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CORRELATION BETWEEN BIOCHEMICAL AND HISTOPATHOLOGICAL PARAMETERS IN PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH PEGYLATED INTERFERON AND RIBAVIRIN

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SUMMARY

Aim: *The main goal of this study was to compare the biochemical and histopathological findings in patients with sustained virological response (SVR) before and two years after the therapy with pegylated interferon α-2a and ribavirin in chronic hepatitis C.*

Subjects and methods: *The study was conducted at the Department of Internal Medicine and the Clinic for Infectious Diseases of the Clinical Hospital Mostar. The study included 48 patients whose treatment for chronic hepatitis C with pegylated interferon α-2a and ribavirin was finished two years prior to the achieved SVR at the end of the treatment. The main criterion for inclusion was a negative result of HCV RNA, determined by the RealTime HCV assay. After taking a history, physical examination, laboratory tests: AST, ALT, GGT, a liver biopsy were performed with the help of the ultrasound. The assessment of necroinflamatory score was determined by histologic activity index (HAI) score, and the stage of fibrosis according to Knodell's numerical score.*

Results: *The values of AST and ALT levels were statistically significantly decreased after the successful treatment ($p<0.001$), as well as the value of HAI score ($p=0.001$) and the stage of fibrosis ($p=0.010$), in contrast to GGT ($p=0.054$). For the components of HAI score like focal necrosis (0.001) and portal inflammation (0.042) the result showed that they were significantly higher before the therapy, which was not true for the piecemeal ($p=0.054$) and confluated necrosis ($p=0.078$). The improvement of HAI score after therapy was found in 36 patients (75.0%), and 27 patients (56.2%) showed an improvement in the degree of fibrosis with the most common improvement of 1 degree (85.7%). One third of patients (31.3%) had the same result in the degree of fibrosis before and after the therapy. Before the treatment, a positive correlation was observed between ALT ($p=0.039$) and AST ($p=0.04$) with HAI, AST and the stage of fibrosis ($p=0.04$). In contrast, after the treatment the only correlation was observed between AST and the stage of fibrosis ($p=0.042$).*

Conclusion: *Virological and biochemical responses in patients with SVR may not reflect the histopathological effects of the treatment and therefore these patients should be monitored for the possible development of the liver cirrhosis and hepatocellular carcinoma.*

Key words: *hepatitis C - pegylated interferon – ribavirin - hepatic fibrosis - hepatocellular carcinoma*

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INTRODUCTION

Despite the fact that hepatitis C, one of the most common chronic liver diseases, causing long-term consequences in the form of liver cirrhosis, hepatocellular carcinoma (HCC) development and premature death is widespread in the world nowadays. Scientific literature gives little information on the long-term outcomes of the patients after completion of the therapy. Patients with HCV infection should be given continuous clinical, biochemical, virological and histological monitoring during and after the therapy (Manns et al. 2001, George et al. 2009). The biochemical response (ALT normalization) is followed by the virological response with a tolerance of a few weeks. Since nowadays hepatitis C is being diagnosed in earlier stages, and the effects of therapy in achieving SVR are getting better, pathohistological improvements have been recorded after the therapy in both, the necroinflammation activity and the stadium of fibrosis.

In the course of the last ten years great progress has been achieved in understanding of the cellular and molecular mechanisms of the liver fibrosis. It has been found that the formation of the scar tissue in the liver fibrosis is neither a static nor a simplex event. The recently increasing clinical and scientific data prove that both liver fibrosis as well as cirrhosis can not be described as incurable liver diseases. The application of antiviral therapy in hepatitis prevents the progression of the disease and leads to the regression of the fibrosis. However, there are grey areas in the field of the individual progress of fibrosis and the regression of fibrosis in each patient (Wright 2002). Pathohistological improvements after administering various therapies were reported, but the best results have been recorded with the pegylated interferon and ribavirin (ref). However, studies monitoring the effects of pegylated interferon are rare.

Given that the histological improvement occurs slowly, it is recommended that the control biopsy should be done in approximately two or three years after the completion of the treatment which would better estimate the histological progress (Shiratori et al. 2005). It is not known whether there is, or what is the discre-

pancy between the liver damage proved by pathohistological findings and the biochemical parameters in patients with chronic hepatitis C two years after the completion of the therapy with the pegylated interferon and ribavirin, with negative values of HCV RNA at the end of the treatment. Therefore, the main aim of this study was to compare the biochemical and pathohistological findings in patients with chronic hepatitis C patients before and two years after the successfully completed treatment with pegylated interferon and ribavirin.

