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REVIEW ARTICLE

Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice

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Keywords
anaemia – direct-acting antiviral – hepatitis C – protease inhibitor – rash – safety

Abbreviations
AEs, adverse events; AGEP, acute generalized exanthematous pustulosis; BOC, boceprevir; BSA, body surface area; DAAs, direct-acting antivirals; DRESS, drug rash with eosinophilia and systemic symptoms; EPO, erythropoietin alfa; PEG-IFN, pegylated interferon; RBV, ribavirin; SCAR, severe cutaneous adverse reaction; SJS, Stevens–Johnson syndrome; SVR, sustained virologic response; TEN, toxic epidermal necrolysis; TVR, telaprevir.

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Abstract
Effective management of adverse events (AEs) is important to prevent treatment discontinuation and optimize hepatitis C virus infection eradication rates. The addition of direct-acting antiviral agents, telaprevir (TVR) or boceprevir to pegylated interferon (PEG-IFN) and ribavirin (RBV) represents a new era of therapy associated with an improvement in treatment response rates and an impairment of the safety profile compared to PEG-IFN/RBV. An increase in the frequency and severity of anaemia was reported in clinical trials for both drugs, and skin disorders including rash and pruritus occurred more frequently with the TVR-based regimen. These AEs are generally manageable and do not lead to early discontinuation. The management of anaemia has not been clearly established, and the impact of RBV dose reductions and erythropoietin alpha use on treatment efficacy and safety must be clarified. The management of rashes, which were mild and moderate in more than 90% of the cases, is well planned, does not require TVR discontinuation and can be treated using emollients and topical corticosteroids. However, approximately 5% of rashes were severe, and a few cases were classified as severe cutaneous adverse reactions leading to treatment discontinuation.

Because of the consequences of treatment failure in patients with chronic hepatitis C virus (HCV) infection, optimizing treatment efficacy and safety is essential to prevent the development of morbidities and increase survival rates (1–3). Managing adverse events (AEs) during antiviral treatment plays an important role in improving adherence and reducing premature treatment discontinuation. In addition, interactions among different drugs in the regimen may affect the efficacy and/or safety of therapy and must be managed appropriately in each patient. While AEs and drug–drug interactions are generally well established for standard peginterferon (PEG-IFN)/ribavirin (RBV) therapy (4–6), the addition of direct-acting antiviral agents (DAAs) to PEG-IFN/RBV as part of a triple therapy regimen will change the factors to be taken into account in patient management. The oral DAA, telaprevir (TVR) and boceprevir (BOC), in combination with PEG-IFN/RBV, have led to a significant improvement in sustained virologic response (SVR) in HCV genotype 1 patients, but have been associated with an increase in several AEs compared with PEG-IFN/RBV alone. In clinical practice, the effective management of safety and drug–drug interactions will be essential to optimize the benefits provided by these agents for patients infected with HCV genotype 1.

Managing safety and tolerance to triple combination therapy

In placebo-controlled phase II/III studies, the most common AEs that occurred more frequently with TVR than with placebo (>5% difference) included pruritus, rash, anaemia and gastrointestinal disorders (anorectal symptoms, nausea and diarrhoea), which were generally

manageable and did not lead to premature discontinuation (7–9). In both BOC phase III studies, the main AEs were an increase in the occurrence of fatigue, anaemia, nausea, diarrhoea, dysgeusia (taste alteration) and neutropenia (10–12).

