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Review article

Triple therapy with first-generation Protease Inhibitors for patients with genotype 1 chronic hepatitis C: Recommendations of the Italian Association for the Study of the Liver (AISF)

Italian Association for the Study of the Liver (AISF)

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ABSTRACT

The first-generation Protease Inhibitors Boceprevir and Telaprevir administered in triple therapy regimens with Peg-interferon alpha and Ribavirin have been proven effective in increasing the rate of Sustained Virological Response in both naive and treatment-experienced patients with chronic genotype-1 hepatitis C. However, at the individual level, the therapeutic advantage of triple therapy is highly variable and results from the combination of multiple factors related to the characteristics of patient, viral status and liver disease.

The recommendations presented are promoted by the Italian Association for the Study of the Liver, with the aim to help the physician in the decision-making process as well as to manage patients during treatment with triple therapy.

Boceprevir (BOC) and Telaprevir (TVR) are the first two direct antiviral agents (DAA) registered for the treatment of patients with chronic genotype 1 hepatitis C virus (HCV) infection. Both, administered with Peg-interferon alpha (Peg-IFN) and Ribavirin (RBV), have been proven to be effective in increasing the rate of Sustained Virological Response (SVR) in naive and experienced chronic HCV genoptype-1 patients [1–8]. However, at the individual level, the therapeutic advantage of a triple therapy regimen is highly variable and results from the combination of multiple factors including patient's characteristics, viral parameters, and liver disease severity.

These Recommendations for the use of triple therapy (Peg-IFN + Ribavirin + first-generation Protease Inhibitor) in genotype 1 chronic hepatitis C, promoted by the Italian Association for the Study of the Liver (AISF), are meant to provide physicians with practical indications on the decision-making process as well as on management of patients during treatment with Protease Inhibitors.

The recommendations were divided into three levels of evidence according to the GRADE system: A (high), B (medium) and C (low), together with 2 recommendation levels: 1 (strong) and 2 (weak).

Members of the AISF Coordinating Committee and of the AISF Consulting Committee on New Antiviral Hepatitis C drugs contributed to the document. The final draft was then submitted to the evaluation of external experts and the text modified according their suggestion and comments.

1. Naive patients

1.1. Selection of naive patients as candidates for triple therapy treatment

The availability of BOC- and TVR-based triple therapy does not change the current indications for hepatitis C treatment, which should be evaluated in all patients, with the exception of those with decompensated cirrhosis or other absolute contraindications to the use of Peg-IFN and RBV [9,10].

Therapy should be considered primarily in patients with significant fibrosis (METAVIR ≥ F2), with priority for those with severe fibrosis (METAVIR F3) and compensated cirrhosis (METAVIR F4), Child–Pugh A class.

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For patients with no or mild fibrosis (METAVIR F0–F1), the indication to treatment must be assessed on a case by case basis, taking into account the risk of disease progression as well as extra-hepatic manifestations related to HCV, potential side effects, patient motivation and high likelihood of the forthcoming availability of new DAAs with higher therapeutic efficacy and better tolerability, especially with the impending arrival of IFN-free regimens.

1.2. Decision-making algorithm

The current knowledge calls for a personalized approach to hepatitis C therapy, which must be assessed according to multiple variables that may influence each patient's case:

1. risk of disease progression
2. likelihood of therapeutic success
3. risk/benefit ratio of treatment

The risk of disease progression, as the mean estimated time to develop cirrhosis or clinical complications of cirrhosis (clinically significant portal hypertension, liver decompensation and hepatocellular carcinoma), is mostly correlated with fibrosis stage. Thus, the assessment of hepatic fibrosis is mandatory, since treatment is more needed over a brief period time in patients with evidence of severe fibrosis or compensated cirrhosis (F3–F4) [11,12]. Appendix 1 focuses on the methods used to evaluate hepatic fibrosis (see Supplementary materials).

The risk of disease progression is also influenced by patient-specific features (age and age at infection, sex, race, genetics), viral parameters (viral load, genotype and heterogeneity), co-factors of liver disease (alcohol use, diabetes, insulin-resistance, obesity) and co-infections with other viruses [13].

Indication for treatment is also expressed according to the likelihood of therapeutic success. This is influenced by treatment schedule, age, disease stage (the likelihood of therapeutic success is inversely related to disease stage), IL28B genotype (its relevance is related to antiviral drug potency, thus lower in triple vs. dual therapy) and the virological profile (viral load, genotype and, in case of triple treatment, viral sub-type by virtue of the lower SVR rates and higher likelihood to develop resistance for the genotype 1a) [1,6,7,14–17].

