

## ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Autoimmune thyroid diseases in patients with chronic hepatitis C treated by pegylated interferon-alpha and ribavirin – A prospective study

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## SUMMARY

**Introduction/Objective** Despite sufficiently explained pathogenesis, today autoimmune thyroid diseases (AITD) are recognized as one of extra-hepatic manifestations of systemic hepatitis C virus infection. The aim of the present study was to determine clinical characteristics and to estimate the success of pegylated interferon- $\alpha$ 2a plus ribavirin (pegIFN- $\alpha$ 2a + RBV) therapy in patients with AITD as an extra-hepatic manifestation of chronic hepatitis C infection (CHC).

**Methods** This prospective study included 91 CHC patients treated with pegIFN- $\alpha$ 2a + RBV from 2010 to 2012 (39 women and 52 men, mean age  $41.6 \pm 11.9$ ). The study group (group A) consisted of 31 patients with CHC and AITD. Control group (group B) consisted of 60 patients with CHC without AITD. We analyzed clinical, biochemical, virological, and histopathological markers of CHC, as well as response and side effects of pegIFN- $\alpha$ 2a + RBV therapy.

**Results** There was a statistically significant difference in sex ( $p = 0.011$ ), age ( $p = 0.001$ ), AST level ( $p = 0.013$ ), level of gamma globulins ( $p < 0.001$ ), level of IgM ( $p = 0.007$ ), IgG ( $p < 0.001$ ), in the success of therapy of CHC with pegIFN- $\alpha$ 2a + RBV between the groups. Odds ratio (OR) for unfavorable outcome in group A was 4.200 [95% confidence interval (CI): 1.545–11.417]. In final multivariate logistic regression analysis in group A, the only factor predicting sustained virological response was patients' age (OR = 0.781; 95% CI: 0.603–0.959). The main side effects in group A were interferon induced thyroiditis (IIT) (41.9% vs. 3.3%;  $p < 0.001$ ) and anemia, which was the only reason for dose reduction of ribavirin (29% vs. 6.7%;  $p = 0.027$ ).

**Conclusion** Patients with AITD as an extra-hepatic manifestation of CHC achieve poorer virological response and their antiviral therapy is inevitably followed by a manifestation of adverse effects, predominantly solvable IITs and anemia.

**Keywords:** chronic hepatitis C; autoimmune thyroid diseases; pegylated interferon alfa; ribavirin

## INTRODUCTION

Autoimmune thyroid diseases (AITD) are the most common group of autoimmune diseases, appearing in 5–10% of the world's population [1]. Besides genetic and exogenous factors as iodine, AITD can appear as 'collateral damage' of the immune system's struggle aimed at eradicating an infective agent [2, 3]. Hepatitis C virus (HCV) infection was one of the first infective diseases to be associated with AITD [4]. Despite sufficiently explained pathophysiological mechanisms, today AITD are recognized as one of extra-hepatic manifestation of systemic HCV infection [5, 6]. It is certain that during chronic hepatitis C (CHC), a thyroid infection develops, followed by a release of pro-inflammatory cytokines (IL-8) and chemokines (CXCL10) which regulate the synthesis of IFN- $\gamma$  and TNF- $\alpha$  activation [6]. Activation of this Th1 immunological response can cause HCV antibodies thanks

to common amino acid sequences with thyroid antibodies (the theory of antigenic mimicry), HCV binding through E2 glycoprotein for the CD81 receptors on thyrocytes' surface, which can be followed by active replication in thyrocytes (the activation theory) or HCV binding by non-structural proteins HCV NS3/4A on TCL3 on thyrocytes [6–9].

Thyroid disorders within CHC are presented in different modalities: more common are higher values of anti-TPO antibodies and anti-TG titres in serum of 15–42% and primary hypothyroidism in 4.5–13%, while prevalence of primary hyperthyreosis and malignant thyroid diseases are significantly lower [5].

The aim of this research was to determine clinical characteristics of CHC and to estimate the success of pegylated interferon- $\alpha$ 2a plus ribavirin (pegIFN- $\alpha$ 2a + RBV) therapy in patients with AITD as extra-hepatic manifestation of CHC.

