Hepatitis C Patient Management Issues in the Era of Protease Inhibitor Based Triple Therapy

INTRODUCTION

Hepatitis C (HCV) affects approximately 180 million people worldwide, with genotype 1 (G1) being the most common as well as the most difficult strain to cure. With the addition of a protease inhibitor (PI) [either Telaprevir (TVR) or Boceprevir (BOC)] to pegylated interferon (PIFN) plus ribavirin (RBV), the percentage of G1 HCV patients capable of achieving a sustained virologic response (SVR), defined as HCVRNA undetectable 24 weeks after treatment termination, has dramatically improved. However, patient management has become increasingly complex. The incidence and severity of side effects including rash, anemia, anorectal problems and dysgeusia have increased. In addition, the clinician must now be aware of an abundance of potential drug-to-drug interactions (DDIs).

This article, the 4th in this series, will review the most commonly encountered side effects associated with BOC or TVR plus PIFN/RBV (triple therapy) and will outline strategies for successful management aimed at increasing adherence without compromising efficacy. Pharmacologic characteristics of TVR and BOC in addition to DDIs associated with triple therapy will also be addressed.
required termination of triple therapy due to rash. (7,8) While rash resolution may take weeks, in clinical trials eventually all dermatologic events resolved after treatment termination.

While serious skin rashes occur infrequently, it is crucial for the clinician to be aware of this potential life-threatening complication, as all patients require triple therapy treatment discontinuation, hospitalization and prompt dermatologic evaluation. Stevens-Johnson Syndrome (SJS) is a dermatologic condition in which cell death leads to the separation of the epidermis from the dermis. Mucous membrane involvement with ulcerations and erosions on lips and conjunctiva may also occur. During clinical trials, SJS was suspected in two patients and confirmed in one patient who received TVR. All reported cases eventually resolved. (6)

Drug-reaction with eosinophilia and systemic symptoms (DRESS) syndrome is considered to be a drug hypersensitivity manifesting as rash, fever, internal organ inflammation, lymphadenopathy, and eosinophilia. As opposed to SJS which has an acute presentation, DRESS has a slower, more progressive course. There were three cases of confirmed and an additional eight cases of suspected DRESS in TVR clinical trials. Of these cases, one patient was lost to follow-up and the other patients recovered. (6)

The clinician must be able to confidently distinguish between and aggressively manage TVR-induced rashes. Inaccurate rash assessment and management may lead to lack of patient adherence to therapy, inappropriate early termination of treatment leading to decreased treatment efficacy or delayed termination of treatment and referral to a dermatologist with potential life-threatening outcomes. It is important to remember that TVR must never be dose-reduced and once TVR has been discontinued, it must never be restarted. (6)

Table 2 provides a summary of the grading and recommended management strategies of TVR-induced skin rashes adapted during Phase 3 clinical trials. (14) Figures 1-4 provide photographs from patients with Grade 1-3 TVR-induced rashes.

### ANEMIA

Anemia is a common side of HCV therapy. In clinical trials of PIFN/RBV mean decline in hemoglobin ranged between 2.5 g/dL and 3.7 g/dL and dose reductions due to anemia were required in 9% -22% of patients. (15,16) The anemia associated with PIFN is due to bone marrow suppression and is slowly progressive such that it typically accounts for the continued decline in hemoglobin concentration during the second and third months of treatment. The anemia associated with RBV is due to dose-dependent red blood cell hemolysis in addition to down-regulation of erythropoietin receptors. RBV-associated anemia typically occurs during the first four weeks of therapy with hemoglobin reductions between 2-3 gm./dL. (15,16) RBV-associated hemolysis is the primary reason for dose reductions and treatment

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### Grade 1 Mild Rash

**Definition**
Localized rash and/or rash with limited distribution, ± pruritus

**Management**
1. Topical corticosteroid cream (avoid oral corticosteroids)
2. Oral antihistamines
3. Oatmeal-based soaps and lotions
4. Hypoallergenic skin products
5. Loose-fitting cotton clothing
7. Adequate hydration
8. Sun avoidance/use sunscreen with high SPF
9. Use mild clothes detergent
10. Observe for worsening or systemic symptoms
11. *Continue TVR*

