Review

Management of HCV Treatment-related Side-effects, Toxicity, and Drug-interactions

Jenna K. Kawamoto, PharmD;[1] Jason P. Smith, PharmD;[1]
Steven-Huy B. Han, MD, AGAF[1,2]*

[1] *Department of Veterans Affairs, Greater Los Angeles Healthcare System, Los Angeles, CA*
[2] *Pfleger Liver Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Direct-acting antiviral (DAA) protease inhibitors, boceprevir (BOC) and telaprevir (TVR) were FDA-approved in 2011 to be used in combination with pegylated interferon (peg-IFN) and ribavirin for the treatment of chronic hepatitis C virus infection (HCV) genotype 1. The addition of these new DAAs increased cure rates but also increased rates of adverse events and drug interactions. This review will evaluate HCV treatment-related side-effects, toxicity, and drug-interactions and management. Understanding and identifying adverse events and drug interactions will help enable the provider to minimize treatment discontinuation, prevent serious adverse events, and optimize treatment for patients. *[N A J Med Sci. 2014;7(1):33-37.* **DOI:** *10.7156/najms.2014.0701033]*

Key Words: *Hepatitis C, protease inhibitors, boceprevir, telaprevir, adverse events, drug interactions*

INTRODUCTION

It is estimated that approximately 170 million people in the world are infected with the hepatitis C virus (HCV).[1] The overall treatment goal in patients with HCV is eradication by obtaining a sustained virologic response (SVR), which is regarded as virologic cure. SVR has been associated with a decrease in all-cause mortality, prevention of long-term complications of cirrhosis, reduction in risk of hepatocellular carcinoma, reversal of liver fibrosis, and reduction in extrahepatic manifestations of HCV.[2-4] Revolutionary direct-acting antiviral (DAA) protease inhibitors, boceprevir (Victrelis®) and telaprevir (Incivek®) were FDA approved in May 2011 for chronic HCV genotype 1 infection to be used in combination with pegylated interferon and ribavirin. The addition of these protease inhibitors have been shown to increase SVR rates from 40-50% with conventional therapies to over 70%.[5-8] However, along with increased cure rates, triple therapy with boceprevir (BOC) and telaprevir (TVR) has added additional adverse side effects and drug interactions which can further complicate treatment.

ADVERSE SIDE EFFECTS

Protease inhibitors, BOC and TVR each have their own unique adverse side effects. BOC is associated with more bone marrow suppression (anemia, neutropenia, thrombocytopenia), and dysguesia. TVR's unique side effects are skin rash, anorectal symptoms, and anemia as well. It is important to remember that BOC and TVR should never be dose reduced in the management of adverse side effects or drug interactions.

Received 01/04/2013; Revised 01/17/2014; Accepted 01/19/2014
***Corresponding Author:** Pfleger Liver Institute, 200 UCLA Medical Plaza, Suite 214, Los Angeles, CA 90095. Tel: 310-794-5970. (Email: sbhan@mednet.ucla.edu)

Anemia

In clinical trials, anemia rates almost doubled in those treated with BOC or TVR compared to those treated with dual therapy (37-52% and 12-32%, respectively).[5-8] Hemoglobin levels decreased by about 4 g/dL with a protease inhibitor compared to about 3 g/dL with dual therapy. Hemoglobin nadirs occurred most commonly during weeks 12 to 16 in patients treated TVR compared to week 24 with BOC treatment.[9] Risk factors for developing anemia include age above 50 years, female gender, low baseline hemoglobin, baseline platelet count < 150,000/µL, baseline creatinine clearance < 1.5 g/dL, no lead-in phase, a decrease in hemoglobin of 2 g/dL or more after 2 weeks of treatment with dual therapy, or the presence of a high function inosine triphosphates (ITPA) genotype.[6,9-12] The mechanisms of anemia include hemolysis from ribavirin and TVR and bone-marrow suppression from pegylated interferon (peg-IFN), BOC, and TVR.

