

Frontiers in the Treatment of Hepatitis C Virus Infection

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Abstract: In the United States, chronic hepatitis C virus (HCV) infection is the leading cause of blood-borne, virus-associated death related to advanced liver disease and the leading indication for liver transplantation. Although the diagnostic test for HCV has been available for more than 20 years, the majority of persons with HCV infection still have not received a diagnosis. This has led to a recent change in screening recommendations by the Centers for Disease Control and Prevention. Moreover, new medications were approved in 2011 after nearly a decade of minimal progress in the development of treatments for HCV infection. This was followed by the highly anticipated approval of sofosbuvir and simeprevir in 2013. In the past 3 years, there has been an explosion of reports on medications from different classes, promising a dramatic expansion to an all-oral regimen for the treatment of HCV genotype 1 infection within the next few years. This article reviews the current screening recommendations and standard of care for treatment of HCV infection and highlights specific agents in the pipeline that should change the landscape of how HCV infection is treated in the near future.

The prevalence of chronic hepatitis C virus (HCV) infection in the United States has been estimated to be between 4 and 7 million persons.^{1,2} In the United States, more than two-thirds of patients infected with HCV are thought to be “Baby Boomers,” born between 1945 and 1965.³ Previously, recommendations for screening had focused only on those persons with risk factors for acquisition of HCV. After more than 20 years, less than 50% of persons infected with HCV have been identified. Thus, the Centers for Disease Control and Prevention (CDC) recently recommended a 1-time screening for chronic HCV infection for everyone in the Baby Boomer cohort regardless of risk factors, recognizing that screening and linkage to care can ameliorate the human and societal costs associated with HCV infection.⁴ Patients of any age with risk factors should still be screened. Fortunately, the US Protective Services Task Force (the independent panel of

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experts in prevention and evidence-based medicine that makes recommendations for primary care physicians in the United States) gave the new screening recommendations for HCV a B recommendation, indicating a high likelihood of payment by payers for this diagnostic test.⁵

Evidence has shown that the diagnosis of chronic HCV infection and achievement of sustained virologic response (SVR) can lead to regression of cirrhosis and reduction in liver-related mortality, hepatic decompensation, hepatocellular carcinoma, and all-cause mortality.⁶⁻⁹ Unfortunately, recent reports from the National Health and Nutrition Examination Survey and the Chronic Hepatitis Cohort Study have found significant shortcomings in the current state of HCV infection care in the United States. Only approximately 50% of persons thought to be infected with HCV have been identified. Of these, one third have been referred for care, 20% have undergone HCV RNA testing, 15% have undergone a liver biopsy, 7% to 11% have initiated treatment, and, of those treated, a mere 5% to 6% have attained SVR.¹⁰

History of Hepatitis C Virus Infection Treatment

Despite recognition that treatment can lead to HCV RNA eradication and cure of HCV infection, progress to improve the therapeutic regimen has been painfully slow and, at times, marked by stagnation. SVR rates were initially 6% to 16% with interferon alpha (IFN- α) monotherapy and, with the addition of ribavirin in the late 1990s, rose to 30% to 40%. Pegylation of IFN in 2001, used in combination with ribavirin, led to a small but statistically significant improvement in SVR of 54% to 56% overall. Patients infected with HCV genotype (GT) 1, the most common GT in the United States, did not do as well as those with GT 2 or 3. Despite many shortcomings with this regimen—including less than satisfactory efficacy, significant toxicity, and numerous contraindications for therapy—10 years passed until the approval of 2 protease inhibitors (PIs), which are the first generation of direct-acting antiviral (DAA) therapies.¹¹

For many years, the main obstacle to the development of new therapeutic products for HCV infection was the absence of a small animal HCV infection model and limitations in cell cultures for studying viral replication.¹² However, in recent years, significant progress has been made. The improvement of cell culture systems has allowed in-depth understanding of the HCV life cycle and genome. Six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) that play critical roles in HCV entry, replication, and proliferation have been identified and serve as possible targets for the development of DAA therapies.¹³

Recent Developments in Hepatitis C Virus Infection Treatment

The recent approval by the US Food and Drug Administration (FDA) of sofosbuvir (Sovaldi, Gilead) and simeprevir (Olysio, Janssen) marks the beginning of a rapidly changing landscape defining the standard of care for patients with HCV infection. Until the end of 2013, the standard of care for patients with either HCV GT 2 or 3 was pegylated (PEG) IFN plus ribavirin for 24 weeks. Expected SVR rates ranged from 69% to 74%.¹⁴ Until 2011, the standard of care for patients with HCV GT 1 also was PEG-IFN plus ribavirin. SVR rates were 40% to 50%.^{15,16} At that time, first-in-class PIs boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex) were approved for patients with GT 1, given in conjunction with both PEG-IFN and ribavirin for a total of 24 to 48 weeks, depending on whether the patient had a robust response.¹⁷ Because the length of therapy is based on individual response to therapy rather than the response of all patients with GT 1 treated similarly, this is called response-guided therapy.