### Grade 2 Moderate Rash

**Definition**
Diffuse rash involving < 50% BSA ± superficial skin peeling, pruritus or mucous membrane involvement with no ulceration

**Management**
Steps 1-10

If rash progresses:
- a. Permanent TVR Discontinuation
- b. If no improvement within 7 days- discontinue RBV
- c. If rash worsens prior to 7 days discontinue RBV earlier

### Grade 3 Severe Rash

**Definition**
Generalized rash involving either > 50% BSA or rash associated with vesicles, bullae or ulceration other than SJS

**Management**
Steps 1-10

Immediate discontinuation of TVR
If no improvement within 7 days- discontinue RBV and/or IFN
If rash worsens prior to 7 days discontinue RBV and/or IFN earlier

Consider consultation with a dermatologist

### Grade 4 Life Threatening or Systemic Involvement

**Definition**
SJS/DRESS

**Management**
Immediate discontinuation of all treatment
Hospitalization
Consultation with a dermatologist

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*Table 2. Management of Telaprevir-Associated Rash* Adapted from reference 14

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termination due to anemia in patients taking PIFN/ RBV. (17) Studies have shown that G1 patients with inosine triphosphatase (ITPA) deficiency, a benign inherited enzymopathy in which inosine triphosphate accumulates in red blood cells, are protected from RBV-associated hemolytic anemia. These patients are less likely to require RBV dose reductions. (18,19)

Avoidance of prolonged dose reductions of PIFN and especially RBV has historically been a crucial factor in optimizing treatment efficacy. Retrospective analysis of PIFN/RBV trials demonstrated that G1 patients not achieving a rapid virologic response (RVR), defined as HCVRNA undetectable four weeks after therapy has begun, were statistically significantly less likely to achieve SVR when cumulative RBV dose exposure (due to dose reduction, premature cessation, or skipped doses) was < 60%. (20) This study also demonstrated that the impact of RBV dose reduction is significantly lessened once the HCVRNA level is undetectable.

The addition of either BOC or TVR to PIFN/ RBV increases the incidence of anemia, which is due to PI – induced bone marrow suppression. In clinical trials of BOC triple therapy versus a control group treated with PIFN/RBV, 49% of patients experienced anemia, defined as a hemoglobin level < 10 g/dL, and 26% of patients required RBV dose reduction due to anemia versus 29% and 13% respectively in controls. Erythropoietin alpha (EPO) was administered to patients (at the investigators discretion) in 43% of patients on BOC triple therapy versus 24% of controls. In patients on BOC triple therapy 3% required blood transfusions and approximately 3% discontinued therapy early due to anemia versus <1% and <1% respectively in controls. (9,10)

In clinical trials of TVR triple therapy versus a control group treated with PIFN/RBV, 32% of patients experienced anemia and 22% of patients required RBV dose reduction due to anemia versus 15% and 9% respectively in controls. EPO use was prohibited in TVR-based studies. In patients on TVR triple therapy, 4.6% required blood transfusions and 2% discontinued therapy early due to anemia versus 1.6% and 0.5% respectively in controls. (7,8)

Sulkowski et al found that patients who developed anemia while on PIFN/RBV were more likely to achieve SVR compared with patients not becoming anemic during combination therapy (21), a trend that was similarly found in BOC triple therapy clinical trials (22) but not in TVR triple therapy clinical trials. (23)

EPO improves quality of life in anemic patients during therapy, (26) which leads to improved adherence, and lessens the need for ribavirin dose reductions. However, studies have revealed conflicting results as to the impact of EPO on SVR. (27,28).

