Research Article

Improvement of the Effectiveness of Antiviral Treatment of Patients with Chronic Hepatitis C and Concomitant Diabetes Mellitus Type II using Alpha-Lipoic Acid and Lactulose

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Abstract

Imbalance of pro-inflammatory and anti-inflammatory cytokines was detected in 104 examined patients with chronic hepatitis C. These changes were the most significant in patients with concomitant diabetes mellitus (DM) type II. Achievement of sustained viral response (SVR) under the influence of antiviral therapy depends on the state of cytokines system. This was evidenced by the detected correlation relationship between the levels of viral load (VL) in patients with concomitant diabetes mellitus type II, namely, direct weak one between IL-4 and VL (r = 0.21) and reverse weak one between the level of IL-2 and VL (r = -0.04). Virus elimination rate and frequency influenced by anti-viral therapy (AVT) depends on the balance of pro-inflammatory and anti-inflammatory cytokines. This was shown in the research by detection of direct medium correlation relationship between VL and IL-4 (r= 0.31) and reverse medium correlation relationship between VL and IL-2 (r= -0.45).

Keywords

chronic hepatitis C; viral load; cytokines; diabetes mellitus

Problem statement and analysis of the recent research

Chronic hepatitis C (CHC) currently remains an extremely important medical and social problem of modern medicine [1, 14, 15]. The peculiarity of the problem is certainly the fact that HCV infection lasts without significant clinical symptoms for a long time causing its late diagnosis in 75-85% of cases at the stage of already developed chronic form with further rapid progression to hepatic cirrhosis (HC) and hepatocellular carcinoma (HCC) [13, 14].

In the 90s of the last century the study of factors influencing the course and efficacy of antiviral therapy (AVT) detected that carbohydrate metabolism disorders such as DM type II, hyperglycemia in the fasted state, impaired glucose tolerance and insulin resistance (IR) disorder were often observed in patients with chronic hepatitis C [1, 5]. Currently, world literary sources provide sufficient data indicating the correlated impact of HCV infection and carbohydrate metabolism disorders [2, 11, 12]. Many studies have found that viral hepatitis C (VHC) is a “metabolic” virus able to induce IR development (especially genotype 1) in case of normal and even underweight body mass regardless of the presence of metabolic factors. The presence of hepatic steatosis regardless of its form (induces, metabolic or combined virus) IR, and diabetes mellitus (DM) type II in this group of patients worsens the prognosis regarding fibrosis progression rate in CHC [1, 2, 3] and are the markers of CHC specific therapy ineffectiveness according to EASL data. Experimental study of foreign scientists [21] has also demonstrated that hyperinsulinemia itself leads to increased replication of HCV in vitro [8, 11, 21].

Peculiarities of CHC course depend on immunopathological reactions [4, 6, 9]. However, unfortunately the immune system in the majority of patients with CHC is unable to eliminate the virus allowing it to replicate in hepatocytes for a long time [7, 20]. In recent years, the immune response as effector phase of immune reactions has been proven to be regulated by soluble mediators, namelt cytokines. Cytokines coordinate important processes in the liver such as hepatocyte growth and regeneration, inflammatory processes, the development of fibrosis and cirrhosis [6, 13, 18]. The majority of domestic and foreign authors studying basic pathogenic mechanisms of disorders in CHC have noted with significant difference the decrease in the concentration of pro-inflammatory cytokines in contrast to their increase in case of normal functioning of the immune system and simultaneous increase in the content of anti-inflammatory cytokines. High level of IL-4 in case of decrease in IL-2 level in blood serum was studied to be asso-
associated with long-term persistence of HCV in the body, high activity of infectious process [9, 10]. In addition, according to many researchers’ data the crucial role in the pathogenesis of many structural and functional disorders in patients with DM (hepatopathy, insulin resistance, vessel wall disorders) belongs to cytokine system imbalance [16].

Thus, we consider the determination of the prevalence of immune response type with the production of certain cytokines to be the basis not only for more accurate understanding of the pathological process and CHC prognosis but also for the effectiveness of treatment [17, 19]. Currently, the need to develop “maintenance” therapy when conducting specific AVT which would provide sustained viral response through the correction of the main pathogenetic changes (namely, cytokine system) is an important therapeutic issue regarding CHC for many foreign researchers.