Boceprevir and telaprevir are linear peptide mimetics that covalently but reversibly bind with and inhibit the NS3/4A protease. That, in turn, diminishes viral replication. The first-generation NS3/4A PIs heralded a new era in HCV infection treatment as the first approved DAA agents. SVR rates in pivotal phase 3 studies of treatment-naïve patients with GT 1 receiving PEG-IFN plus ribavirin plus a PI ranged from 63% to 75%, compared with 38% to 44% in controls receiving PEG-IFN plus ribavirin.^{18,19} In patients who previously received PEG-IFN plus ribavirin but did not achieve SVR, superior SVR rates of 75% to 83% were achieved in relapsers, 52% to 59% in partial responders, and 29% to 38% in null responders receiving PEG-IFN plus ribavirin plus a PI compared with 24% to 29% in relapsers, 7% to 15% in partial responders, and 0% to 5% in null responders receiving PEG-IFN plus ribavirin.^{20,21}

Limitations of the Recent Standard of Care

Despite FDA approval of the first-generation DAA agents, major limitations remain. First, boceprevir and telaprevir are only approved for use in patients infected with GT 1 HCV. The PIs are administered thrice daily with food (boceprevir with any food and telaprevir with 20 g of fat), have significant pill burden (6-12 pills daily), and have significant drug-drug interactions because of metabolism by CYP3A4, through which many other commonly used medications also are metabolized. Despite the high potency of these PIs, there is a low barrier for the development of resistance and subsequent treatment failure,

requiring concomitant antiviral therapy with PEG-IFN plus ribavirin, which serves as a resistant barrier against the breakthrough of resistant HCV quasiespecies.

The continued need for PEG-IFN plus ribavirin in PI-based regimens means that contraindications to the previous, pre-PI-era standard of care for treatment of HCV infection—including psychiatric issues such as severe depression and bipolar disease, autoimmune disease, advanced cardiovascular disease, decompensated liver disease, and renal failure—remain in play. Furthermore, many other patients without absolute contraindications to therapy, such as liver transplant recipients, do not tolerate PEG-IFN plus ribavirin or tolerate it poorly. Finally, many patients are unwilling to undergo therapy with an IFN-based regimen.

For patients who are eligible and willing to receive PI therapy, improvements in SVR rates come with significant toxicity. For boceprevir, the frequency and severity of anemia is greater than that observed in control groups. For telaprevir, anemia is also problematic. In addition, rash (occasionally severe) is noted in some patients. Anorectal symptoms also occur in treated patients. The cost of these regimens is also high. Thus, although first-generation PI regimens offer higher SVR rates than PEG-IFN plus ribavirin alone and although the adverse effects are manageable in most cases, there is a need for more effective and better-tolerated pangenotypic regimens that have more favorable dosage schedules, have fewer or no drug-drug interactions, and are suitable for patients with medical comorbidities.

Unmet Needs and Challenges in Hepatitis C Virus Infection

The large majority of HCV infections in the United States—perhaps up to 75% of cases—remain undiagnosed.²² Persons on the fringes of society, such as the homeless or incarcerated and those otherwise unable to access healthcare, remain the most vulnerable group.^{4,23} Serving special populations—including children, the elderly, HIV-coinfected patients, patients with decompensated liver disease, liver transplant recipients, and patients on dialysis—remains a challenge for clinicians. Difficult-to-treat populations—such as cirrhotic patients, null responders to previous PEG-IFN plus ribavirin, and patients who have failed or have been intolerant to boceprevir or telaprevir—require better approaches to therapy. In the French CUPIC study, a cohort of patients with advanced liver disease treated with PEG-IFN plus ribavirin plus a PI (telaprevir or boceprevir) had SVR rates of approximately 40% and rates of treatment discontinuation due to adverse events that exceeded 40%.²⁴ In particular, patients with lower-than-normal albumin

levels and thrombocytopenia at baseline experienced the most toxicity. In addition, reports of hepatic decompensation and death associated with PI-based therapy have led to temperance on proceeding with treatment in cirrhotic patients with significant portal hypertension.

Resistance to first-generation PIs develops in the majority of patients who do not achieve SVR after exposure. A concern is that, if the resistant variants persist, future PI-based regimens could be adversely affected. However, it appears that resistant variants do not persist over the long term, probably because HCV replicates in the cytoplasm, has no DNA intermediate, and does not integrate with host DNA. In patients with detectable resistant variants who have failed PI treatment, the majority had a return to wild-type variants at long-term follow-up of more than 16 months.^{25,26} However, the long-term impact of PI-resistant variants and subsequent response to regimens containing second-generation NS3/4A PIs remains unclear.

New Treatments for Hepatitis C Virus Infection

Fortunately, efforts to develop effective HCV medications have been robust. Current efforts are focused on the NS HCV proteins NS3, NS4A, NS5A, and NS5B. Because HCV rarely recurs if it is undetectable 12 weeks after discontinuation of therapy, the FDA recently approved SVR at 12 weeks after the end of treatment (SVR12), rather than SVR after 24 weeks of therapy, as the new primary objective for regulatory approval of HCV studies.²⁷

When interpreting data on the new therapeutic agents in development for HCV infection, it is important to keep in mind the current limitations of therapy and the features of an ideal regimen. Table 1 outlines these issues. Regarding the new regimens for HCV infection, much of the data are preliminary. A few phase 3 studies of the new regimens have been published, but the majority of data consist of phase 2 (or earlier) studies. Data have frequently been presented in abstract form or press releases. Relatively few patients have been included in trials, and many difficult-to-treat populations, such as cirrhotic patients, patients who have failed DAA agents, HIV-coinfected patients, and null responders to PEG-IFN plus ribavirin, are underrepresented. Many groups, such as patients with decompensated liver disease, those with HCV infection after liver transplantation, dialysis patients, and children with HCV infection, have not been assessed at all. When reviewing the data, excitement must be tempered because, until a drug completes the approval process, there is a possibility of potential rare toxicities, such as those found in BMS-986094 (renal and cardiac toxicity) or PSI-938 (hepatotoxicity).

