Clinical, biological and evolutionary characteristics of patients with advanced liver fibrosis under direct acting antivirals

PhD student: FOFIU CRINA STEFANIA

PhD coordinator: PROF. DR. DOBRU DANIELA

The increasing prevalence of hepatitis C virus infection is a matter of global concern. With the introduction of direct acting antivirals, the primary goal of HCV treatment is to achieve a sustained virological response (SVR), which is associated with an improvement in quality of life by reducing the risk of hepatocellular carcinoma, liver decompensation and liver related deaths.

The choice of the present research topic is fully justified, proving it's up to date and of practical importance. Since the introduction of direct acting antivirals (DAAs) many studies have been concerned about the optimization of these treatment regimens. Because of the high efficacy, safety and better tolerability of these new antivirals, WHO aims to eliminate HCV as a public health threat by 2030. Consequently, romanian health care system approved the IFN-free regimen containing Ombitasvir, Paritaprevir, ritonavir, Dasabuvir and Ribavirin (PODr+R), as a first therapeutic protocol for HCV in 2015.

The first part of our thesis describes the current stage of knowledge about the importance and complexity of HCV treatment, as well as the disease progression without therapy. The literature review summarized the history of hepatitis C virus breakdown, viral structure, epidemiological data, HCV diagnostic criteria, complications, HCV treatment over time, and approved treatment in Romania, based on 156 bibliographic titles.

Patients with chronic hepatitis C virus infection (HCV) and cirrhosis have a higher risk for liver related complications and have historically been more difficult to cure than patients without cirrhosis. Therefore, the aim of the present thesis was to evaluate the clinical, biological and evolutional characteristics of patients with advanced liver fibrosis. The primary objective was to assess the efficacy of PODr+R regimen in patients with chronic HCV genotype 1b infection and compensated cirrhosis, regardless of previous treatment with IFN. The secondary objective was to evaluate the predictive factors of severe complications in cirrhotic patients. And finally the tertiary objective of the thesis was to note the severe complications which led to early treatment discontinuation. In order to meet the present objectives three separate studies were conducted.

In the first study, we assessed the efficacy of Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir and Ribavirin (PODr+R) therapy in 59 patients with chronic HCV genotype 1b infection and compensated cirrhosis, with and without prior treatment experience with pegylated interferon and ribavirin (PegIFN/RBV). Analysis of previous exposure to PegIFN/RBV treatment allowed us to divide patients into two groups: previously experienced IFN-based treatment and naive patients. Thus, more than half were previously treated with IFN (59.3%, n = 35). Of them 51.4% (n = 18) had null response to PegIFN/RBV, 11.4% (n = 4) had partial response and 37.2% (13) were relapsers. All patients had HCV genotype 1b and

grade F4 liver fibrosis. Forty four (74.5%) individuals were previously diagnosed with liver cirrhosis Child Pugh score 5, while the remaining 15 patients (25.4%) were diagnosed with Child Pugh score 6. The initial distribution of demographics, clinical and biological characteristics have led to arguments supporting the framing of patients in different groups. Females were more commonly distributed in the naïve patients group (F / B = 15/9), while men were more common in treatment experienced patients. Treatment naïve patients were significantly older than patients previously treated with PegIFN/RBV (p=.013). Comparing pre-treatment laboratory analyzes, treatment experienced patients showed significantly higher mean level of ALT than naïve patients, although mean AST, ALT and GGT values were found to be above normal in both groups. While number of platelets was significantly lower among naïve patients, there was no difference in HCV RNA levels or Child Pugh score between the groups. Changes in patients HB and TBIL values were observed under the treatment. Mean TBIL value increased after 2 weeks of treatment while mean Hb levels decreased after 2-4 weeks. After 12 weeks of treatment with PODr+R, 100% of patients in each cohort achieved SVR12. We noted post-treatment hyperbilirubinemia in 15 of the 39 previously experienced patients (38%), while only 3 cases (12.5%) in naive group.

The second study was designed to evaluate risk factors for liver complications and liver-related death in cirrhotic patients, with particular attention to hepatocellular carcinoma. We retrospectively analyzed 282 patients diagnosed with cirrhosis of various etiologies. We considered severe complications: grade III ascites, encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis and we ranked patients in two groups based on the presence of these. The presence of hepatocellular carcinoma has been analyzed as a separate complication. From the analysis of demographic indices, the presence of smoking only significantly increased the risk of serious complications. Alcohol consumption and viral infection were also found to be risk factors for complications. Concerning HCC, viral infection has been shown to be a predictive factor in our group of patients.

The third study assessed the severe complications that led to early DAAs discontinuation, as well as the efficacy of shorter period of therapy, by observing SVR12. We reported two cases of PODr early disscontinuation, the first one due to hepatic decompensation with ascites and hyperbilirubinemia and the second one due to allergic reaction. The first case achieved SVR12 after 6 weeks of PODr+R only, despite the presence of cirrhosis.

The main original aspect of the thesis is that we describe the first experience results of our country with approved IFN-free therapeutic protocol in a special group of patients. Moreover our results report the highest rate of sustained virological response (SVR12 of 100%) achieved under PODr+R regimen in a group of patients with compensated cirrhosis. We report also two cases of early discontinuation due to adverse events, among patients with low risk for complications. The identification of high-risk cirrhotic patients for the development of complications is another feature of this study. By identifying this category of patients, careful monitoring and application of specific intensive care should be undertaken.