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Experience of Using Metformin in Patients Infected with HCV Genotype 3 with Concomitant Metabolic Disorders

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Abstract

Summary: The so-called "metabolic syndrome" is among the most significant factors that influence the natural course of Chronic Hepatitis C (CHC) and the effectiveness of specific Antiviral Therapy (AVT).

Materials and methods: 34 patients with chronic hepatitis C (genotype 3) treated with standard AVT (PEGylated interferon in combination with ribavirin) were included in the study. The study group included 18 patients with chronic hepatitis C in combination with metabolic disorders, namely the Insulin Resistance (IR). They received metformin 20 mg/kg for 24 weeks. The control group included 16 patients with chronic hepatitis C and IR, who did not receive metformin. The patients' age (35.7 ± 1.5) and sex prevalence were matched in both groups. The diagnosis criteria of CHC included: clinical and laboratory signs of the disease, the presence of RNA HCV determined by PCR, with a specific genotype 3. The presence of IR was assessed by HOMA-index (HOMA-IR), fasting insulin levels (IU/ml) × fasting glucose (mmol/L)/22.5. IR was diagnosed in case of HOMA index>2.

Conclusion: IR frequently follows the course of CHC in patients with or without metabolic syndrome. Metformin administration leads to weight loss in overweight patients with chronic hepatitis C, reduces the severity of metabolic disorders, such as IR, in these patients, resulting in increased frequency of achieving rapid and early virological responce and biochemical remission. The administration of metformin had a positive effect on liver steatosis, resulting in a decrease of its severity according to ultrasonography.

Keywords: Chronic hepatitis C; Insulin resistance; Liver cirrhosis; Hepatic steatosis

Introduction

Chronic Hepatitis C (CHC) was and still is one of the greatest problems in infectology. Medical and social significance of hepatitis C is determined by its wide spread, progressive increase of new incidence, diversity of clinical manifestations and high probability of developing chronic liver disease and extrahepatic lesions. According to expert estimates, 1 billion people worldwide are infected with hepatitis C and the number of patients with chronic hepatitis C is about 200 million. At this stage, we are experiencing a pandemic of hepatitis C, which is almost 5 times higher than the prevalence of HIV infection [1,2].

According to modern ideas, there are number of factors that may influence the natural course of CHC and the effectiveness of specific Antiviral Therapy (AVT), such as coinfection with other hepatotropic viruses, various toxic factors, so-called "patient factors", which include: age, sex, race, genetic features, as well as viral factors, such as its genotype and viral load. However, despite the large number of studies on the problem of chronic hepatitis C, the mechanisms of disease progression are not fully understood particularly in case of various comorbidities [3].

A lot of studies are now focusing on the factors that may affect not only the natural course of chronic hepatitis C, but also contribute to the progression of the disease to liver cirrhosis and reduce the effectiveness of specific antiviral therapy, reducing the frequency of achieving Sustained Virological Response (SVR).

The so-called "metabolic syndrome" is among the most significant factors that attract the attention of the world's medical community over the past 20 years. In 1980, M. Henefeld and W. Leonhardt M. suggested the term "metabolic syndrome", which included such symptoms as abdominal obesity, hyperinsulinemia, glucose intolerance, low level of cholesterol of low density lipoproteins and Arterial Hypertension (AH). This syndrome was caused by presence of Insulin Resistance (IR) with compensatory hyperinsulinemia [4].

According to WHO, obesity has an epidemic spread now and is found in about 30% of the population of the European Region. IR is defined as a state characterized by the need for higher insulin concentrations than the norm for the implementation of its biological effects, or as a condition in which the normal insulin content does not provide its metabolic function [5,6].

IR in patients with CHC has its own features not only because its considered to be a central pathogenetic part of Metabolic Syndrome (MS), but because it is assumed that HCV-infection itself can lead to the development of IR. The cause - effect relationship between HCV-infection and IR indicates the fact that the incidence of IR in patients with chronic hepatitis C ranges from 30% to 70%, while the overall distribution of IR is only 10-25% of the population [6,7].

