HEPATITIS C

Update on the Treatment of Hepatitis C Genotype 1

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ABSTRACT

- **Objective:** To review treatment of hepatitis C viral (HCV) infection genotype 1.
- **Methods:** Review of the literature in the context of 4 clinical cases.
- **Results:** HCV infection affects over 180 million people worldwide with the majority of individuals exposed to the virus developing chronic infection. The success rate of treatment of HCV genotype 1 has increased over the years with the evolution of therapeutic regimens, including the recent addition of direct-acting antiviral agents (DAAs). The sustained virologic response rate has increased from about 10% with initial treatment regimens to over 75% with triple therapy with a DAA and pegylated interferon/RBV combination. In addition, the treatment duration has been shortened without significant reduction in response rate. Adding new drugs to HCV treatment regimen increases the complexity of the treatment algorithms, associated side effects, and cost of the therapy.
- **Conclusion:** HCV treatment has significantly changed over the past decades with success rates dramatically increasing. This success is expected to reduce the number of patients infected with HCV and subsequently reduce the prevalence of HCV-induced cirrhosis, liver failure, and hepatocellular carcinoma.

Hepatitis C viral (HCV) infection affects over 180 million worldwide with the majority of individuals exposed to the virus developing chronic infection. One third of patients with chronic hepatitis C progresses to develop cirrhosis with subsequent liver failure and hepatocellular carcinoma [1,2]. The success rate of treatment of HCV genotype 1 has increased over the years with the evolution of therapeutic regimens including interferon (IFN) monotherapy, interferon/RBV combination, pegylated interferon (P-INF) monotherapy, and P-INF/RBV combination, and then with the recent addition of direct-acting antiviral agents (DAAs). The sustained virologic response (SVR) rate has increased from around 10% with initial treatment regimens to over 75% with triple therapy with a DAA and P-INF/RBV combination. In addition, the treatment duration has been shortened without significant reduction in SVR rate. The addition of a third drug to P-INF/RBV therapy has increased the complexity of the treatment regimen, side effects and cost [3–6].

DIRECT-ACTING ANTIVIRAL AGENTS

HCV is a single-strand RNA virus which encodes for a single polyprotein. This protein is subsequently cleaved by proteases with resultant production of 4 structural and 6 nonstructural proteins. Inhibition of the NS3/4A protease has been shown to significantly affect HCV viral replication. Two selective inhibitors of this protease have recently been approved by the FDA: telaprevir (TVR) and boceprevir (BOC). Neither of these protease inhibitors (PI) can be used as a single agent due to the rapid development of viral resistance [7,8].

HCV is a highly variable virus with various genetically different viral species coexisting in the same infected individual. As in the case of other micro-organisms, the wild type virus is more capable of replicating than mutant variants. Thus in an untreated individual the wild virus predominates. Since the active site of NS3/4A protease is a three-amino-acid residue, drug resistance can occur as a consequence of using inhibitors of this protease. Studies have shown that resistant HCV mutants can be detected within a few days of DAA monotherapy with TVR or BOC. Lower rates of viral resistance have been noticed in HCV genotype 1b in comparison to genotype 1a [8–10].

Boceprevir

Phase III clinical trials have shown that both TVR and BOC are safe and effective drugs in achieving SVR when combined with P-INF and RBV. The BOC-based regimen has a 4 week lead-in phase where patients receive P-INF and RBV. This strategy has been shown to
reduce the rate of viral breakthrough and is associated with higher SVR rates. At the beginning of week 5, BOC 800 mg po every 8 hours is added to the treatment regimen. The duration of the treatment varies based on presence of cirrhosis, prior response to P-INF/RBV therapy, and viral load at week 4 and 8 [3] (Figure 1). The BOC-based treatment regimen has been shown to increase the SVR rate in treatment-naive patients. In the SPRINT-2 trial, the BOC response-guided therapy arm achieved SVR in 63% of patients as compared with only 38% of the control group receiving 48 weeks of standard P-INF/RBV. Furthermore, the relapse rate in BOC response-guided therapy was 8% as compared to 23% in the control arm [5,6,11].

Treatment experienced patients (defined as those with prior history of failed treatment with P-INF/RBV due to partial response or relapse but not null response) have also been shown to benefit from BOC-based triple therapy. RESPOND-2 trial showed that 59% of patients in the BOC response-guided treatment arm achieved SVR in comparison to only 21% of patients receiving P-INF/RBV therapy [12].