Anaemia

Anaemia is a well-known RBV-related event which is exacerbated by the addition of TVR and BOC. The mechanism of anaemia with both DAA was not because of haemolysis but was thought to be the result of a bone-marrow suppressive effect. In clinical trials, triple therapy with TVR or BOC was associated with an increase in the incidence (approximately 20%) and severity of anaemia compared to PEG-IFN/RBV alone (Table 1). The frequency of anaemia, defined as haemoglobin levels below 10 g/dl, was about 50% for triple therapy with BOC and 40% with TVR. Haemoglobin values gradually improved after the end of TVR dosing at week 12 and were similar to those with PEG-IFN/RBV alone by week 20. The impact of anaemia on the SVR rate was different for the two drugs. Anaemia had no effect on efficacy outcomes in treatment-naïve patients (13) with TVR (Fig. 1). In contrast, for BOC, the SVR rate was more frequently achieved in patients with anaemia than in those without in treatment-naïve and -experienced patients (14) (Fig. 2). Premature discontinuation of antiviral treatment because of anaemia remained rare (Table 1). The management of anaemia in TVR and BOC clinical trials is summarized in Table 1. In BOC trials, 43% of patients received erythropoietin alpha (EPO) for the management of anaemia, *de facto* using a quadruple combination therapy (10–12). This may be problematic in clinical practice, as BOC will have to be administered for 24 or 44 weeks. In phase II/III TVR trials, the use of EPO was generally prohibited, but EPO was used in 1% of patients only (9). Blood transfusion was required in less than 5% of the patients for both drugs. A similar proportion of patients underwent RBV dose reductions to manage anaemia, approximately 22–26% (Table 1) (7–12). The retrospective analysis of phase III clinical trials with BOC and TVR showed that RBV dose reduction did not seem to have a negative impact on SVR (Figs 1 and 2) (13, 14). In addition, the use of EPO did not seem to have a positive impact on SVR rate in BOC studies.

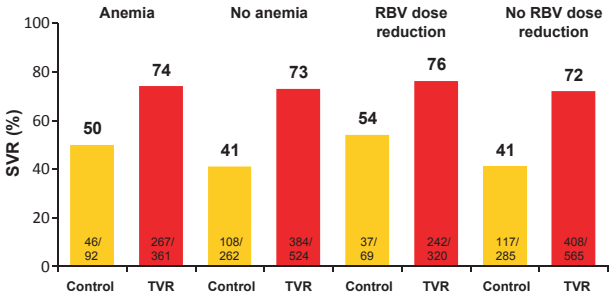


Fig. 1. Impact of anaemia and RBV reduction dose on SVR rate in treatment-naïve patients receiving triple therapy with TVR or PEG-IFN/RBV alone (13).

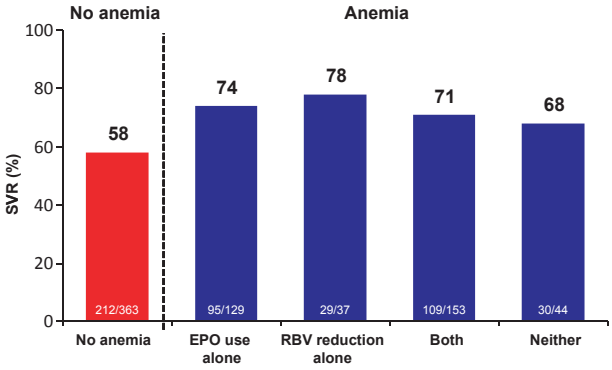


Fig. 2. Impact of anaemia and management of anaemia RBV on SVR rate in treatment-naïve and -experienced patients receiving triple therapy with BOC (14).

These initial analyses must be discussed in relation to the results of large retrospective studies of patients treated with PEG-IFN/RBV. These studies have shown that a dose reduction of RBV only has a negative effect on the efficacy of outcomes when the cumulative dose is less than 60% of the initially planned dose. If the dose reduction of RBV occurs when HCV RNA is undetectable, the impact on SVR seems to be reduced (15). When EPO is used, the full dose of RBV can often be maintained and the quality of life is improved (16). In a *post hoc* analysis of a controlled study involving more than 3000 patients, it has been shown that patients who developed anaemia during a course of PEG-IFN/RBV

Table 1. Incidence and management of anaemia with TVR and BOC in triple combination compared with PEG-IFN/RBV alone in controlled clinical trials (7–12)