SUBJECTS AND METHODS

The study included 48 HCV RNA negative patients, two years after the completion of the therapy for chronic hepatitis C (CHC) with pegylated interferon α-2a and ribavirin. Patients were treated in Clinical Hospital Mostar from January 1, 2005 to December 31, 2008. There were 39 males (81.3%) and 9 women (18.7%). The average age of the monitored patients was 36. The length of the treatment, which involved only therapy-naïve patients, depended on the genotype of the virus. Pegylated interferon α-2a (Pegasys®) was administered in a dose of 180 μg, and was applied subcutaneously once a week. Ribavirin (Copegus®) pills were administered in a daily dose of 15 mg /kg for the genotypes 1 and 4, and 800 mg per day for the genotypes 2 and 3. Patients with viral genotypes 1 and 4 were treated for 48 weeks, while the genotype 2 and 3 patients were treated for 24 weeks. Three viral genotypes were recorded in patients who participated in the study: 1,3 and 4, among them the genotype 3, found in 27 (56.3%) patients being the most common, which proved statistically relevant. The basic criterion for the inclusion of patients in this study was a negative finding of HCV RNA two years after the successful therapy. The study included patients of both sexes, aged over 18.

The exclusion criteria for the participation in the study were: a positive finding of HCV RNA two years after the completion of the therapy, a simultaneous presence of HBV DNA virus or HIV, active addiction to alcohol and drugs, nonalcoholic steatohepatitis, autoimmune hepatitis, alcoholic liver disease, uncompensated liver cirrhosis, hemochromatosis, Wilson's disease, patients with cancer and those who used immunosuppressive therapy, including corticosteroids.

All subjects have confirmed their participation in the study by signing an informed consent. The examination was conducted in accordance with the ethical principles and the principles of the Declaration of Helsinki as well as according to the Guidelines of good clinical practice (World Medical Organization 1996). After the diagnosis of chronic hepatitis C was confirmed, which included a qualitative and quantitative assessment of the HCV RNA by polymerase chain reaction PCR HCV RNA (IU/ml) (Ghany et al. 1994) patients' biochemical findings of AST, ALT, GGT were assessed and liver biopsy was done in order to assess the necro-inflammatory response (HAI index) and the stage of fibrosis (Desmet et al. 1994, Ishak et al. 1995). After the diagnosis, patients were treated with pegylated interferon α-2a and ribavirin whereas the length of the treatment was dependent on the viral genotype.

RESULTS

The values of AST and ALT were significantly higher at the first examination in relation to control examination. Median values of AST at the first examination was 40, and at the control examination it was 21 ($p<0.001$). At the first examination the median ALT was 61.5, while in the control one it was 21.5 ($p<0.001$). In contrast, median GGT was 29 at the first examination, and 25.5 at the control examination ($p=0.054$).

There were no statistically significant differences in AST and ALT values between male and female patients at the first and at the control examination.

In contrast to these findings, GGT in men was significantly higher than in females, both in the first and in the control examination, although both values were within the reference interval.

By comparing the pathohistological findings of the liver biopsy at the first and the control examination the values of HAI index and the degree of fibrosis were significantly higher at the first examination. Looking at individual values of the HAI index, the values of C (focal necrosis) and D (portal inflammation) were statistically higher at the first examination than at the control examination. The values of A (piecemeal necrosis) and B (bridging necrosis) were not significantly different (Table 1).

Two years after the completion of the therapy, patients were divided into three groups depending on the pathohistological findings: a) improvement, b) deterioration c) without changes in pathohistological findings. Comparing the initial and control pathohistological findings of the liver, expressed in the HAI index and the degree of fibrosis, we found the following: a) the group with the improvement of pathohistological findings, 36 or 75% of patients according to HAI index, and 27 or 56.2% of the patients according to the degree of fibrosis, b) the group with the deterioration of the pathohistological findings, 10 or 20.8% of the patients according to HAI index, and six or 12.5% according to the degree of fibrosis c) the group with unchanged pathohistological findings 2 or 4.2% according to the HAI index, and 15 or 31.3% according to the degree of fibrosis. It should be mentioned that the control values of liver enzymes in all patients were in the normal range (Table 2, Table 3).