Both SPRINT-2 and RESPOND-2 studies have shown that patients with poor interferon response, defined as a viral load reduction of less than 1 log at week 4, are at higher risk to develop BOC resistance and subsequently achieve a lower SVR rate [6,11,12].

Adverse effects associated with BOC-based triple therapy are similar to those observed in patients receiving P-INF/RBV-based dual therapy. BOC use has been shown to be associated with higher rates of anemia than dual therapy regimen. Anemia was reported in 45% and 50% of patients randomized to BOC in SPRINT-2 and RESPOND-2 trials in comparison to 20% and 29% of patients receiving standard dual therapy. Most of the cases of anemia were successfully managed by RBV dose reduction and/or the use of erythropoietin. The rate of erythropoietin use was almost double in the BOC arm [5,6,11,12].

Telaprevir
Phase III clinical trials have shown that TVR combined with P-INF and RBV is associated with increased SVR rate. TVR (750 mg po every 8 hours taken with high fat meal) is taken as part of triple therapy for 12 weeks. This is followed by P-INF/RBV dual therapy for another 12-36 weeks based on presence of cirrhosis, prior history of P-INF/RBV treatment, and VL at week 4 and 12 of therapy (Figure 2). The ADAVCE clinical study revealed an SVR rate of 75% in treatment-naive patients randomized to TVR-based response-guided triple therapy in comparison to 44% in the standard P-INF/RBV group. The relapse rate in the TVR group was 9% while it reached 28% in the dual therapy group. Similar findings were observed in the ILLUMINATE study [4,14,15].

Treatment experienced patients (defined as those with prior history of failed treatment with P-INF/RBV due to null response, partial response, or relapse) have also been shown to benefit from TVR based triple therapy. The REALIZE phase III clinical trial demonstrated that patients treated with 12 weeks of triple therapy followed by 36 weeks of dual therapy achieved SVR in 66% in comparison to 17% of patients receiving 48 weeks of standard P-INF/RBV therapy. Among prior null responders, TVR based therapy achieved SVR in 33% of the cases in contrast to 5% of patients in the standard dual therapy retreatment group [15,16].

In addition to known adverse effects associated with P-INF/RBV therapy, almost 50% of patients receiving TVR developed skin rash. Although the majority of these cases were mild to moderate in severity, in 3% to 6% of the cases the rash can be severe. The severity of skin rash ranges from mild cases that can be managed by local therapy to severe cases, including Stevens-Johnson syndrome, that require prompt discontinuation of the treatment and urgent evaluation by a dermatologist [3,17].

**CASE 1**
**Initial Presentation**

A 57-year-old Caucasian female with chronic genotype 1a HCV infection presents for possible therapy. A recent liver biopsy showed stage II/IV fibrosis. She does not have clinical, laboratory, or sonographic evidence of cirrhosis. She was recently diagnosed with HCV infection upon routine laboratory testing that included abnormal liver function tests. Her medical history is remarkable for mild depression, hypertension, and dyslipidemia. Her medication list includes escitalopram, amlodipine, and simvastatin. She does not smoke tobacco, consumes 1 drink of alcohol
Figure 1. Treatment algorithm using boceprevir (BOC) and pegylated interferon (P-INF)/ribavarin (RBV) combination.
Figure 2. Treatment algorithm using telaprevir (TVR) and pegylated interferon (P-INF)/ribavirin (RBV) combination.
per week, and denies any recent illicit drug use though admits to remote history of snorting cocaine for a few months. Baseline laboratory tests showed normal complete blood count (CBC), comprehensive metabolic panel (CMP) except for mildly elevated transaminases, and HCV viral load (VL) of 2,080,000 IU/mL.

- **What treatment plan is recommended?**

This patient is treatment-naive with no evidence of cirrhosis and no contraindication for triple therapy. She would be a good candidate for either TVR- or BOC-based therapy. She does have mild depression, thus close follow up with a psychiatrist is recommended. She may qualify for shortened treatment duration since she is treatment naive and does not have cirrhosis (Figures 1 and 2).

**Case Continued**

The patient was started on P-INF alfa-2a (Pegasys 180 mcg), weight-based RBV (1200 mg/day), and TVR (750 mg every 8 hours). Her medication list was reviewed for potential interaction with TVR. At week 4, HCV VL was undetectable. Per the treatment paradigm she qualifies for 12 weeks of triple therapy followed by 12 weeks of dual therapy.

