Management algorithm for genotype 1 hepatitis C virus

F1000Prime REPORTS

Published: 01 July 2013

Management algorithm for genotype 1 hepatitis C virus

Arthur Y. Kim

Address: Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA

Email: akim1@partners.org

F1000Prime Reports 2013, **5**:24 (doi:10.12703/P5-24)

Abstract

Hepatitis C virus (HCV) infection is the most common etiology of chronic liver disease in Western countries. Morbidity and mortality due to HCV-related end-stage liver disease are increasing, just as novel therapeutics arrive with the promise of better cure rates that prevent these complications. However, substantial barriers to successful application of these novel treatments remain, including the lack of providers with sufficient knowledge to address this epidemic. To address these deficits, this article aims to provide a general framework with algorithms to guide initial management decisions for HCV genotype 1 infection, the most commonly found genotype, based on therapies approved as of 2013.

Introduction

Hepatitis C virus (HCV) usually establishes a chronic viral infection that infects 1-2% of the United States population or about 3-4 million people [1]. HCV has emerged as a leading killer of adults who were predominantly infected in the 1970s and 1980s, but decades later suffer from complications due to cirrhosis and end-stage liver disease. Mortality attributable to HCV currently exceeds that of human immunodeficiency virus (HIV) in the United States [2]. Cure of HCV, termed a sustained virologic response (SVR), is associated with a substantial decline in liver-related morbidity and mortality [3]. From 2002 to 2011, the standard of care for antiviral treatment was a combination of injectable pegylated interferon (PegIFN) and oral ribavirin, a treatment regimen only effective in ~50% of individuals [4]. Treatment uptake has been low for a variety of reasons, including lowered efficacy against genotype 1, the most commonly found HCV in the United States, Europe, and Japan, and significant side effects associated with treatment.

In 2011, two novel agents that potently inhibit the viral protease, boceprevir and telaprevir, were approved for use against HCV genotype 1 infections in the United States (see Table 1). One of these oral medications may be added to the standard regimen as part of a "triple therapy" regimen and increase response rates substantially [5]. For the patient naïve to therapies, response rates improved from ~40% for PegIFN/ribavirin to 65-70% when one adds either of these protease inhibitors to the regimen [6,7]. However, these agents add substantial complexity to management due to pill burden (multiple pills consumed every 7-9 hours), drug-drug interactions, and additive side effects.

Future regimens active against genotype 1 HCV are on the horizon, promising both improved efficacy and tolerability [8,9]. A significant proportion of candidates for treatment in 2013 may elect to wait for these novel therapies, due in the coming years. Therefore, a first step is to provide guidelines for selecting treatment candidates for current versus future therapies in the context of a rapidly changing field. Then, if treatment is recommended, management algorithms are needed for providers to treat with "triple therapy."

The focus of this article is the management of genotype 1 HCV infection in those naïve to interferon-based therapies. Guidelines are available for non-genotype 1 HCV infection and those with prior treatment experience [4,10,11]. While algorithms and checklists may be helpful, treatment decisions are ultimately individualized.

Table 1. Antiviral medications for genotype 1 infection

PegIFN	RBV	Protease inhibitor
PegIFN alfa-2a 180 μg per week Or PegIFN alfa-2b 1.5 μg/kg per week	RBV (in two divided doses) with food: <75 kg: 1,000 mg per day or ≥ 75 kg: 1,200 mg per day; alternative weight-based dosing: <65 kg: 800 mg per day 65-85 kg: 1,000 mg per day >85-105 kg: 1,200 mg per day, >105 kg: 1,400 mg per day	TVR 750 mg (two 375 mg tablets) orally every 8 h with food (20 g fat) Or BOC 800 mg (four 200 mg capsules) orally every 8 h with food.

Abbreviations: BOC, boceprevir; PegIFN, Pegylated interferon; RBV, ribavirin; TVR, telaprevir

Goals of antiviral therapy

The primary goal of interferon-based therapies against HCV is achievement of SVR, defined as an undetectable viral load in the plasma weeks after therapy. The measurement traditionally occurred at least 24 weeks after cessation of therapy, but recently it has been appreciated that undetectable virus measured at 12 weeks after cessation correlates extremely well with the 24-week measurement [12], which in turn is associated with a durable cure [13]. A durable cure achieves a substantial reduction in liver-related morbidity and mortality [3,14,15]. Other objectives of antiviral therapy may be to treat conditions and symptoms that may rarely occur in relation to chronic infection (such as cryoglobulinemia), to reduce further transmission risk, to facilitate the application of other hepatotoxic therapies [16,17] and to improve quality of life.