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## METHODS

This prospective study included 91 CHC patients treated with pegIFN- $\alpha$ 2a + RBV, at the Clinical Centre of Vojvodina, Novi Sad, Serbia, from 2010 to 2012. We treated 39 women and 52 men, with the mean age of 41.6 (SD  $\pm$  11.9). Patients with HCV infection genotype 1 and 4 were treated for 48 weeks with pegIFN- $\alpha$ 2a 1800 $\mu$ g s.c. weekly + RBV 800–1200 mg (depending on the body weight) daily. Patients with HCV infection genotype 2 or 3 were treated for 24 weeks – the same regime of pegIFN $\alpha$ 2a + RBV 800 mg daily.

Estimation of CHC severity was done on the basis of complete blood count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, histopathological examination of liver biopsy specimens, HCV genotype and quantitative PCR HCV RNA test. Detection of viral particles and HCV genotype were done by the reverse transcriptase-polymerase chain reaction (RT-PCR) method, highly sensitive and specific commercial tests (Roche Diagnostics systems, Basel, Switzerland): Amplicor HCV test whose analytic sensitivity is from  $1 \times 10^2$  to  $10^3$  copies/ml and Monitor HCV version 2.0 with analytic sensitivity from  $5 \times 10^3$  to  $1 \times 10^4$  copies/ml. In order to estimate thyroid gland function, the levels of anti-thyroglobulin (anti-TG Ab), anti-thyroid peroxidase antibodies (anti-TPO Ab), serum-free tetra- and free tri-iodothyronine (fT4 and fT3) and thyroid stimulating hormone (TSH) were obtained prior to therapy (chemiluminescent microparticle immunoassay). In order to estimate presence of parameters of the B cells activation, the levels of rheumatoid factors (RF), immunoglobulins M, G, A (IgM, IgG, IgA), gamma globulins, and autoantibodies [antinuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (ASM), anti-cardiac (ACA), and anti-parietal antibody (APA)], were determined by commercial tests.

Patients were divided into two groups, according to the presence or absence of thyroid function disorders prior to introduction of antiviral therapy. Group A comprised patients with thyroid function disorders, included 31 patients, 19 (38.7%) females and 12 (61.3%) males, mean age 45.39 (SD  $\pm$  11.91); group B comprised patients without thyroid function disorders and without any extra-hepatic manifestations of CHC, included 60 patients, 20 (33.3%) females and 40 (66.6%) males, mean age 37.38 (SD  $\pm$  10.52).

Complete blood count and ALT activity assessment were performed every month during the therapy. Anti-TG Ab, anti-TPO Ab, fT4, fT3, and TSH assessment were done every three months during the therapy and six months after its discontinuation. Quantitative PCR HCV RNA test was done six months after the therapy, with the same diagnostic system.

Data analysis was done in SPSS for Windows, Version 10.0 (SPSS Inc., Chicago, IL USA). Among descriptive statistical methods measures of central tendency (mean, x-bar), standard deviation (SD), and measures of variability, absolute and relative frequency were done. Fore date analysis, parametric (Student's t-test) and nonparametric tests (Mann-Whitney U-test, Kruskal-Wallis H-test,  $\chi^2$  test, and multivariate logistic regression analysis) were performed. Multivariate analysis included the implementation of a binary logistic regression model, where we used the ratio

of chances (odds ratio) with 95% confidence interval (CI), as well as the sensitivity and specificity of the model, for the interpretation of the results. The selected chosen levels of significance were the following: statistically significant  $p < 0.01$ , and  $p > 0.05$  without statistical significance.

## RESULTS

In group A, anti-TG and/or anti-TPO positivity without clinically overt thyroid gland disorder was found in 20/31 (64.5%) patients, autoimmune hypothyroidism in 7/31 (22.6%) and autoimmune hyperthyroidism in 4/31 (12.9%) patients. There were seven patients with autoimmune thyroiditis treated with levothyroxine replacement therapy prior to combined antiviral therapy initiation. Four patients with autoimmune hyperthyroidism were receiving methimazole thyrosuppressive therapy. These patients were euthyroid before the initiation of pegIFN- $\alpha$ 2a + RBV therapy. In this group, the presence of other autoantibodies was estimated in 4/31 (12.9%) patients, three patients were ANA positive, and one patient was AMA positive.

