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Emerging Therapeutic Targets for Hepatitis C Virus Infection

ARUN B. JESUDIAN,* YPE P. DE JONG,*,‡ and IRA M. JACOBSON*

*Division of Gastroenterology and Hepatology, Center for the Study of Hepatitis C, New York–Presbyterian Hospital, Weill Cornell Medical College, New York; and ‡Laboratory of Virology and Infectious Disease, Center for the Study of Hepatitis C, Rockefeller University, New York, New York

Therapy for hepatitis C virus (HCV) is a rapidly evolving field wherein traditional treatment with the nonspecific antiviral agents pegylated interferon (IFN)-alfa and ribavirin has been and will continue to be supplanted by combinations of targeted therapies against HCV with and without concomitant pegylated IFN and/or ribavirin, resulting in markedly superior rates of viral clearance. Exhaustive study of HCV structure and replication through the development of in vitro systems has enabled the development of numerous novel direct acting antiviral agents that currently are undergoing clinical trials. As our understanding of the HCV virus and its antiviral targets increases, the future of HCV therapy holds the promise of high rates of viral eradication in all patient populations, many or all of whom will be treatable with IFN-free combinations of all-oral agents.

Keywords: Hepatitis C; Direct Acting Antivirals; Interferon-free Therapy; Telaprevir; Boceprevir.

Hepatitis C virus (HCV) is a member of the *Flaviviridae* family of positive-stranded RNA viruses that was identified as the cause of non-A, non-B hepatitis in 1989. It affects up to 200 million persons worldwide and approximately 4 million persons in the United States alone.[1,2] The viral genome encodes for a polyprotein that is cleaved into 3 structural and 7 nonstructural (NS) proteins by viral and host proteases. In 1999, the subgenomic replicon system was established, which is an in vitro system that allows for the replication of a partial genome in a human hepatoma cell line.[3] The replicon system has led to the screening of small molecules that can inhibit viral replication, facilitating the development of many drugs that directly inhibit viral proteins, so-called direct acting antivirals (DAAs). Inhibitors of the viral protease NS3/4A, the polymerase NS5B, and the multifunctional protein NS5A have shown great promise in clinical studies and are discussed in detail later. Inhibitors of other viral proteins, such as the NS2 and NS4B, or the helicase domain of NS3, are in preclinical or early phase clinical investigation and are discussed in detail elsewhere.[4] Hampered by the lack of model systems, drugs directed against other parts of the viral life cycle could not be studied until the discovery of an infectious clone in 2005.[5,6] This cell culture system has proven indispensable in our understanding of the viral life cycle, including viral entry and innate immunity against HCV in hepatocytes, and may in the future lead to clinically useful interventions.[7,8] Last, experiments with chimpanzees, the only natural host besides human beings, have been used for in vivo studies. These experiments have led to a better understanding of the adaptive immune response against HCV, and the chimpanzee model, although costly and increasingly controversial, remains the best model for vaccine development.[9–11] Targets that are the focus of currently available or investigational antiviral strategies are illustrated in Figure 1.

Current Standard of Care

Although the incidence of HCV infection is decreasing in the United States, the burden of liver disease resulting from chronic hepatitis C continues to increase.[12] The goal of HCV therapy has been to achieve sustained virologic response (SVR), defined as an undetectable serum HCV RNA level at 24 weeks after conclusion of treatment, which portends a more than 99% likelihood of remaining HCV RNA–negative long term.[13] Host factors influencing response include genetics, particularly interleukin (IL)-28B polymorphisms, race, obesity, insulin resistance, and severity of hepatic fibrosis, whereas viral characteristics include viral genotype and viral load at initiation of therapy.[14–18] Genotype 1 HCV, the most common in the United States, has been more difficult to treat with interferon-based therapy than other prevalent genotypes.[19–21] Until recently, the standard of care for patients with chronic HCV infection had been treatment with pegylated-interferon-alfa (Peg-IFN) in combination with ribavirin (RBV), given for 24 to 48 weeks, depending on viral genotype. SVR rates after treatment with Peg-IFN/RBV in genotype 1 HCV-infected patients have been 40% to 50%.[22]

A milestone in the evolution of HCV therapy occurred in 2011 with the approval of the first 2 DAAs: the NS3/4A serine protease inhibitors telaprevir (Incivek; Vertex, Cambridge, MA) and boceprevir (Victrelis; Merck, Whitehouse Station, NJ). The dramatic improvement in SVR rates when these agents are added to Peg-IFN and RBV has led to a new standard of care in patients with genotype 1 HCV infection.