Selecting treatment candidates

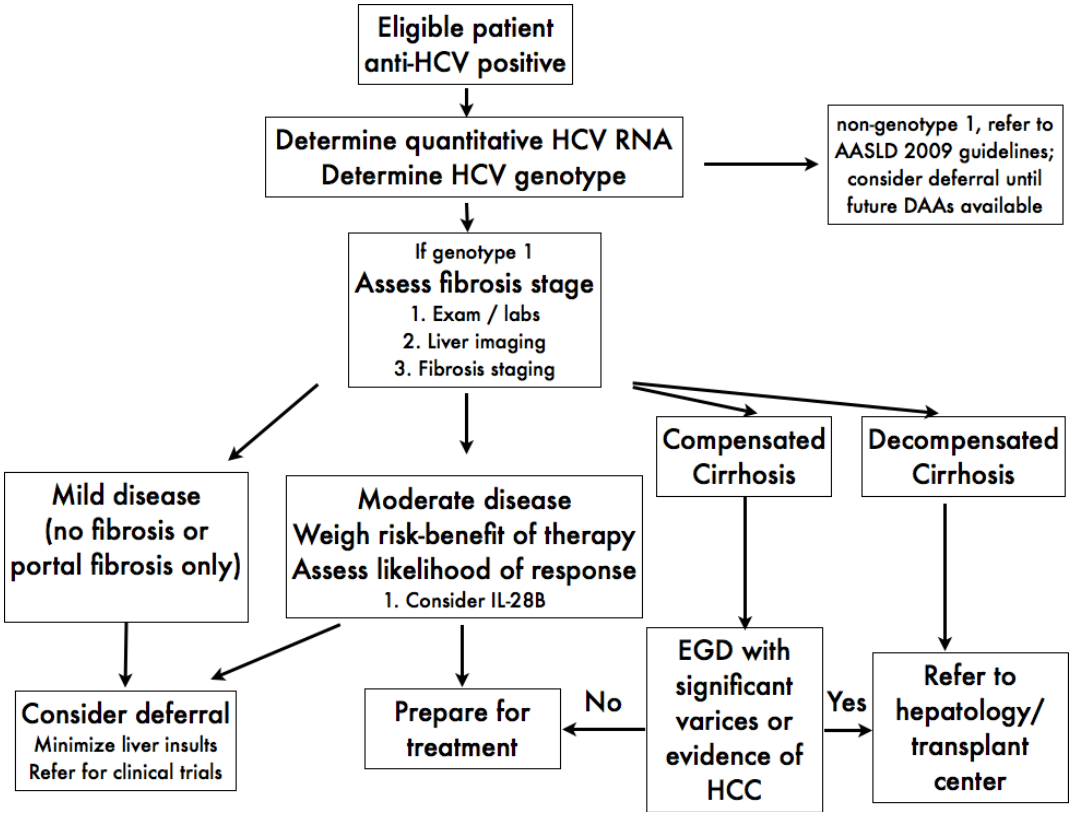
As chronic HCV infection is a progressive disease that does not remit spontaneously and may carry substantial burden to the individual, one starting point is that all infected patients may eventually be candidates for cure, but everyone does not require treatment immediately. Thus, questions of when and how treatment should be applied remain open, especially given the rapidly evolving therapeutic landscape.

The decision to initiate treatment for chronic HCV infection remains complex and is ultimately individualized to the patient situation. Disease severity is the primary factor, as the prognosis for those with mild to moderate liver damage is much better than those with cirrhosis. Therefore, virtually all treatment candidates with chronic HCV infection should receive some assessment of fibrosis. Patients with evidence of milder disease (stage 1 out of 4, METAVIR staging) can safely await future therapy. Unfortunately, compared with those with mild disease, those with advanced liver disease (defined as stage 3 or 4 out of 4, and therefore in greater need of a cure) are less likely to respond, suffer more frequently from certain side effects and are at risk of decompensation while on therapy. Nonetheless, due to the risk of life-threatening events associated with not achieving an SVR, those with advanced liver disease should be strongly considered for treatment, after appropriate risk stratification for those with confirmed cirrhosis (i.e endoscopy, screening for hepatoma, consideration of transplantation referral). Extreme caution should be exercised for those with evidence of mild decompensation; treatment by experienced centers is highly advised after determining candidacy for liver transplantation. For those with moderate disease (stage 2 out of 4), an individualized decision should be made, with deferral possible or even preferable given the novel therapies on the horizon. An algorithm detailing the decision to treat based on the primary factor of liver fibrosis is presented in Figure 1, again re-emphasizing that the decision-making process should occur on a case-by-case basis.

The provider should screen for advanced fibrosis/cirrhosis via physical examination, basic laboratory tests (examining platelet counts, the AST/ALT ratio, prothrombin time, albumin) and screening by ultrasound [18]. Results from the above evaluation may increase the likelihood of cirrhosis if abnormal but lack sensitivity. Given the importance of the liver fibrosis stage in these treatment decisions, a more formal fibrosis assessment can be considered rather than an assessment determined by history, physical and basic laboratory values/imaging. For genotype 1 infection, there remains controversy regarding whether all patients should undergo liver biopsy, the most accurate assessment of fibrosis, or whether some can be assessed and monitored using noninvasive testing. A staged approach utilizes noninvasive testing first: F0-1 and F4 may skip the more invasive liver biopsy as these tests perform well at these ends of the spectrum. For F2-3, many would proceed with liver biopsy due to the imprecision of results in this range, which may either underestimate or overestimate fibrosis. The details of these noninvasive approaches are reviewed elsewhere [19,20].

The need for treatment must be weighed carefully against the likelihood of success and the potential risks and toxicities associated with therapy. The provider must screen for baseline conditions that may be exacerbated by

Figure 1. Algorithm for the initial evaluation of the patient with genotype 1 HCV infection who is treatment-naïve



Principles that govern this decision tree include the importance of assessing fibrosis stage, the consideration of prognostic testing (such as quantitative viral load, IL28b), and provision of appropriate care to prevent fibrosis progression and related complications. Abbreviations: AASLD, American Association for the Study of Liver Diseases; IL28b, interleukin-28 beta subunit; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; EGD, esophagogastroduodenoscopy.

Table 2.