- **What potential drug-drug interactions are of concern?**

Both TVR and BOC have potential drug interaction with many medications which could significantly alter drug levels of PIs or the other drugs. Concomitant use of a statin (such as simvastatin in this case patient) and TVR or BOC is contraindicated. TVR also interacts with escitalopram and amlodipine potentially altering their levels. On the contrary, BOC does not significantly interact with escitalopram. Lowering escitalopram levels may result in worsening of depression thus this patient would require close follow up and monitoring by a psychiatrist. Due to their metabolism via cytochrome P450 3A4 (CYP3A4), PIs have potential interaction with over half of the drugs available in the market. Thus, close evaluation of the patient’s drug list is recommended prior to initiating HCV triple therapy. Multiple websites that assist in checking for potential drug interactions with TVR or BOC are available (eg, www.hep-druginteractions.org) [3,4,11,15].

- **What are possible treatment-associated complications?**

HCV treatment with P-INF and RBV has a list of known potential adverse effects including skin rash. The addition of PIs to the treatment regimen has been shown to increase the risk of skin rash. Studies have shown this to be more common with TVR than BOC-based regimens. The mechanism of dermatologic adverse effects of PIs is not clear. Skin rash has been reported in more than half of patients receiving TVR. Although most cases of rash have been mild, severe cases with potential life-threatening dermatologic reactions have been noted. The majority of patients with drug induced skin reaction have eczematous dermatitis associated with xerosis and pruritus. Phase III clinical studies have shown that up to 55% of patients receiving TVR develop rash and 51% have pruritus in comparison to 33% and 26% of patients receiving placebo. Half of the rash cases start in the first 4 weeks of treatment and the remaining half are noted up to week 12 of therapy. More than 90% of TVR-associated rash is grade 1 or 2, and in 92% of the cases the rash does not progress to worse grade [4,14,16].

Aggressive skin care should be recommended to all patients treated with triple therapy. This includes frequent hydration and use of emollients. Patients should be counselled about skin eruptions and the need to report that to the treating physician. Special attention should be oriented towards identifying and reporting blisters, oral ulcers, ocular inflammation, or fever. The manufacturer’s package grades TVR-associated rash into 4 degrees of severity. The treatment of skin rash is based on its severity, and drug interruption or discontinuation may be required [17].

Two forms of severe cutaneous adverse reactions (SCAR) associated with TVR use require immediate discontinuation of TVR, P-INF, and RBV with emergent evaluation by a dermatologist. Both of these reactions, Stevens-Johnson syndrome (SJS) and drug reaction eosinophilia with systemic symptoms (DRESS),
have been reported in a small percentage of patients in the initial drug trials. Review of phase III drug trials showed that among 221 patients with grade 3 skin rash 14 patients (6%) had SCAR (3 cases of SJS and 11 cases of DRESS). The mortality rate of SCAR is estimated to be between 10% and 13%. Although no fatal cases due to TVR associated rash have been reported, SJS and DRESS can lead to fatal outcomes if they are not suspected and diagnosed in timely fashion with subsequent early discontinuation of the offending drug [17].

**Case Continued**

At the end of week 10, the patient developed a mildly pruritic macular papular rash involving the extensor surfaces of the elbows and knees and scattered over the abdomen. The severity of the rash was grade 1. She was started on cetirizine (10 mg po daily) in addition to local treatment with hydrocortisone 1% ointment. She was continued on triple therapy. Within 4 days the rash progressed to grade 2; hydrocortisone was discontinued and a more potent topical steroid (triamcinolone acetonide 0.1% ointment) was started. Despite this, her rash continued to worsen and TVR was discontinued and dual therapy with P-INF/RBV was continued with careful monitoring of the rash. The severity of the rash continued to worsen over the next few days and it reached grade 3 in 5 days. At this point treatment with P-INF and RBV was interrupted for 1 week until improvement of the rash was noted. The patient was able to finish her treatment course and her VL continued to be undetectable at 24 weeks and 48 weeks.