Table 1. Limitations of Current HCV Treatment and Features of an Ideal Regimen

| Current Treatment Limitations of BOC and TVR | Features of an Ideal Regimen |
|---|--|
| <75% efficacy (although improved compared with PEG-IFN + RBV) | High efficacy |
| 24 to 48 weeks | Short duration of treatment (≤ 12 weeks) |
| GT 1 alone | Pangenotypic |
| Low barrier to resistance | High barrier to resistance |
| Significant adverse events: anemia, rash, constitutional symptoms | Minimal, easily tolerated adverse events |
| Three-times-a-day dosing | Once-daily dosing |
| Complex treatment algorithm | Straight-forward regimen |
| Injection + oral | Oral |
| Expensive | Affordable |
| Limited availability in developing countries | Widely available |

BOC, boceprevir; GT 1, genotype 1; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

NS5B RNA-Dependent RNA Polymerase Nucleotide Inhibitor Plus Ribavirin with or without PEG-IFN

Nucleotide inhibitors (NIs) are analogues of purine or pyrimidine nucleotides that compete for incorporation into the virus and function as active site inhibitors of the NS5B RNA-dependent RNA polymerase (RdRp). They act as chain terminators that block the RdRp active site and lead to termination of RNA replication and HCV virion production. The NIs are moderately potent but have a very high barrier of resistance because mutations in the NS5B RdRp conferring resistance to the NI lead to changes in the catalytic site of the RdRp, reducing the viability and fitness of the resistant variant.²⁸ Because the RdRp is preserved across GTs, these NIs have broad genotypic efficacy.

Mericitabine, a nucleoside analogue of the NS5B RdRp with a first phosphorylation step for activation as a triphosphate uridine or cytidine form, is associated with a slow first-phase decline in HCV RNA. Mericitabine was reported in the first proof-of-concept DAA study in conjunction with danoprevir, a NS3/4A PI, in patients infected with GT 1 HCV.²⁹ Subsequent large phase 2 studies combining mericitabine with PEG-IFN plus ribavirin revealed SVR rates that were similar to the 50% SVR rate obtained in the control arms of PEG-IFN plus ribavirin.^{30,31} Mericitabine was less effective even though it was well tolerated, due to a

high relapse rate despite on-treatment suppression of HCV replication. Mericitabine, at least in combination with PEG-IFN plus ribavirin, will likely not be a prominent agent for antiviral therapy in the United States.

Sofosbuvir is metabolized to the same uridine triphosphate analogue as mericitabine and acts as a non-obligate chain terminator. However, sofosbuvir bypasses the first phosphorylation step and has a more rapid onset of action and higher potency. Sofosbuvir is pangenotypic and is dosed orally at 400 mg once daily without food requirements. Sofosbuvir is excreted by the kidneys and has not demonstrated any significant drug-drug interactions to date. More than 2000 patients have been treated with sofosbuvir without any significant safety signals reported, nor has there been identification of significant resistance mutations that have altered efficacy.³²⁻³⁴

Four phase 3 studies of sofosbuvir have been published: NEUTRINO, FISSION, FUSION, and POSITRON.^{32,33} Table 2 highlights the results of these studies. The NEUTRINO study involved treatment-naïve patients with mainly GT 1 HCV infection.³² There was no control group; rather, a prespecified historical control SVR rate of 60% was used for comparison. The regimen of PEG-IFN plus ribavirin plus sofosbuvir for 12 weeks was well tolerated and had a statistically significant improvement in SVR, with an overall rate of 90% and a rate of 80% in patients with cirrhosis. Patients infected with GT 1a HCV had a better overall SVR rate at 92% vs 82% for patients with GT 1b HCV infection.

The FISSION study assessed treatment-naïve patients with GT 2 or 3 HCV infection, comparing an IFN-free regimen of ribavirin plus sofosbuvir for 12 weeks with 24 weeks of PEG-IFN plus ribavirin.³² Noninferiority objectives were met. The ribavirin-plus-sofosbuvir regimen was well tolerated with no reported resistance, and it was associated with a superior SVR12 rate in patients infected with GT 2 HCV, with a SVR rate of 97% vs 78% for the control arm of PEG-IFN plus ribavirin. However, in patients infected with GT 3 HCV, response in the ribavirin-plus-sofosbuvir group was inferior to that of the group receiving PEG-IFN plus ribavirin, with overall SVR rates of 56% vs 63%, respectively. Twelve weeks of ribavirin plus sofosbuvir appeared to be sub-optimal for treatment of GT 3 HCV infection.

