IL03 MANAGEMENT OF PATIENTS WITH CHRONIC HEPATITIS C - OUR EXPERIENCE

Todorovska B, Caloska I. V, Dimitrova G. M, Popova R, Trajkovska M, Stardelova G. K, Curakova E, Licoska J. F, Joksimovic N.
University Clinic of Gastroenterohepatology, Skopje, R. of Macedonia

INTRODUCTION: Chronic infection with hepatitis C virus (HCV) is a chronic liver disease that is found in 2.8% of world population and leads to a more advanced form of liver damage or cirrhosis requiring liver transplantation, but there is an increased occurrence rate of hepatocellular carcinoma associated with HCV infection. So far in the literature lot has been written about the factors that affect the progression of the disease and the virological response, which are factors associated with the virus as genotype and viraemia and factors related to the host, such as age, sex, genetic polymorphisms, consumption alcohol, co-infection with the hepatitis B virus or HIV and the presence of metabolic abnormalities (increased insulin resistance, obesity, changes in lipid status, fatty liver, metabolic syndrome etc.). There are many ways of transmission of the virus, where the most common mode of transmission is through contaminated needle with virus among intravenous consumers of drugs and rarely mentioned are sexually transmissions, by hemodialysis, tattoos, surgical interventions, blood transfusion at the time they were not tested for HCV and transmission at health professional. In Macedonia, the most common mode of transmission of HCV infection is through intravenous drug use (at 62.3%), within 32% the virus is transmitted by hemodialysis, and other modes of transmission are found in 5.7%.

AIM OF STUDY: Overview of our experience in the treatment of patients with chronic hepatitis C in the last six years, the analysis of the efficacy of antiviral therapy with pegylated interferon and ribavirin and analysis of the impact of several factors on achieving sustained virological response (SVR).

PATIENTS AND METHODS: In Macedonia the treatment of patients with chronic C hepatitis is combination therapy of pegylated interferon alpha and ribavirin, therapy which was several years ago the gold standard worldwide, but in recent years superior therapy especially for genotype 1 is considered to be direct acting anti-viral drugs (Direct acting antivirals DAAs) which unfortunately are not available for patients in Macedonia.

Before starting antiviral therapy all patients should take full range of tests that yield insight into the activity of the virus and the range of advanced stage liver disease, which are the following in:

- genotyping (genotype determination of HCV RNA by PCR technique)
- quantification of virus (viremia or viral load)
- ultrasound of the abdomen which verifies the presence of hepatic steatosis (graduated from Grade 0-2, 0-absence of steatosis, grade 1-mild degree of steatosis, with quite easy increased ehogenicity of the hepatic parenchyma and clear visualization of the diaphragm and walls of intrahepatic vessels and level-3 fatty expressed low or no visualization of the previously described parameters)

- Biochemical laboratory (hematology, hepatological, lipid, carbohydrate status, insulinemija (by calculating the HOMA-IR according to the formula: fasting insulin (μU / mL) x plasma glucose (mmol / L) /22.5.),
- analysis of thyroid status (TSH, fT4)
- analysis of auto-antibodies (ANA, AMA, AsMA, LKM1, SLA) to exclude the presence of autoimmune disease of the liver that may be a contraindication to interferon therapy
- body weight and height to calculate the BMI according to the formula: weight in kilograms / (height in meters) at the beginning and at the end of treatment
- liver biopsy under ultrasound control for histological assessment of the degree of inflammation and fibrosis (expressed through Knodell scale, 0 = no inflammation; 1-4 = minimal inflammation, 5-8 = mild inflammation; 9-12 = moderate inflammation, and 13-18= significant presence of inflammation and fibrosis in the liver where 0 = no fibrosis, and 4= significant fibrosis or cirrhosis).
- After all above mentioned investigations will be made, patients are placed on a standard antiviral therapy, the combination of pegylated interferon alpha (peg-IFN alpha-2a or peg-IFN alpha-2b) and ribavirin, and duration of treatment is dependent on the genotype of virus, so patients with genotype 1 and 4 received 48 weeks of therapy with pegylated interferon alpha (peg-IFN α) subcutaneously once a week at a dose of 180 μg of peg-IFN α2a or 1,5 μg / kg of peg-IFN α2b, and patients with genotype 2 and 3 receive the above treatment in duration of 24 weeks, while ribavirin is receiving per os at a daily dose of 1200 mg per genotype 1 and 4 or 800 mg per genotype 2 and 3. All subjects are then evaluated in terms of achieved virological response, and for sustained virological response is considered undetectable levels of HCV RNA in the blood after six months of therapy.
- The electronic database of University Clinic of Gastroenterohepathological is used to be taken for analysis only patients where we have data regarding the achieved or absent of sustainede virological response for the period 2009 to 2015. We have analyzed 226 patients, who are then divided into groups of patients with sustained virological response (SVR) and a group of patients Non virus responders (NVR) which do not have adequate virological response.