Abbreviations used in this paper: **DAA, direct acting antiviral; HCV, hepatitis C virus; IL, interleukin; NS, nonstructural; Peg-IFN, pegylated interferon; quad, quadruple; RBV, ribavirin; RGT, response-guided therapy; SVR, sustained virologic response; SVR12, undetectable HCV RNA at 12 weeks after termination of therapy.**

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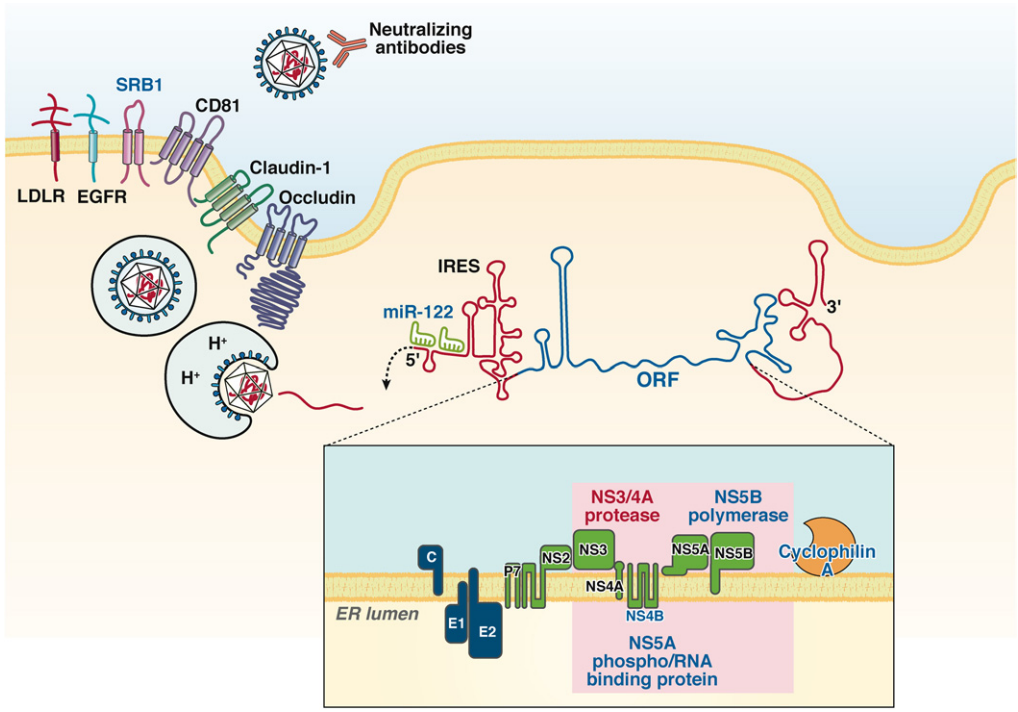

Figure 1. Current antiviral targets in the HCV life cycle. HCV requires several entry factors to infect hepatocytes. After the virus has entered the cell, its RNA genome, which contains the 5' untranslated region where the microRNA 122 (miR-122) binds, is released. Subsequent translation of one open reading frame (ORF) results in the expression of the polyprotein. This is cleaved into structural proteins core, E1, and E2, and the NS proteins p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. The proteins NS3 through NS5B form the replication complex (*shaded pink*), which also includes host factor cyclophilin A. Currently approved DAAs target the NS3/4A serine protease. Additional protease inhibitors, as well as NS5B polymerase and NS5A inhibitors, have completed or currently are being evaluated in phase 3 trials; other drugs in these classes are in earlier phases of development. Inhibitors of cyclophilin A, miR-122, NS4B, and SRB1, or other entry factors represent alternative strategies that have been studied to variable degrees and may become useful in the future. Adapted with permission from C.M. Rice. C, core protein; CD81, cluster of differentiation 81; E1/E2, envelope protein 1/2; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; IRES, internal ribosome entry site; LDLR, low density lipoprotein receptor; NS, nonstructural; SRB1, scavenger receptor B1.