Treatment arms of the FUSION study included 12- vs 16-week regimens of ribavirin plus sofosbuvir in treatment-experienced patients infected with GT 2 or 3 HCV.³³ A historical control SVR rate of 25% was used for comparison. For noncirrhotic patients infected with GT 2 HCV, 12 weeks of ribavirin plus sofosbuvir was effective and well tolerated, whereas for patients infected with GT 3 HCV and for cirrhotic patients in general, the 16-week regimen of ribavirin plus sofosbuvir was superior. However, it is not clear from this study whether the optimal

Table 2. Summary of Sofosbuvir Phase 3 Studies

| Study | Regimen | Duration, weeks | N | Group | Characteristics | SVR12 | Discontinued due to AE |
|------------------------|--------------------------------|-----------------|-----|-------------------------|--|--|------------------------|
| NEUTRINO ³² | SOF + PEG-IFN + RBV | 12 | 327 | GT 1, 4, 5, 6; Tx-naïve | <ul style="list-style-type: none"> • IL-28 CC: 29% • GT 1: 89% • Cirrhosis: 17% | <ul style="list-style-type: none"> • 90% overall • 80% in cirrhosis • 92% in GT 1a; 82% in GT 1b • 96% in GT 4 | 1.5% |
| FISSION ³² | SOF + RBV | 12 | 256 | GT 2, 3; Tx-naïve | <ul style="list-style-type: none"> • IL-28 CC: 43% • GT 3: 72% • Cirrhosis: 20% | <ul style="list-style-type: none"> • 67% overall • 97% in GT 2; 91% in cirrhosis • 56% in GT 3; 34% in cirrhosis | 1% |
| | vs PEG-IFN + RBV control group | 24 | 243 | | | <ul style="list-style-type: none"> • 67% overall • 78% in GT 2; 62% in cirrhosis • 63% in GT 3; 30% in cirrhosis | 11% |
| FUSION ³³ | SOF + RBV | 12 | 103 | GT 2, 3; Tx-experienced | <ul style="list-style-type: none"> • IL-28 CC: 30-31% • GT 3: 62% • Cirrhosis: 33-35% | <ul style="list-style-type: none"> • 50% overall • 86% in GT 2; 60% in cirrhosis • 30% in GT 3; 19% in cirrhosis | 0% |
| | | 16 | 98 | | | <ul style="list-style-type: none"> • 73% overall • 94% in GT 2; 78% in cirrhosis • 62% in GT 3; 61% in cirrhosis | |
| POSITRON ³³ | SOF + RBV | 12 | 207 | GT 2, 3 | <ul style="list-style-type: none"> • IL-28 CC: 47% • GT 3: 47% • Cirrhosis: 15% | <ul style="list-style-type: none"> • 78% overall • 93% in GT 2; 94% in cirrhosis • 61% in GT 3; 21% in cirrhosis | 2% |
| | Placebo | 12 | 71 | | | 0% | 4% |

AE, adverse events; GT, genotype; IL, interleukin; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; Tx, treatment.

regimen for treatment-experienced patients infected with GT 3 HCV and cirrhotic patients infected with GT 2 or 3 HCV is 16 weeks or whether a longer duration of treatment will be required to provide an optimal SVR.

The POSITRON study was a double-blind, placebo-controlled, phase 3 trial that assessed patients infected with GT 2 or 3 HCV who were either ineligible, intolerant, or unwilling to take IFN therapy.³³ Patients received ribavirin-plus-sofosbuvir therapy or placebo. An SVR rate of 78% was observed with ribavirin plus sofosbuvir (vs 0% in the control arm).

This finding was consistent with the phase 2 ELECTRON trial, which reported a SVR24 rate of 100% for patients with GT 2 or 3 HCV infection treated with ribavirin plus sofosbuvir.³⁴ The addition of PEG-IFN did not improve the SVR24 rate but was associated with an increase in adverse events. Among patients infected with

GT 1 HCV who received ribavirin plus sofosbuvir, the SVR24 rate was 84% (21/25) in treatment-naïve patients and 10% (1/10) in null responders.

At the 2013 annual meeting of the American Association for the Study of Liver Diseases, the results of several sofosbuvir studies that addressed questions regarding the optimal treatment combination and duration for patients infected with GT 3 HCV were reported. The VALENCE study reported a SVR12 rate of 93% overall for patients infected with GT 2 HCV who were treated with 12 weeks of sofosbuvir plus ribavirin and a SVR12 rate of 85% overall for patients infected with GT 3 HCV treated with 24 weeks of sofosbuvir plus ribavirin.³⁵ The LONESTAR-2 trial evaluated sofosbuvir plus PEG-IFN plus ribavirin in treatment-experienced patients infected with GT 2 or 3 HCV who were treated for 12 weeks.³⁶ SVR12 rates of 96% and 83% were reported in patients

with GT 2 or 3 HCV infection, respectively, with a SVR12 rate of 83% in both cirrhotic and noncirrhotic patients infected with GT 3 HCV. These findings suggest that another option for cirrhotic patients infected with GT 3 HCV may be a 12-week regimen of sofosbuvir plus PEG-IFN plus ribavirin.