**CASE 2**

**Initial Presentation**

A 60-year-old Caucasian male with HCV-genotype 1b and alcohol-induced liver cirrhosis with no prior HCV treatment presents for possible therapy. A liver biopsy 4 years ago showed stage III/IV fibrosis. The patient was recommended HCV treatment at that time yet he failed to follow up. Currently he has clinical evidence of cirrhosis (Child-Pugh A) with portal hypertension. He has not consumed any alcohol over the past 6 months. His past medical history is significant for diabetes mellitus (DM) type 2. He does not have a history of psychiatric illness. His medication list includes pioglitazone and glimepiride. Esophagogastroduodenoscopy showed no esophageal or gastric varices. Abdominal ultrasound showed no ascites. Recent ophthalmologic evaluation showed no evidence of diabetic retinopathy. Baseline electrocardiogram and cardiac stress test revealed no evidence of coronary artery disease. Pretreatment labs showed leukopenia (WBC 3500/µL), thrombocytopenia (123,000/µL) and HCV viral load of 2460 IU/mL.

- **What treatment plan is recommended?**

This patient is a good candidate for HCV treatment with triple therapy. Either BOC or TVR could be used in this setting. Since the patient has cirrhosis he would require 48 weeks of treatment and would not qualify for response-guided therapy (ie, shortened treatment duration) as per package insert for BOC and TVR and AASLD guidelines [3] (Figures 1 and 2).

This patient has well compensated cirrhosis, and HCV treatment could result in decompensation of liver function. We recommend that treatment of such patients should be performed in institutions with liver transplant centers or after a referral to a transplant center. These patients would require close monitoring for evidence of hepatic failure. Eradication of HCV infection at this stage would prevent post-transplantation recurrence with associated potential for graft failure. Thus patients with compensated cirrhosis should be strongly considered for HCV treatment.

Pretreatment leukopenia and thrombocytopenia raise the possibility of having to reduce the dose of P-INF. Patients with DM are at risk of having coronary artery disease (CAD) and diabetic retinopathy; thus we recommend that these patients get cardiac and ophthalmologic evaluation prior to initiating interferon-based treatment.

**Case Continued**

The patient was started on P-INF alfa-2a (Pegasys 180 mcg), weight-based RBV (1000 mg/day), and TVR (750 mg, every 8 hours). At weeks 4 and 12, HCV VL was undetectable. VL was again undetectable at weeks 24 and 48 (end of treatment). As per recommendations, the patient received 12 weeks of triple therapy (TVR/P-INF/RBV) followed by 36 weeks of dual therapy (P-INF/RBV). Of note, despite achieving a SVR, patients with established cirrhosis would continue to require interval screening for compli-
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cations of cirrhosis including hepatocellular carcinoma and varices.

Case Continued

The patient developed anemia on triple therapy, with hemoglobin (Hgb) decreasing to below 10 g/dL from a pre-treatment baseline of 14.6 g/dL. The management options include either decreasing the dose of RBV, using erythropoietin, or combining both options; rarely blood transfusion may be required. We opted to use erythropoietin in order to avoid RBV dose reduction after counseling the patient about the possible side effects of erythropoietin-stimulating agents. The patient was treated with 40,000 units of erythropoietin per week starting at week 9. This resulted in improvement of Hgb levels. At week 12 the patient finished his TVR and continued on dual therapy. Following this his Hgb improved further and erythropoietin was discontinued at week 15. Should his anemia have worsened further despite of erythropoietin injections, then the dose of RBV would have to be reduced. Our patient developed leukopenia and worsening degree of thrombocytopenia during his treatment course. This improved with INF dose reduction performed due to concomitant leukopenia.

• What treatment complications may be seen?

Anemia

Anemia is a common complication associated with RBV and PIs. It is more commonly seen with BOC than TVR, most likely due to the longer duration of triple therapy with BOC [4,12]. Studies have shown that treatment-induced anemia may be a favorable indicator of higher SVR. This has been shown in the case of BOC in SPRINT-2 trial. In this study, patients who developed anemia (Hgb < 10g/dL) achieved a 72% SVR rate in contrast to 58% of patients who had Hgb ≥ 10 g/dL. A similar finding was noted in TVR studies, ADVANCE and ILLUMINATE, where patients whose week 12 Hgb decreased by ≥ 3 g/dL from baseline achieved a 76% SVR rate in contrast to 55% in patients who had a Hgb drop of < 3 g/dL. The difference in SVR among patients with and without anemia seems to reflect adequate RBV dosing in patients who developed higher degree of anemia. Studies have shown that RBV dose reduction for management of anemia may not reduce the likelihood of achieving SVR with BOC- or TVR-based therapy [11,12]. Based on that it is our practice to use erythropoietin as the first-line drug in treatment of anemia and if this fails, then we would reduce the dose of RBV.