Telaprevir

The ADVANCE (A New Direction in HCV Care: A Study of Treatment Naïve Hepatitis C patients with Telaprevir) study showed significantly higher SVR rates in treatment-naive patients who were given telaprevir-based regimens compared with those who received Peg-IFN/RBV alone.[23] The duration of therapy was determined by viral response to treatment, a concept known as response-guided therapy (RGT). The REALIZE (Retreatment of Patients with Telaprevir-based Regimen to Optimize Outcomes) trial showed that treatment-experienced patients achieved higher SVR rates when telaprevir was added to the re-treatment regimen compared with Peg-IFN and RBV alone, with prior relapsers having higher rates of SVR than responders.[24] The most significant side effects of telaprevir are anemia and rash.

Telparevir is now approved for use at a dose of 750 mg 3 times a day given in combination with Peg-IFN/RBV for 12 weeks followed by RGT (Peg-IFN/RBV for an additional 12 or 36 weeks, depending on viral response) in noncirrhotic treatment-naive patients and prior relapsers or followed by 36 weeks of Peg-IFN/RBV in prior partial or null responders, as well as patients with cirrhosis.[25] Recent results from the OPTIMIZE study in treatment-naive patients showed that twice-daily dosing of telaprevir 1125 mg had equivalent efficacy to 3 times per day dosing.[26]

Boceprevir

The benefit of adding boceprevir to Peg-IFN/RBV in treatment-naive patients was established in the SPRINT-2 (Serine Protease Inhibitor Therapy) trial, and in prior partial responders and relapsers in the RESPOND-2 trial (Retreatment with HCV Serine Protease Inhibtor Boceprevir and PegIntron/Rebetol).[27,28] These trials also established the foundation for RGT with boceprevir treatment. The most significant side effect of boceprevir is anemia.

Boceprevir is now approved for the treatment of genotype 1 HCV at a dose of 800 mg 3 times per day in combination with Peg-IFN/RBV.[29] All patients receive a 4-week lead-in period of Peg-IFN/RBV, and boceprevir in combination with Peg-IFN/RBV is added thereafter. Duration is determined by RGT based on the HCV RNA level at treatment weeks 8 through 24. Total treatment duration ranges from 28 weeks to 36 or 48 weeks based on prior treatment status and viral response.

Upcoming Direct Acting Antiviral Therapies

Telaprevir and boceprevir will be followed by other oral targeted therapies with various combinations of potency, barrier to resistance, side-effect profiles, and convenience of administration. These newer agents are being evaluated for use in

combination with Peg-IFN/RBV and also in combination with other DAAs in IFN-free regimens. A recurrent theme with the protease and NS5A inhibitors is the difference in barrier to resistance and, in some cases, difference in potency between genotype 1 subtypes. HCV genotype 1a has a greater propensity to become resistant to either of these classes than genotype 1b, resulting in higher rates of response in patients with genotype 1b to several agents in these classes either combined with peg-IFN and RBV (including telaprevir and boceprevir) or in some IFN-free regimens studied to date. Nucleotide polymerase inhibitors have a higher barrier to resistance than the other classes of drugs enumerated earlier. The following is a brief summary of many of the most promising new DAAs currently in development, categorized by type of regimen, with emphasis placed on larger trials or those illustrating proof of concept.

One Direct Acting Antiviral Plus Peg-Interferon/Ribavirin

Regimens containing DAAs from several classes combined with Peg-IFN/RBV have resulted in SVR rates that are significantly higher than those attained by Peg-IFN/RBV alone. These classes include protease inhibitors, nucleotide polymerase inhibitors, and NS5A inhibitors. The most extensively studied class studied has been the protease inhibitors.

Simeprevir (formerly TMC435) is an NS3/4A protease inhibitor in an advanced stage of development. In the PILLAR study in treatment-naive patients, SVR rates were 75% to 86% across 4 arms of simeprevir-containing therapy vs 65% with Peg-IFN and RBV alone.[30] In the ASPIRE study in prior treatment-experienced patients, simeprevir at a dose of 150 mg/d combined with Peg-IFN and RBV yielded an SVR in 85% of prior relapsers, 75% of partial responders, and 51% of null responders compared with 37%, 9%, and 19% with Peg-IFN/RBV alone.[31] Simeprevir is administered once daily and is unassociated with incremental anemia or rash, which can complicate therapy with the currently available protease inhibitors. Hyperbilirubinemia associated with an effect of the drug on transporters may be seen. Phase 3 trials have been completed and results are pending at the time of writing.

