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.

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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 genotype-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. **Naïve patients**

1.1. Selection of naïve 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.
For patients with no or mild fibrosis (METAIVIR 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 DAAIs 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 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

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of treatment and the possible alternative therapeutic options to become available in the short/mid-term.

2.2. Decision-making algorithm

The likelihood of SVR with triple therapy varies remarkably depending on the non-response profile to previous dual therapy (higher in relapers, lower in null responders and intermediate in partial responders) and the extent of virological response (at least 1 log UI/mmol drop of serum HCV RNA levels) after 4 weeks of dual treatment with Peg–IFN + RBV before adding DAA. Additional predicting factors from post hoc analyses are the stage of liver fibrosis and the viral subtype [3,8,23,24].

According to previous response profile and virological response, SVR rate with BOC was higher in patients with HCV RNA decline >1 log UI/mL both among partial responders (61% vs. 37%) and relapers (81% vs. 37%) [3]. In case of TVR treatment, SVR rate was higher in patients with HCV RNA decline >1 log UI/mL in null responders (54% vs. 15%) and relapers (94% vs. 62%), while it was basically similar among partial responders (59% vs. 56%) [23].

Based on the above mentioned data, relapers are very good candidates to triple treatment regimens, given the high likelihood of reaching SVR. The same may also apply to partial responders, even though response rates are lower and influenced, to a variable extent with the two DAAs, by fibrosis stage and sensitivity to IFN. In these patients, for BOC regimens a viral load decline <1 log UI/mL after 4 weeks of dual therapy provides an additional tool to determine the likelihood of therapeutic response at the individual level [3,22].

In null responders, the therapeutic advantage of triple therapy with BOC and TVR is generally lower. In this setting, a reduction <1 log UI/mL of serum HCV RNA after 4 weeks of dual therapy allows to select a subgroup of patients whose potential response rate appears to be quite low, particularly when associated with other negative predictors (high viral load, advanced fibrosis, genotype 1a), reducing the therapeutic advantage vs. dual therapy to a limited or even arguably nonexistent level.

In real-life practice many patients who previously failed to respond to treatment with Peg–IFN + RBV do not have an exact record of the type of failure. In this setting, an initial 4-week course of Peg–IFN + RBV is useful to predict the efficacy of triple therapy.

Finally, patients with virological breakthrough during a previous treatment with Peg–IFN + RBV (reappearance of HCV RNA during therapy, after achieving undetectability) can be assimilated to relapers, since they have shown some degree of sensitivity to IFN.

Recommendations

1. BOC or TVR triple therapy is currently the reference treatment for patients with previous Peg–IFN + RBV failure (A1). Similarly to naive patients, the indication to therapy should be assessed considering the risk of liver disease progression and consequently priority to treatment, likelihood of response, potential treatment side effects, patient motivation and future therapeutic options (A1).

2. In relapers, triple therapy is strongly indicated in the presence of severe fibrosis (F3) or compensated cirrhosis (F4) in Child–Pugh class A; it is indicated in patients with moderate fibrosis (F2), while it should be discussed on a case by case basis for patients with no or mild fibrosis (F0–F1) (A1).

3. In partial responders, triple therapy is strongly indicated in the presence of severe fibrosis (F3) or compensated cirrhosis (F4) in Child–Pugh class A; it is indicated in patients with moderate fibrosis (F2), while it should be discussed a case by case basis for patients with no or mild fibrosis (F0–F1) (B1). A 4-week lead-in phase with Peg–IFN + RBV contributes to define the likelihood of SVR in patients receiving BOC (B1).

4. In null responders, the indication to triple therapy must be carefully assessed considering the risk/benefit ratio. The evaluation of serum HCV RNA decline during the first 4 weeks of dual therapy is particularly useful to identify those patients with low likelihood of SVR (B1). If the reduction is <1 log UI/mL, the decision to add a DAA and continue a triple therapy regimen must be re-assessed individually by weighting the poor response likelihood and the risk of disease progression with the therapeutic “urgency” (B1).