The objective of the research was to study the impact of alpha-lipoic acid and lactulose on the effectiveness of antiviral therapy in patients with CHC and concomitant diabetes mellitus type II.

1. Methods

104 patients with CHC were examined. The course of the disease associated with diabetes mellitus type II was observed in 84 patients. 20 patients with CHC without comorbidities constituted the experimental group. 84 patients with combined pathology underwent the specific combined antiviral therapy with pegylated interferon alpha-2b and alpha-2a in combination with ribavirin according to international recommendations for the treatment of chronic hepatitis C EASL (2006, 2009, 2012, 2013) and “Chronic Hepatitis C” (2014), unified clinical protocols of primary, secondary (specialized) care for adults and children. Treatment duration constituted 48 weeks according to international recommendations as the study included patients with genotype 1b. The dose of pegylated interferon alpha-2b was determined in an amount of 1.5 µg/kg once per week. Ribavirin dose required for combination therapy with pegylated interferon alpha-2b was calculated according to patient body weight. In combination with antiviral therapy (AVT) the patients were prescribed alpha-lipoic acid in a dose of 300 mg/day intravenously by drop infusion per 200.0 ml of 0.9% sodium chloride solution for 10 days with subsequent transition to oral administration of the medication in a dose of 1 capsule (300 mg) in the morning for 60 days. Taking into account the impact of intestinal dysbacteriosis on the severity of major clinical symptoms the intensity of the imbalance of lipid peroxidation / antioxidant defense systems and cytokines, we used lactulose in the treatment regimen in a dose of 6.66 g once daily in the morning for two months.

Patients with CHC and concomitant DM type II were divided into 4 groups depending on the treatment. 20 patients (Group I) received only AVT. 21 patients (Group II) received alpha lipoic acid (ALA) in addition to AVT. 23 patients (Group III) received lactulose in addition to AVT. 20 patients (Group IV) received ALA and lactulose according to the proposed regimen along with AVT. The control group consisted of 20 apparently healthy individuals.

Monitoring of AVT effectiveness and safety was conducted on the basis of international recommendations on the management of patients with CHC undergoing standard AVT (EASL 2006, 2012-2014) on the 4th week of treatment (rapid viral response – RVR), after 12th week (early virological response – EVR), 24th week after the therapy completion (sustained viral response – SVR).

Along with the assessment of viral response, the assessment of biochemical responses achievement was conducted according to EASL (2006, 2012-2014) recommendations. Efficacy of the treatment was assessed according to the dynamics of viral load reduction during the treatment and 24 weeks after the treatment.

The main role in the pathogenesis of disorders and development of complications and extrahepatic manifestations, virus elimination and the disease progression in HCV infection is known to belong to the balance of the cytokine system. The importance of studying this mechanism of changes is caused also by the fact that DM type II, hepatopathy and multisystemic changes in this pathological condition are also based on IL system disorder. Therefore, the levels of IL-2 and IL-4 were determined in all patients in 2 weeks, 6 and 12 months of treatment in addition to general clinical methods of examination.

Titers of cytokines were determined by ELISA test on the analyzer “Stat Fax 303 Plus” (USA) using standard reagents kit “Vektor Best” (Russia) in the Central laboratory for HIV infection, toxoplasmosis, venereal diseases and viral hepatitis diagnostics at the Regional Center of HIV Infection Prevention and AIDS Control at Regional Clinical Infectious Hospital in Ivano-Frankivsk.

All patients were included into the research after signing an informed consent.

Statistical processing of the research results was conducted on a PC using a standard package Statistica 5. Mean values (M), mean error (m), significance of differences according to Student’s t-test were assessed. Pearson correlation coefficient was used to assess interrelation between the studied characteristics.

2. Results and Discussion

According to the results of the conducted research, the level of IL-4 was increased in all groups of patients before the treatment in comparison with that in healthy individuals (p<0.001).