Widely recognized and leading mechanism of IR is an imbalance of adypocytokins with present abdominal obesity which is known as the so-called metabolic insulin resistance. However, in patients with chronic hepatitis C it was shown that there is direct and indirect (via proinflammatory cytokines) inhibitory effect of HCV (mostly in case of genotype 1) on the insulin cascade leading to the development of "viral" insulin resistance [6]. Such IR in combination with insulin resistance associated with metabolic syndrome can accelerate the progression of disorders of carbohydrate metabolism until the development of type II

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diabetes. Moreover, some researchers consider IR and diabetes type 2 to be extrahepatic manifestations of chronic hepatitis C [8,9].

There were developed many methods to determine the level of insulin but most experts use a quantitative description of the degree of severity of IR which is HOMA-index (HOMA-Homeostatic Model Assessment), proposed by Matthews D.R. et al in 1985. It takes into account the concentration of glucose and insulin on an empty stomach. HOMA index is calculated by the formula: fasting serum insulin × fasting serum glucose/22.5. In healthy persons HOMA index is less than 2.7 [10].

In 2003, the American Association of Clinical Endocrinology added Hepatic Steatosis (HS) to metabolic syndrome as a manifestation of Nonalcoholic Fatty Liver Disease (NAFLD). HS in patients with chronic hepatitis C is detected in approximately 50% of those who is infected [11]. Previously, it was assumed that the presence of hepatic steatosis causes hepatic injury only in a rather small percentage of individuals in the absence of other concomitant liver disease. In fact, only in 2% of the total population presence of hepatic steatosis leads to the formation of clinically significant liver disease (nonalcoholic steatohepatitis) which is accompanied by the elevated levels of aminotransferase level and progression to fibrosis/cirrhosis (10-20% according to different authors).

Its presence is necessary to consider as a co-factor that is able to influence the course and progression of liver disease as well as therapeutic prospects of management such patients [12,13]. It should be noted that patients with chronic hepatitis C may have two main forms of HS: virus-induced and metabolic. Metabolic steatosis may be determined in case of all genotypes of the virus and often occurs in the presence of known risk factors of NAFLD such as obesity, hyperlipidemia, glucose intolerance. Development of metabolic steatosis is not directly associated with HCV-infection, but the presence of liver disease may be associated with accelerated progression of fibrosis [14].

The second form of steatosis in patients with chronic hepatitis C may occur as a result of direct exposure to the virus and more frequently observed in patients with genotype 3 [14,15]. This type of hepatic steatosis also leads to more rapid disease progression.

Association between HCV infection, hepatic steatosis and IR, as components of metabolic syndrome, and their impact both individually and in combination on the progression of fibrosis/cirrhosis and effectiveness of treatment indicates the need for its detection and correction [6,12,16].

Metformin is most widely used among the drugs for the correction of IR [17]. A number of works by both foreign and local researchers has shown that long-term use of metformin in dosage of 1000 mg/per day for at least for 3 months in patients with metabolic syndrome without diabetes reduces body weight, waist size, normalize lipid profile and decreases insulin levels [17,18]. However, metformin only partially reduces IR, acting mainly on reducing processes of gluconeogenesis and glycogenolysis in the liver with no significant effect on IR caused by changes in muscle and fatty tissues. Given that CHC is closely linked to IR, development of hepatic steatosis and increased risk of type 2 diabetes as a result of both metabolic disorders and virus-induced factors that may cause the self-development of hepatic steatosis and IR, the use of these drugs is of particular interest in patients with CHC.

The aim of our work is to assess and evaluate the effectiveness of impact of metformin on the dynamics of IR and HS severity and to analyze their correlation with Rapid Virological Response (RVR) and Early Virological Response (EVR) in patients with CHC.

Materials and Methods

34 patients with chronic hepatitis C (genotype 3) treated with standard AVT (PEGylated interferon in combination with ribavirin) were included in the study. All patients were divided into two groups. The main group included 18 patients with chronic hepatitis C in combination with metabolic disorders, namely the IR. They received metformin 20mg/kg for 24 weeks. The control group included 16 patients with chronic hepatitis C and IR, who did not receive metformin. The patients' age (35.7 ± 1.5) and sex prevalence were matched in both groups. The diagnosis criteria of CHC included: clinical and laboratory signs of the disease, the presence of RNA HCV determined by PCR, with a specific genotype 3. The presence of IR was assessed by HOMA-index (HOMA-IR), fasting insulin levels (IU/ml) × fasting glucose (mmol/L)/22.5. IR was diagnosed in case of HOMA index>2. Body Mass Index (BMI) was calculated as a ratio of body weight to height (kg/m^2). BMI>25 kg/m^2 is considered high, and BMI>30 kg/m^2, is considered as obesity. Also, all patients have undergone the ultrasonographic diagnostics, during which the presence of HS was evaluated.