In addition, there is new hope for special populations, such as HIV-coinfected patients. PHOTON-1 was an open-label study of sofosbuvir plus ribavirin in both treatment-naïve and treatment-experienced patients coinfecting with HIV and GT 1, 2, or 3 HCV.³⁷ SVR12 was reported in 76% of patients infected with GT 1 HCV, 88% of those infected with GT 2 HCV, and 67% of those infected with GT 3 HCV.

The strengths of sofosbuvir-based regimens are high SVR rates, a lack of significant adverse events, simple dosing regimens with a 12-week course of triple therapy for patients with GT 1 HCV infection, a lack of drug-drug interactions, and pangenotypic efficacy. Sofosbuvir was approved by the FDA in December 2013 for HCV-monoinfected and HIV/HCV-coinfected patients with HCV genotypes 1, 2, 3, and 4. For GT 1 or 4, sofosbuvir was approved for 12 weeks in combination with PEG-IFN and ribavirin. For GT 2 HCV infection, sofosbuvir plus ribavirin was approved for 12 weeks, whereas, for GT 3 HCV infection, sofosbuvir plus ribavirin was recommended for 24 weeks. In addition, sofosbuvir plus ribavirin was approved for PEG-IFN-ineligible patients for 24 weeks. Lastly, sofosbuvir plus ribavirin was approved for up to 48 weeks (or until liver transplantation, if it occurs first) in patients with hepatocellular carcinoma awaiting liver transplantation.

The availability of sofosbuvir represents a major breakthrough in the treatment of HCV infection. Phase 3 trials assessing sofosbuvir plus drugs in other classes will further advance treatment of HCV infection toward an even shorter duration of treatment and simplification of pill burden with minimal adverse effects. However, further work must be done to confirm the effectiveness of sofosbuvir outside of research settings and to clarify the optimal regimens for patients in difficult-to-treat subpopulations that have not yet been fully examined.

Protease Inhibitors Plus PEG-IFN Plus Ribavirin

PIs inhibit the key initial cleavage of the HCV polyprotein by the NS3/4A protease. The second generation of PIs is better tolerated than the first, requires once-daily dosing, and retains high potency in comparison with boceprevir and telaprevir. Asunaprevir, simeprevir, faldaprevir, and vaniprevir are examples of second-generation PIs.³⁸⁻⁴⁰

Simeprevir combined with PEG-IFN plus ribavirin resulted in a SVR12 rate of approximately 80% compared with a rate of 50% for PEG-IFN plus ribavirin alone

in patients with GT 1 HCV who are treatment-naïve. Simeprevir was noted to have an improved hematologic profile compared with first-generation PIs, although transient increases in total bilirubin levels and slight increases in photosensitivity and rash were noted in patients receiving this regimen compared with those receiving PEG-IFN plus ribavirin.^{38,39} In November 2013, simeprevir was approved by the FDA for use in combination with PEG-IFN plus ribavirin in fixed-dose regimens for 12 weeks followed by PEG-IFN plus ribavirin for 12 weeks in treatment-naïve patients and prior relapsers and for 36 weeks in prior nonresponders in patients with GT 1 HCV. However, the FDA strongly recommended that, prior to initiating treatment with simeprevir, patients infected with GT 1a HCV be screened for the NS3 Q80K polymorphism because its presence was found to be a strong predictor of suboptimal response to simeprevir.⁴¹

Faldaprevir also has been studied in GT 1 HCV infection in treatment-naïve patients, with a reported SVR12 rate of approximately 80%. It was generally well tolerated, although a transient increase in total bilirubin levels at higher doses was noted.⁴⁰

NS5B Nonnucleoside Inhibitors

Unlike NS5B NIs, non-NIs (NNIs) target the NS5B RdRp and bind the enzyme at areas away from the active catalytic site. This leads to conformational changes in the enzyme or interference with the active catalytic site by allosteric hindrance that decreases the ability of RdRp to replicate HCV. Although this offers another mechanism of attacking the NS5B RdRp, NNIs are more prone to the development of resistance and, thus, have reduced genotypic coverage compared with NIs. NNIs are currently not under development for use with PEG-IFN plus ribavirin; however, because NNIs have different resistance variants than NS3/4A PIs and NS5B NIs, they are hypothesized to be valuable potential combination partners in IFN-free regimens. Table 3 lists the currently evaluated NNIs. ABT-333 is currently under investigation in IFN-free regimens and is the agent furthest along in development in this class at this time.⁴²

NS5A Inhibitors Plus PEG-IFN Plus Ribavirin

The NS5A protein has an unknown function but appears to be essential for HCV replication and viral assembly.⁴³ NS5A inhibitors are postulated to inhibit HCV replication by altering the localization and proper assembly and function of the NS5A protein. These inhibitors are potent and have a broad genotypic efficacy but have a low barrier to resistance.^{44,45}

Daclatasvir is the furthest along among the multiple NS5A inhibitors in development. It is given at a dosage of 60 mg once daily and does not have known drug-drug interactions. Daclatasvir also has been used with asuna-

Table 3. NS5B Nonnucleoside Inhibitors in Development

| |
|---|
| Thumb I TMC-647055, BMS-791325 Stopped: MK-3281, BI-207127 |
| Thumb II Stopped: Filibuvir (PF-868554), lomibuvir (VX-222), GS-9669, VX-759, VX-916 |
| Palm 1 Setrobuvir (RG-7790), ANA-598, ABT-333 Stopped: ABT-072 |
| Palm 2 Stopped: Tegobuvir (GS-9190), IDX375, HCV-796 |

NS, nonstructural.

previr in combination with PEG-IFN plus ribavirin in treatment-experienced patients infected with GT 1 HCV (nonresponders).⁴⁶ There was significant excitement with reports of SVR rates of 100%.