The likelihood of achieving SVR has been found to be independent of RBV dose reductions or EPO use during therapy. (Figures 5 and 6) This important finding demonstrates that SVR rates are not adversely impacted by managing side effects by decreasing RBV dose, especially once HCVRNA levels become undetectable. (29) It should be noted that RBV dose reduction criteria differed in BOC and TVR clinical trials. In TVR-based trials RBV was dose reduced to 600 mg/day while in BOC-based trials RBV was dose reduced by 200 mg intervals. While predictors of anemia with BOC triple therapy have yet to be determined, predictors of anemia during TVR triple therapy include older age, lower BMI, lower HGB, advanced liver disease, genotype 1b, and (GFR) peg/ribavirin.
lower BMI, lower hemoglobin, advanced liver disease and genotype 1b. (29) (Table 3) Thus, patients with these characteristics, especially those with advanced liver disease, should be monitored for anemia at more frequent intervals. It is contraindicated to dose reduce BOC or TVR, or to use BOC or TVR as monotherapy under any circumstances. RBV dosages may be held for up to fourteen days. Permanent discontinuation of RBV requires permanent discontinuation of BOC or TVR due to the risk of developing drug resistance.

Anorectal Disorders

Anorectal adverse events including hemorrhoids, pruritus, pain, burning and diarrhea occur more commonly in TVR-based regimens compared to PIFN/RBV alone (29 % vs. 7% respectively), and have not been a significant problem with BOC-based regimens. (30) While the exact mechanism of anorectal events is unknown, it is postulated that it may involve the 20 gram fat diet requirement necessary for absorption of TVR, although this has not been confirmed. There are no predictors for the development of anorectal disorders, and there is no correlation with skin rash. In clinical trials, most anorectal adverse events occurred within the first two weeks of TVR triple therapy and were considered to be mild to moderate in severity. Only 1% of patients discontinued therapy due to anorectal symptoms.

A baseline anorectal exam prior to initiation of therapy with treatment of pre-existing anorectal disorders is recommended. In clinical trials on-treatment anorectal exam typically revealed hemorrhoids and non-specific pruritus-induced erythema. General clinical symptomatic care should be recommended to patients. This may include sitz baths, topical corticosteroid creams, topical numbing preparations such as lidocaine gel, calmsoneptine topical cream, pramoxine topical cream, diarrheal management, loperamide, stool softeners, and fiber. Oral antihistamines and mild analgesics have also been used. Good anorectal hygiene should be discussed with the patient. This includes avoiding scented lotions and/or toilet paper, as well as nylon and tight fitting undergarments that can contain moisture. Anorectal symptoms typically resolve either during TVR therapy or after TVR is completed, thus all attempts should be made to prevent early TVR termination.

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Dysgeusia

Dysgeusia, an altered taste sensation, occurred in approximately 40% of patients taking BOC triple therapy and in 10% of those patients taking TVR triple therapy in clinical trials. While typically mild to moderate in intensity, it is a side effect that can be quite bothersome to patients, and thus could potentially lead to decreased patient compliance with therapy. While there have been no clinical studies specifically addressing dysgeusia treatment in HCV patients on triple therapy, it is advantageous for the healthcare practitioner to be familiar with commonly recommended therapies. Zinc supplementation has been used successfully in the treatment of idiopathic dysgeusia. (31) Since oral zinc supplementation may slow HCV disease progression, may reduce the incidence of HCV-related hepatocellular carcinoma (HCC) and may improve response to antiviral treatment, it seems reasonable to suggest...
**Table 5. Examples of Foods with ≥ 20g of Fat (42)**

- Bagel with cream cheese
- 1/2 cup of nuts
- 3 tablespoons of peanut butter
- 1 cup of ice cream
- 2 ounces of American or cheddar cheese
- 2 ounces of potato chips
- 1/2 cup of trail mix
- 1 cup of granola (33 g)
- 3 slices of homemade French toast
- 2 cups 3.3% whole milk
- 2 oz. chocolate candy bar with almonds or peanuts
- 2 2oz. plain doughnuts
- 1 slice pecan pie
- 1 medium avocado
- 3.5 oz. lean hamburger in bun
- 3.5 oz. salami
- 4 slices of bologna
- 1 3.5 oz broiled pork chop
- 3 3.5 oz. sausage patties
- 2 cups chow mein noodles
- 1 7 oz. fried chicken breast
- 2 small roasted chicken legs

**Table 6. Pharmacologic Characteristics of BOC and TVR**

**Boceprevir**
- TID (q 7-9 hours)
- Must be dosed with food (high fat not a requirement)
- 4 (200 mg) tabs TID
- Cannot be used as monotherapy
- Cannot be dose reduced
- No dose adjustment with renal impairment

**Telaprevir**
- Q 8 hours (q 7-9 hours)
- With high fat food (≥ 20 grams of fat required)
- 2 (375 mg) tabs q8h
- Cannot be used as monotherapy
- Cannot be dose reduced
- No dose adjustment with renal impairment

Zinc as a treatment option for dysgeusia. (32,33,34) It should also be kept in mind that while daily dosages up to 100mg of zinc may boost the immune system and improve response to interferon, an excess of this amount of zinc may be immunosuppressive. (35).

