CHRONIC HEPATITIS C VIRUS INFECTION IN 2013 – QUO VADIS?

Chronic hepatitis C virus infection affects over 180 million people, that is approximately 3% of world population (1). Worldwide, the prevalence of chronically evolving hepatitis is 0.1% to 5%, while in Romania it is 4.9%, genotype 1b being the most common.

Acute hepatitis C virus infection is self-limited in only 25% of cases, in the remaining 75% becomes a chronic condition. In most patients the course of chronic infection is characterized by few or no symptoms for a long period of time. Signs of chronic liver condition occur 20 to 30 years after infection, so that 27% of liver cirrhosis cases and 25.5% of hepatocellular carcinomas are the result of chronic hepatitis C virus infection, making it the most common indication for liver transplantation (2, 3).

Given the incomplete knowledge, treatment included, hepatitis C remains a complex issue with epidemiological, social and economic implications. We here cover the main aspects of chronic hepatitis C treatment in different geographical areas and in Romania.

The main goal of treatment in chronic hepatitis C virus infection is viral eradication, obtaining sustained virologic response (SVR) - undetectable viremia 6 months after treatment - equivalent to “cure” of hepatitis C virus infection. Secondary goals are to reduce inflammation, fibrosis progression, and the risk of complications, especially hepatocellular carcinoma occurrence.

"Standard care" in the treatment of chronic hepatitis C viral infection

Interferon was introduced in the etiopathogenic treatment of chronic hepatitis C virus infection in 1997; later it was associated with ribavirin, which has improved SVR. In the USA and Western Europe the combination of pegylated interferon and ribavirin remained the standard therapy until the spring of 2011. This dual combination is administered for 48 weeks in treatment-naive patients with HCV genotypes 1, 4, 5 and 6, and for 24 weeks in those with genotypes 2 and 3. SVR rates are 40-50% for patients infected with genotype 1, 55-65% for those with genotype 4, and 85% with genotypes 2 and 3 (4). Retreatment with this combination therapy in patients with genotype 1 infection is recommended in case of relapse (undetectable viremia at the end of treatment but detectable later), and partial responders (more than 2 log viral load drop at week 12 but present through treatment end). Non-responders (less than 2 log viral load drop at 12 weeks), generally those with advanced fibrosis, may benefit from re-treatment, but with very low SVR.

In Romania, SVR rate is similar to that in the literature both in treatment-naive and treatment-experienced patients; the initial treatment as well as re-treatment are free of charge, being covered by the health insurance company.

Early monitoring of HCV RNA dynamics (protocol applied in Romania) facilitates virologic response- guided therapy. When a rapid virologic response (RVR = undetectable viral load at 4 weeks) is achieved in patients with mild fibrosis and baseline viral load below 600000 IU treat-
As in the case of dual therapy, triple therapy is virologic response-guided. Patients begin boceprevir treatment after a 4-week lead-in treatment with pegylated interferon and ribavirin. This phase serves to assess the response to interferon and ribavirin in terms of diminished viral resistance and viral breakthrough. Induction phase is followed by 24 or 44 weeks of triple therapy. In treatment-naive non-cirrhotic patients with undetectable viral load at weeks 8 and 24, treatment duration may be reduced to 28 weeks (4 weeks induction phase and 24 weeks triple therapy). But if HCV RNA is >100 IU at week 12 or detectable at 24 weeks treatment should be discontinued. Telaprevir triple therapy lasts 12 weeks and is followed by 12 or 36 weeks of treatment with pegylated interferon and ribavirin. In treatment-naive non-cirrhotic patients on telaprevir treatment duration may be reduced to 24 weeks if viral load is undetectable at weeks 4 and 12. Conversely, if HCV RNA is >1,000 IU at weeks 4 or 12, or detectable at week 24, treatment should be discontinued.