Patients were analyzed in terms of several parameters, such as:

- sex,
- age,
- genotype
- drug abuse as a way of transmission of the virus (patients were divided into two groups: Group 1 - Patients who used intravenous drugs, group 2 - patients who received the virus otherwise)

- viral load,
- histological changes of liver biopsy (used Knodell score for measuring the degree of inflammation, HAI-histological activity index, which is numbered 1 to 18; and attending fibrosis, according to which patients are divided into three groups: group 1- no fibrosis, group 2- evident fibrosis and group 3 - with liver cirrhosis)
- the presence of steatosis (patients were divided into three groups: group 0-no steatosis; group 1 - mild degree of steatosis and group 2 - severe steatosis)
- weight expressed through BMI, and depending on the value of the index a division of the patients into four group was made: group 1 - underweight (where BMI <20 kg / m2), group 2 normal weight (BMI between 20-24.9 kg / m2), group 3 overweight (BMI between 25 and 29.9 kg / m2) and a group 4-obese (BMI over 30 kg / m2)
- laboratory parameters, such as aminotransferases activity (AST, ALT), then the lipid status (TG, total cholesterol, HDL, LDL, and for dyslipidemia according to the recommendations of the National Cholesterol Education Program Adult Treatment Panel III considering the following cut off values : for TG ≥150 mg / dL or ≥ 1.7 mmol / L; for total cholesterol ≥ 200 mg / dL or ≥ 5.17 mmol / L, LDL ≥ 130 mg / dL or ≥ 3.36 mmol / L and HDL <40 mg / dL or <1.03 mmol / L), the glucose status and insulinemia (calculation of HOMA-IR according to the formula: fasting insulin (μU / mL) x plasma glucose (mmol / L) /22.5., and the insulin resistance value is considered ≥2).

Then a comparison between the two groups in terms of all the above parameters is made. The obtained data were processed using a statistical computer program SPSS for Windows, where the following statistical tests are used:

- arithmetic mean, standard deviation, standard error, median and inter-quarter interval for quantitative measures
- frequencies and percentages for categorical measures
- for testing the difference in the analyzed parameters between the two groups independent parametric and non-parametric tests are used (Student T test, Chi-square test, Mann-Whitney test).
- Multivariable logistic regression analysis is used to detect independent predictors of SVR
- For all analyzes p value <0.05 was considered statistically significant, and p <0,01 for highly significant.

RESULTS: From the 226 patients analyzed, 189 patients achieved SVR or 83.6%, and 37 patients belong to the group NVR which means 16.4% of the sample size. Males are dominating, or about 75% of patients (177 of 226 patients) are men and 49 are women (25%). Patients age is between 18 and 66 years, with a mean age of 33.8 years. Regarding the manner of transmission of the virus prevalent group is the one who were former intravenous drug abusers or 63% of the sample size, other modes of transmission account for 37%. In our patients dominant genotype is 3 (present in 67.3%), following genotype 1 (at

31.4%), while genotype 2 and 4 very rare, or at 0.9% and 0.4% respectively. There are major differences in terms of viral load, which ranges between 101 IU / ml and 59,159,152 IU / ml, with a mean of 1,804,828 IU / ml, where 51.2% of patients have low viral load (<800,000 IU / m), and 48.8 % of patients with high viral load (> 800,000 IU / ml). In histological analysis of the biopsy Knodell score-HAI in our patients ranges between 1 and 13, where the majority of patients have Knodell score of 3 and 4, and for the presence of fibrosis in 73.6% of the patients have an absence of fibrosis; in 21.3% fibrotic changes are found, while veryfied cirrhosis in 5.1% of the sample size. Steatosis is present in about 45% of patients, of which at 5% steatosis is highly expressed, while 55% of patients are without steatosis. Analysis of weight expressed as BMI indicated the presence of overweight in a large percentage of the patients, or 46% (37.2% are overfed, and 8.8% were obese). The remaining 49.6% had normal body weight and underweight are 4.4%. Aminotransferases AST and ALT are average of 63.2 U / L (14-582 U / L) and 97.1 U / L (10-591 U / L) respectively. Dyslipidemia is found in 53.8% of patients, with a mean value of TG, tot. chol.HDL, LDL with the following values: 1.3 mmol / L (0.4-5.4 mmol / L), 4.2 mmol / L (1.9-8.7 mmol / L), 1.2 mmol / L (0.4-2.5 mmol / L), 2.5 mmol / L (0.6-6.8 mmol / L), respectively. Fasting glucose is between 3.4 and 11.9 mmol / L, with a mean of 5.3 mmol / L, but insulin resistance is present in 43.6% of the patients (mean insulinemija of 12.74 μIU / ml). When we made a comparison between the two groups (with or without adequate virological response) compared to the previously described parameters, we obtained statistical significance in terms of age, actually the age of the patients who do not achieve adequate virological response is significantly higher than the group with SVR ($p < 0.001$), and this highly significant difference was obtained in terms of way of transmission of the virus, i.e. 90.44% of patients who were former intravenous drug abusers have achieved SVR ($p < 0.001$). Then patients with genotype 3 achieved significantly more SVR compared to patients with other genotypes ($p = 0.002$), and patients who are not achieving SVR have higher Knodell score-HAI, with a mean of 4,258 ± 2,828 and $p = 0,028$. The greater weight or higher BMI is an important factor for inadequate virological response so that patients with SVR have a mean BMI of 24.3 ± 3.9, while patients with NVR 26.6 ± 5.2 or statistical significance is for $p = 0.022$. Glucose status meets significant statistical significance of fasting glucose, fasting insulin and HOMA IR results are significantly higher in the group NVR corresponding to $p = 0.02$, 0.037 and 0.039 respectively. For all other parameters statistical significance between the groups is not detected. Using the multivariable logistic analysis we obtained that independent predictors of SVR are the genotype and the BMI.

CONCLUSION: In our study there is a high rate of sustained virological response of 83.6%, which is statistically significantly more frequent in patients with genotype 3 (90.54%), unlike in genotype 1 it is 71.01%, and these two genotypes are typically represented genotypes in analyzed patients. A high percentage of SVR is seen in former intravenous drug addicts (even at 90.44%). Age, higher HAI and BMI are factors affecting adversely the virological response. Also an important factor for the absence of virological response is increased insulin resistance, which is present in a large percentage of the sample size (43.6%). In our study independent predictors of SVR are the genotype and the BMI.