	TVR phase II/III placebo-controlled trials (7–9)	BOC phase III clinical trials (10–12)
Incidence of anaemia	32% (TVR) vs 15% (control)	49% (BOC) vs 29% (control)
RBV dose reductions because of anaemia	22% (TVR) vs 9% (control)	26% (BOC) vs 13% (control)
EPO use	Not allowed (1% use in TVR arms)	43% (BOC) vs 24% (control)
Blood transfusions	4.6% (TVR) vs 1.6% (control)	3% (BOC) vs <1% (control)
Premature discontinuation	TVR/placebo alone: 2 vs 0.5% All treatment at the same time: 1% (TVR) vs 0.5% (control)	0–3% (BOC) vs 0–1% (control)

had higher SVR rates than those who did not develop anaemia (17). In this study, EPO increased the chance of eradicating HCV when it was administered in the first 8 weeks, probably when HCV RNA was still detectable. After the eighth week of treatment, EPO had no beneficial effect on the SVR rate. If these results are extrapolated to triple therapy, it may be necessary to maintain the full dose of RBV until HCV RNA becomes undetectable. Thus, EPO could be used according to the local regulations of each country. If anaemia occurs when HCV RNA is undetectable, the RBV dose could be reduced by stages of 200 mg daily. The value of administering EPO or reducing the dose of RBV in patients with haemoglobin levels below 10 g/dl is under investigation in a prospective clinical trial with BOC. The results of this important study will be available in 2012. The initial dose of protease inhibitors must be maintained in all cases. Finally, a few patients with cirrhosis were included in phase III clinical trials with BOC and TVR (7, 8, 10, 11). The first safety report of the CUPIC cohort, related to the French early access programme and including a large number of treatment experienced patients with cirrhosis treated with triple therapy, showed a poor safety profile. BOC or TVR in combination with PEG-IFN/RBV was associated with high rates of serious AEs (40–57%) with a median treatment period of 84–89 days. EPO was used in 41–45% of patients, and blood transfusions were required in 4–17% of patients, suggesting that triple therapy must be administered cautiously with intensive safety monitoring, including anaemia, in patients with cirrhosis (18).

Dermatological adverse events

Dermatological reactions with PEG-IFN/RBV are well established and tend to be a uniform entity of dermatitis: generalized pruritus and skin xerosis, with eczematiform lesions accentuated by erythematous papules and microvesicles that are often excoriated, predominantly located on the extremities and on truncal skin sites exposed to friction (19). These eruptions can be managed using the same approach as for chronic eczema (topical corticosteroids, gradually replaced by emollients), and there is usually no need to discontinue antiviral treatment (20). The new treatment era with DAA is accompanied by additional patient management considerations for HCV-treating physicians. In particular, skin disorders are expected to be more frequent and more severe with triple combination regimens than with PEG-IFN/RBV alone.

In clinical trials, dermatological AEs have been reported at higher frequencies with TVR-based and sometimes with BOC-based therapy, compared with PEG-IFN/RBV alone (7–12). In placebo-controlled TVR phase II/III studies, in which 2012 patients received at least one dose of TVR and 764 patients received at least one dose of placebo, 55% of TVR-treated patients developed a rash compared with 33% of patients treated with PEG-IFN/RBV alone (9). Although it was more extensive and severe, the typical rash in people who received a TVR-based regimen was virtually indistinguishable from the PEG-IFN/RBV rash visually and on histopathology. Rashes were primarily pruritic and eczematous, although some had an additional maculopapular component, which is not consistent with a typical hypersensivity. Histologically, the rash appeared to be a spongiform dermatitis, with predominantly lymphatic or eosinophilic perivascular infiltration. Most (>90%) rashes were mild or moderate (grade 1 and 2), involving less than 30% of the body surface area (BSA), and progression to more severe rash was infrequent (<10%) (9, 21). Approximately 50% of rashes developed within the first 4 weeks of treatment, with the remaining 50% starting between 5 and 12 weeks and the median time to onset of rash (any grade) was 25 days (range 1–350) (21). Therefore, skin eruptions can occur at any time during TVR treatment. Following the end of TVR treatment at week 12, all patients continued to receive PEG-IFN/RBV, and the incidence of rash was similar between TVR and placebo-treated patients.