The goal of anemia management is to maintain a safe hemoglobin level to mitigate symptoms while optimizing ribavirin and peg-IFN dose to maintain SVR. Strategies for the management of anemia include ribavirin and peg-IFN dose reduction, erythropoietin (EPO)-stimulating agents (ESAs), and blood transfusions. The initial recommended strategy for anemia management is ribavirin dose reduction. Package labeling recommends decreasing ribavirin by 200 mg/day increments or to 600 mg/day when hemoglobin falls below 10 g/dL, but remains > 8.5 g/dL. If hemoglobin falls below 8.5 g/dL, package labeling recommends discontinuing ribavirin until resolution. However, if ribavirin is stopped for seven days or more while receiving BOC or TVR, treatment must be permanently discontinued. In a randomized trial of ribavirin dose reduction versus EPO in patients treated with BOC, patients who received less than 50% of their total

milligram dose of ribavirin had a significantly lower SVR compared to those patients who received 50% or more of their total milligram dose of ribavirin.[13] In patients treated with TVR, it was shown that there was no difference in SVR in treatment-naïve patients who had a ribavirin dose reduction of 600 mg or less compared to those with no dose reduction.[14] Therefore, in patients treated with TVR, it may be advisable to dose reduce ribavirin rather than using EPO as EPO use was prohibited in TVR phase III clinical trials. This extensive reduction of ribavirin dose without effect on SVR may be adequate due to increased ribavirin plasma and intracellular concentrations when used with TVR.[15]

An adjunct to ribavirin dose reduction is using ESAs. ESAs are theorized to improve Hgb by increasing reticulocytosis to overcome bone marrow suppression induced by peg-IFN, BOC, and TVR. It is important to note that ESAs are not FDA-approved for the indication of management of HCV-induced anemia and carry a black box warning for increased thromboembolic events. Therefore, their use should be minimized. It is recommended to initiate an ESA when hemoglobin falls below 10 g/dL and after iron, vitamin B-12, and folate deficiency have been ruled out. In practice, EPO-alfa is started at 40,000 units weekly or darbepoetin alfa 1.5 µg/kg/week and titrated to maintain hemoglobin levels around 10 g/dL. If the patient is clearly not responding to an ESA or if hemoglobin increases to 12 g/dl or above, then the ESA should be discontinued. It is important to remember that the full effect of ESA administration may take a couple weeks; therefore, early administration of ESAs may be appropriate for anticipated hemoglobin drops. If the anemia is primarily due to bone marrow suppression, an ESA will not likely be effective and should be discontinued. At best, ESA use allows maintenance of optimal ribavirin and peg-IFN dosing and improves the patient's quality of life by increasing hemoglobin levels. However there has no conclusive evidence that EPO use increases SVR compared to ribavirin dose reduction when using a protease inhibitor.

Packed red cell transfusions are recommended if hemoglobins fall below 7.5 g/dL and/or clinical symptoms develop. Red blood cells should be given in 2-3 unit infusions per episode as to avoid complications from overload.

Neutropenia

Recommended management of HCV treatment induced neutropenia is peg-IFN dose reduction. Package labeling recommends reducing peg-IFN alfa-2a dose to 135 mcg per week if the absolute neutrophil count (ANC) falls below 750 cells/µL and to discontinue peg-IFN alfa-2b if the ANC falls below 500 cells/µL.[16] However, a study in patients treated with peg-IFN and ribavirin has shown that interferon-induced neutropenia, even when ANC < 500 cells/µL, does not increase the risk of infections.[17] Rather, other factors such as cirrhosis, hyperglycemia, and age > 55 years at baseline significantly increased the risk of infection during HCV treatment regardless of ANC.[17] In general, maintaining peg-IFN doses above 60% of the maximal dose does not compromise efficacy rates in patients treated with dual therapy; however, there is limited data on the impact of SVR rates and peg-IFN dose reduction in patients receiving BOC or TVR.[18] An alternative to peg-IFN dose reduction is the use of granulocyte colony stimulating factor (GCSF). GCSF may be considered in cases of severe neutropenia (< 500 cells/µL) or if patients have risk factors for infection. The target ANC is between 500 and 1000 cells/µL. Close monitoring of the patient's complete blood cell count (CBC) is indicated, and blood should be drawn right before the next dose of GCSF since the ANC may be falsely elevated if checked after the dose of GCSF.