In the phase 2 COMMAND-2/3 study, PEG-IFN plus ribavirin plus daclatasvir was given for 12 or 16 weeks and compared with standard 24 weeks of PEG-IFN plus ribavirin in treatment-naïve patients infected with GT 2 or 3 HCV.⁴⁷ The SVR24 rate was 83% in patients infected with GT 2 and 67% to 69% in patients infected with GT 3 HCV, with similar results observed with 12 or 16 weeks of therapy. Daclatasvir was well tolerated.

COMMAND-1 reported SVR12 rates of 80% to 85% for PEG-IFN plus ribavirin plus daclatasvir administered for 12 to 24 weeks; the SVR rate was higher in patients infected with GT 1b than those infected with GT 1a.⁴⁸ A phase 3 trial investigating PEG-IFN plus ribavirin plus daclatasvir in patients infected with GT 1b HCV is underway.

The NS5A inhibitor ledipasvir, formerly GS-5885, which has improved potency against GT 1a as well as GT 1b HCV infection, is being pursued in further studies with sofosbuvir. It is also dosed once daily. Although ledipasvir has not been used in combination with PEG-IFN plus ribavirin alone, it has been studied with GS-9451, a PI, plus PEG-IFN plus ribavirin with 6 to 12 weeks of total therapy. Patients with favorable treatment characteristics, such as having GT 1 infection, being treatment-naïve, and having the interleukin (IL)-28B CC genotype, had SVR rates as high as 98% in the 12-week arm.⁴⁹

ABT-267, another NS5A inhibitor that is dosed once daily, also is under study with IFN-free regimens. It has not been studied with PEG-IFN plus ribavirin.

Host System Targets

In addition to NS protein targets, research is also underway on host system targets. Cyclophilin A interacts with NS5A to facilitate HCV replication. Alisporivir (DEB-025) is a

cyclophilin A inhibitor that has a high barrier to resistance and activity against HCV GT 1 through 4.⁵⁰ However, further development has been delayed due to reports of severe pancreatitis in phase 3 studies involving IFN.⁵¹

IL-29 (IFN- λ) is an endogenous type 3 IFN that stimulates an antiviral response. Although IFN- α receptors are virtually expressed in all cell types, resulting in the widespread adverse effects seen with PEG-IFN treatment, *IL-29* receptors are found in hepatocytes in higher levels. IFN- λ , which has been developed in a pegylated form, is reported to cause less constitutional symptoms and cytopenias from bone marrow suppression than IFN- α . Thus, fewer dose reductions were observed compared with PEG-IFN- α in HCV infection treatment.^{52,53}

MicroRNA inhibitors also have been reported to be a potential host target for treatment of HCV infection. MiR222 is a liver-specific microRNA that binds to HCV to facilitate HCV replication. MiR222 binding sites are conserved across HCV genotypes and subtypes and, thus, represent a potentially high-yield target for inhibition.⁵⁴ A recently reported phase 2a dose-escalation study demonstrated significant HCV RNA reduction without dose-limiting adverse events or development of escape mutants in 27 of 27 patients given MiR222.⁵⁵ The concept that this unique mechanism of action could complement different classes of DAA agents is intriguing, and further studies are awaited.

Combination Regimens without PEG-IFN

The final frontier of HCV infection therapy is development of effective and well-tolerated regimens that are PEG-IFN-free and all-oral. Combination regimens that use different classes of agents have been investigated.

NS5B Nucleotide Inhibitors Plus NS5A Inhibitors

Among the most intriguing data presented to date are studies combining sofosbuvir and daclatasvir, with or without ribavirin, in IFN-free regimens. In treatment-naïve patients with HCV infection, SVR rates of 100% (44/44) in GT 1 and 91% (40/44) in GT 2 or 3 were reported.⁵⁶ Furthermore, a phase 2 trial involving patients who failed therapy with PEG-IFN plus ribavirin plus boceprevir/telaprevir with daclatasvir plus sofosbuvir with or without ribavirin yielded a SVR rate of 100%.⁵⁷ The regimen was well tolerated.

Ledipasvir has been investigated in combination with sofosbuvir plus ribavirin in the phase 2 ELECTRON trial.⁵⁸ Treatment-naïve and treatment-experienced patients infected with GT 1 HCV received sofosbuvir plus ledipasvir plus ribavirin. The SVR12 rate was 100% (25/25) in treatment-naïve patients and 100% (9/9) in previous null responders.

Protease Inhibitors Plus NS5A Inhibitors

Asunaprevir plus daclatasvir was the first IFN-free regimen examined in treatment-experienced patients with GT 1 HCV infection and yielded a SVR rate of 36% (4/11).⁴⁶ More recently, the C-WORTHY study reported high SVR12 rates of 89% to 100% in patients treated with MK-5172 (NS3/4A PI) plus MK-8742 (NS5A) with or without ribavirin.⁵⁹ There were no early discontinuations, and the treatments were safe and otherwise well tolerated.