Patients with advanced liver fibrosis (F4 - compensated liver cirrhosis) have lower SVR rates in both double and triple therapy. In case of triple therapy patients who respond favorably will follow the 48-week treatment regardless of the protease inhibitor used.

Re-treatment is considered in relapsers or partial responders to pegylated interferon and ribavirin therapy (for non-responders only studies on telaprevir are available). Boceprevir triple therapy should be discontinued if HCV RNA >100 IU at week 12, and telaprevir triple therapy if HCV RNA >1,000 IU at weeks 4 and 12 due to the increased risk of developing viral resistance (6,7).
Selection and prioritization of patients for triple therapy

Ideally, any patient diagnosed with hepatitis C virus infection should receive treatment. In the year triple therapy became the "standard of the care" we wonder which patients should be treated immediately and which can wait for better, more effective and side effect-free treatments. When attempting to prioritize and individualize the treatment, several factors should be quantified: race, genotype, severity of fibrosis, patient type - treatment-naïve or treatment-experienced, prior response to treatment, compliance and adherence with previous treatment, age, marital status, co morbid conditions, and economic status. There is general agreement that treatment should be immediate for treatment-naïve genotype 1 patients and relapers with advanced fibrosis (F3-F4) or extrahepatic manifestations. Low-stage fibrosis (F1-F2), relapers with poor tolerance to previous dual combination therapy, contraindications to interferon or ribavirin, are factors that determine putting the patient on the waiting list for other types of treatment (8).

Recent year researches have been focused on identifying a genetic marker with predictive value in assessing the response to antiviral therapy in chronic hepatitis C patients. Recently, it has been shown that interleukin 28B polymorphism (interferon, lambda 3 on chromosome 19) is a strong predictor of SVR in dual therapy with pegylated interferon and ribavirin, CC IL-28B type is associated with a 2-fold higher SVR rate as compared to TT and CT types (69%, 33%, 27%, respectively) (9). With the introduction of triple therapy as the standard model, the predictive role of IL-28B polymorphism has diminished. Also, the predictive value of IL-28 genetic polymorphism in "interferon free" regimes is unknown. Currently, both the national and international guidelines do not recommend the use of IL-28B testing as a pre-treatment predictor or for individualization of antiviral therapy in chronic hepatitis C patients. However, it remains a predictive factor that may increase patient compliance and adherence to treatment (9).

Therapeutic goals

Triple therapy can be considered a success in treating genotype 1 chronic hepatitis C patients (the most common and difficult to treat) due to significant increase in SVR in treatment-naïve and treatment-experienced patients as compared to dual therapy. However, triple therapy is far from ideal therapy: treatment costs are very high and there are patients in which the therapeutic response is not satisfactory (advanced fibrosis, non-responders with cirrhosis, intolerance or contraindication to pegylated interferon and/or ribavirin). Also, there are no data on therapeutic results when other viral genotypes than 1 were involved.

Studies are currently underway to discover other direct antiviral agents and perhaps "interferon free" regimens. The common denominator of current researches on triple therapy is SVR rate increase (> 80%), less side effects, and shorter treatment duration. The most recent direct acting antivirals include, among others, the second-generation protease inhibitors, nucleoside polymerase inhibitors, non-structural protein inhibitors, of which the best known are daclatasavir and alisporivir, in phase 3 trials. "Interferon free" combinations of 2, 3 or 4 direct antiviral agents with/without ribavirin, are currently studied in clinical trials.

In conclusion it can be said that the progress in recent years in the treatment of
chronic hepatitis C virus infection (triple therapy, IL28 B gene polymorphism) shows that we are still far from the ideal therapy. Ideal drug should address all viral genotypes and various categories of patients regardless of age, with 90% SVR, negligible side effects, should not induce viral resistance and to be administered to patients with various major co-morbid conditions (co-infections with hepatitis B virus or HIV, liver failure or renal transplant recipients).

REFERENCES

1. World Health Organization (WHO), Hepatitis C. Fact Sheet No164 Revised October 2000.

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