Current contraindications to therapies including interferon/ ribavirin
Adapted from AASLD Practice Guidelines[4]
Major uncontrolled depressive illness
Solid organ transplant (renal, liver, lung)
Autoimmune hepatitis or other autoimmune condition known to be exacerbated by interferon
Untreated thyroid disease
Pregnant or unwilling to comply with adequate contraception (due to ribavirin's teratogenicity)
Severe concurrent medical disease
Age less than 2 years
Known hypersensitivity to drug used to treat HCV

Table 3.

Populations in which more data are needed regarding triple therapies
Decompensated cirrhosis
HIV co-infection
Renal insufficiency/dialysis
Infants and children
Liver transplant recipients
Active injection drug use/substance abuse

interferon-based treatments and, thus, limit or preclude therapy. Absolute contraindications are listed in Table 2 [4]. Another limitation is the paucity of data regarding triple therapies for certain subgroups, such as those with HIV co-infection, renal disease, solid-organ transplantation, and active injection drug users (Table 3). A detailed discussion of each of these special populations with HCV is beyond the scope of this report but it is advisable to seek the guidance of providers with experience of treating these "special" populations.

This decision is also influenced by the likelihood of a response to the above therapies. A higher likelihood of SVR is associated with factors that are easily modifiable,

such as non-African-American race, lower viral titers, the subtype of virus (1b responding better to protease inhibitor-based therapy than 1a), and host single nucleotide polymorphisms related to the interleukin-28-beta subunit (IL28b) [21,22]. Host IL28b genotyping for rs12979860 is commercially available in the United States and may be additionally useful in predicting whether patients might be eligible for PegIFN/ribavirin without protease inhibitor, and for shortened duration of treatment based on early response kinetics [23,24]. Specifically, those with a favorable host genotype (homozygous for the C-allele at rs12979860, or CC) have the best response to interferon-based therapies and, therefore, treatment should be more favourable. These factors are probably most useful in decision-making for those with moderate fibrosis.

Deferral of therapy

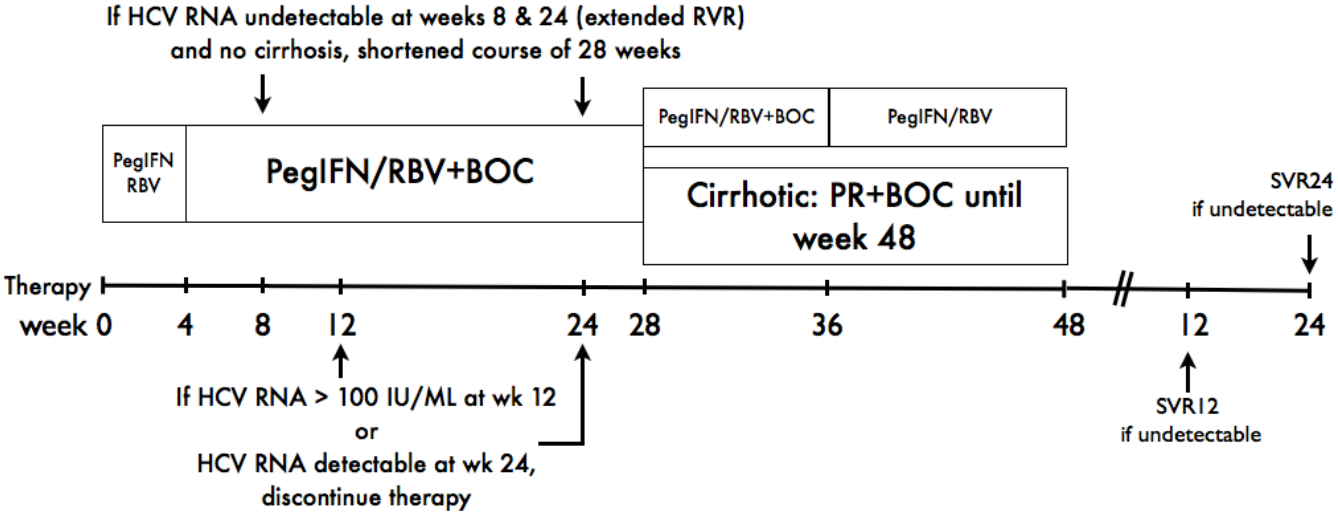
If the provider and patient decide to await emerging novel therapies due to low levels of fibrosis and/or concern about toxicities, they should work together in the meantime to minimize disease progression (i.e. avoiding other hepatic insults such as alcohol or steatosis due to weight gain, and preventing co-infections such as HIV). If available, enrolment into clinical trials should be discussed.

Preparing the patient for antiviral treatment

Triple therapy regimens are schematized in Figures 2 and 3. There are no head-to-head trials to inform the choice of which protease inhibitor to add for chronic genotype 1 infection [5]. The choice may, however, be guided by factors such as specific side effects, duration of protease inhibitor therapy, or formulary issues. Of note is that use of a lead-in therapy period of 4 weeks prior to protease inhibitor addition is recommended for boceprevir [25]. Also, for telaprevir, a similar lead-in period does not compromise sustained virologic response or add toxicity according to one trial of prior nonresponders [26]. Therefore, for selected individuals at high risk of additive toxicities, one might elect to use a lead-in period even if using triple therapy with telaprevir. Also, selected patients with favourable characteristics for interferon-responsiveness (IL-28b C-C genotype, low viral load) could be considered for initial dual therapy without protease inhibitor [10,27]; if a rapid virologic response (undetectable HCV RNA at week 4) is not achieved in this subgroup then either protease inhibitor could be added.