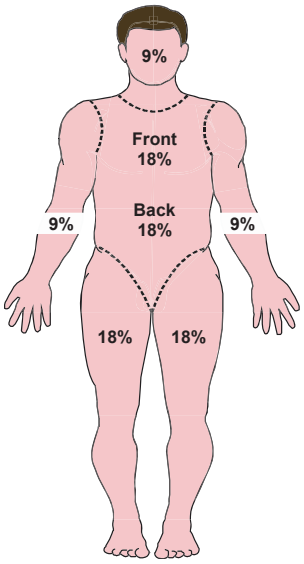
Overall, the incidence of severe or grade 3 rash (primarily eczematous, pruritic and involving more than 50% of BSA) was 4.8 vs 0.4% with PEG-IFN/RBV alone (9). Rash led to premature discontinuation of TVR alone in 5.8% of patients and of TVR combination therapy in 2.6% of patients compared with none of those receiving PEG-IFN/RBV. Following the end of TVR treatment or discontinuation, symptoms improved and usually resolved, although rashes may take several weeks to resolve.

A few cases of rash were classified as severe cutaneous adverse reactions (SCAR), which can be life-threatening if unrecognized or unmanaged, and require immediate discontinuation of antiviral treatment. In placebo-controlled phase II and III trials, 11 patients (0.4%) were recorded as having drug reactions with eosinophilia and systemic symptoms (DRESS) and three patients (<0.1%) had suspected Stevens–Johnson syndrome (SJS) (9, 21). Among the 11 reported cases of DRESS, three were confirmed by a systematic retrospective assessment by expert dermatologists. One of these cases has been reported separately (22). Among the three SJS cases, one occurred 11 weeks after TVR was discontinued and was not considered to be related to TVR. Of the two cases of suspected SJS that occurred during the TVR treatment phase, one was considered to be possible SJS by expert dermatologists and the other probable SJS. All of these severe reactions resolved when treatment was discontinued (9, 21). Finally, the mechanism of TVR-related rash remains unknown and no predictors have been identified.

The second dermatological AE that was frequently reported with TVR was pruritus. This event was generally reported when rash was present, but could also be seen without it. Pruritus may be invalidating and cause rare treatment discontinuations.

Guidance for managing rashes

The goal of physicians should be to give patients the best chance of eradicating HCV, i.e. to continue antiviral therapy when possible in accordance with treatment and rash management protocols. However, to avoid exposing patients to the risk of severe drug-induced cutaneous reactions, physicians treating HCV should be able to easily distinguish between dermatitis and SCAR. The recommendations for grading and monitoring of dermatological reactions and for discontinuation of TVR, PEG-IFN and RBV because of such events are summarized in Table 2 (9). Figure 3 provides a guide to estimate BSA as an indicator of the severity of a dermatological reaction (23). A number of clinical and biological criteria should help physicians to distinguish between TVR-related dermatitis and potential SCAR. If drug rash with eosinophilia and systemic symptoms (DRESS) alert criteria are present, including an onset between 5 and 10 weeks after the first dose of TVR that rapidly progresses to exanthema with a prolonged fever (>38.5°C) that is not related to the PEG-IFN injection and facial oedema, the following confirmation criteria should be assessed: enlarged lymph nodes (at least two sites), eosiniphilia ($\geq$ 700/μl or $\geq$ 10%), atypical lymphocytes, internal organ involvement (liver and kidney) (21). Patients presenting with rapidly progressing exanthema, skin pain, atypical or typical target lesions, mucosal involvement in at least two sites or with blisters or epidermal detachment should be suspected of having SJS and toxic epidermal necrolysis (21).



Adult body	BSA
Perineum	1%
Arm	9%
Head (front and back)	9%
Leg	18%
Chest	18%
Back	18%

Fig. 3. Estimating body surface area (23).