According to the criteria of the Italian Drug Agency (AIFA), no reimbursement for triple therapy is provided in patients with F0–F2 fibrosis presenting a <1 log reduction in viral load after 4 weeks of dual therapy.

5. Patients in which treatment is deferred must be followed over time in order to rule out disease progression, which would determine a re-assessment for treatment indication (A1).

6. In case of unknown response profile to previous dual therapy, an initial 4-week course of Peg–IFN + RBV would help to predict the efficacy of a triple treatment regimen (B2).

3. Therapeutic schedules

Therapeutic schedules of BOC or TVR triple therapy regimens have been allowed by regulatory Agencies as shown in Appendix 2 (see Supplementary materials). Naive patients without cirrhosis and relapers may follow a response-guided schedule with both DAAs, while patients with cirrhosis and non-responders need to receive a longer fixed regimen (see Supplementary materials).

4. Stopping rules during treatment and viral resistance

Based on registration studies, the European Medicines Agency (EMA) suggests to discontinue treatment with BOC in case of HCV RNA ≥100 UI/mL at week 12 or detectable HCV RNA at week 24 [25]; treatment with TVR in case of HCV RNA ≥1000 UI/mL at weeks 4 or 12 or detectable HCV RNA at week 24 [26].

However, a recent post hoc analysis has shown that none of the patients BOC-treated with <1 log HCV RNA reduction vs. baseline after a 4-week lead-in and <3 log reduction after 4 weeks of triple therapy obtained SVR (negative predictive value: 100%) [27].

This data, if confirmed in larger cohorts, will arguably lead to a change in the BOC discontinuation stopping criteria. Pending this, for patients in triple therapy with BOC it is advisable to perform an additional serum HCV RNA assay at week 8, for the purpose of considering an early discontinuation, especially in subjects displaying poor treatment tolerance.

For TVR therapy, it may be advisable to adopt a serum HCV RNA threshold of 100 UI/mL at weeks 4 and 12 as a cut-off for drug discontinuation for the purpose of containing the risk of selecting resistant viral strains, particularly when TVR is started after 4 weeks of dual therapy. However, if triple therapy with TVR is started from the beginning, we still suggest to follow the EMA indications until stronger evidence will support more stringent discontinuation criteria [26].

To guarantee an adequate virological monitoring, HCV RNA assays should have a lower detection limit of 15 UI/mL and the results should be available within 3 working days. Rapid availability of HCV RNA results is needed to promptly apply the stopping rules, thus limiting the risk of developing viral resistance.

At present, the clinical meaning of selection of resistant variants is controversial. If therapeutic failure with BOC- and TVR-based therapies is invariably associated with the selection of resistant viral strains, studies with prolonged follow-up have shown that
the variants progressively decline over time with a restoration of the “wild type” population [28–30]. Furthermore, the impact of resistant variants on the efficacy of future therapeutic approaches is uncertain.

Recommendations

1. According to the indications approved by the EMA, triple therapy with BOC must be discontinued in case of HCV RNA >100 UI/mL at week 12 or detectable at week 24; triple therapy with TVR in case of HCV RNA >1000 UI/mL at weeks 4 or 12 or detectable at week 24 (B1).
2. In patients receiving BOC with HCV RNA decrease <1 log after the 4-week lead-in, an additional HCV RNA dosing should be performed at week 8 and, in case of a <3 log reduction vs. baseline, it is acceptable to stop treatment (B2).
3. In patients receiving TVR after 4 weeks of dual therapy, it could be reasonable to stop TVR in case of HCV RNA >100 UI/mL at weeks 8 or 12, in order to avoid selection of resistant viral strains (C2).
4. Determination of BOC and TVR viral resistance should be restricted to patients treated within research protocols (B1).
5. Side effect management in patients with cirrhosis

A main concern with the use of triple therapy is the higher incidence of adverse events, particularly serious in patients with advanced disease, and responsible for early treatment discontinuation (11–25% of the cases in registration studies). It is therefore mandatory, before starting therapy, to perform comprehensive patient “counselling”. Patients must be informed of the risk, type and severity of treatment-related adverse events, on the need of tight clinical and laboratory monitoring and on management of adverse events.