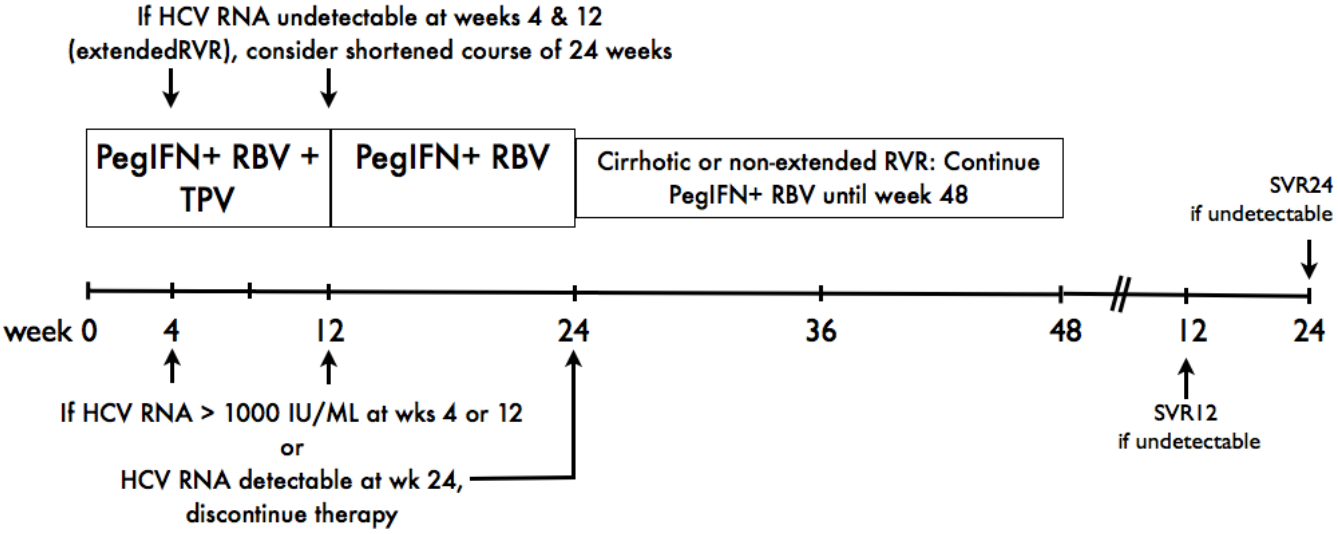
A partial checklist regarding key elements of a pre-treatment evaluation is shown in Table 4. Known medical conditions should be optimized (such as control of diabetes, hypertension, or thyroid disease) and others anticipated (such as unmasking of cardiac angina due to onset of anemia). Some patients with risk factors may require cardiac risk stratification. Baseline anemia should be worked up and, if feasible, reversed prior to antiviral treatment. It is also highly advised to assess depression to screen for modifiable mood disorder, consider potential referral and establish a baseline for monitoring while on interferon.

Figure 2. Guide for using triple therapy with boceprevir and response-guided therapy



The regimen consists of a lead-in period of PegIFN/RBV for 4 weeks followed by either 24, 32 or 44 more weeks of triple therapy with boceprevir (BOC). The shorter course can be used if HCV RNA is undetectable at weeks 8 and week 24. Stopping rules are also shown: if HCV RNA > 100 IU/ml at wk 12 or HCV RNA detectable at wk 24, therapy should be discontinued.

Figure 3. Guide for using triple therapy with telaprevir and response-guided therapy



The regimen consists of a 12 weeks of PegIFN/RBV/TVR for 12 weeks followed by either 12 or 36 more weeks of dual therapy. The shorter course can be used if HCV RNA is undetectable at weeks 4 and week 12. Stopping rules are also shown: if HCV RNA > 1000 IU/ml at wks 4 or week 12 or HCV RNA detectable at wk 24, therapy should be discontinued.

Table 4.

Sample checklist of items before starting patient on triple therapies
Obtain baseline HCV RNA (within 6 months of planned start date)
Obtain baseline laboratory tests (i.e. complete blood count plus differential, renal function, liver function tests, metabolic panel, thyroid stimulating hormone, prothrombin time)
Consider additional prognostic testing (i.e. IL-28b genotype)
Screen for other infectious diseases that share transmission routes (HIV antibody, HBsAg)
Screen for other liver diseases (i.e. autoimmune hepatitis, iron overload)
Psychiatric history, screen for active depression and, if necessary, refer
Catalogue and treat comorbid conditions (i.e. substance abuse, anemia, thyroid abnormalities)
Cardiac risk-stratification for those with multiple cardiac risk factors
Obtain baseline ophthalmologic examination (for those with hypertension, diabetes)
Ensure adequate contraception for women of child-bearing age and for sexually-active men
Counsel regarding avoidance of alcohol while on treatment
Counsel regarding common and serious side effects
Keep up-to-date medication lists and screen for drug-drug interactions
Plan for interruption of work or other duties
Plan laboratory monitoring schedule, transportation, communication, and other logistics

As ribavirin is associated with teratogenicity in animal models and is labeled as category X by the U.S. Food and Drug Administration, a female should not become pregnant and a male should not impregnate while on this medication. Use of two forms of contraception is current standard of care during therapy and for six months afterwards.