Table 2. Grading and recommendations for managing dermatological reactions with TVR-based triple combination therapy (9, 21)

Extent and features of dermatological reactions	Recommendations for monitoring of dermatological reactions and discontinuation of TVR, PEG-IFN and RBV
Mild rash (grade 1) Localized skin eruption and/or a skin eruption with a limited distribution (up to several isolated sites on the body)	-Monitor for progression or systemic symptoms until the rash is resolved.
Moderate rash (grade 2) Diffuse rash < 50% of BSA	-Monitor for progression or systemic symptoms until the rash is resolved. -Consider consultation with a dermatologist. -For moderate rash that progresses, permanent discontinuation of TVR should be considered. If the rash does not improve within 7 days following TVR discontinuation, RBV should be interrupted. Interruption of RBV may be required sooner if the rash worsens despite discontinuation of TVR. PEG-IFN may be continued unless interruption is medically indicated. -For moderate rash that progresses to severe, permanently discontinue TVR (see below).
Severe rash (grade 3) Extent of rash > 50% of BSA or associated with significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment	-Permanently discontinue TVR immediately. -Consultation with a dermatologist. -Monitor for progression or systemic symptoms until the rash is resolved. -PEG-IFN and RBV may be continued. If improvement is not observed within 7 days of TVR discontinuation, sequential or simultaneous interruption or discontinuation of RBV and/or PEG-IFN should be considered. If medically indicated, earlier interruption of discontinuation of PEG-IFN and RBV might be needed.
SCAR Generalized bullous eruption, DRESS, SJS/TEN, AGEP, erythema multiform	-Permanent and immediate discontinuation of TVR, PEG-IFN and RBV. -Consider consultation with dermatologist.

AGEP, acute generalized exanthematous pustulosis; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

In the case of grade 1 or 2 rash, patients can benefit from guidance on optimal skin care techniques that may limit symptoms and allow optimal antiviral therapy to be continued for as long as possible. Emollient cream, rather than lotions or ointments, may be effective in relieving eczematous reactions. Cream should be applied for at least 15 min, beginning with areas around the joints and progressing with broad strokes across the rest of the skin. This should be begun 15 min after showering or bathing and should be applied daily. Rashes can be primarily treated with topical corticosteroids. Permitted systemic antihistaminic drugs may also be used for the treatment of pruritus. Regular follow up is important, and the patient should be advised to limit exposure to sun/heat. Baking soda or oatmeal baths and loose-fitting clothes can be suggested. If grade 3 rash is present, TVR must be discontinued immediately and can be managed with topical corticosteroids without antiviral treatment (PEG-IFN/RBV) discontinuation. In case of SCAR, all antiviral treatment must be discontinued immediately, and the patient must be hospitalized in an appropriate department.

Anorectal disorders

In placebo-controlled TVR phase II/III trials, anorectal AEs occurred more frequently in TVR arms than in control arms: 26.2 vs 5.4% respectively (7–9). Events usually developed within the first 2 weeks of treatment. Reported events included haemorrhoids, anal pruritus, anal discomfort or rectal burning. Most of these events were mild to moderate, very few led to treatment discontinuation, and they resolved after completion of TVR dosing. The mechanism is unknown and no evident association was found with either generalized pruritus or skin rash. An anal examination should be performed to exclude lesions that could explain the symptoms, especially haemorrhoids, fissure nor fistula. Generally, an anal examination shows non-specific erythema secondary to itching. Standard symptomatic care may be considered for managing anorectal disorders, including short-term use of non-specific topical ± including local anaesthetic in case of rectal burning. Topical corticosteroids and allowed systemic antihistaminic drugs may also be used for the treatment of pruritus.

Managing drug–drug interactions

Drug–drug interactions that lower antiviral or concomitant medication drug levels to below therapeutic ranges can result in a loss of efficacy, with suboptimal drug pressure potentially leading to drug resistance (24). In contrast, drug–drug interactions that elevate drug levels and exposure can increase the risk of AEs (24). Both of these effects may reduce the chances of treatment success, but with effective management they can be lessened.