Management of anaemia, skin rash and ano-rectal discomfort are reported in Appendix 3 (see Supplementary material). Specific indications for cirrhotic patients, those with higher risk of developing severe adverse reactions, are provided below.

Registration studies with both DAs enrolled a limited number of cirrhotic patients. Further information on the safety of these drugs are currently available thanks to increased access to BOC and TVR regimens, showing that the incidence of adverse events, including those requiring hospitalization, is significantly higher than reported in previous studies. It has been also reported that the monitoring and management of side effects requires a great effort by physicians [31–33].

Besides anaemia which often requires erythropoietin (Epo) therapy and blood transfusion, cirrhotic patients are also predisposed to develop bacterial infections and liver decompensation, which were also responsible for treatment deaths, with a reported mortality of 1–3% [31–33].

A very recent analysis of the French Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC) identified a series of clinical/laboratory variables associated with a higher risk of developing severe clinical complications and death, which includes: age >65 years, serum albumin <3.5 g/dL, thrombocytopenia <100,000/mmc, clinically significant portal hypertension, previous ascites, functional impairment or digestive bleeding, decline of albuminemia during therapy, and lack of lead-in with dual therapy. Moreover, patients with albumin levels <3.5 g/dL and platelet <100,000/mmc present a risk of severe adverse events and death above 40% [31]. Similarly, a recent monocentric German prospective study, has shown that patients with a platelet level <110,000/mmc and Child–Pugh score >5 have a higher risk of hospitalization [32].

However, preliminary data from 609 patients (20% Italian) in the Expanded Access Programme (EAP) to TVR for patients with advanced fibrosis (F3) or cirrhosis (F4) seem to provide more encouraging data on treatment tolerability, reporting a lower incidence of severe anaemia, bacterial infections, liver decompensation, hospitalization and mortality [33]. A rather accurate and consistent patient selection (only those with compensated cirrhosis and platelets >90,000/mmc were enrolled) seems to be one of the possible explanations for the better safety profile in the EAP compared to the CUPIC compassionate trial.

Recommendations

1. The management of BOC- and TVR-based triple therapy in patients with cirrhosis is particularly difficult and requires a great commitment from physicians (A1).
2. Patients with compensated cirrhosis are a heterogeneous population. Several clinical/laboratory variables (e.g., combination of platelet count <100,000/mmc and serum albumin levels <3.5 g/dL) may be used to identify those with the higher risk for severe adverse events and death (B2).
3. An initial 4-week dual therapy before the addition of the DAA can be used as tolerability test to identify subjects with low tolerance to Peg-IFN and/or RBV and therefore potentially unsuitable to sustain a triple therapy regimen (C1).
4. Patients with cirrhosis receiving triple therapy should be stringently monitored in order to promptly diagnose and manage adverse reactions (A1). Besides the typical side effects related to triple therapy (anaemia, skin rash), special attention must be devoted to the risk of infectious diseases and hepatic decompensation (A1).
5. Given the above reasons, in the presence of risk factors for severe adverse events, cirrhotic patients should be treated in centres with considerable expertise in management of antiviral therapy in patients with advanced liver disease. The enrolment of these patients in clinical trials using second generation antiviral drugs with fewer side effects should be encouraged (B1).

6. Special populations

6.1. Patients with HIV/HCV co-infections

As a result of the high efficacy of the current antiretroviral treatments, hepatitis C has become an important cause of morbidity and mortality in patients with HIV/HCV co-infection [34,35]. In these patients, liver disease progression is faster and the response rate to dual therapy lower, with a SVR rate equal to 15–29% for genotype 1 [36].

The concerns regarding possible drug-to-drug interactions, related to the common metabolic pathway through cytochrome CYP3A4 of BOC and TVR with antiretroviral drugs, contraindicated the inclusion of HIV patients in DAA registration studies.

However, phase II studies and other reported series have shown a similar efficacy and safety profiles for triple therapy in HIV/HCV and HCV-monoinfected patients [37,38]. Nevertheless, the incidence of anaemia was higher with both drugs and, in the TVR group, skin rash (approximately 56%) caused early drug discontinuation in 5–7% of cases [37,38].