Faldaprevir is a protease inhibitor administered once daily. Treatment-naive genotype 1 patients were evaluated in the SILEN-C1 study, yielding SVR rates of 71% to 83%, with the highest SVR seen in patients receiving 240 mg daily without a 3 day lead-in arm.[32] The control group had an SVR rate of 56%. In the SILEN-C2 study of prior nonresponders (relapsers excluded), response rates ranged from 27% to 41% across 3 active treatment arms.[33] Side effects of faldaprevir include rash and predominantly indirect hyperbilirubinemia. Phase 3 data are awaited.

Danoprevir is an NS3/4A protease inhibitor that was studied in the DAUPHINE trial in combination with Peg-IFN/RBV in treatment-naive genotype 1 and 4 HCV patients.[34] When given at doses of 200, 100, or 50 mg boosted by ritonavir 100 mg twice daily for 24 weeks, preliminary undetectable HCV RNA at 12 wks after termination of therapy (SVR12) (now generally considered equivalent to SVR at 24 weeks) were 93%, 83%, and 67%, respectively, in genotype 1 (analysis with missing data excluded), and 100% in genotype 4. Rates of withdrawal because of adverse events were similar between the danoprevir and control arms.

Daclatasvir (formerly BMS-790052) is an NS5A replication complex inhibitor that is being studied in combination with Peg-IFN/RBV in treatment-naive patients with genotypes 1 and 4 HCV in the COMMAND-1 trial.[35] When given at a dose of 20 or 60 mg daily in combination with Peg-IFN/RBV for 48 weeks, SVR rates were 64% to 65% in genotype 1 patients compared with 36% in patients receiving Peg-IFN/RBV alone. Higher SVR rates were seen in genotype 1b than in genotype 1a patients. The 60-mg dose has been selected for further development.

Sofosbuvir (formerly GS-7977) is a nucleotide NS5B polymerase inhibitor that combines potency with a high barrier to resistance that was studied in combination with Peg-IFN/RBV in the PROTON study, with a 90% rate of SVR with a response-guided regimen that resulted in nearly all the patients receiving 24 weeks of therapy.[36] In the subsequent ATOMIC trial, when sofosbuvir was given at a dose of 400 mg daily in combination with Peg-IFN/RBV for 12 or 24 weeks in treatment-naive patients with genotypes 1, 4, and 6 HCV, SVR12 rates were 90% or greater.[37] Sofosbuvir generally was well tolerated with no identified serious adverse events and low rates of discontinuation secondary to adverse events. A phase 3 trial of Peg-IFN, RBV, and sofosbuvir for 12 weeks is in progress.

Two Direct Acting Antivirals Plus Peg-Interferon/Ribavirin (Quadruple Therapy)

Recent studies have demonstrated high SVR rates when a combination of 2 distinct DAAs with different protein targets are added to Peg-IFN/RBV in what is now referred to as 4-agent or quadruple (quad) therapy. Treatment-naive patients were treated with a quad regimen in the ZENITH study, which evaluated a combination of telaprevir and a non-nucleoside polymerase, VX-222, with Peg-IFN/RBV.[38] Lower and higher doses of VX-222 resulted in SVR rates of 83% and 90%, respectively.

The results of quad therapy in prior nonresponders have been notable. When the NS5A replication complex inhibitor, daclatasvir, was combined with asunaprevir, an NS3 protease inhibitor, along with Peg-IFN/RBV in prior null responders with genotype 1 HCV, SVR rates were 90% to 95%.[39] Danoprevir with ritonavir boosting and mericitabine, a nucleotide NS5B polymerase inhibitor, were combined with Peg-IFN/RBV in prior partial and null responders with genotype 1 HCV in the MATTERHORN study.[40] In patients who received the 4-drug regimen, SVR rates were 86% and 84% in prior partial and null responders, respectively. These rates of response were significantly higher than in those patients who received only 3 drugs as opposed to quad therapy, whether it was Peg-IFN/RBV plus danoprevir or the 3 oral drugs without Peg-IFN. Response rates were higher in genotype 1b than in genotype 1a patients.