Good oral hygiene should be encouraged. Meticulous, but not excessive brushing (3-4 times per day) and gentle flossing is crucial, unless gums are already inflammed. The mouth should be rinsed with baking soda, but not commercial mouthwashes as many of these contain alcohol. Mucositis may be diminished by lubricating the corners of the mouth and the lips with petroleum jelly on a regular basis, especially prior to bedtime. A topical corticosteroid such as fluocinomide (Lidex) 0.05%, or clobetasol (Temovate) 0.05% may enhance the healing process. A corticosteroid mouth rinse such as dexamethasone elixir may also be helpful. Use of oral corticosteroids is contraindicated due to potential DDIs with BOC or TVR. Topical anesthetics such as Xylocaine or Orabase B, or an anesthetic mouthwash or spray such as Hurricane liquid should also be considered.

Mouth infections such as herpes or fungal infections may occur due to neutropenia, which is increased in incidence with BOC-based triple therapy compared with PIFN/RBV (23% versus 18% respectively). (36) Oral thrush requires mycostatin, usually taken as a swish and swallow preparation. Diflucan (fluconazole) should be used with caution due to potential DDIs. Increasing the flow of saliva, which contains antibacterials, can be achieved by recommending chewing sugarless
### Table 7. Drugs with Absolute and Relative Contraindications for use with BOC or TVR

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<tr>
<th>Drugs with Absolute Contraindications</th>
<th>Drugs with Relative Contraindication</th>
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<tr>
<td>Alfuzosin</td>
<td>Alprazolam</td>
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<td>Atorvastatin (TVR)</td>
<td>Amiodarone</td>
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<tr>
<td>Carbamazepine (BOC)</td>
<td>Atorvastatin (BOC)</td>
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<tr>
<td>Cisapride</td>
<td>Amlodipine (TVR)</td>
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<tr>
<td>Didanosine (contraindicated with ribavirin)</td>
<td>Bepridil</td>
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<td>Dihydroergotamine</td>
<td>Bosentan</td>
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<td>Drospirenone (BOC)</td>
<td>Budesonide (inhaled)</td>
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<tr>
<td>Ergonovine</td>
<td>Buprenorphine (BOC)</td>
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<tr>
<td>Ergotamine</td>
<td>Carbamazepine (TVR)</td>
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<tr>
<td>Lovastatin</td>
<td>Clarithromycin</td>
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<td>Methylergonovine</td>
<td>Colchicine</td>
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<td>Midazolam (orally administered)</td>
<td>Cyclosporine</td>
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<td>Phenobarbital (BOC)</td>
<td>Desipramine</td>
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<td>Phenytoin (BOC)</td>
<td>Dexamethasone (systemic)</td>
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<td>Pimozide</td>
<td>Digoxin</td>
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<tr>
<td>Rifampin</td>
<td>Diltiazem (TVR)</td>
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<td>St. John’s wort</td>
<td>Efavirenz</td>
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<td>Sildenafil or tadalafil (when used for the treatment of pulmonary arterial hypertension)</td>
<td>Ethinyl estradiol</td>
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<td>Simvastatin</td>
<td>Erythromycin (TVR)</td>
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<td>Triazolam</td>
<td>Escitalopram (TVR)</td>
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<td>Felodipine</td>
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<td>Methadone</td>
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<td>Methylprednisolone (systemic)</td>
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<td>Midazolam (intravenous)</td>
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<td>Rifabutin</td>
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<td>Ritonavir (Norvir) in combination with atazanavir (Reyataz) or darunavir (Prezista), or with Kaletra (lopinavir/ritonavir)</td>
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<td>Salmeterol (inhaled)</td>
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<td>Sildenafil (contraindicated if for pulmonary arterial arterial hypertension)</td>
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<td>Sirolimus</td>
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<td>Tacrolimus</td>
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<td>Tadalafil (contraindicated if for pulmonary arterial hypertension)</td>
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<td></td>
<td>Tenofovir disoproxil fumarate (TVR)</td>
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<td>Trazodone</td>
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<td>Vardenafil</td>
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<td>Verapamil (TVR)</td>
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<td>Voriconazole</td>
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<td>Warfarin</td>
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<td>Zolpidem (TVR)</td>
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*(continued on page 44)*
Gum and drinking plenty of fluids throughout the day. Additional management strategies for dysgeusia are listed in table 4. (37,38,39)