The main ultrasonographic signs of HS are: increased echogenicity of the liver parenchyma, sound conduction abnormality that manifests with the phenomenon of ultrasound distal attenuation and reduce of visualization of intrahepatic vessels' walls. Mild, moderate and severe HS are distinguished according to those features. Stage of liver fibrosis was determined by ultrasound diagnostics using 3D + PD mode (Patent of Ukraine # 32 829 from 19.03.2008) [19]. Biochemical and virological criteria of treatment efficacy were determined. Biochemical criteria included normalization or reduction of ALT and AST activity in biochemical blood tests. Virological criteria included the rapid virological responsev - the absence of RNA HCV after 4 weeks of AVT and the early virological response - the absence of RNA HCV after 12 weeks of therapy. All the mentioned tests were performed before the start of treatment and on the 4th and 12th weeks of it.

Summarizing all the above inclusion criteria were as follows: age of the patients from 18-65 years, confirmed chronic HCV-infection, genotype 3, the presence of concomitant insulin resistance, steatohepatitis. Exclusion criteria were coinfection with other viruses (HIV, hepatitis B, D), alcohol abuse, intravenous drug use.

For statistical treatment Microsoft Excel and package Statistica were used. Interval indicators presented as "mean ± standard error". Test for normality of distribution was evaluated using Shapiro-Wilkie criterion. Fisher's criterion and minimum mean square error were used to estimate the data.

Results and discussion

At the start of AVT the average transaminase activity were: ALT-127.9 ± 16.4 U/l and AST-101.3 ± 10.7 U/l in the study group and ALT-154.2 ± 19.7 U/l, AST-87.7 ± 8.7 U/l in the control group. HOMA-IR was higher than 2.7 in all patients, that confirmed the presence of IR. BMI was increased (>25 kg/m^2) in 12 patients (66.6%) of the study group and in 10 patients (62.5%) of the control group. As it can be seen, not all patients with increased BMI developed IR. It is explained by many researchers that HCV is "metabolic" virus and can induce the development of IR at normal or even low body weight. HS of different severity was diagnosed in almost all patients, both study and control groups, in 16 (88.8%) patients and in 13 (81.5%) patients, respectively. 5 (27.7%) patients of the study group were diagnosed with mild HS, 9 (50%) - with moderate HS, and 4 (22.2%) patients - with severe HS. Almost the same distribution was in the control group: moderate HS

was defined in 9 patients (56.2%), mild HS was diagnosed in 5 (31.3%) patients, and severe HS - in 2 (12.5%). It was also found that the majority of patients in both groups developed liver fibrosis at the stages F2-3 (in 10 (55.5%) patients of the study group and in 8 (50%) of the control group). Stages F0-1of liver fibrosis was diagnosed in 7 (38.8%) patients of the study group and in 6 patients (37.5%) of the control group. Liver fibrosis stage F4 was found in 1 (5.6%) patient of the study group and in 2 (12.5%) patients of the control group.

After 4 weeks of treatment the normalization ALT (27.4 ± 1.8 U/l) and AST (25.7 ± 1.6 U/l) activity was found in 17 (94.4%) patients of the study group, even in patients with severe HS and liver fibrosis F 3-4, in contrast to the patients of the control group. Only 1.5-2 times decrease of transaminases' activity (ALT-79.4 ± 10.2 U/l, AST-47.5 ± 4.0 U/l) was found in 9 (56.3%) patients of the control group with moderate/severe fibrosis and HS, despite administration of standard specific AVT ($p<0.05$). Moreover, in 10 (83.3%) patients of the study group with high BMI (>25 kg/m^2) a reduction or normalization of BMI (≤25 kg/m^2) was observed. In the control group decrease in the IR was noted, but it was not as significant as one in the study group, where only 5 (31.3%) patients did not show the presence of IR after 4 weeks of the treatment. According to the literature data, standart AVT itself is an example of association between HCV and IR development. Insulin sensitivity can significantly improve in patients who achieved RNA HCV clearance, unlike patients with persistent viral replication. Even if BMI decreases during specific AVT, insulin sensitivity doesn't change in this group of patients.