The two groups of patients were compared by demographic, biochemical, virological and histological parameters (Table 1). There was statistically significant difference in sex ( $p = 0.011$ ), age ( $p = 0.001$ ), AST level

**Table 1.** Clinical characteristics of chronic hepatitis C patients studied

Variable	Patients with AITD	Patients without AITD	p
Age	45.39 $\pm$ 11.91	37.38 $\pm$ 10.52	0.001
Sex			0.011
Male	12/31 (38.7%)	40/60 (66.7%)	
Female	19/31 (61.3%)	20/60 (33.3%)	
ALT IU/l	89 (62–149)	80 (60–126.7)	0.530
AST IU/l	81 (47–105)	48 (38.2–80.7)	0.013
Gamma GT IU/l	45 (31–106)	44.5 (29–82)	0.857
ALP IU/l	76 (56–102)	75.5 (54.5–93)	0.706
TBIL mmol/l	10 (8–14)	11 (8–15)	0.802
RF IU/l	9.42	6.37	0.255
C3 g/l	1.11	1.21	0.147
C4 g/l	0.21	0.25	0.059
Gamma glob g/l	17.44	12.92	< 0.001
IgM g/l	1.77	1.49	0.007
IgG g/l	15.56	11.42	< 0.001
IgA g/l	2.26	2.03	0.667
Fibrosis			0.174
No	3 (10.3)	11 (18.6)	
Mild	19 (65.5)	42 (71.2)	
severe or cirrhosis	7 (24.1)	6 (10.2)	
VL			0.727
< 400,000 IU/ml	12/31 (38.7%)	21/60 (35%)	
> 400,000 IU/ml	19/31 (61.3%)	39/60 (65.0%)	
Genotype			0.071
1	71.2%	58.4%	
Non 1	29%	41.6%	

ALT – alanine aminotransferase; AST – aspartate aminotransferase; Gamma GT – gamma glutamyl transferase; ALP – alkaline phosphatase; TBIL – total bilirubin; RF – rheumatoid factor; IgM – immunoglobulin M; IgG – immunoglobulin G; IgA – immunoglobulin A; AITD – autoimmune thyroid diseases

**Table 2.** Outcome of treated HCV patients

Variable	Patients with AITD n = 29 (%)	Patients without AITD n = 55 (%)	p
SVR	15 (51.7%)	45 (81.8%)	0.011
NR	9 (31.0%)	8 (14.5%)	
Relapse	5 (17.2%)	2 (3.7%)	

SVR – sustained virological response; NRT – null-responders; AITD – autoimmune thyroid diseases

**Table 3.** Clinical modalities of side effects of combined antiviral therapy in patients involved in the research

Side effects of combined antiviral therapy	Patients with AITD n = 29 (%)		Patients without AITD n = 55 (%)	
	Cytopenias	13	41.9	19
Psychiatric	1	3.2	7	11.7
Pulmonary	0	/	1	1.7
GIT	0	/	1	1.7
AIIT	13	41.9	2	3.3
AIH	0	/	1	1.7
RA	0	/	1	1.7
SLE	0	/	1	1.7
Vasculitis	0	/	0	0.0
Alopecia	1	3.2	1	1.7
Allergies	1	3.2	5	8.3

GIT – gastrointestinal tract; AIIT – autoimmune interferon induced thyroiditis; AIH – autoimmune hepatitis; RA – rheumatoid arthritis; SLE – systemic lupus erythematosus