It has been speculated that quad regimens might find a place in the treatment of particularly difficult to cure populations with HCV infection. Recent developments with IFN-free therapy (see later) have seemingly made it less likely that quad therapy will occupy a durable position during the upcoming evolution of HCV therapy, but it remains a possibility. Peg-IFN-λ, the receptor for which has a less widespread tissue distribution than that for interferon-alfa, has shown early promise of at least equal potency to interferon-alfa with less hematologic toxicity.[41] It is possible that this form of interferon

could play a role in quad regimens in the future should there be a role for them.

Interferon-Free Regimens

Since its inception, IFN-based HCV therapy has been plagued by poor tolerability and significant side effects. Until very recently, patients with contraindications or an inability to tolerate therapy with Peg-IFN had no alternative options for treatment of their HCV infection. The development of DAAs has enabled investigators to pursue the most coveted goal in the history of HCV therapy, the ability to eradicate HCV without IFN in an all-oral combination of anti-HCV agents. The era of IFN-free therapy was ushered in by the INFORM-1 study, which showed marked viral suppression with 2 weeks of treatment when the protease inhibitor danoprevir was combined with the nucleotide polymerase inhibitor mericitabine.[42]

Lok et al[43] showed proof of concept for the curability of HCV infection without IFN by combining the NS5A replication complex inhibitor daclatasvir with the NS3 protease inhibitor asunaprevir in 11 patients with genotype 1 HCV who previously had not responded to Peg-IFN/RBV. In this small phase 2a study, 4 patients treated with 24 weeks of the 2-DAA combination achieved SVR without IFN: 2 of 9 with genotype 1a and 2 of 2 with genotype 1b. Chayama et al[44] validated these findings by showing a 100% SVR rate in 9 prior null responders with genotype 1b HCV who completed therapy with 24 weeks of the identical IFN-free regimen of daclatasvir and asunaprevir alone. In a larger cohort of null responders given 24 weeks of daclatasvir 60 mg once daily and asunaprevir 200 mg daily or twice daily, SVR occurred in 65% and 89% of genotype 1b–infected patients, respectively.[39] In contrast, high rates of virologic breakthrough and low rates of SVR were observed in genotype 1a patients given the same regimen even when RBV was added. Another study showing markedly disparate results between genotype 1a and 1b patients was the INFORM-SVR trial, which evaluated a combination of danoprevir, mericitabine, and RBV for 24 weeks.[45] Compared with an SVR rate of 71% in genotype 1b patients, SVR occurred in only 26% of those with genotype 1a.

Along with the initial study by Lok et al,[43] early evidence for the curability of HCV infection without Peg-IFN came from the ELECTRON study of the nucleotide polymerase inhibitor sofosbuvir.[46] Forty patients with genotypes 2 or 3 infection received sofosbuvir 400 mg daily plus RBV for 12 weeks with varying durations of Peg-IFN in 3 arms, and, in 1 arm, no Peg-IFN. All (100%) of patients had SVR. In an additional group of 10 patients who received sofosbuvir monotherapy, all patients responded, but 4 patients relapsed, yielding an SVR rate of 60%. In 2 additional arms of the study evaluating patients with genotype 1 infection, 21 of 25 (84%) previously untreated patients had an SVR with 12 weeks of sofosbuvir plus RBV, whereas only 1 in 10 (10%) of prior null responders had SVR. Two additional studies of sofosbuvir plus RBV have yielded lower SVR rates in previously untreated patients. In the QUANTUM study, SVR rates of 59% were obtained, whereas in a study conducted at the National Institutes of Health the SVR rate was 72%.[47,48]