It is critical to anticipate drug-drug interactions and additive toxicities while on triple therapy for genotype 1 infection. Both boceprevir and telaprevir are potent inhibitors of the cytochrome P450 pathway (specifically CYP3A4), which metabolizes a whole host of prescribed medications. It is, therefore, prudent for the provider to carefully and regularly reconcile a medication list and, if complicated, enlist the advice of a clinical pharmacist to anticipate changes in drug levels that might be significant. Herbal supplements and alternative medications should also be reviewed. Newly emerging data regarding safe use with commonly encountered medications and online resources (such as http://www.hep-druginteractions.org) should be examined. For instance, in HIV co-infected patients, treatment of genotype 1 with protease inhibitors has been tested with only a fairly limited subset of antiretroviral regimens [28]. The patient should also be instructed to inform providers of any medication recommended while on therapy for HCV.

Logistical issues should also be explored prior to treatment, as successful treatment may be limited by insufficient insurance coverage, transportation to monitoring visits, poor access to additional specialists, and cultural/language barriers. The patient may need to plan for missed time from work or family duties, and support systems should be maximized. Those with cirrhosis should be informed of the risk of decompensation on interferon-based therapies that necessitates the interruption of treatment.

Response-guided therapy

Response-guided therapy describes the adjustment or cessation of the treatment course based on viral kinetics after initiation (Figures 2 and 3). Response-guided therapy criteria are shown in Figures 2 and 3. For those without advanced fibrosis/cirrhosis, it is possible that if certain benchmarks are met, the course may be significantly shortened. In the case of PegIFN/ribavirin/telaprevir, HCV RNA at weeks 4 and 12 should both be undetectable (defining an extended rapid virologic response) to allow a shortened total course of 24 weeks [29]. For PegIFN/ribavirin/boceprevir, the testing is done at weeks 8 and 24; if both timepoints are completely negative for virus, then the total course can be shortened to 28 weeks [25].

An important feature of applying response-guided therapy for shortening treatment is the use and interpretation of sensitive assays. Recommended assays should have a lower limit of quantification of 25 IU/mL of HCV RNA and a lower limit of detection of around 10-15 IU/mL. These assays may, therefore, report levels <25 IU/mL, which can be detected but are unquantifiable. Response-guided therapy that results in shortened therapy should be based on results of "undetectable" or "target not detected" [30].

In 2013, based on the algorithm presented in Figure 1, those with advanced fibrosis/cirrhosis are most likely to be treated with current regimens. Those with cirrhosis are at a particularly high risk of lower response rates if therapies are shortened; thus, currently, the full duration of 48 weeks is recommended (Figures 2 and 3).

The other principle of response-guided therapy is the cessation of therapy based on viral measurements revealing insufficient response and ultimately futility of further treatment. These "stopping rules" are also described in Figures 2 and 3. For PegIFN/ribavirin/boceprevir, if HCV RNA is greater than 100 IU/mL at week 12 or detectable at week 24, then all three medications should be stopped. For PegIFN/ribavirin/telaprevir, if HCV RNA is greater than 1000 IU/mL at week 4 or 12 or is detectable at week 24, then medication should be stopped.

Optimal management of side effects

Since therapy is prolonged (24-48 weeks), the provider should aim to actively diagnose and manage side effects to minimize their impact on the patient. There are many potential side effects to therapy; common complications that require active management are reviewed here.

Cytopenias

Anemia

All three medications used in either regimen can cause anemia, which occurs at rates of approximately 40% in phase III trials of telaprevir-containing regimens, and ~50% of those of boceprevir-containing regimens. Given the high-prevalence of this side effect, several management strategies have been used including dose reduction (particularly of ribavirin), erythropoietic agents, and transfusion.

Multiple trials of telaprevir-containing regimens excluded the use of erythrocyte-stimulating agents and managed anemia with ribavirin dose reduction as the first-line manuever [31]. For many trials of boceprevir, erythrocyte-stimulating agents were typically used at the discretion of the providers; however, a recent randomized controlled trial comparing erythrocyte-stimulating agents versus ribavirin dose reduction in the context of PegIFN/ribavirin/boceprevir treatment showed no difference in SVR between the two groups [32]. Given the excellent response rates of these trials and the lower cost and fewer side effects, ribavirin dose reduction should, therefore, be the first-line management. For those with rapid onset significant anemia (generally those with cirrhosis), reduction of the daily dose by more than 200 mg increments from starting dose to ~600 mg/day is prudent. If significant anemia persists despite ribavirin dose reduction, strategies include addition of erythrocyte-stimulating agent, blood transfusion, or PegIFN dose reduction. The dose of protease inhibitor should never be reduced [25,29,32]. A minimum haemoglobin level <10 mg/dL is a precipitant for considering action, but the goal haemoglobin level may be individualized to the patient based on symptoms and comorbidities.

Neutropenia

Neutropenia is common during therapy and is most often attributed to PegIFN. Thus far, despite drops of absolute neutrophil counts below 500 cells/μL, trials have not detected an associated increased risk of infection [33,34]. Nonetheless, it is standard to counsel patients with neutropenia on taking precautions to prevent infection and to maintain absolute neutrophil counts with combined use of filgrastim and PegIFN dose reduction. Thresholds for such interventions differ based on individual providers and guidelines [11,35]; one option is to react to intervene when absolute neutrophil counts drop below 750 cells/μL for those with known cirrhosis (who are at generally higher risk of bacterial complications) and when absolute neutrophil counts drop below 500 cells/μL for those without cirrhosis [35]. If absolute neutrophil counts cannot be maintained above 500 cells/μL then PegIFN discontinuation should be considered.