Thrombocytopenia

Thrombocytopenia is also a dose limiting adverse effect of peg-IFN that may necessitate peg-IFN dose reduction or discontinuation of treatment. The addition of BOC and TVR increases the risk of thrombocytopenia. Package labeling recommends decreasing peg-IFN alfa-2a to 90 mcg per week if platelets fall below 50,000/µL and to discontinue peg-IFN if platelets fall below 25,000/ µL.[16] Reassuringly, in one study by Roomer et al, severe bleeding events did not occur in patients whose platelet counts dropped below 50,000/µL when treated with peg-IFN and ribavirin.[17] Patients with HCV-related cirrhosis often have baseline platelet counts < 150,000/µL, which prohibits initiating antiviral treatment, results in early IFN dose reductions, or results in premature discontinuation of antiviral treatment. Eltrombopag is an oral thrombopoietin receptor agonist, FDA-approved for use in patients with chronic hepatitis C and thrombocytopenia, to allow patients to initiate and maintain interferon-based therapy.[19] In clinical trials with eltrombopag, SVR rates were significantly higher in patients with thrombocytopenia who were started on eltrombopag prior to initiation of peg-IFN and ribavirin.[20,21] However, in both studies, patients receiving eltrombopag had more thromboembolic events, progression of cataracts, and hepatobiliary adverse events. The package labeling for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation.[19]

Dermatologic Events

The typical rash associated with peg-IFN and ribavirin therapy is generalized pruritus, zerosis, and eczematous lesions. Skin disorders occurred at a higher rate with the addition of TVR and less frequently with BOC. In TVR trials, approximately half of the patients experienced rash with the majority of cases being mild to moderate and did not progress. However, there were a few reported cases of severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Rash may occur any time during treatment, even after discontinuation of TVR with a median time to onset of 25 days.[22] The mechanism of TVR-induced rash is unknown.

Grade 1 (mild) rash is defined as localized skin eruptions limited to one or several sites with or without pruritus. Grade 2 (moderate) rash is defined as diffuse skin eruptions involving up to 50% of body surface area with no ulcerations. Grade 3 (severe) rash is defined as generalized skin eruptions

involving more than 50% of body surface area or associated with significant systemic symptoms such as rash with bullae, vesicles, mucous membrane ulcerations, target lesions, purpura, or epidermal detachment.[5,6] For mild to moderate rash, the TVR prescribing information does not require TVR discontinuation and can be treated with topical emollients/moisturizers, topical corticosteroids, or oral antihistamines. For severe rash, discontinuation of TVR is recommended and peg-IFN and ribavirin may be continued. During this time, if symptoms worsen or do not improve within 7 days of stopping TVR, then discontinuation of ribavirin and peg-IFN is recommended. Symptomatic treatment for mild to moderate rash may be instituted as previously described. If a life-threatening or systemic reaction such as SJS, TEN, or DRESS is suspected, then all antiviral medications should be discontinued and treatment with systemic corticosteroids considered.[5,6]

If patients develop rash, it may be prudent to refer patients to an experienced dermatologist. Furthermore, for all dermatologic reactions, it is important to counsel patients to keep all areas clean to prevent bacterial translocation, systemic infection, and possible sepsis.

Anorectal Adverse Events

Anorectal symptoms are associated with TVR use. These symptoms occur in approximately 25% of patients receiving TVR and include hemorrhoids, anorectal discomfort, anorectal pruritus, and anorectal burning.[5,6] These symptoms rarely require treatment discontinuation and are manageable with topical steroids or local anesthetics. To prevent these symptoms, it is important to stress that TVR should be taken with at least 20 grams of fat to optimize drug absorption into the systemic circulation and decrease elimination through the gastrointestinal tract.

Elevated Uric Acid Levels

Elevated uric acid levels are associated with TVR use. Onset occurred during the first 2 weeks of therapy and peaks within 6 to 8 weeks. If the patient is at high risk for gout flares, the addition of allopurinol may be considered if uric acid levels exceed 10 mg/dl. In clinical trials, less than 1% of patients who experienced hyperuricemia experienced clinical events of gouty arthritis.[23]

Elevated Bilirubin Levels

Elevated bilirubin levels (conjugated and unconjugated) are associated with TVR use. 41% of patients treated with TVR experienced elevations in total bilirubin as compared to 28% of patients treated with peg-IFN and ribavirin. Peak levels occurred during the first 2 weeks of treatment but were not due to liver dysfunction.[23] The mechanism of this adverse event is likely multifactorial including ribavirin induced hemolysis which would increase unconjugated bilirubin, inhibited uptake of unconjugated bilirubin, and inhibited excretion of conjugated bilirubin.

