The majorities of patients were males (60%) and had viral GT1 (56.6%). Significantly fewer subjects (34.2%) had low level of HCV RNA (<800.000 IU/mL). Viral GT3 had 32.2% of patients, while GT2, GT4 and mixed genotypes were presented in 5.4%, 4.5% and 1.2% of patients, respectively. Liver cirrhosis occurred in a minority of patients (17.3%). The frequency of patients younger than 40 year was not significantly different from that of older patients.

Epidemiological investigation showed that routes of Hepatitis C Virus (HCV) transmission were as follows: transfusion of blood and blood products (31.3%), Intravenous Drug Use (IVDU) (23.2%), inoculation during medical interventions (11.6%), infection of health care workers (2.9%) and unknown (33.9%). A few patients had simultaneous different ways of infection.

All pre-treatment values of ALT were at the Upper Limit of Normal (ULN) with a Median 90; SE 5.073; range from 41 U/l -882 U/l. According to the clinical significance, ALT values were divided into three categories: >40 U/l- 2 x ULN; >2-5x ULN and >5x ULN). The relative numbers of patients categorized into these three groups are presented in Table 1. The majority of them (58.1%) had moderate elevated ALT values of >40 U/l- 2 x ULN.

The frequency of ALT normalization and successful virologic responses six months after treatment are presented in Figure 1. The majority of patients showed normalization of ALT values (219/310). Furthermore, most patients (225/310) with SVR had normal values of ALT.

A strong relation between BR and SVR was found (p<0.001, Fisher's Exact Test; r = 0.938, p< 0.001, Spearman Correlation Test). Further analysis using the binary logistic regression test revealed high

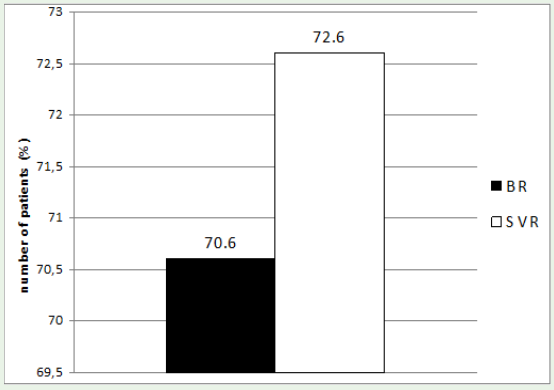

Figure 1: The prevalence of ALT normalization in comparison to successful virologic response after treatment of chronic hepatitis C patients.
BR: biochemical response six months after stopping treatment; SVR: sustained virologic response six months after stopping treatment.

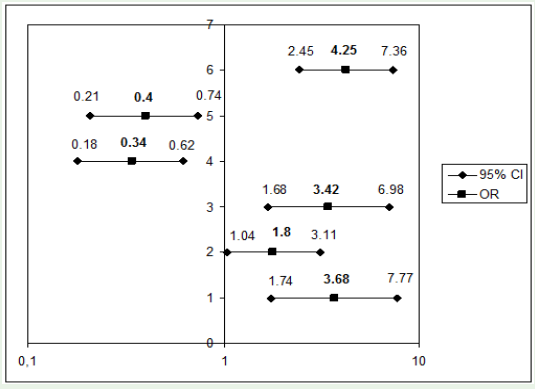

Figure 2: The prevalence of ALT normalization in comparison to successful virologic **response** after treatment of chronic hepatitis C patients.
Odd ratio (OR) for the following variables: 4.25: < 40 year; 3.68: low HCV RNA; 3.42: GT3; 1.8: IVDU; 0.4: cirrhosis; 0.34: GT1.

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significance for BR as the positive variable for SVR (p<0.001; OR = 2616.0; 317.05-21585.03).

Statistical significances concerning frequency of ALT normal values was noted for the following demographic and virologic variables: age <40 year, IVDU, cirrhosis, GT1, GT3, and low RNA (p<0.001, p<0.001, p=0.006, p=0.001, p<0.001 and p=0.036, respectively) (Fischer's Exact Test).

Normalization of ALT analyzed with the binary regression analysis is presented logarithmically in Figure 2. Age younger than 40, GT3, IVDU, and low viral load were independent positive variables (p<0.001, p=0.001, p=0.001 and p=0.034, respectively), while GT1 and liver cirrhosis (p=0.001 and p=0.004, respectively) were significant negative variables. The most significant variable in multivariate analysis was age younger than 40 (p<0.001; OR=3.026; 1.64-5.58).