Recommendations

1. Hepatitis C treatment should be considered in all patients with HIV/HCV co-infection (A1).
2. Triple therapy in patients is indicated in naive or relapsing patients with significant fibrosis (≥F2) (B1). Given the limited data in non responder patients (partial or null responders), in this setting the indication to triple therapy should be assessed on a case by case basis, taking into account the individual risk/benefit ratio (B1).

3. Patients should be treated in centres with specific expertise, with strict clinical and laboratory monitoring. Enrollment in study protocols should be encouraged (B1).

4. Triple therapy is currently not recommended for patients with mild or no fibrosis (F0–F1), due to reduced tolerability of co-infected patients to Peg-IFN + RBV and the impending availability of interferon-free regimens with better efficacy and safety profiles (B1).

6.2. Liver transplant recipients

Hepatitis C infection recurs invariably after liver transplantation and evolves rapidly: about 30% of patients develop cirrhosis within 5 years and, in those with cirrhosis, about 50% progress to liver failure within 1 year [39]. Treatment with Peg-IFN + RBV is indicated in patients with significant fibrosis (META VIR ≥ F2), although SVR rates are lower than those observed in immunocompetent patients [40].

Preliminary results regarding the use of triple therapy with BOC and TVR have been reported in several series indicating a total of about 250 patients, mainly non responsive to previous dual therapy [41–43].

As a whole, the data available today indicate that undetectable serum HCV RNA after 3 months of treatment is achieved in 40–90%, a promising result considering the positive predictive value, which an early viral response implies for the achievement of SVR [41–43].

In the post-transplant setting, the main concern in DAA use refers to the interaction with Cyclosporin and Tacrolimus, as BOC and particularly TVR are responsible for greatly increasing the serum levels of both immunosuppressors [44,45].

As far as tolerability is concerned, the most frequent reported side effect was anaemia, treated by reducing RBV dosage, use of Epoetin in 50–100% of cases and blood transfusion in 50% of cases. Other severe adverse events included neutropenia, skin rash, renal function worsening and bacterial infections. Overall, 25% of the patients prematurely discontinued treatment due to side effects or viral breakthrough; several cases of death were also reported [41–43].

Recommendations

1. Triple therapy with BOC or TVR should be considered for recurrent hepatitis C in liver transplant recipients, in case of at least moderate fibrosis (≥F2) (B1).

2. Even in absence of available data, transplant recipients who develop a fibrosing cholestatic hepatitis can be treated with triple therapy, due to therapeutic urgency (C1).

3. In patients receiving BOC and TVR, Cyclosporin and Tacrolimus plasma levels should be closely monitored in order to maintain immunosuppression within the therapeutic range through dose adjustments (A1). Switch from Tacrolimus to Cyclosporin may be also considered due to lower interaction of the latter with BOC and TVR (B2).

4. Liver transplant recipients receiving triple therapy should be rigorously monitored to promptly diagnose and manage adverse reactions (A1).

5. For the above mentioned reasons, triple therapy with BOC and TVR should be managed by hepatologists with specific expertise in antiviral therapy in close connection with transplant centres (C1).

6.3. Patients with cryoglobulinemia

In a preliminary experience, triple therapy with BOC in 24 non responder patients to dual therapy with advanced fibrosis or cirrhosis and symptomatic mixed cryoglobulinemia produced a rapid cryocrit negativization in 19 cases and purpura and arthralgia remission during treatment, even though SVR rate was lower compared to the control group without cryoglobulinemia [46].

Recommendations

1. Due to limited available experience, patients with symptomatic cryoglobulinemia should be treated with triple therapy only in centres with specific expertise in the management of extra-hepatic syndromes (B1).

2. DAA triple based regimens are not recommended for patients with severe cryoglobulinemia (B1).

7. Drug-to-drug interactions

BOC and TVR are metabolized through cytochromes P450 3A4 and 3A5 (CYP3A4/5). Moreover, both Protease Inhibitors are strong inhibitors of the same P450 cytochrome family, which accounts for over 30% of total liver P450 cytochrome. According to this, the risk of interactions with drugs, with the same metabolic pathways, is a main concern in clinical practice [47].