After analyzing the dynamics of viral load, it was found that RVR was observed in 12 (66.6%) patients of the main group and in 7 (43.8%) patients of the control group. Patients who remained IR, HS and liver fibrosis F3-4 haven't reached RVR. The resulting Figures 1 and 2 show the negative impact of IR, HS and liver cirrhosis in RVR frequency that corresponds with the data of world literature.

After 4 weeks of treatment no significant dynamics in HS and liver fibrosis was found.

After 12 weeks of treatment all the 18 (100%) patients of the study group reached biochemical response (ALT-24.4 ± 1.8 U/L, AST-24.2 ± 1.8 U/l, $p<0.05$). But in the control group biochemical response was achieved only in 11 (68.8%) patients with the average activity of ALT and AST-39.8 ± 5.2 U/l and 35.1 ± 4.3 U/l, correspondingly. In 17 (94.4%) patients of the study group HOMA-index decreased to ≤2, compared with patients in the control group where IR wasn't determined in 10 (62.5%) patients after 12 weeks of treatment ($p<0.05$). In 5 (41.7%) patients of the study group BMI normalization was observed, in other 7 (58.3%) patients of the study group BMI decreased more than 2.5 times. Only 3 (30%) patients of the control group had normalization of BMI (≤25 kg/m^2), and 5 (50%) patients with a BMI

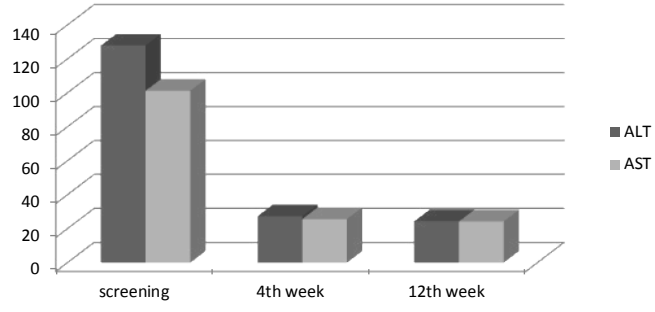

Figure 1: ALT and AST dynamics in patients who received AVT with metformin.

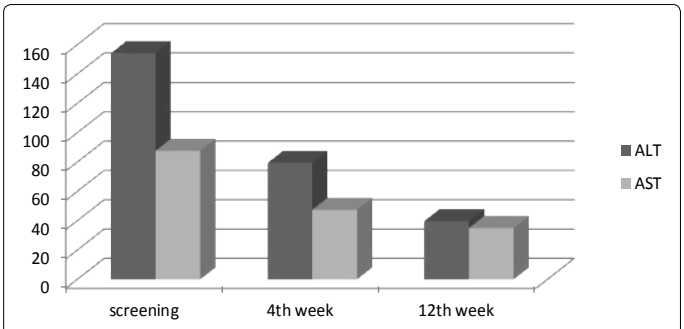

Figure 2: ALT and AST dynamics in patients who received AVT without metformin.

decreased in 2 times. The BMI of the rest of the patients didn't change. EVR was achieved by all the patients of the study group, but only by 13 (81.5%) patients of the control group.

Conclusions

IR follows the course of CHC frequently in patients with or without metabolic syndrome and its main component, such as obesity, confirming the link between HCV-infection and the development of glucose intolerance. The results suggest that HCV is a "metabolic" virus that is able to induce the development of IR in patients with normal or even decreased body weight. Moreover, metformin administration leads to weight loss in overweight patients with chronic hepatitis C, reduces the severity of metabolic disorders, such as IR, in these patients, resulting in increased frequency of achieving RVR, EVR and biochemical remission. The administration of metformin had a positive effect on HS, resulting in a decrease of its severity according to the ultrasonography. Summarizing all the above, it may be said that metformin was effective as an additional component of AVT in patients with chronic hepatitis C (3 genotype) and IR, significantly improving its efficiency, that also corresponds with other researchers' data.

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