The treatment risk/benefit ratio is mainly bound to the incidence and severity of the side effects, which are significantly increased with the triple therapy, mostly in patients with advanced fibrosis or cirrhosis [4,6].

Even though the role of positive predictive factors (low viral replication rate, CC homozygosis for the IL28B rs12979860 polymorphism, mild fibrosis) has been described both for dual and triple therapy, no pre-treatment parameter is able to predict SVR with a diagnostic accuracy higher than 90%.

At present, Rapid Virological Response (RVR), defined as undetectable HCV RNA at week 4 of Peg-IFN + RBV therapy, is the most accurate predictive factor of SVR [18,19]. It follows that 4 weeks of dual therapy for assessing RVR is a valuable mean to identify those patients with high IFN-responsiveness and high probability to achieve SVR. In such cases, it is reasonable to continue treatment with dual therapy without adding the Protease Inhibitor, avoiding the risk of additional side effects. Nevertheless, it should be considered that the likelihood of reaching RVR decreases progressively from 34–23% in patients without advanced fibrosis, to 21–11% in subjects with advanced fibrosis/cirrhosis [20,21] and that the positive predictive power of RVR is reduced in patients with severe fibrosis, and it does not exceed 50% in cirrhotic patients [21].

The initial 4-week course of dual therapy is also helpful to define the risk/benefit ratio of triple therapy in patients with more advanced disease and a lower likelihood to achieve SVR. Indeed, in cirrhotic patients treated with BOC, the reduction of HCV RNA < 1 log after the 4-week lead-in with Peg-IFN + RBV is an unfavourable prognostic indicator of SVR [6]. There is currently no information regarding the use of TVR after a 4-week dual therapy in naive patients.

Finally, regardless of the DAA used, the 4-week initial dual therapy may be used as a "tolerability test" for the purpose of identifying the patients, mostly represented by those with an advanced disease, who develop adverse reactions with dual therapy and who will likely not be able to sustain a triple therapy course (see paragraph 5).

Recommendations

1. **The availability of triple therapy in naive patients does not change the indications for hepatitis C treatment, which must be evaluated in all patients, except those with decompensated cirrhosis (A1).**
2. **Patients with severe fibrosis (F3) or compensated cirrhosis (F4) in Child–Pugh class A are the main candidates to BOC or TVR triple based therapy. Those patients have higher clinical priority for treatment, to prevent the progression of liver disease (A1). In some, mostly non-cirrhotic patients, continuing treatment with dual therapy upon accomplishing RVR may be considered in the presence of favourable predictive factors (e.g., IL28B CC or low viral load) and/or high risk of developing side effects (B2). In cirrhotic patients (F4) with viral load reduction <1 Log UI/mL after the first 4 weeks of lead-in with dual therapy, addition of BOC should be assessed on a case by case basis, given the lower likelihood to reach SVR (B1).**
3. **In patients with moderate fibrosis (F2), triple therapy is indicated, while, in those with mild or no fibrosis (F0–F1), indication is more controversial and must be assessed individually, taking into account the low short-mid term risk of disease progression, extra-hepatic manifestations of HCV infection, potential side effects, patient motivation and future therapeutic options with more effective drugs with fewer side effects (B1). In patients with F0–F2 fibrosis, an initial 4-week lead-in with Peg-IFN + RBV allows to customize treatment based on on-treatment virological response. If RVR is present it is appropriate to contain dual therapy, as the likelihood of SVR is very high. If RVR is not obtained, patients with moderate fibrosis (F2) should continue with a triple therapy regimen; in patients with no or mild fibrosis (F0–F1), the choice between stopping antiviral treatment or continuing with triple therapy should be assessed individually (B1).**
4. **Patients in which treatment is deferred must be monitored periodically according to their disease stage, in order to identify progression of liver disease and thus reconsider the need for treatment (A1).**

2. Patients with failure to previous dual therapy (experienced)

2.1. Selection of "experienced" patients as candidates for triple therapy

BOC- or TVR-based triple therapy significantly increases SVR rates in patients with previous failure to dual therapy [3,5,8,22]. Thus, experienced patients are suitable candidates for triple therapy regimens.

However, even in this setting, the indication must be weighed in each patient considering in mind the risk of disease progression in the short-term, likelihood of therapeutic success, risk/benefit ratio