Protease Inhibitors Plus NS5B Nonnucleoside Inhibitors

In the COSMOS trial, the SVR8 rate in null responders infected with GT 1 HCV who received simeprevir plus sofosbuvir plus ribavirin was 96% vs 92% in null responders receiving simeprevir plus sofosbuvir.⁶⁰ No safety signals or significant adverse events were reported. In the SOUND-C2 and SOUND-C3 trials, faldaprevir plus deleobuvir (BI 207127), a nonnucleoside NS5B polymerase inhibitor, plus ribavirin resulted in high SVR12 rates of 95% in treatment-naïve patients infected with GT 1b HCV.^{61,62} However, in patients with GT 1a, a low SVR12 rate of 17% was reported. Studies are now focusing on patients with GT 1b, comparing 16 vs 24 weeks of treatment.

Protease Inhibitors Plus NS5A Inhibitors Plus Nonnucleoside Inhibitors

The regimen of ABT 450/R (PI) with or without ABT 267 (NS5A) with or without ABT 333 (NNI) with or without ribavirin has been investigated in treatment-naïve and treatment-experienced patients infected with GT 1 HCV. A phase 2 study reported very high SVR24 rates of 83% to 96% across GT 1 subtypes, *IL-28B* genotypes, baseline HCV RNA levels, and fibrosis levels.⁴² The combination was well tolerated, with mild adverse events of headache (31%), fatigue (30%), nausea (23%), and insomnia (20%). There was a transient elevation of total bilirubin levels, which peaked in the first week and declined despite continued treatment without dose modification or interruption. Drug-drug interactions with the ritonavir component of the combination may be an issue in some patients.

Daclatasvir plus asunaprevir plus BMS-791325 (NNI) was investigated in treatment-naïve patients infected with GT 1 HCV, with a SVR12 rate of 92%.⁶³ Table 4 chronicles studies that have assessed these early combinations.⁶⁴⁻⁶⁶

Future Directions

The challenge of treating HCV infection has been daunting over the past 20 years. Physicians have struggled to identify persons with HCV infection and patients eligible

for therapy and have struggled to treat patients because of challenges related to treatment toxicity as well as cost of therapy and access to care. The new screening recommendations of the CDC offer hope that the majority of persons in the United States who are infected with HCV will be identified. However, it remains to be seen whether the new recommendations will have traction, and, if so, how long it will take before significant results are seen. A coordinated educational campaign must be implemented and directed to the appropriate stakeholders so that screening takes place and patients with HCV infection are identified and treated appropriately.

Three new regimens were approved at the end of 2013: PEG-IFN plus ribavirin plus sofosbuvir, PEG-IFN plus ribavirin plus simeprevir, and sofosbuvir plus ribavirin. The regimen of PEG-IFN plus ribavirin plus sofosbuvir for 12 weeks has been approved for treatment-naïve and treatment-experienced patients infected with GT 1 or 4 HCV. Although PEG-IFN and ribavirin remain in the regimen, patients with relative contraindications may still be eligible for therapy because only 12 weeks of treatment will be required. In addition, for PEG-IFN-ineligible patients, sofosbuvir plus ribavirin can be considered.

The regimen of PEG-IFN plus ribavirin plus simeprevir has been approved in treatment-naïve and treatment-experienced patients infected with GT 1 HCV. Because simeprevir is dosed once daily and is better tolerated than boceprevir and telaprevir, it is likely to replace the first-generation PIs. However, treatment still requires 24 to 48 weeks. Moreover, the presence of a significant portion of patients infected with GT 1a HCV with the baseline Q80K polymorphism may limit simeprevir's use.

In the longer term (late 2014 to early 2015), regimens such as PEG-IFN plus ribavirin plus faldaprevir for GT 1 HCV infection and PEG-IFN plus ribavirin plus daclatasvir for GT 1b infection are expected to be available. The role of these regimens is unclear, given the recent approval of sofosbuvir and simeprevir and the expected availability of IFN-free options in the near future. Many healthcare providers have been awaiting IFN-free regimens for GT 1 HCV infection. Such regimens will also likely be available in late 2014 or early 2015.

The National Institute of Allergy and Infectious Diseases SYNERGY trial studied the fixed-dose combination of sofosbuvir plus ledipasvir for 12 weeks vs sofosbuvir plus ledipasvir plus GS9669 (NS5B NNI) or GS9451 (NS3/4 PI) for 6 weeks and reported SVR rates of 90% to 100% in patients with poor prognostic factors for traditional IFN-based therapy.⁶⁷ This trial gives a preview of the regimens that are likely to be approved for both treatment-naïve and treatment-experienced patients with GT 1 HCV infection: sofosbuvir plus ledipasvir with or without ribavirin for 12 weeks and ABT 450/R plus

