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Serum autoantibody positivity and its impact on the treatment response of the genotype 1 chronic hepatitis C.

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Abstract

Background: Autoantibody positivity is a common finding in chronic hepatitis C infection. The data about the clinical and prognostic significance of the presence of these autoantibodies is still controversial. The aim of this study is to investigate the clinical significance of the presence of autoantibodies on the treatment response of the genotype 1 chronic hepatitis C.
Methods: The research relies on the data collected retrospectively through the outpatient clinic files and the hospital's automation system. A total of 249 Anti-HCV and HCV-RNA positive patients (91 male, 158 female) who were admitted to our outpatient clinic between the years 2010 and 2013, were included in this study. All of the patients in this study had conventional treatment for hepatitis C.
Results: A total of 85 patients (64.3%) were anti-nuclear antibody positive. Anti-smooth muscle antibody was detected in 15 patients (9.9%) whereas anti-liver kidney microsomal antibody and anti-microsomal antibody in 1 patient (0.6%). The sustained virological response rate was not statistically different among autoantibody positive and autoantibody negative patients (41% *vs.* 58%).
Conclusion: In conclusion, in this study, we did not detect a negative effect of autoantibody positivity on the sustained virological response obtained by conventional treatment of genotype 1 chronic hepatitis C.

Keywords: Hepatitis C, Antibodies, Antinuclear antibody (ANA), Sustained virological response.

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Introduction

Hepatitis C may be involved in the loss of tolerance to the self-antigens and may start the autoimmunity cascade which can be the cause of many different type of autoimmune diseases detected in chronic hepatitis C (CHC) [1]. Non organ specific autoantibody positivity is common in CHC. Autoantibody positivity is reported in 20-40% of Chronic Hepatitis C (CHC) patients. The most common autoantibody detected in CHC is SMA (anti-smooth muscle antibody). It was reported as high as 66% of the CHC patients. ANA (anti-nuclear antibody) positivity was reported up to in 41%. The least common type is LKM-1 (anti-liver kidney microsomal antibody) reported in 1-11% of CHC patients [2]. In Turkey more than 90% of CHC patients are genotype 1b [3]. The data about the effect of autoantibodies positivity on sustained virological response (SVR) rate in the genotype 1 patients is limited. In a study from Taiwan it was reported that the SVR was not different among ANA positive or ANA negative patients who have genotype 1. The percentage of genotype 1 patients was 36% in this study 4. In another study which reported the negative effect of autoantibody positivity on SVR, the data about the genotype 1 was given combined with genotype [4,5]. In one study it was reported that ANA positivity was more prevalent in genotype 1 patients, but in this study antibody positivity has had no effect on SVR rate [6]. Our aim in this study is to investigate the effect of autoantibody positivity on the sustained virological response rate in patients who had conventional therapy for chronic hepatitis C.

Material and Methods

We retrospectively reviewed the charts of CHC patients who were regularly coming to the outpatient clinic visits between the years 2010 to 2013. Disease duration, laboratory results, serological findings, abdominal imaging results and results of the autoimmune markers ANA (anti-nuclear antibody), AMA (anti-mitochondrial antibody), ASMA (anti-smooth muscle antibody), anti-LKM (anti-liver kidney microsomal antibody) were recorded from patient files or from the data automation system of our hospital. For autoantibody detection indirect immunofluorescence method was used. Among the patients with CHC, those who had chronic hepatitis B, metabolic liver disease or any autoimmune related disease (systemic lupus erythematosus, Sjogren's syndrome, Hashimato's thyroiditis, connective tissue diseases) were not included in the study. All patients who had medical treatment for hepatitis C in this study were treated with conventional treatment: Pegylated interferon

alpha or beta once a week plus ribavirin at standard doses. In patients who received treatment, those who had positive results for HCV-RNA at the end of the treatment, those who did not have a 100 fold decrease in HCV-RNA levels at the 3rd month of the treatment and those who did not have negative results for HCV-RNA at the 6th month were accepted as unresponsive, those who were still HCV-RNA negative at 6th months after the end of therapy were accepted to have sustained virological response. Detection of HCV-RNA positivity after the end of the treatment was accepted as relapse. The Mann-Whitney U test was used for comparison of the continuous data, Chi square test was used for qualitative variables.

Table 1. *Age and sex distribution of ANA-positive CHC patients.*

	ANA (+)		ANA (-)	
	N (%)	Mean age	N	Mean age
Female (n)	55 (61.7%)	62.9 ± 11.1	34	57.3 ± 12.4
Male (n)	30 (69.7%)	59.2 ± 9.4	13	51.7 ± 11.3
All group	85 (64.3%)	61.6 ± 10.6	47	56.7 ± 16.4

Results

A total of 165 patients were tested for autoimmune hepatitis markers (109 female, 55 male, mean age: 58.9 ± 12.6 years) among 249 chronic hepatitis C patients. Results of ANA test were available in 132 patients, 85 of these patients were ANA (+) (64.3%). One hundred fifty one patients were tested for ASMA, LKM and AMA, of which 15 were ASMA (+) (9.9%). Only one patient had AMA positivity, whom was also positive for LKM-1. Mean age of the patients who were positive for ANA was significantly higher than ANA (-) patients.