Thrombocytopenia

Many patients with advanced liver disease start with abnormally low platelet counts that then drop further due

to the marrow-suppressive effects of interferon, typically during the first weeks after initiation of treatment [36]. Some authorities suggest discontinuation of therapy if platelet counts are lower than 20,000/μL, and for those with counts between 20,000 and 50,000/μL PegIFN dose reduction should be considered [35]. Recently, the Food and Drug Administration approved elthrombopag, a platelet growth factor, as an adjunctive therapy to boost platelet counts, thus allowing HCV initiation or maintenance of therapy [37,38]. Downsides of this therapy include its cost and its association with potentially dangerous complications (hepatotoxicity and thromboembolic complications, the latter including the portal vein). The provider should select patients carefully for elthrombopeg and discuss the risks and benefits fully.

Dermatologic issues

Telaprevir, in particular, is associated with rashes, but it is important to remember that both PegIFN and ribavirin may cause dermatologic reactions. PegIFN may result in both local reactions, generalized dermatitis, and, in particular, worsened psoriasis. Rashes due to ribavirin may occur any time during therapy but usually during the first few months. This overlaps with the timeframe when telaprevir is administered, sometimes making it difficult to determine the offending agent.

Mild to moderate rashes associated with telaprevir are common. Up to 56% of patients treated with PegIFN/ribavirin/telaprevir may suffer from rashes, compared with about one-third of patients receiving PegIFN/ribavirin alone [29]. The majority of these eruptions are pruritic, resemble eczema and are classified as mild to moderate, often starting in the first 4 weeks of treatment. Severe rashes were reported in up to 5% of patients, and may progress to life-threatening exanthems such as drug rash with eosinophilia and systemic symptoms (DRESS) or Stevens-Johnson Syndrome (SJS), resulting in a warning by the Food and Drug Administration to providers [39].

Thus, patients on telaprevir-based therapy must be instructed to quickly report any skin eruptions to the provider (who can also monitor), and the rash should be carefully graded in severity and extent. Mild to moderate rashes are managed with antihistamines, topical steroids and skin care. Systemic steroids may interact with telaprevir and are thus not recommended [29]. Rashes may take several weeks to resolve. Criteria requiring cessation of telaprevir includes rashes affecting more than 50% of body surface area, lesions indicative of SJS, or with worsening systemic symptoms. Substitution of boceprevir for telaprevir successfully resolved rashes in a case report [40], but more data are needed to assess this strategy. If cessation of telaprevir occurs after 8 weeks but before 12 weeks, significant benefit is still likely, as indicated by a trial that included an arm of 8 weeks treatment (69% cured with 8 weeks PegIFN/ribavirin/telaprevir versus 44% PegIFN/ribavirin alone) [41]. A diagnosis of DRESS or SJS requires prompt referral for urgent hospitalization, dermatologic consultation, and cessation of all antiviral medications [29].

Anorectal complications

Anorectal side effects including discomfort, pruritus, and hemorrhoids are commonly reported, particularly with regimens including telaprevir. Insufficient absorption of telaprevir may be one contributor, so ensuring adequate fat intake with each dose and avoiding medications that may interfere with absorption is critical. Over-the-counter ointments including hydrocortisone or zinc oxide may provide relief, in addition to keeping the area clean and dry. For more severe cases, prescription ointments may be utilized. Both internal and external hemorrhoids may also become symptomatic, with pain, itchiness, or bleeding. Patients should avoid constipation and straining while defecating, as well as maintaining water intake; laxatives or stool softeners may also be useful. Rarely, surgical referral is warranted for severe cases.

Psychiatric complications

Depression is the most commonly encountered psychiatric condition found in HCV patients, and may be exacerbated in about 20% of patients undergoing therapy. As mentioned, active depression at baseline should be treated prior to initiation of HCV therapy. Placebo-controlled trials of pre-emptive antidepressant therapy for all patients undergoing interferon-based treatment for HCV have shown variable results, but recent trials of escitalopram have shown some efficacy [42-44]. For those with prior history of depression, one should reconsider institution of an agent that has elicited a clinical response in the past. For those already stable on antidepressants, dose adjustments may need to be considered. Repeated application of validated questionnaire-based instruments such as the Beck Depression Inventory or the Patient Health Questionnaire may reveal changes in mood while on therapy. While providers of interferon-based therapies should be familiar with basic management of depression, psychiatric expertise is helpful for more complicated cases.

Conclusion

Since 2011, the addition of direct-acting antivirals boceprevir and telaprevir to the previous standard of care provides great hope for the curing of most genotype 1 HCV infections. Consequently, the goal of preventing liver-related complications, substantial morbidity and reduced life expectancy may be more easily achieved in the future.

Management with current triple therapies has become more complicated; thus, clear and concise guidelines and principles governing these regimens will help guide the practitioner navigate this first era of direct-acting antivirals against HCV. The decision to treat will be made in the context of future regimens in development that promise higher cure rates with fewer side effects.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; DRESS, drug rash with eosinophilia and systemic symptoms; IL28b, interleukin-28 beta-subunit; PegIFN, pegylated-interferon; SJS, Stevens-Johnson Syndrome.

Disclosures

Arthur Kim has served as a consultant for Vertex (2011), Abbvie (as of 25/06/2013) and Gilead (as of 18/07/2013).

Acknowledgements

Funding sources: Dr. Kim is supported by the National Institutes of Health, grants U19 AI066345, R01 DA033541, R01 DA031056 and R01 DA031059. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ: **The prevalence of hepatitis C virus infection in the United States, 1999 through 2002.** *Ann Intern Med* 2006, **144:**705-14.