Recommendations

Before starting a BOC or TVR triple therapy, a detailed pharmacological history is mandatory to avoid potential dangerous drug-to-drug interactions (A1). Moreover, during triple therapy, physicians are required to refer to specific periodically updated databases (e.g., www.hep-druginteractions.org) and search for alternative drugs not metabolized by CYP3As (A1).

8. Conclusions

The advent of the first-generation Protease Inhibitors BOC and TVR, administered with Peg-IFN and RBV, has significantly improved the SVR rate both in naive and experienced patients with chronic genotype 1 hepatitis C.

Nevertheless, their use is partly offset by the high incidence of side effects and the complexity of their management requiring a great effort by clinical staff, as well as by the lower efficacy in difficult to treat-patients (cirrhotics and non-responders to Peg-IFN + RBV). Taken together, all these factors can result in limited access to therapy, particularly in patients with more advanced disease.

Moreover, the expectation for new antiviral agents, which will be available in the next years and appear to be safer, simpler and more effective, introduces the possibility to defer the therapy, sometimes making the decision to treat the patient with the current triple regimens even more complex.

At present, hepatologists have the ethical obligation to share with the patient both risks and benefits related to the current treatment as well as to its deferral, taking into account the limitations in accurately staging liver disease and in predicting clinical progression. Furthermore, physicians and patients must be aware that for many promising agents in the HCV pipeline there is no predictable time to market or reimbursement in many parts of the
Conflict of interest

Alessia Ciancio is in Speaker bureau for Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, and MSD Italia. Maria Rendina is in Speaker bureau for Grifols Italia, Kedrion, Gilead Sciences, and Bristol-Myers Squibb. Salvatore Petta is in Speaker bureau. Raffaele Bruno is in Advisory boards and Speaker bureau for Abbott/AbbVie. Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, and MSD Italia. Alessio Aghemo is in Research grants, Advisory boards, and Speaker bureau for Roche, Gilead Sciences, Janssen-Cilag, and MSD Italia. Alfredo Alberti is in Research grants, advisory boards, Speaker bureau, and unrestricted sponsorships for Bristol-Myers Squibb, Novartis, MSD Italia, Roche, Gilead Sciences, Janssen-Cilag, Tibotec, and Abbott. Pietro Andreone is in Research grants and advisory boards for Roche, MSD Italia, Janssen-Cilag, and Bristol-Myers Squibb. Ferruccio Bonino is in Advisory boards, consulting fees, speakers bureau and support for meeting organization. Savino Bruno is in Advisory boards and Speaker bureau for MSD Italia Roche, Bristol-Myers Squibb, and Novartis. Massimo Colombo is in Research grants, advisory boards, Speaker bureau for MSD Italia, Roche, Novartis, Bayer, Bristol-Myers Squibb, Gilead Sciences, Tibotec, Vertex, Janssen-Cilag, Achillion, Lundbeck, Abbott, Boehringer Ingelheim. Antonio Craxi is in Research grants, advisory boards, consulting fees, and Speaker bureau for Bayer, Bristol-Myers Squibb, and Novartis. Giovanni Battista Gaeta is in Research grants, advisory boards, and Speaker bureau for MSD Italia, Gilead Sciences, AbbVie, Boehringer Ingelheim, and Bristol-Myers Squibb. Alessandra Mangia is in Research grants, advisory boards, and Speaker bureau for MSD Italia, Gilead Sciences, Novartis, and Janssen-Cilag. Massimo Puoti is in Research grants, advisory boards, and Speaker bureau for AbbVie, MSD Italia, Janssen-Cilag, Gilead Sciences, Bristol-Myers Squibb, ViV, Vertex, Novartis, Roche, and Boehringer Ingelheim. For Paolo Caraceni, Barbara Coco, Marco Marzioni, Luca Valenti, and Davide Bitetto, these are not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.dld.2013.08.243

References