( $p = 0.013$ ), level of gamma globulins ( $p < 0.001$ ), level of IgM ( $p = 0.007$ ) and IgG ( $p < 0.001$ ) (Table 1). The rate of sustained virological response (SVR) was statistically significantly lower in group A (51.7% vs. 81.8%;  $p = 0.011$ ) (Table 2). The odds ratio (OR) for unfavorable outcome in group A was 4.200 (OR = 4.200, 95% CI: 1.545–11.417). According to the model of multivariate logistic regression in the AITD patient group with CHC (dependent variable includes SVR, while independent variables include sex, age, genotype, fibrosis, anti-TPO, gamma globulin, IgG, RF, and anti-TPO below 5.6 IU/ml (negative) six months after the discontinuation of treatment), a patient's age stands out as the only significant variable in the model (OR = 0.600, 95% CI: 0.394–0.913). With the age increase of five years, the SVR chances decrease by 40%.

Incidence of side effects of pegIFN- $\alpha$ 2a + RBV was not statistically significantly higher in group A (64.5% vs. 53.3%;  $p = 0.104$ ) (Table 3). In group A, antiviral therapy had to be discontinued due to interferon adverse events in 2/31 (6.4%) patients (pegIFN- $\alpha$ 2a allergic reaction, agranulocytosis). In group B, therapy was discontinued in 5/60 (8.4%) patients on the following grounds: acute psychosis (two patients), rheumatoid arthritis (one patient), systemic lupus (one patient), and autoimmune hepatitis (one patient). Incidence of interferon induced thyroiditis (IIT) was statistically significantly higher in group A (41.9% vs. 3.3%;  $p < 0.001$ ). All patients developed autoimmune IIT (defined by rise of the anti-TPO/anti-TG levels and thyroid decompensation), recognized in the 12th week of therapy. In group A, among 13 patients who developed AIIT, in 2/13 (15.4%) patients the treatment of hypothyroidism repealed six months after the completion of antiviral therapy. In group B, 2/55 (3.3%)

patients developed AIIT, but there was no remission of the thyroid diseases after the pegIFN- $\alpha$ 2a + RBV cessation.

In both groups of patients, neutropenia and thrombocytopenia were the only reason for dose reduction of pegIFN- $\alpha$ 2a ( $p = 0.924$ ). Anemia was the reason for dose reduction of ribavirin statistically significantly more often in group A (29% vs. 6.7%;  $p = 0.027$ ).

## DISCUSSION

Even AITD are today recognized as extra-hepatic manifestation of CHC, there are still controversies about of their influence on the course and, in particular on the outcome of the pegIFN- $\alpha$ 2a + RBV therapy of CHC [5].

Since the generation of autoantibodies is a consequence of specific and persistent immune response in the course of HCV infection [8], statistically significant older CHC patients with AITD (group A) are expected ( $p = 0.001$ ). The higher incidence of women in group A ( $p = 0.011$ ) is certainly explicable by a more potent immune response caused by estrogen [10]. However, recent literature identifies *TLR7* gene on the X chromosome, responsible for *TLR7* receptor expression on B lymphocytes [11]. Binding of RNA components (RNA HCV for example) to these receptors leads to the production of IFN- $\alpha$  and IFN- $\lambda$  in B lymphocytes, and subsequent activation of the immune system [12]. It is clear that women are susceptible to excessive *TRL7* expression, hyperstimulation of B lymphocytes, and, thus, the production of autoantibodies [11, 12]. Although the more potent immune response in women (Th2 cytokine profile with production of IL10, presence of *TLR7* receptors on B lymphocytes) results in a higher level of spontaneous elimination of HCV after an acute infection, in case of already established persistent HCV infection, it presents a predisposition for triggering autoimmunity [13].

Even though we are aware of the two-way interaction between the liver and the thyroid gland, the issues of causal relationship between AITD and clinical course of CHC still remains unresolved [14]. As well as other authors, we have determined no statistically significant difference between the examined groups either based on biochemical CHC parameters (ALT  $p = 0.530$ ) or histological CHC indicators (liver activity  $p = 0.154$  and fibrosis  $p = 0.174$ , according to the METAVIR score). These data support the idea that the appearance of antithyroid antibodies is a consequence of an independent, active inflammatory process taking place in the thyroid gland during an HCV infection, rather than a passage of antigenic stimuli, from the liver tissue through porto-systemic anastomoses, which is possible only when there is severe liver fibrosis [4, 5, 15]. Statistically significantly higher AST activity ( $p = 0.013$ ) in group A can be a consequence of damage to the liver parenchyma in the form of cholestasis, ischemic hepatitis and steatohepatitis, as well as myopathy within the manifested AITD [14], present in 41.9% of patients involved in the research.