F1000Prime RECOMMENDED

2. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD: **The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007.** *Ann Intern Med* 2012, **156:**271-8.

F1000Prime RECOMMENDED

3. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HLA: **Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis.** *Ann Intern Med* 2007, **147:**677-84.

F1000Prime RECOMMENDED

4. Ghany MG, Strader DB, Thomas DL, Seeff LB: **Diagnosis, management, and treatment of hepatitis C: an update.** *Hepatology* 2009, **49:**1335-74.

5. Cooper C, Lester R, Thorlund K, Druyts E, El Khoury AC, Yaya S, Mills EJ: **Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis.** *QJM* 2013, **106:**153-63.

F1000Prime RECOMMENDED

6. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ: **Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.** *N Engl J Med* 2009, **360:**1827-38.

F1000Prime RECOMMENDED

7. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, Davis MN, Galati JS, Gordon SC, Ravendhran N, Rossaro L, Anderson FH, Jacobson IM, Rubin R, Koury K, Pedicone LD, Brass CA, Chaudhri E, Albrecht JK: **Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.** *Lancet* 2010, **376:**705-16.

F1000Prime RECOMMENDED

8. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM: **Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C.** *N Engl J Med* 2013, **368:**34-44.

F1000Prime RECOMMENDED

9. Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, Koev G, Tripathi R, Pilot-Matias T, Bernstein B: **Exploratory study of oral combination antiviral therapy for hepatitis C.** *N Engl J Med* 2013, **368:**45-53.

F1000Prime RECOMMENDED

10. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB: **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:**1433-44.

11. Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, Monto A: **Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office.** *Am J Gastroenterol* 2012, **107:**669-89; quiz 690.

F1000Prime RECOMMENDED

12. Martinot-Peignoux M, Stern C, Maylin S, Ripault M, Boyer N, Leclere L, Castelnau C, Giuily N, El Ray A, Cardoso A, Moucari R, Asselah T, Marcellin P: **Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin.** *Hepatology* 2010, **51:**1122-6.

F1000Prime RECOMMENDED

13. Payne DW, Talalay P: **Isolation of novel microbial 3 alpha-, 3 beta-, and 17 beta-hydroxysteroid dehydrogenases. Purification, characterization, and analytical applications of a 17 beta-hydroxysteroid dehydrogenase from an Alcaligenes sp.** *J Biol Chem* 1985, **260:**13648-55.

14. Berenguer J, Alvarez-Pellicer J, Martín PM, López-Aldeguer J, Von-Wichmann MA, Quereda C, Mallolas J, Sanz J, Tural C, Bellón JM, González-García J: **Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus.** *Hepatology* 2009, **50:**407-13.

F1000Prime RECOMMENDED

15. Morgan TR, Ghany MG, Kim H, Snow KK, Shiffman ML, de Santo JL, Lee WM, Di Bisceglie AM, Bonkovsky HL, Dienstag JL, Morishima C, Lindsay KL, Lok ASF: **Outcome of sustained virological**

responders with histologically advanced chronic hepatitis C. *Hepatology* 2010, **52:**833-44.

F1000Prime RECOMMENDED

16. Uberti-Foppa C, de Bona A, Morsica G, Galli L, Gallotta G, Boeri E, Lazzarin A: **Pretreatment of chronic active hepatitis C in patients coinfected with HIV and hepatitis C virus reduces the hepatotoxicity associated with subsequent antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2003, **33:**146-52.

17. McGovern BH, Birch C, Zaman MT, Bica I, Stone D, Quirk JR, Davis B, Zachary K, Basgoz N, Graeme-Cook F, Gandhi RT: **Managing symptomatic drug-induced liver injury in HIV-hepatitis C virus-coinfected patients: a role for interferon.** *Clin Infect Dis* 2007, **45:**1386-92.

18. Brau N: **Evaluation of the HCV-Infected Patient: The Initial Encounter.** *Clin Infect Dis* 2012.

19. Manning DS, Afdhal NH: **Diagnosis and quantitation of fibrosis.** *Gastroenterology* 2008, **134:**1670-81.

20. Smith JO, Sterling RK: **Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C.** *Aliment Pharmacol Ther* 2009, **30:**557-76.

21. Thompson AJ, McHutchison JG: **Will IL28B polymorphism remain relevant in the era of direct-acting antiviral agents for hepatitis C virus?** *Hepatology* 2012, **56:**373-81.

F1000Prime RECOMMENDED

22. Berger CT, Kim AY: **IL28B polymorphisms as a pretreatment predictor of response to HCV treatment.** *Infect Dis Clin North Am* 2012, **26:**863-77.

23. Kwo PY: **Phase III results in Genotype 1 naïve patients: predictors of response with boceprevir and telaprevir combined with pegylated interferon and ribavirin.** *Liver Int* 2012, **32**(Suppl 1):39-43.

24. Poordad F, Bronowicki J, Gordon SC, Zeuzem S, Jacobson IM, Sulkowski MS, Poynard T, Morgan TR, Molony C, Pedicone LD, Sings HL, Burroughs MH, Sniukiene V, Boparai N, Goteti VS, Brass CA, Albrecht JK, Bacon BR: **Factors that predict response of patients with hepatitis C virus infection to boceprevir.** *Gastroenterology* 2012, **143:**608-18.e1-5.

F1000Prime RECOMMENDED

25. **Victrelis™ (boceprevir; package insert). Schering Corporation: Whitehouse Station, NJ;** 2011.

26. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, van Heeswijk R, de Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M: **Telaprevir for retreatment of HCV infection.** *N Engl J Med* 2011, **364:**2417-28.

F1000Prime RECOMMENDED

27. Thompson AJ, Shiffman ML, Rossaro L, Ghalib R, Han SB, Beavers KL, Pianko S, George J, He L, Wu X, *et al.*: **Six weeks of a NS5A inhibitor (GS-5885), protease inhibitor (GS-9451) plus peginterferon/ribavirin (PR) achieves high SVR4 rates in genotype 1 IL28B CC treatment naive HCV patients: interim results of a prospective, randomized trial.** *Hepatology* 2012, **56:**556A.

28. Naggie S, Sulkowski MS: **Management of patients coinfected with HCV and HIV: a close look at the role for direct-acting antivirals.** *Gastroenterology* 2012, **142:**1324-1334.e3.

F1000Prime RECOMMENDED

29. **Incivek™ (telaprevir; package insert). Vertex Pharmaceuticals Inc: Cambridge, MA;** 2011.

30. Lontok E, Mani N, Harrington PR, Miller V: **Closing in on the target: sustained virologic response in hepatitis C virus genotype 1 infection response-guided therapy.** *Clin Infect Dis* 2013, **56:**1466-70.

F1000Prime RECOMMENDED

31. Sulkowski MS, Roberts S, Afdhal NH, Andreone P, Diago M, Pol S, Poordad F, Zeuzem S, Bengtsson L, Luo D, *et al.*: **Ribavirin dose modification in treatment-naïve and previously treated patients who received telaprevir combination treatment: no impact on sustained virologic response in phase 3 studies.** *European Association for the Study of the Liver 47th Annual Meeting; Barcelona, Spain, 2012.*

32. Poordad F, Lawitz EJ, Reddy KR, Afdhal NH, Hézode C, Zeuzem S, Lee SS, Calleja JL, Brown RS, Craxi A, *et al.*: **A randomized trial comparing ribavirin dose reduction versus erythropoietin for anemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin.** *European Association for the Study of the Liver 47th Annual Meeting; Barcelona, Spain, 2012.*

33. Antonini MG, Babudieri S, Maida I, Baiguera C, Zanini B, Fenu L, Dettori G, Manno D, Mura MS, Carosi G, Puoti M: **Incidence of neutropenia and infections during combination treatment of chronic hepatitis C with pegylated interferon alfa-2a or alfa-2b plus ribavirin.** *Infection* 2008, **36:**250-5.

F1000Prime RECOMMENDED

34. Roomer R, Hansen BE, Janssen HLA, de Knegt RJ: **Risk factors for infection during treatment with peginterferon alfa and ribavirin for chronic hepatitis C.** *Hepatology* 2010, **52:**1225-31.

F1000Prime RECOMMENDED

35. Sherman KE: **Managing adverse effects and complications in completing treatment for hepatitis C virus infection.** *Top Antivir Med* 2012, **20:**125-8.

F1000Prime RECOMMENDED

36. Roomer R, Hansen BE, Janssen HLA, de Knegt RJ: **Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C.** *J Hepatol* 2010, **53:**455-9.

F1000Prime RECOMMENDED

37. **GSK press release: FDA approves new indication for PROMACTA® (eltrombopag).** [http://www.gsk.com/media/press-releases/2012/FDA-approves-new-indication-for-PROMACTA-eltrombopag.html]

38. **FDA News Release: FDA announces changes to risk strategy requirements for 2 drugs to treat low platelet counts – Nplate (romiplostim) and Promacta (eltrombopag).** [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm282502.htm]

F1000Prime RECOMMENDED

39. **Incivek (telaprevir) In combination with drugs peginterferon alfa and ribavirin (Incivek combination treatment): drug safety communication - serious skin reactions.** [http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm332860.htm]

40. Carlson A, Gregorich Z, Striker R: **Telaprevir to boceprevir switch highlights lack of cross-reactivity.** *Clin Infect Dis* 2013, **56:**552-4.

41. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS,

Zeuzem S: **Telaprevir for previously untreated chronic hepatitis C virus infection.** *N Engl J Med* 2011, **364:**2405-16.

F1000Prime RECOMMENDED

42. Morasco BJ, Loftis JM, Indest DW, Ruimy S, Davison JW, Felker B, Hauser P: **Prophylactic antidepressant treatment in patients with hepatitis C on antiviral therapy: a double-blind, placebo-controlled trial.** *Psychosomatics* 2010, **51:**401-8.

F1000Prime RECOMMENDED

43. de Knegt RJ, Bezemer G, van Gool AR, Drenth JPH, Hansen BE, Droogleever Fortuyn HA, Weegink CJ, Hengeveld MW, Janssen HLA: **Randomised clinical trial: escitalopram for the prevention of psychiatric adverse events during treatment with peginterferon-alfa-2a and ribavirin for chronic hepatitis C.** *Aliment Pharmacol Ther* 2011, **34:**1306-17.

F1000Prime RECOMMENDED

44. Schaefer M, Sarkar R, Knop V, Effenberger S, Friebe A, Heinze L, Spengler U, Schlaepfer T, Reimer J, Buggisch P, Ockenga J, Link R, Rentrop M, Weidenbach H, Fromm G, Lieb K, Baumert TF, Heinz A, Discher T, Neumann K, Zeuzem S, Berg T: **Escitalopram for the prevention of peginterferon-α2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease: a randomized trial.** *Ann Intern Med* 2012, **157:**94-103.

F1000Prime RECOMMENDED