**Pharmacologic Characteristics of BOC and TVR**

BOC and TVR must be administered three times per day due to their short half-lives and poor gastrointestinal (GI) absorption. BOC requires twelve pills per day, dosed as four 200 mg pills three times per day (every 7-9 hours). TVR requires six pills per day, dosed as two 375 mg pills every 8 hours (range 7-9 hours). It should be noted that studies of TVR dosed at four pills every 12 hours proved to be equally efficacious. (40) While both PIs must be taken with food, in contrast to BOC, TVR must be taken within 30 minutes of consuming a high fat (>20 grams of fat) meal in order to enhance GI absorption (41) Examples of foods containing 20 grams of fat are detailed in Table 5. (42) Neither PI can be dose reduced or used as monotherapy. No dose adjustment is required for renal impairment. (Table 6)

Both BOC and TVR are strong reversible inhibitors of cytochrome P 450 (CYP) 3/4 A and the CYP 3 A, respectively, and are substrates and inhibitors of P-glycoprotein, a protein that transports a variety of drug substrates. Due to their mode of metabolism and transport, the likelihood for DDIs is increased, which in turn can cause serious drug toxicity and/or decreased drug efficacy. Since more than half of all medications are metabolized via CYP 3A, (43) prior to starting BOC or TVR triple therapy, health-care practitioners must take a meticulous medication history with attention to both prescription and over-the-counter medications including herbal therapies. Since there are hundreds of potential DDIs an exhaustive review is beyond the scope of this article and there are many easy to use apps and websites such as Epocrates that comprehensively address DDIs with BOC and TVR. A list of drugs with absolute and relative contraindications can be found in Table 7.

Examples of medications that are absolutely contraindicated during BOC or TVR triple therapy are the HMG-CoA reductase inhibitors simvastatin and lovastatin. When combined with inhibitors of CYP 3/4A, HMG-CoA reductase inhibitor toxicities can increase leading to severe myopathies or even rhabdomyolysis. (44) Thus, using an alternative lipid-lowering agent is recommended during BOC or TVR therapy. If a drug on the relative contraindicated list is used its dose must be adjusted in the appropriate manner. For example, the antianxiolytic effect of alprazolam is prolonged when combined with either TVR or BOC, and therefore alprazolam requires a dose reduction prior to its use.
The effectiveness of estrogen-containing birth control pills is reduced when used with either BOC or TVR, thus two alternative forms of contraception are required during therapy.

CONCLUSION

With the FDA approval of BOC and TVR, treatment of HCV has become more rewarding, yet much more complex for both the patient and the healthcare practitioner. Adapting to new concepts such as stringent dosing requirements, awareness of drug-drug interactions, avoidance of PI dose reductions, and more liberal use of RBV dose reductions are necessary. Patient education surrounding these issues, as well as prompt and aggressive management by the healthcare provider of adverse events will result in a decreased incidence of premature discontinuation, a reduction of drug toxicities, improvements in treatment adherence and overall success of therapy.

References

29. Foster, Graham et al. Impact Of Anemia And Ribavirin Dose Reduction On Svr To A Telaprevir-Based Regimen In Patients With Hcv Genotype 1 And Prior Peginterferon/Ribavirin Treatment Failure In The Phase 3 Realize Study Presented at the 22nd Conference of the Asian Pacific Association for the Study of the Liver (APASL) Taipei, Taiwan February 16-19, 2012.
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