Table 4. Phase 2 Trials of Combination DAAs in Development

| Study | NS3/4A PI | NS5A Inhibitor | NS5B NI | NS5B NNI | Host Target/ Misc | SVR rate |
|-----------------------------|-----------------------------|------------------|---------------------------|---------------|----------------------|-------------------------|
| INFORM-1 ²⁹ | Danoprevir (RG-7227) | | Mericitabine (RG-7128) | | | |
| SOUND-C2 ⁶⁵ | FDV (BI-201335) | | | BI-207127 | RBV | 52%- 69% |
| Pol et al ⁶⁴ | GS-9451 | | | TGV (GS-9190) | PEG-IFN + RBV | |
| QUAD ⁵⁶ | GS-9451 | LDV (GS-5885) | | TGV (GS-9190) | RBV | |
| COPILOT ⁶⁶ | ABT-450 | | | ABT-333 | RBV, ritonavir | 93%- 95% Tx-naive |
| AVIATOR ⁴² | ABT-450 | ABT-267 | | ABT-333 | RBV, ritonavir | 83%- 96% |
| Lok et al ⁴⁶ | Asunaprevir (BMS-650032) | DCV (BMS-790052) | | | | |
| Everson et al ⁶⁸ | Asunaprevir (BMS-650032) | DCV (BMS-790052) | | BMS-791325 | | 88% |
| AA-444040 ⁵⁷ | | DCV (BMS-790052) | SOF (GS- 7977) | | RBV | 91%- 100% |
| ELECTRON ⁵⁵ | | LDV (GS-5885) | SOF (GS- 7977) | GS-9669 | RBV | |
| VITAL-1 ⁵⁰ | | | | | Alisporivir + RBV | 88% |

DCV, daclatasvir; FDV, faldaprevir; LDV, ledipasvir; NI, nucleotide inhibitor; NNI, nonnucleotide inhibitor; NS, nonstructural; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TGV, tegobuvir; Tx, treatment.

ABT 267 plus ABT 333 plus ribavirin for 12 weeks. Phase 2 trial results indicate that SVR rates in both populations of patients infected with GT 1 HCV may well exceed 90%. In the interim, the availability of simeprevir and sofosbuvir may lead to their combined, off-label use, given the promising data that have been reported in the COSMOS study.⁶⁰

Caveats

Are the regimens that may be available in the near future the final answer for chronic HCV infection? Will physicians soon be able to eliminate HCV infection completely? Although the data look exceedingly promising, it is important to keep in mind several issues. First, phase 3 trials have not been completed for the IFN-free regimens and for products used in combination with PEG-IFN plus ribavirin aside from the recently approved agents of sofosbuvir and simeprevir. Until phase 3 studies are completed and the safety of new medications has been confirmed, one cannot necessarily count on approval. Second, new therapies in many difficult-to-treat populations, such as HIV/HCV-coinfected patients, patients on dialysis, patients with hepatic decompensation, patients after liver transplantation, the elderly, and children, have not

yet been examined, and only a limited number of patients with compensated cirrhosis have been studied. Patients infected with GT 3 HCV with or without cirrhosis may require better approaches than what is currently available or in the pipeline. Furthermore, little study has been conducted on treatments for GT 4, 5, and 6 HCV infections, which are more prevalent elsewhere in the world and, thus, require additional investigation from a worldwide perspective.

The capacity of the healthcare system also is an issue. Currently, HCV infection is treated primarily by gastroenterologists and hepatologists. Because the number of patients eligible for therapy will be substantial, it is likely that groups of providers without significant experience in treatment of HCV infection will be involved in therapy, including primary care providers. Although the new IFN-free regimens should be easy to administer, it is likely that different regimens for different lengths of time will be appropriate for different groups of patients. Education of the new providers regarding these issues will be a significant undertaking.

Warehousing

There is anecdotal evidence that many providers in the United States are recommending deferral of antiviral therapy

until newer and improved regimens are available. Although it is true that HCV infection is generally slowly progressive, even in the worst cases, healthcare providers must pull the trigger at some point and treat the patients that they can. Patients with stage 0 to 2 fibrosis are not in urgent need of therapy; however, patients with stage 3 to 4 fibrosis face the risk of hepatic decompensation and/or hepatocellular carcinoma. Treatment should certainly not be deferred for long.

Finally, it is likely that cost and availability of new medications will become the new challenges faced in care of patients with HCV infection. Will healthcare providers be able to mix and match DAA agents to provide optimal regimens for patients, or will they be constrained by labeling restrictions and cost concerns? Will certain regimens be dictated to healthcare providers by third-party payers based on cost issues, such that optimal regimens may be unavailable or provided at an increased tier? Will third-party payers cover the new medical regimens for all patients, or will therapy be rationed only to patients most in need?

Cost and availability of the new regimens should be considered prior to deferral of therapy for appropriate patients. It would be quite sad to warehouse patients for future regimens, only to find that, in the future, those patients cannot receive the therapy because of restrictive policies.

Conclusion

The long war on HCV infection should soon reach a resolution, as short-term, effective therapies were approved in late 2013, and IFN-free regimens are poised to enter the market in late 2014 and in 2015. Significant issues remain, however. Strategies must be developed to implement the recent CDC screening recommendations. Treatments in special populations of patients with HCV infection that have been traditionally difficult to treat need to be explored. Groups of healthcare providers outside the fields of hepatology need education on the importance of screening and how to treat patients with HCV infection. Finally, obstacles related to the cost and availability of the new regimens must be addressed.

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