The importance of both viral and host factors with some antiviral regimens targeting genotype 1 HCV was illustrated by the SOUND-C2 trial, which combined the NS3/4A protease inhibitor faldaprevir with the non-nucleoside NS5B inhibitor BI 207127 with and without RBV in treatment-naive patients with genotype 1 HCV.[49] The SVR12 rate in patients given all 3 drugs for 28 weeks in the arm receiving the non-nucleoside agent twice daily was 69%, which was significantly higher than the SVR12 rate of 39% observed in those patients receiving the 2 DAAs without RBV. Response rates were much higher in genotype 1b than 1a patients (85% vs 43%), and much higher in genotype 1a patients with the favorable IL-28B CC genotype than the less favorable CT or TT genotypes. A subset analysis of cirrhotic patients showed encouraging rates of response.[50]

Further studies using various combinations of DAAs provided additional evidence for the importance of host factors in addition to viral factors in determining response to IFN-free regimens, including IFN nonresponsiveness and IL-28B genotype. When Poordad et al[51] combined the NS3 protease inhibitor ABT-450 (combined with low-dose ritonavir) with the nonnucleoside NS5B polymerase inhibitor ABT-333 and RBV, treatment-naive patients had higher SVR rates (93%–95%) than prior nonresponders (47%).

In the initial wave of IFN-free trials suggesting that both viral and host factors were involved in mediating response to several regimens, it was particularly surprising that prior nonresponse to IFN-based therapy was an adverse predictor of response to IFN-free regimens. These observations posed the compelling question of whether optimized antiviral regimens could overcome the impact of both viral and host factors on response. The most recently studied regimens indeed appear to diminish the impact of both viral and host factors by showing extremely high SVR rates across genotype subtypes regardless of prior treatment status. Increasingly, it appears that such combinations of all-oral agents will attain SVR in most patients with HCV infection.

In the AVIATOR trial, studying the IFN-free combination of 3 DAAs (ABT-450/r, an NS3/4A protease inhibitor with ritonavir boosting + ABT-267, an NS5A inhibitor + ABT-333, an NS5B polymerase inhibitor) in combination with RBV in treatment-naive and prior null -responders with genotype 1 HCV, treatment with the all-oral, 4-drug regimen resulted in SVR12 in 98% of patients who received all 4 drugs (n = 75): 100% in genotype 1b patients and 96% in genotype 1a patients.[52] SVR rates were 85% to 90% in patients who received ABT-450/r plus 2 of 3 of the other drugs, as well as in an arm containing all 4 drugs given for only 8 weeks. In prior null responders receiving all 4 drugs for 12 weeks, the SVR12 rate was 93%: 100% in genotype 1b and 89% in genotype 1a (42 of 45 patients). The nucleotide inhibitor sofosbuvir was studied in combination with the NS5A inhibitor GS-5885 and RBV in genotype 1 patients in an extension of the ELECTRON study.[53] The 3-drug regimen achieved SVR4 in 100% (25 of 25) of treatment-naive genotype 1 HCV patients and also in 100% (9 of 9) of prior null responder genotype 1 patients.

The combination of the NS5A inhibitor daclatasvir with the NS5B polymerase inhibitor sofosbuvir, with or without RBV, has yielded equally remarkable SVR rates in treatment-naive patients.[54] SVR24 was observed in 100% of treatment-naive genotype 1 patients treated with a 24-week course of the IFN-free regimen, with the exception of only 1 patient who appeared to be re-infected with a different virus at week 24, and in 93% of treatment-naive genotypes 2 and 3 patients treated with the 24-week course. In a group with genotype 1 treated for only 12 weeks, with or without RBV, SVR4 rates were 95% to 98%, with

all 3 patients who failed to have SVR4 going on to have SVR12 (2 patients were missing data at week 4, and 1 patient had undetectable HCV RNA at post-treatment week 2 and low-level viremia at week 4). The implication of these results is that a 2-drug, RBV-free regimen can achieve nearly universal SVR with 12 weeks of therapy, at least in treatment-naive noncirrhotic patients. A study of this regimen in patients who have failed protease inhibitor therapy is ongoing. As with most of the studies cited here, cirrhotic patients were not included and further studies in these patients with IFN-free therapy are essential.