Cirrhosis

The safety profiles of BOC and TVR as seen in phase III trials were similar between patients with cirrhosis and those without cirrhosis. However, a French Early Access Programme study, CUPIC, was conducted in a cohort of patients with cirrhosis treated with BOC or TVR. Patients receiving BOC and TVR experienced significantly more serious adverse events, including 6 deaths, hepatic decompensation, and severe infections, when compared to published clinical trials (32.7%-45.2% in CUPIC versus 9%-14% in clinical trials).[10] Predictors of severe complications were albumin of < 3.5 g/dl and platelet count ⩽ 100,000/ μL. Although patients with cirrhosis are most in need of therapy, real-life adverse events as seen in CUPIC have shown that these patients are at high risk of severe complications, questioning whether it is safe for them to be treated with triple therapy including BOC and TVR.

DRUG INTERACTIONS

Both BOC and TVR are strong CYP3A4 inhibitors and CYP3A4 substrates which impose significant potential for drug-drug interactions. BOC is metabolized by aldoketoreductase 1C2 and 1C3 and to a lesser extent CYP3A4, whereas TVR is primarily metabolized by CYP3A4. Coadministration with drugs that are highly dependent on CYP3A4 for clearance increases levels of the coadministered drugs, which have important clinical implications if these coadministered drugs have a narrow therapeutic index. If the coadministered drugs are strong inhibitors of CYP3A4, elevated concentrations of BOC and TVR may occur increasing risks of adverse events associated with treatment. Also, potent CYP3A4 inducers significantly reduce the concentration of BOC and TVR which reduces efficacy of HCV treatment. Additionally, both BOC and TVR are substrates and inhibitors of P-glycoprotein (P-gp), thereby increasing concentration of other drugs that are substrates of P-gp.[23,24]

Common classes of drugs used in combination with BOC and TVR that may pose significant drug interactions are antiretroviral drugs, immunosuppressants, HMG-Coa reductase inhibitors, oral contraceptives, psychotropic agents, cardiovascular agents, analgesics, sedatives, antimicrobials, and anitfungals. Certain drugs in these classes are contraindicated with BOC and TVR.[23,24] When prescribing these protease inhibitors, it is always important to look for potentially significant and harmful drug-interactions by using useful websites (www.hep-druginteractions.org), medication databases, prescribing information, or consulting with a pharmacist.

Immunosuppressants

Large studies have not been performed in post-transplant patients on immunosuppressants treated with BOC or TVR. However, BOC and TVR have been studied in healthy volunteers with cyclosporine and tacrolimus. The area under the curve (AUC) of tacrolimus increased 17.1-fold to 70.3-fold when administered with BOC and TVR, respectively. TVR also increased the mean half -life of tacrolimus from 40 hours to 186 hours. The AUC of cyclosporine increased 2.7-fold to 4.64-fold when administered with BOC and TVR, respectively. TVR increased the mean half-life of cyclosporine from 12 hours to 53 hours. Therefore, it

recommended to empirically reduce the dose of cyclosporine by 75% if administered with BOC or TVR and use therapeutic drug monitoring to decide on the appropriate dose and frequency of cyclosporine.[25] Sirolimus has not been studied, but is theorized to behave like tacrolimus.

Systemic corticosteroid use should be avoided with BOC and TVR based therapy. Dexamethasone has been shown to decrease the concentrations of BOC and TVR and, therefore, coadministration is not recommended. BOC increased prednisone concentrations; however, no dose adjustment of prednisone is recommended. If possible, concurrent use of inhaled budesonide and fluticasone should be avoided due to increased steroid concentrations which can result in reduced serum cortisol levels.[23,24]

Antiretrovirals

BOC and TVR are not FDA-approved to treat co-infected patients with HIV. However, there have been multiple, small pharmacokinetic cohort studies in healthy patients given BOC or TVR with antiretrovirals. Co-administration of TVR is not recommended with ritonavir-boosted darunavir, fosamprenavir, or lopinavir due to significant interactions altering drug concentrations. TVR co-administered with ritonavir-boosted atazanavir may result in decreased TVR concentrations with concomitant increase in atazanavir concentrations. Co-administration of BOC can lead to decrease in concentrations of ritonavir-boosted atazanavir, darunavir, and lopinavir concentrations. BOC should be avoided with efavirenz, which may decrease BOC concentration. Ritonavir may also decrease BOC concentration.