According to the findings of Hsieh et al. [7], the induction of AITD is a result of a simultaneous presence of several genotypes, which differ in their antigenic determinants

continually stimulating immune response. Genotypes 1 and 4 are dominant in both studied groups ( $p = 0.071$ ), as a consequence of the epidemiological profile of HCV infection in Serbia [16]. There have been no mixed genotypes determined in any of the 91 CHC patients included in our research, which can be a result of methodology used for the HCV genotype determination.

AITD often appear together with other autoimmune phenomena and diseases, for example the presence of non-organ specific antibodies (NOSA), systemic lupus erythematosus (SLE), Sjögren's syndrome, rheumatoid arthritis [17]. In 12.9% of the patients, our research has determined a simultaneous presence of NOSA in three patients, ANA on Hep2 cells and AMA in one patient. Presence of anti-thyroid antibodies is just one of the consequences of polyclonal proliferation of B lymphocytes within CHC, so finding other autoantibodies is expected [18]. However, since we determined no statistically significantly higher values of RF in group A, as the most important marker of polyclonal proliferation of B lymphocytes ( $p = 0.255$ ) [19], nor a higher incidence of the complement components consumption (C3  $p = 0.147$ ; C4  $p = 0.059$ ), our research is more supportive of the theory that AITD are isolated, organ-specific autoimmune processes within CHC. Higher incidence of hypergammaglobulinemia ( $p < 0.001$ ), dominant due to higher IgG fraction ( $p < 0.001$ ) in group A, can be explained by excessive stimulation of thyrocytes by TSH, especially in patients in the hypothyroid state [20]. Hashimoto's thyroiditis within IgG4-related sclerotic disease is a much-discussed topic today [21]. So far it has been established that this clinical entity is triggered by an infection in predisposed persons, and that the pathogenic mechanism is similar to HCV induced AITD. Our results were obtained on a sample too small to allow explaining higher IgG values, but they give grounds for further investigation.

Our results are contradictory to the attitude of the professional public that AITD presence within CHC does not decrease the success of IFN-based antiviral therapy [4, 7, 22, 23]. In our research, patients with CHC and AITD have over four times higher chances for unfavorable outcome of antiviral therapy (OR 4.200; 95% CI 1.545–11.417). According to the model of multivariate logistic regression, this result is primarily a consequence of the older age of patients in this group. With an increase of patients age by 5 years, the chances for achieving SVR decrease by 40% (OR = 0.600, 95% CI: 0.394-0.913), while the group of AITD patients is on average eight years older in comparison to the control group of patients.

Although the research has determined no statistically significant difference in the incidence of treatment side effects ( $p = 0.104$ ), patients with AITD within CHC should remain marked as a group 'difficult to treat' because of the possibility of the development of IFN-induced thyroiditis, primarily AIIT, which was registered in 41.9% of patients in group A. According to Tran et al. [24], AIIT manifestation is a predictive factor of a favorable outcome of antiviral therapy, where the thyroid lesion is a consequence of effectiveness and efficiency of the immune system triggered

by IFN during HCV elimination. On the other hand, it is known that the presence of thyroid hormone increases the effect of IFN, probably by changing the expression of the MHC class II epitopes. Sudden exposure to higher concentrations of thyroid hormones, which happens within AIIT, may contribute to the immune-modulatory effect of IFN, and subsequently achieving SVR [25]. AIIT can be marked both as a mediator and as a consequence of achieving SVR. However, by the model of multivariate logistic regression in group A, the AIIT induction has not been marked as a variable significant for achieving SVR. It must be noted that in our research, there were no instances of IIT being the reason for discontinuing the IFN therapy. It is estimated that in 40–50% of patients with AIIT there will be a complete remission of thyroid diseases after the withdrawal of IFN, as a result of the disappearance of pharmacological effects of IFN [26]. In our study of 13 patients who developed AIIT, in only two patients (15.4%) the treatment of hypothyroidism repeated six months after the completion of antiviral therapy.