Alternative Strategies

Most patients are expected to respond to a combination of the 3 DAA classes described earlier. However, several hard-to-treat populations may require alternative or additional therapies. There are many alternative antiviral strategies under investigation, some of which already have progressed into clinical trials. These include DAAs directed against other viral proteins, drugs that interfere with host factors required in the HCV life cycle, and entry inhibitors. New DAA classes currently being studied are directed against NS2, the helicase domain in NS3 and NS4B. Of these, the NS4B inhibitor clemizole has been started in clinical studies, the results of which are pending, whereas NS2 and NS3 helicase inhibitors currently remain in preclinical development.[55]

A second strategy is to interfere with host factors that are essential for HCV replication. The most advanced in clinical studies is alisporivir (formerly debio-025), a cyclophilin A antagonist. Cyclophilins are a family of ubiquitously expressed peptidyl-prolyl isomerases that accelerate protein folding and assembly. Cyclophilin A is inhibited by cyclosporin A and subsequent investigations showed it to interact both with the NS5B polymerase to enhance its affinity for viral RNA and enzymatically modify domains 2 and 3 of NS5A.[56–58] Alisporivir, a nonimmunosuppressive cyclosporin A analogue, was shown to have clinical efficacy and achieve an SVR rate of 75% when combined with Peg-IFN/RBV for 48 weeks in naive patients.[59] Early observations also suggested activity of this agent in patients who had failed to respond to a previous course of Peg-IFN/RBV.[60] Moreover, it also has shown promise against genotypes 2 and 3 in a trial in which the drug was administered with or without RBV, with Peg-IFN added (along with RBV in the RBV-free arm) from weeks 6 to 24 if HCV RNA was greater than 25 IU/mL at week 4.[61] Somewhat fewer than half the patients continued without Peg-IFN through the end of therapy, with SVR rates up to 90% in these patients. A cluster of pancreatitis cases in the phase 3 development program containing interferon-based regimens resulted in this combination being put on hold. The high barrier of resistance and pangenotypic coverage of this drug leave open the possibility that it, or other drugs in this class, will be studied further in IFN-free regimens, even if studies of alisporivir with Peg-IFN/RBV are not resumed.

A different approach is represented by the antisense oligonucleotide miravirsen, which interferes with micro-RNA-122, a liver-specific micro-RNA that is essential for HCV replication.[62] Miravirsen monotherapy was able to suppress HCV RNA in a dose-dependent fashion and at the highest dose, 4 out of 9 patients became undetectable.[63] Irrespective of the amount of viral suppression no breakthrough was observed, illustrating that interfering with host factor may be less prone to viral escape.

Another potential strategy is the prevention of viral entry into hepatocytes, either through broadly neutralizing antibodies or by blocking one of the entry factors.[64–66] One of these strategies led to the development of ITX-5061, a small molecule inhibitor of the entry factor SRB1, which currently is in phase 2 trials. These novel therapeutic strategies are unlikely to become standard of care, but may serve a need in certain difficult-to-treat subpopulations.

Safety Considerations

As we progress toward the removal of interferon from our treatment regimens, the safety features, pharmacokinetics, metablic pathways, and potential for drug-drug interactions of new drugs require close attention. Anemia, though less pronounced without interferon, will still be an issue in some patients if ribavirin is a component of therapy, along with the drug's teratogenicity. Unlike telaprevir or boceprevir, the newer protease inhibitors do not appear to be associated with incremental hemoglobin declines, and rash is either less common or not seen with greater frequency than peginterferon and ribavirin alone. While cases of ALT elevation have been reported with certain investigational protease inhibitors, the isolated hyperbilirunemia induced by others in advanced development, related to a transporter effect and/or interactions with UDP-glucuronyl transferase, is of minimal clinical significance. The NS5A inhibitor class appears to combine potent viral suppression with an excellent safety profile thus far. The experience with INX-189, a guanosine nucleotide polymerase inhibitor which had its development halted because of cardiac and renal toxicity, has been a sobering reminder of how quickly a drug can fall from the perception of great promise to nonviability. The development of at least one other guanosine analogue, which had not been associated with toxicity thus far, was halted based on the experience with INX-189. Reassurance about the nucleotide polymerase class in general is provided by the favorable safety profile of sofosbuvir, a uridine analogue, after extensive studies. Another uridine analogue, VX-135, is earlier in development.