HMG-CoA Reductase Inhibitors

Simvastatin, lovastatin, and atorvastatin are lipophilic HMG-CoA reductase inhibitors that are metabolized by CYP3A4. Increased statin concentrations may result in increased risk of myopathy and rhabdomyolysis. Simvastatin and lovastatin use is contraindicated with BOC and TVR. Atorvastatin dose should not exceed 40 mg when administered with BOC, and although not contraindicated, atorvastatin should be avoided when administered with TVR. Pravastatin and rosuvastatin may be safer options, as both are not dependent on CYP3A4 for metabolism; however, it is advisable to start at a low dose and titrate up as needed.[23, 24]

Oral Contraceptives

Ribavirin is highly teratogenic and rated "pregnancy category X". Patients on HCV treatment are advised to use at least 2 forms of birth control during treatment up to six months after treatment with peg-IFN and ribavirin. BOC and TVR may decrease plasma concentrations of ethinyl estradiol; therefore, 2 forms of barrier contraceptives are recommended while on treatment with BOC and TVR. Drospirenone is contraindicated with BOC due to potential hypokalemia.[24] Increased levels of drospirenone have also been associated with increased risk of clot formation,[26]

Other

Phosphodiesterase-5 enzyme (PDE5) inhibitor use is contraindicated with BOC and TVR. However, doses used for erectile dysfunction (sildenafil 25 mg every 48 hours, tadalafil 10 mg every 72 hours, and vardenafil 2.5 mg every 24 hours) are acceptable. Providers should monitor patients for potential PDE5 inhibitor-associated adverse events such as visual disturbances, hypotension, prolonged erection, and syncope.

Future Drugs

Increased adverse effects and significant drug interactions placate BOC and TVR's increased efficacy. Newer agents with different mechanisms of actions are being developed with less drug interactions and toxicities. Two agents that were FDA approved in December 2013 are sofosbuvir and simeprevir.

Simeprevir is a second generation NS3/4A protease inhibitor indicated for the treatment of chronic HCV genotype 1 infected patients to be used in combination with Peg-IFN and RBV. Unique adverse events associated with simeprevir are photosensitivity and rash. Both usually occur during the first four weeks of therapy, although it may occur at any time during treatment. Simeprevir induced photosensitivity may appear as an exaggerated sunburn in areas exposed to light. Symptoms include burning, erythema, exudates, blisters, and edema. Patients should be advised to use sun protective measures and limit exposure to sunlight while on treatment. Discontinuation of simeprevir is recommended if symptoms are severe.[27]

At baseline, it is recommended that patients with genotype 1a be screened for the Q80K polymorphism. In a pooled analysis from 2 phase 3 trials, patients with GT1a and the Q80K polymorphism experienced reduced efficacy compared to those without this polymorphism. Therefore, the use of alternative therapy is recommended if the Q80K polymorphism is present.[27]

Simeprevir is metabolized by CYP3A4 posing similar drug interactions as described with BOC and TVR. Simeprevir also mildly inhibits CYP1A2 and intestinal CYP3A4 which may increase concentrations of calcium channel blockers, most statins, and PDE-5 inhibitors.[27]

Sofosbuvir is a nucleotide NS5B polymerase inhibitor indicated for the treatment of chronic HCV infection as a component of a combination antiviral treatment regimen. Efficacy has been established in HCV GT 1, 2, 3 and 4, including those with HCC meeting Milan criteria and those co-infected with HIV. Common adverse events (incidence $\geqslant$ 20%) with treatment with sofosbuvir and RBV include fatigue and headache. Common adverse events observed with sofosbuvir in combination with RBV and Peg-IFN include fatigue, headache, nausea, insomnia, and anemia.[28]

Sofosbuvir is a substrate of P-glycoprotein (P-gp). Co-administered drugs that are inducers of P-gp may decrease sofosbuvir plasma concentrations and decrease its therapeutic effect and, therefore, are not recommended. Unlike BOC, TVR, and simeprevir, sofosbuvir does not interact with the

cytochrome P450 enzymes; therefore, drugs such as cyclosporine, tacrolimus, darunavir, efavirenze, lamivudine, raltegravir, rilpivirine, tenofovir, and methadone do not require dose adjustments.[28]

Other classes of drugs that are being developed are non-nucleoside polymerase inhibitors, NS5A inhibitors, and cyclophilin inhibitors. These new drugs gives us hope for regimens that do not contain interferon, have better efficacy, minimal side effects, and less drug interactions.

CONCLUSION

Efficacy has improved with the addition of BOC and TVR to peg-IFN and ribavirin; however, this comes at a price of more treatment related adverse events and drug interactions. Management of adverse events and prevention of drug interactions is key to optimized treatment. Emerging DAAs will have differing characteristics, but hopefully less adverse effects and less drug interactions than current treatment with triple therapy including BOC and TVR.