Table 1. Pathohistological findings at the first and the control examination

Features	C (Q) values		Mann – Whitney U	p
	first examination	control examination		
HAI	6.0 (4)	4.0 (4)	706.500	0.001
A	2.0 (2)	1.0 (2)	896.000	0.054
B	0.1 (2)	0.1 (1)	942.500	0.078
C	2.0 (1)	1.0 (1)	708.000	0.001
D	2.0 (1)	2.0 (1)	888.500	0.042
The degree of fibrosis	2.7 (2)	1.9 (2)	811.500	0.010*

C (Q): median (interquartile range); HAI: histological activity index; A: piecemeal necrosis; B: bridging necrosis; C: focal necrosis; D: portal inflammation

Table 2. Pathohistological findings expressed through HAI index and the stage of fibrosis

Features	Number of patients			χ^2 test	p
	improvement	without change	deterioration		
HAI	36	2	10	39.500	<0.001
The degree of fibrosis	27	15	6	13.875	0.001*

*χ= chi-square test; HAI-histological activity indeks

Table 3. Values of the liver enzymes compared to pathohistological findings of the liver after the treatment of patients with CHC

Laboratory findings	C (Q) values according to change of the HAI system			Kruskal-Wallis	p
	without change	improvement	deterioration		
AST	22.5 (0)	22.0 (11)	19.5 (5)	1.003	0.606
ALT	29.0 (0)	22.5 (23)	20.0 (11)	0.523	0.770
GGT	33.5 (0)	26.5 (21)	18.0 (19)	3.585	0.167*

*C (Q): median (interquartile range); AST-aspartate aminotransferase; ALT alanine aminotransferase; GGT gamma-glutamyl transferase

There were no significant differences in liver enzyme values and pathohistological findings according to the HAI system.

Analyzing the individual biochemical parameters and their mutual correlation with pathohistological findings at the first examination, a significant positive correlation between the values of AST with the HAI (p=0.04) and with the degree of fibrosis (p=0.04) was found. By analyzing the individual parameters of pathohistological findings the positive correlation between AST (p=0.01), A (p=0.01) and D (p=0.05) was found, while the other values of B and C were not statistically significant (B p=0.205; C p=0.624).

During the control examination, looking at the correlation of AST with pathohistological findings of the liver, a statistically significant positive correlation with the degree of fibrosis (p=0.046) was recorded, while no positive correlation was found for the HAI value (p=0.398), not even for the individual HAI values (A p=0.158; B p=0.512; C p=0.334; D p=0.517).

At the first examination a statistically significant positive correlation between ALT and HAI (p=0.039) was found, whereas it was not found for the degree of fibrosis (p=0.266). Analyzing the individual components of the HAI index, a statistically significant positive correlation was found between ALT and A (p=0.026), while no statistically positive correlation was found for the other variables B, C and D. During the control examination, there was no significant positive correlation between ALT and HAI (p=0.066), nor between the ALT and the degree of fibrosis (p=0.068). The only statistically significant positive correlation was found for the values of A (p=0.026).

For the GGT values, during both the first and the control examination no significant positive correlation with the HAI index and its individual variables, nor with the degree of fibrosis was found.

Two years after the successfully completed therapy for chronic hepatitis C with pegylated interferon α-2a and ribavirin, all negative HCV and RNA patients were checked for biochemical values of AST, ALT and GGT and the liver biopsy was repeated in order to make a quantitative assessment of the degree of inflammation and the stage of fibrosis.

DISCUSSION

The study included 48 successfully cured CHC patients who remained continuously HCV RNA negative for two years after having been treated with pegylated interferon α 2a and ribavirin.

Monitoring the cured patients with SVR for two years from the completion of the therapy, we noticed that 100% of patients remained HCV PCR negative. There is little information in the literature indicating the outcome of the patients with SVR, although this problem has been recently actualised and research on this field has started (McHutchison et al. 2001). The studies observing the patients through four years have shown that SVRwas viable in 99-100% of the patients (Giannini et al. 2010, Swain et al. 2003). However, there are also studies that show a higher proportion of late return of the virus (about 4%), especially in previously treated patients (Maylin et al. 2009, Ciancio et al. 2006, Castillo et al. 2009).

Increased levels of serum aminotransferases indicate liver damage and are of great importance for confirmation of liver disease, including hepatitis. The high concentration of the ALT enzym is the most specific indicator of liver damage. Statistically relevant and significant for our research were lowered levels of AST and ALT two years after the successfully completed treatment, whereas the GGT levels did not vary significantly. It has been proved that hepatocyte necrosis is not necessary for the release of serum aminotransferases and that the correlation between the levels of liver aminotransferases and the degree of the damage to hepatocytes is weak (Sánchez Tapias 2009). While some studies show normal histological findings in patients with normal ALT levels (Piton et al. 1998), other studies showed that the viraemia in patients with normal ALT levels is associated with liver damage (Brillanti et al. 1993, Stanley et al. 1996, Nutt et al. 2000, Inglesby et al. 1999).