Leukopenia

Reduction in WBC is a known complication of INF-based HCV treatment. Management options include INF dose reduction with or without the use of neupogen.

Thrombocytopenia

Thrombocytopenia is a known side effect of INF and could present a challenge in patients with cirrhosis. Its treatment is based on INF dose reduction.

CASE 3

Initial Presentation

A 41-year-old African-American patient presents for possible HCV treatment. He has genotype 1b and a liver biopsy 2 years ago showed stage II/IV fibrosis. His infection has relapsed after a full course of P-INF/RBV. He does not have clinical or radiologic evidence of cirrhosis. He does not have any other medical or psychiatric problems. He smokes cigarettes and does not drink alcohol or use illicit drugs.

• What treatment plan is recommended?

This patient is a good candidate for HCV treatment with triple therapy. Either BOC or TVR could be used in this setting. Since the patient does not have cirrhosis and he is treatment experienced with prior relapse after dual therapy, he qualifies for response-guided therapy with TVR as per package insert and AASLD guidelines [3]. If his VL is undetectable at weeks 4 and 12 then he would receive a total of 24 weeks of treatment. On the other hand, if these VLs are detectable but ≤ 1000 IU/mL then he would require a 48 week course of treatment. If he was a partial or null responder, then he would not qualify for response-guided therapy (Figure 2).

Case Continued

The patient was started on weight-based P-INF alfa-2b (Pegintron 150 mcg/week), weight-
based RBV (1200 mg/day), and TVR (750 mg, every 8 hours). Pretreatment HCV VL was 1,840,000 IU/mL. The VL decreased to being detectable but not quantified at week 4 and then undetectable at week 8. Unfortunately it became detectable but not quantified at week 12. As per treatment recommendations, if the VL is < 1000 IU/mL at week 4 and 12, then treatment should be continued. After finishing 12 weeks of triple therapy, he was continued on dual therapy and VL was rechecked at week 24. Unfortunately, HCV VL at this time was 2230 IU/mL thus P-INF and BRV were discontinued. His treatment course was complicated by development of anal burning sensation at week 4. This was controlled by topical over-the-counter antihemorrhoidal steroid foam. Although the burning sensation improved with this treatment it did not completely resolve, yet the patient was able to finish 12 weeks of TVR. After finishing TVR the anal discomfort gradually faded away.

• What treatment-associated issues are notable?

Viral Breakthrough

Current treatment guidelines for TCV recommend discontinuing treatment if the VL is >1000 IU/mL at weeks 4 or 12 and/or if the VL is detectable at week 24. The treatment paradigm is different for BOC as treatment should be stopped if VL is ≥ 100 IU/ml at week 12 or detectable at week 24. Retreatment with a different PI or the same PI should not be considered. This is essential to prevent development of resistant viral variants which could complicate or prevent future therapies. As with other viruses and microorganisms, treatment failure selectively results in predominance of resistant strains over wild type organisms. Phase III studies have shown that around 75% of patients who did not achieve SVR on TVR based triple therapy had resistant viral variants. Similar findings were noted in patients who did not achieve SVR with BOC [8,18].

Anorectal Complaints

Anorectal complaints have been reported in up to 29% of patients treated with TVR. Most of these patients complain of discomfort, pruritus, burning sensation, or hemorrhoids. Studies have shown that only 1% of the patients may need to discontinue TVR due to anorectal complaints. Management options include topical steroids, lidocaine, or oral antihistamines [15].

CASE 4

Initial Presentation

A 45-year-old African-American female presents for possible retreatment of HCV infection. She has genotype 1a and a liver biopsy 3 years ago showed stage III/IV fibrosis. Interleukin-28B (IL28B) genotype was determined to be CT. She does not have evidence of cirrhosis on clinical examination, laboratory data or sonographic imaging. She had a partial response to prior treatment with P-INF/RBV. Her medical history is significant for chronic lower back pain due to motor vehicle accident. She has been on methadone for the last 5 years. She does not smoke cigarettes, drink alcohol or use illicit drugs.