The level of pro-inflammatory cytokine IL-2 in serum was significantly lower (by 3.2 times on average) in patients with CHC and concomitant DM type II compared to the control group (p<0.001) (Fig. 1). Comparison of IL-2 indices in patients with CHC and concomitant DM type II and in patients with CHC without comorbidity detected that IL-2 level in the main group was 1.2 times lower than in the comparison group (3.85±0.37 pg/ml and 3.12±0.15 pg/ml (p<0.01) (Fig. 1).
Improvement of the Effectiveness of Antiviral Treatment of Patients with Chronic Hepatitis C and Concomitant Diabetes Mellitus Type II using Alpha-Lipoic Acid and Lactulose — 3/4

Reverse weak correlation relationship between the levels of IL-2 and IL-4 ($r=-0.23$) was also observed in the main group.

Thus, the presence of concomitant DM type II in patients with CHC affects the provision of cellular response to the presence of HCV infection, therefore contributing to the disease progression.

Clear direct weak correlation relationship between the level of viral load in patients with concomitant DM type II and IL-4 ($r=0.21$) and reverse weak correlation relationship between the level of IL-2 and VL ($r=-0.04$) was established in the course of the research. That is, the process activity, pathogen elimination and the effectiveness of AVT depend on interleukins system balance, especially in case of combined pathology which enhances the inhibition of cell protection system.

The frequency of virologic response achievement by patients with CHC and concomitant DM type II depending on the treatment regimen is shown in Figure 2.

RVR was achieved with almost the same frequency in all studied groups. Negative result of PCR RNA VHC was recorded in 10 patients of Group I (50.00±10.95%), 12 patients of Group II (57.14±10.80%), 10 patients of Group III (43.48±10.34%), 14 patients of Group IV (70.00±10.25%) in 4 weeks of the treatment. RVR in the patients of group IV occurred with the same frequency as in patients with CHC without comorbidities ($p>0.05$), which was not observed in the other groups. RVR was recorded in 45% of patients of group I, 47.62% of patients of group II, 39.13% of patients of group III and in 50% of patients of group IV with no significant difference between groups.

SVR was achieved in 8 patients (40.00%) who were prescribed ALA and lactulose in addition to AVT which was 2 times higher in comparison with group I (40.00±4.47% versus 20.00±8.94%), 2.09 times higher than in group II (40.00±4.47% versus 19.05±8.22%), 2.2 times higher in comparison with group III (40.00±4.47% versus 18.18±8.57%) ($p>0.05$). Significant difference between the study groups was not detected ($p>0.05$).

Dependence of virus elimination rate and frequency on the balance of pro-inflammatory and anti-inflammatory cytokines was proven as a result of detection of direct medium correlation relationship between VL and IL-4 ($r=0.31$) and reverse medium correlation relationship between VL and IL-2 ($r=-0.45$).

3. Conclusions

- Increase in IL-4 level by 3.8 times and decrease in IL-2 level by 2.6 times was observed in patients with CHC compared to the control group.

- Imbalance of pro-inflammatory and anti-inflammatory cytokines was the most significant in patients with concomitant diabetes mellitus type II. Comparison of these interleukins levels between the groups proved that IL-4 index was 1.3 times higher in patients with concomitant DM type II than in the group without comorbidities (9.87±0.19 pg/ml versus 7.63±0.37 pg/ml, $p<0.001$) and IL-2 level was 1.3 times lower than in the comparison group (3.85±0.37 pg/ml and 3.11±0.16 pg/ml ($p<0.05$).

- Sustained viral response was achieved in 25.00% of patients who were prescribed AVT, in 28.57% of patients who were prescribed ALA in addition to AVT and in 26.09% of patients who were treated with lactulose in addition to AVT. Inclusion of ALA and lactulose into the treatment increased SVR to 45%.

- Dependence of virus elimination rate and frequency on the balance of pro-inflammatory and anti-inflammatory cytokines was proven as a result of detection of direct medium correlation relationship between VL and IL-4 ($r=0.31$) and reverse medium correlation relationship between VL and IL-2 ($r=-0.45$).
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