CONFLICT OF INTEREST
None.

REFERENCES

1. Lavanchy D. The global burden of hepatitis C. Liver Int. 2009;29 (Suppl 1):74-81.
2. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(4):1433-1444.
3. Backus LI, Boothroyd DB, Phillips BR, et al, A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9(6):509-516.
4. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308(24):2584-2593.
5. Jacobson IM, McHutchison JG, Dusheiko G, et al., Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med, 2011. 364(25): 2405-2416.
6. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med, 2011. 364(25): 2417-2428.
7. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med, 2011. 364(13): 1207-1217.
8. Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13): 1195-1206.
9. Sulkowski MS, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon Alfa-2b/ribavirin and boceprevir: Analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial. Hepatology. 2013; 57(3):974-984.
10. Hezode C, Fontaine H, Dorival C, et al, Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013;59(3):434-441.
11. Fellay J, Thompson AJ, Ge D, et al., ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. Nature. 2010;464(7287):405-408.
12. Thompson AJ, Clark PJ, Singh A, et al., Genome-wide association study of interferon-related cytopenia in chronic hepatitis C patients. J Hepatol. 2012;56(2):313-319.
13. Poordad F, Lawitz E, Reddy KR, et al. Effects of Ribavirin Dose Reduction vs Erythropoietin for Boceprevir-Related Anemia in Patients with Chronic HCV Genotype 1 Infection-a Randomized Trial. Gastroenterology. 2013;145(5):1035-1044.
14. Sulkowski MS. Anemia had no effect on efficacy outcomes in treatment-naive patients who received telaprevir-based regimen in the ADVANCE and ILLUMINATE phase 3 studies. Journal of Hepatology. 54(Suppl 1):S195.
15. Hammond KP, Jimmerson L, MacBrayne CE, et al. Increased Plasma and Intracellular Ribavirin Concentrations Associated With Telaprevir Use. Atlanta: 29th Conference on Retroviruses and Opportunistic Infections, 2013.
16. Pegasys (peginterferon alfa-2a) package insert, Hoffmann-La Roche Inc, Nutley, NJ, 2011.
17. Roomer R, Hansen BE, Janssen HL, de Kneqt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. J Hepatol, 2010. 53(3): 455-459.
18. Howell CD, Jeffers LS, Cassidy W, et al. Peginterferon alfa-2a and ribavirin for chronic hepatitis C genotype 1 infections in black patients: safety, tolerability and impact on sustained virologic response. J Viral Hepat. 2006;13(6):371-376.
19. Promacta (Eltrombopag) [package insert]. GlaxoSmithKline. Research Triangle Park, NC, 2012.
20. Afdhal N. Final Results of ENABLE 1, a Phase 3, Multicenter Study of Eltrombopag as an Adjunct for Antiviral Treatment of Hepatitis C Virus-Related Chronic Liver Disease Associated With Thrombocytopenia [abstract]. In: 62nd Annual Meeting of the American Association for the Study of Liver Disease; 2011. 4-8; San Francisco, California (CA): AASLD; 2011. Abstract LB-3.
21. Dusheiko G. Results of ENABLE 2, a Phase 3, Placebo-controlled, Multicenter Study of Eltrombopag, Peginterferon Alfa-2b, and Ribavirin Treatment in Patients with Hepatitis C and Thrombocytopenia [abstract]. In: 47th Annual European Association for the Study of Liver; 2012 April 20; Barcelona, Spaon: EASL; 2012. Abstract #279.
22. FDA Antiviral Drugs Advisory Committee. Telaprevir briefing document April 28, 2011. http://www.fda.gov/downloads/Advisory-Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisory-Committee/UCM252562.pdf, 2011. Accessed 10/5/2012.
23. Incivek (Telaprevir) [package insert], Vertex Inc.Cambridge MA. April 2013.
24. Victrelis (Boceprevir) [package insert], Merck Inc. February 2013.
25. Garg V, van Heeswijk R, Lee JE, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011;54(1):20-27.
26. World Health Organization. Drospirenone-containing combined oral contraceptives: possible increased risk of blood clots. WHO Pharm Newslett. 2011;6:5.
27. Simeprevir [package insert]. Janssen-Cilag, SpA, Latina, Italy. Janssen Products, LP, 2013.
28. Sofosbuvir [package insert]. Foster City, CA: Gilead Sciences, Inc, 2013.