• What treatment plan is recommended?

This patient is a good candidate for HCV treatment with triple therapy. Either BOC or TVR could be used in this setting. Treatment with BOC was decided. Reviewing her medication list for drug interaction with BOC indicates a potential interaction with methadone. Boceprevir is metabolized principally by aldolko-reductase (AKR) enzymes and partially by CYP3A4. In vitro studies have shown BOC to be a potent inhibitor of CYP3A4. Methadone is partially metabolized by CYP3A4. Although no studies on the effect of co-administration of BOC and methadone have been reported, prior studies on other potent inhibitors of the CYP3A4 (such as HIV medications) have indicated reduced levels of methadone in these patients. Thus it is recommended to clinically monitor these patients while receiving BOC and adjust the dose of methadone accordingly [19].

Since the patient is treatment experienced with prior partial response to dual therapy, she would qualify for response-guided therapy as per package insert for BOC and AASLD guidelines [3]. It is important to note that null responders were not included in BOC clinical trials while TVR trials included this patient population. If these patients are treated with BOC-based therapy, then they would be treated as patients with cirrhosis and would require a 48-week course of treatment (Figure 1).
**What is the significance of IL28 genotype?**

There is adequate evidence in recent literature to support that IL28B genotype is a strong predictor of SVR in patients treated with P-INF/RBV dual therapy and that this is a reflection of responsiveness to interferon [20]. The role of IL28B as a predictor of SVR with triple therapy is not as clear. In both ADVANCE and REALIZE, SVR rates were increased across all IL28B genotypes in patients receiving TVR. In the SPRINT-2 trial of BOC, patients with IL28B CC genotype experienced similarly high rates of SVR in both triple and dual therapy arms. However, patients with the CT and TT genotypes who received BOC had significantly higher SVR rates than those receiving dual therapy. RESPOND-2 study revealed higher SVR rates in patients with favorable IL28B genotype. The current AASLD guidelines indicate that testing for IL28B may be considered if the results are expected to affect the patient’s or provider’s decision about treatment or its duration [3]. Thus IL28B genotyping may be of some value in predicting response to triple therapy. Yet since the SVR rate with triple therapy is already encouragingly high even with unfavorable IL28B genotypes we do not routinely check IL28B genotype.

**Case Continued**

The patient was started on weight-based P-INF alfa-2b (Pegintron 150 mcg/week) and weight-based RBV (1000 mg/day) as a lead-in phase. Pretreatment HCV VL was 1,225,000 IU/mL. At week 4, BOC (800 mg, every 8 hours) was started and HCV VL was obtained. The VL was noted to have decreased by 2 logs. According to the current treatment guidelines, patients with less than 1 log of decrease in VL at week 4 are considered to have poor interferon response and thus would require 48 weeks of treatment (Figure 1). Since our patient had an adequate VL response at week 4 she was continued on the response-guided regimen. Subsequently, repeat VL was 12,540 IU/mL at week 8 and undetectable at week 24. As per current guidelines, our patient finished BOC at week 36 and continued P-INF/RBV dual therapy until week 48. At the end of therapy (week 48) the VL was again undetectable.

The patient developed a mild drop in Hgb level that significantly worsened after BOC was started, with Hgb decreasing to below 9.5 g/dL from a pre-treatment baseline of 12.3 g/dL. As discussed earlier, the management options at this stage include either decreasing the dose of RBV, using erythropoietin, or combining both options. The patient was treated with 40,000 units of erythropoietin per week starting at week 6. The following week showed an Hgb of 8.5 g/dL and thus RBV dose had to be transiently reduced and erythropoietin frequency was increased to 3 times per week. Eventually the dose of RBV was increased back to target dose and the patient was able to finish the full course of treatment. As discussed earlier, SPRINT-2 has shown that anemia may be a favorable indicator of higher success rate in achieving SVR.

**CONCLUSION**

HCV treatment has significantly changed over the last few decades, with success rates dramatically increasing with the recent introduction of triple therapy, raising cure rates from 1 in 10 patients to over three-quarters. This success is expected to reduce the number of patients infected with HCV and subsequently reduce the prevalence of HCV-induced cirrhosis, liver failure, and hepatocellular carcinoma. Adding new drugs to the HCV treatment regimen increases the complexity of the treatment algorithms, associated side effects, and cost of the therapy.

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