A discrepancy between elevated post-treatment ALT values and SVR was noted in eight patients. Among the seven patients who did not attain a normal ALT value, two had liver cirrhosis and two had severe fibrosis. Six these patients were older than 40 years and four of them had GT1.

A SVR was achieved in 58.8% of patients with liver cirrhosis while BR had 54.9% of patients from the same group.

Elevated pre-therapy ALT values and normalization of ALT after therapy were not significantly related (p= 0.249, Mann-Whitney Test).

Discussion

In this prospective study of demographic and clinical data of patients with CHC who had undergone successful antiviral treatment were evaluated. As well, pre-treatment and post-treatment normalization of ALT values were assessed in relation to treatment response.

In general, the enzyme alanine aminotransferase occurs primarily in liver cells. Ordinarily, this soluble enzyme is present at low levels in sera when liver function is normal. Elevated ALT values are usually seen in parenchymal liver diseases characterized by destruction of hepatocytes. Generally, ALT activity is more specific for the liver than AST and its increased serum concentrations are rarely observed in conditions other than parenchymal liver disease [11-13].

In progressive chronic viral disease with lasting liver injury, ALT leaks from the liver causing persistently enhanced serum activity. Consequently, normalization of ALT after therapy generally serves as a leading biomarker for absence of hepatocellular injury. Therefore, it is regularly accepted that that elevation of ALT by at least 2 x UNL is mandatory for screening individuals for liver disease, particularly when other risk factors are present (alcohol consumption, IVDU, homosexuality, blood/blood derivates transfusion, maternal positivism, etc.) [14].

Our study showed strong association between normal ALT values and SVR (70.6% vs. 72.6%, respectively), which confirms similar results of other authors [15-17]. Moreover, a recent report from Korea showed that normalization of ALT was a useful response predictive factor for viral elimination not only for SVR but also for a Rapid Viral Response (RTR) after 4 weeks of treatment [18].

Furthermore, many authors found that nearly 20% of CHC patients with persistently normal ALT levels (measured three times in 6 months) usually present with minimal/mild fibrosis and stable disease [19-21]. This suggests that normalization of ALT simultaneously with post-therapy viral eradication yields a favorable prognosis with a low rate of liver disease progression in the future. Moreover, elevation of ALT in the late course of therapy with negative viral RNA was shown to be notably associated with viral relapse [22]. Thus, any increase of ALT during follow-up of successfully treated patients arouses suspicion of viral rebound, which has considerable importance in clinical practice.

In this investigation only 7/225 (3.1%) patients who achieved SVR remained with high ALT values. This rare occurrence might indicate the possibility of pre-existence of other liver diseases (autoimmune hepatitis, alcohol damage, etc). This option ought to be unlikely due to clinical and laboratory pre-treatment exclusion of nearly all other potential liver diseases. Related to this, it should be also taken into account that ALT levels can be influenced by different factors, such as gender, race, obesity, diet, etc. [12,13]. Moreover, clinicians are aware that liver cirrhosis per-se can cause hepatocyte necrosis even when etiological factors are already removed (e.g. viral elimination, alcohol abuse, etc) (two of our patients had cirrhosis and two patients had severe fibrosis). Therefore, although ALT is an imperative indicator for hepatic injury, its specificity and sensitivity is sometimes low in chronic liver disease.

It is also crucial to note that all seven patients with elevated of post-treatment ALT who achieved SVR in this study were older than 40 years. It is expected as the finding in this investigation establishes age less than 40 as the most critical positive predictor for a successful biochemical response [3,4]. The situation is similar with GT1 that was found in four of these patients.

In addition, this investigation also suggests that pre-treatment ALT levels do not influence the biochemical response related to normalization of ALT. Indeed, most authors agree that levels of ALT before treatment are not an important independent predictor for successful biochemical response [5,21,23-25].

Conclusion

This study confirms that successful antiviral treatment leads to normalizing of ALT activity in the majority of patients, which can be used as a positive "surrogate marker" for prediction of viral elimination. It also reflects diminishing liver necrosis as the most essential benefit of treatment for CHC. Among other characteristics of patients for this opportunity, younger age is the most important predictive factor.

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