Table 2. *Comparison of autoantibody positive and negative groups for laboratory parameters in patients who had treatment.*

	Autoantibody positive group	Autoantibody negative group	P
Age	57.2 ± 9.4	53.9 ± 12.9	0.1
Sex (female/male)	33/20	34/14	0.4
Genotype 1 (%)	92.40%	93.70%	0.7
RNA levels	2.600.000 ± 3.800.000	1.700.000 ± 3.400.000	0.2
AST	59.3 ± 42.6	57.6 ± 46.5	0.8
ALT	74.8 ± 52.6	66.4 ± 49.8	0.4
Total Bilirubin	0.8 ± 0.4	0.7 ± 0.4	0.5
Albumin	4 ± 0.4	4 ± 0.4	0.8
INR	1.1 ± 0.1	1 ± 0.1	0.1

Mean age in ANA (+) female patients was higher than ANA (-) female patients, whereas there was no age difference between ANA (+) and ANA (-) male patients. Frequency of ANA positivity was not different among male and female as shown in Table 1. We calculated international autoimmune hepatitis score retrospectively, none of the 85 ANA positive patients had a moderate or high risk score for autoimmune hepatitis, the score range was between 2 to 8 points [7]. One hundred and one patients have received conventional treatment regime for chronic hepatitis C. Mean age of the treated patients was 55.6 ± 11.3 years. There was no difference in viral load and laboratory parameters among antibody positive and negative patients groups as shown in Table 2.

Effect of autoantibody positivity on treatment response

Autoantibody positivity was significantly more frequent in the relapser group compared to the sustained virological response group. There was no difference between autoantibody positive and negative groups regarding unresponsiveness. The results are summarized in Table 3.

Table 3. *Autoantibody positivity and response rate.*

	Autoantibody positive	Autoantibody negative	P
Sustained Virological Response (SVR)	22 (41%)	28 (58%)	0.11
Relapse	15 (28%)	6 (12.5%)	0.041
Unresponsiveness	16 (30%)	14 (29%)	0.42
SVR+Relapse	37 (69%)	34 (70%)	0.53

Table 4. *Treatment response in genotype 1 patients who received INF +RBV treatment.*

	Autoantibodies positive	Autoantibodies negative	P
Sustained virological response (SVR)	18 (43%)	23 (56%)	0.4
Relapse versus SVR	12 (29%)	6 (14%)	0.091
Unresponsiveness	11 (26%)	12 (29%)	0.42

Subgroup examinations in patients who received treatment

They were 14 patients who had chronic renal failure requiring dialysis. These patients received only peglayted interferon alpha 2A without ribavirin. Among patients who received treatment, those who were other than genotype 1 and those who had renal failure were excluded in order to obtain a group of patients who had conventional therapy for genotype 1. According to the analysis with this new group, response rates in autoantibody positive patients were similar with autoantibody negative patients summarized in Table 4.

Discussion

Autoantibody positivity is a common finding in CHC patients. Studies from different countries have reported the rate of the antibody positivity in CHC patients in a large range: ANA and ASMA positivity were reported as 3.6-54% and 4.3-78% respectively [1]. If a CHC patient who has autoantibody positivity has also a high IgG level, autoimmune liver disease should be ruled out. For the clinician the possible association of CHC and autoimmune hepatitis may become a real challenge since even with liver biopsy there are no clear cut rules to differentiate these two entities [8]. The clinician should decide whether immunosuppressive or antiviral therapy is more accurate on a case-based strategy. In our study none of the patients who had autoantibody positivity had a high serum IgG titer, and moreover none of them had a high autoimmune hepatitis score either. It is debatable to investigate autoantibody routinely in CHC. Actually in the real life experience, we see that the patients have already autoantibodies results at the time of their admission to our clinic. Should we change our practice according to a positive autoantibody test result in a chronic hepatitis C patient? It was reported that autoantibody positivity has a negative impact on SVR rate [4,5,9,10]. On the other hand some researchers did not found a negative effect of the autoantibody positivity on the SVR rate [6,11,12]. In our study we did not detect an association between autoantibody positivity and the response rate of the conventional chronic hepatitis C treatment. Although recurrence rate was higher in autoantibody positive group, when we excluded the patients who have another genotype than genotype 1 and the patients who did not receive ribavirin the difference was not significant anymore. As a result we think that the presence of autoantibodies should not change our treatment decision in CHC and it is not necessary to test autoantibodies routinely in CHC patients. There are some weak points in our study that we should mention: This is a retrospective study, so there are missing data, we have the result of autoantibodies in 66% of CHC patients. We have no data about the change of autoantibodies positivity rate during or after the end of the treatment. The power is not sufficient to prove or disprove a relation between treatment response and autoantibodies positivity. These results are reliable only for genotype 1 CHC patients. Lastly the authors are aware that the interferon based therapy for hepatitis C is completely abandoned in some countries. But due to financial and health insurance related problems interferon based treatment is still an option in some parts of the world as it is in our country.

In conclusion in this study we did not find a difference at the sustained virological response rate among the genotype 1 CHC patients who had autoantibody positivity compared to those who didn't have antibody positivity.

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