The patients in group A were at a higher risk of developing cytopenias ( $p = 0.001$ ). Although not indicated as a relevant therapy outcome predictor, it is possible that the unfavorable therapy outcome was influenced by the reduction of cumulative ribavirin dose ( $p = 0.027$ ) [27]. What remains inconclusive is whether CHC patients with AITD could make yet another group for which the administration of erythropoietin would be cost/benefit justified [28].

## CONCLUSION

Based on our results, patients with CHC and AITD are a group difficult to treat using the IFN-based therapy. They achieve poorer SVR, and their antiviral therapy is inevitably followed by a manifestation of undesirable effects (94.4%). New "IFN-free" therapy protocols with direct active antiviral drugs would be certainly more appropriate and cost/benefit justified for this group of patients.

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## NOTE

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## Аутоимунска болест штитасте жлезде код оболелих од хроничног хепатитиса Ц лечених пегилованим интерфероном алфа и рибавирином – проспективна студија

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### САЖЕТАК

**Увод/Циљ** Упркос недовољно разјашњеном патофизиолошком механизму развоја, данас је аутоимунска болест штитасте жлезде препозната као једна од екстрахепатичних манифестација хроничне ХЦВ инфекције.

Циљ студије је да се утврде клиничке карактеристике и да се процени успех терапије пегилованим интерфероном - $\alpha$ 2а и рибавирином (*pegIFN- $\alpha$ 2a* + РБВ) код оболелих од хроничног хепатитиса Ц (ХХЦ) са аутоимунском болешћу штитњаче, као њеном екстрахепатичном манифестацијом.

**Методe** Проспективна студија је обухватила 91 оболелог од ХХЦ леченог *IFN- $\alpha$ 2a* + РБВ од 2010. до 2012. (39 жена и 52 мушкараца, просечне старости  $41,6 \pm 11,9$ ). Испитивану групу (групу А) чинило је 31 оболелих од ЦХЦ и АИТД. Контролну групу (групу Б) чинило је 60 оболелих од ХХЦ без АИТД. Анализирани су клинички, биохемијски, вирусолошки и хистопатолошки маркери ЦХЦ, одговор и појава нежељених дејстава на терапију *pegIFN- $\alpha$ 2a* + РБВ.

**Резултати** Између посматраних група болесника утврђена је статистички значајна разлика у полној дистрибуцији

( $p = 0,011$ ), старости ( $p = 0,001$ ), нивоу АСТ ( $p = 0,013$ ), гама глобулина ( $p < 0,001$ ), *IgM* ( $p = 0,007$ ), *IgG* ( $p < 0,001$ ), као и успеху терапије *pegIFN- $\alpha$ 2a* + РБВ. *Odds ratio* за неповољан исход терапије у групи А је био 4,2 ( $OR = 4,200$  (95% *CI*: 1,545–11,417)). Мултиваријантном анализом логистичке регресије предикторни фактор успостављања СВР у групи А је старост болесника ( $OR = 0,781$ ; 95% *CI*: 0,603–0,959). Најчешћи нежељени ефекат терапије у групи А је био интерфероном индукован тиреоидитис (*IIT*) (41,9% *vs.* 3,3%;  $p < 0,001$ ) и анемија, која је уједно била и једини разлог за редукцију дозе рибавирина (29% *vs.* 6,7%;  $p = 0,027$ ).

**Закључак** Оболели од ХХЦ и АИТД као екстрахепатичном манифестацијом постижу слабији вирусолошки одговор на терапију *pegIFN- $\alpha$ 2a* + РБВ, која је и неизоставно праћена манифестацијом нежељених ефеката, на првом месту *IIT* и анемијом.

**Кључне речи:** хронични хепатитис Ц; аутоимунска болест штитњаче; пегиловани интерферон алфа; рибавирин