By observing the biochemical outcomes we noticed that most patients with SVR normalized the values of biochemical parameters unless some other liver disease or or a relapse (EASL Clinical Practice Guidelines 2011, McHutchison 2004), were present which our research confirmed.

Comparing histopathological findings before and two years after the completion of the therapy in SVR patients, the significant improvement in histopathological findings expressed in both the HAI index and the degree of fibrosis was found. Improvements expressed in the HAI index were recorded in 75% of patients ($p<0.001$), and the degree of fibrosis was improved in 56% of patients ($p=0.001$).

Marcellin and his associates in France (Marcellin et al. 1997, Rumi et al. 2002, Wiley et al. 2002) were the first to publish that SVR records in patients not only reduced the risk of worsening liver fibrosis, cirrhosis and hepatocellular carcinoma, but even histological improvements, reduction of inflammation and an improvement in the degree of fibrosis were present.

During the four years of their follow-up 93% of patients continued to have normal ALT values/levels, while 96% of patients had undetectable HCV RNA values.

Comparing the histological findings before the therapy with those made up to 6 years after the completed therapy, improvement in 94% of patients was proved.

Some studies have shown that pegylated interferon reduces inflammation and fibrosis in patients with SVR, and even in those who have recorded relapse, but not in the nonresponders (Veldt et al. 2007, Maruoka et al. 2012, Cammà et al. 2004, Ghany et al. 2003).

The interconnection between the progression of liver fibrosis and the necroinflammatory stage is controversial, since it has been found that there is no or very little correlation between the necroinflammatory activity and the stage of fibrosis. Most studies whose aim was to monitor the patients after ETR have recorded a faster and better improvement in the inflammatory index in relation to the stage of liver fibrosis (Zeuzem et al. 2011, Poynard et al. 2002, Tsubota et al. 2007, Camma et al. 1998, Veldt et al. 2004, Saracco et al. 1993). This is explained by the fact that the necroinflammatory activity is a dynamic process fluctuating over time, which shows the severity of necrosis and inflammation at a given time. So far the relationship between ALT and histological findings in patients with CHC has been the subject of controversy.

Some studies indicate that there is no statistically significant difference in histological findings between patients with normal and those with elevated ALT levels (Morgan et al. 2010), what was confirmed in our research. On the other hand, there are studies which showed that patients with chronic hepatitis C and normal ALT levels/values had a significantly lower rate of proliferation of hepatocytes and showed a tendency toward a lower rate of apoptosis compared to the patients with the elevated ALT levels.

Bonis and associates conducted a meta-analysis in order to monitor the correlation between the biochemical response to interferon α and the histological improvement in hepatitis C, and found that the histological improvement, in the strict sense of its meaning, ocurred in 28% of patients after the treatment with interferon. Sensitivity and specificity of ALT levels to determine the histological changes were 70% and 66%. Even 17% of the patients with pathologic ALT recorded histological improvement by the end of the interferon therapy However, Bonis proved that ALT does not always reflect the accurate pathohistological picture/ state of the liver after the treatment with interferon alfa and may underestimate the histological improvement (Bonis et al. 1997).

Although chronic hepatitis is a diffuse liver disease, fibrosis itself is not homogeneous throughout the liver, and a tissue sample taken by biopsy may not be representative for assessing the degree of fibrosis, which

represents a limitation of our study/research. Therefore, the puncture site in the control biopsy was the same as in the previous one. In the pointing system to assess the degree and stage of the disease visual assessment of pathologists was used, which is not entirely objective. Also, the rating scale is not an adequate indicator, because fibrosis can not progress linearly as a scoring system, eg progression from stage 1 to stage 2 may be far more important and requires a longer period of progression from system 3 to 4, or vice versa. The research results would be more representative with a larger number of subjects.

CONCLUSION

Results from our study showed that, despite the fact that usual levels of liver enzymes tend to normalize by the end of the therapy and during the follow-up monitoring of the SVR patients , pathohistological outcome does not fully correlate with reduction in concentration of liver enzymes. Considering that pathological deterioration, development of liver cirrhosis and HCC can be found in patients with SVR, it is important to identify the factors affecting this processes, in order to have the proper evaluation of disease progress and its prevention.

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Conflict of interest : None to declare.

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