The mechanisms of drug–drug interactions include absorption, gastrointestinal metabolism or transport, and hepatic metabolism or transport. For example, liver enzymes such as cytochrome P450 (CYP) 3A and transporters such as P-glycoprotein (P-gp) may affect plasma drug concentrations. Ultimately, whether an interaction takes place is dependent upon characteristics of both the drug and the patient.

Table 3 summarizes the key pharmacological characteristics of TVR and BOC that need to be accounted for when considering the risk of drug–drug interactions (9, 12).

As a result of these characteristics, TVR and BOC are contraindicated with a number of drugs, in particular those that are highly dependent on CYP 3A (TVR) or CYP 3A4/5 (BOC) for clearance and for which elevated plasma concentrations are associated with serious of life-threatening events. Concomitant administration of TVR with active substances that strongly induce CYP 3A, and thus may lead to lower exposure and loss of efficacy of TVR, is also contraindicated (Table 4) (9, 12).

In summary, it is important to review all medications prior to initiation of triple combination therapy. Once this information has been collected, a key source of information and recommendations regarding co-administration with different compounds is the drug product label (9, 12). As with HIV, online tools are now also becoming available to help healthcare professionals predict, avoid and manage drug interactions in HCV.

Conclusion

The addition of DAA (TVR or BOC) to PEG-IFN/RBV therapy will change the spectrum of elements to be taken into consideration for patient management

Table 3. Summary of key pharmacological characteristics of TVR and BOC (9, 12, 25, 26)

Drug	Dosing regimen	CYP	P-glycoprotein	Non-CYP metabolism
TVR	q8h No significant boosting by ritonavir	CYP 3A4: ■ Substrate ■ Inhibitor	■ Substrate ■ Inhibitor	_
BOC	tid No significant boosting by ritonavir	CYP 3A4/5: ■ Substrate ■ Inhibitor	■ Substrate	■ Substrate (aldo-keto reductase 1C2/1C3)

q8h, every 8 h; tid, three times daily.

Table 4. Contraindications to TVR and BOC (9, 12)

Class	Agent	TVR (9)	BOC (12)
Alpha-1 receptor antagonists	Alfuzosin	Contraindicated	No recommendation
Antiarrhythmics	Amiodarone, bepridil, quinidine	Contraindicated (with class Ia/III, except IV lidocaine)	Bepridil contraindicated Caution with amiodarone/quinidine
Anticonvulsants	Carbamazepine, Phenobarbital, phenytoin	Contraindicated	No data available not recommended
Antihistamines	Astemizole, terfenadine	Contraindicated	No recommendation
Antimalarials	Lumefantrine, halofantrine	No recommendation	Contraindicated
Antimycobacterials	Rifampicin	Contraindicated	No data available not recommended
Antipsychotics	Pimozide	Contraindicated	No data available not recommended
Benzodiazepines	Oral midazolam, oral triazolam	Contraindicated	Contraindicated
Digestive motility stimulants	Cisapride	Contraindicated	No recommendation
Ergot rye derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Contraindicated	Contraindicated
Herbal products	St John's wort (Hypericum perforatum)	Contraindicated	No recommendation
HMG-CoA reductase inhibitors	Atorvastatin, simvastatin, lovastatin	Contraindicated	No data available. Therapeutic monitoring recommended (atorvastatin, simvastatin)
PDES inhibitors	Sildenafil, tadalafil	Contraindicated	No recommendation
Tyrosine Kinase inhibitors	Not specified	No recommendation	Contraindicated

compared to PEG-IFN/RBV alone (27). The main AEs reported in clinical trials evaluating the efficacy and safety of TVR or BOC in combination with PEG-IFN/RBV were generally manageable and did not lead to premature discontinuation, although an increase in the frequency and severity of anaemia and skin disorders relative to PEG-IFN/RBV alone were noted. In clinical practice, monitoring and effective management of AEs and drug–drug interactions will be essential to optimize treatment with TVR and BOC and improve cure rates across different patient populations.

Conflicts of interest

Christophe Hézode is a speaker and adviser for BMS, Gilead, Merck, Roche and Janssen.

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