Conclusions

The era of DAA therapy in the treatment of hepatitis C is evolving rapidly. The leap forward from the initial proof of concept that HCV infection can be cured without IFN to showing that cure can be attained in an extraordinarily high proportion of patients has occurred more quickly than most observers had anticipated. We have an increasingly clear understanding of what components of an antiviral regimen are necessary to maximize SVR across patient groups. Whether a nucleotide-containing regimen requires 1 to 2 fewer drugs to optimize the chance of response, particularly across genotype 1 subtypes as suggested thus far, remains to be fully determined. Additional studies are needed to establish whether an optimized regimen in treatment-naive patients will suffice in prior nonresponders. Patients with cirrhosis who have impaired responses to interferon-based therapy, require evaluation to determine whether they require additional drugs or longer durations of therapy. Other groups requiring specific focus include HIV co-infected persons, decompensated cirrhotic patients, liver transplant recip-

ients, and patients with renal disease. Allowing for some variability between HCV genotypes, it seems likely that there will be a transition period during which several new drugs will each be approved for use in combination with interferon and ribavirin, followed by the advent of interferon-free regimens which will become the standard of care for most, if not all, patients.

Supplementary Material

Note: The references for the Appendix will be available online only. To access the references, please visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2013.04.003.

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Reprint requests

Address requests for reprints to: Ira M. Jacobson, MD, 1305 York Avenue, 4th Floor, New York, NY 10021. e-mail: imj2001@med.cornell.edu; fax: (646) 962-0433..

Conflicts of interest

This author discloses the following: Dr Jacobson recieves grant/research support from AbbVie, Achillion Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Novartis, Pfizer, Roche/Genentech. Schering/Merck, Tibotec/Janssen, and Vertex. He is also on the speakers' bureau for Bristol Myers Squibb, Gilead, Roche/Genentech, and Vertex. Additionally, he is a consultant/advisor for AbbVie, Achillion,

Boehringer Ingelheim, Bristol Myers Squibb, Enanta, Gilead, Glaxo Smith Kline, Idenix, Kadmon, Novartis, Presidio, Roche/Genentech, Schering/Merck, Tibotec/Janssen, and Vertex. The remaining authors disclose no conflicts.

Appendix

The following is a brief summary of some of the most notable studies presented at the 48th Annual Meeting of the European Association for the Study of the Liver (EASL) held April 24–28, 2013, in Amsterdam. References are online only (available at www.cghjournal.org).

Phase 3 data on simeprevir were reported in 2 studies in treatment-naive genotype 1 patients. In both trials, patients were given 24 or 48 weeks of simeprevir + Peg-IFN/ribavirin (PR) depending on response-guided therapy (RGT) criteria. Overall SVR12 with simeprevir was 80%–81% vs 50% with PR alone.[1,2] In a phase 3 trial of faldaprevir + PR in similar patients, either of 2 doses of faldaprevir resulted in SVR12 in 79%–80% vs 52% with PR alone.[3] With both drugs, most patients were eligible to stop therapy after 24 weeks. There is no incremental anemia and at most slight increment in rash, with some increase in photosensitivity, with either of these once-daily protease inhibitors. Both can cause hyperbilirubinemia in the absence of hepatotoxicity.

Results from four phase 3 trials of sofosbuvir (SOF) were presented. In the FISSION trial, a 12-week regimen of SOF/RBV was compared to 24 weeks of PR in treatment-naive genotype 2 and 3 patients.[4] The overall SVR 12 rate was 67% in both groups—97% and 78% with SOF/RBV and PR, respectively, in genotype 2 and 56% and 63%. Cirrhosis impacted upon SVR rates in genotype 3 patients, especially those with cirrhosis. In the FUSION trial, treatment-experienced genotype 2 and 3 patients were treated with 12 or 16 weeks of SOF/RBV.[5] SVR12 rates were 86% and 94% with 12 and 16 weeks, respectively, and 30% and 62%, respectively, in genotype 3 patients. The largest increment in SVR from 12 to 16 weeks was in genotype 3 cirrhotic patients. In the POSITRON trial, IFN-ineligible, -intolerant, or -unwilling genotype 2 or 3 patients received a 12-week regimen of SOF/RBV.[6] SVR12 rates were 93% in genotype 2, 61% in genotype 3, 81% in patients without cirrhosis, and 61% in those with cirrhosis, with cirrhosis having an impact only in genotype 3 patients. A common theme of SOF/RBV therapy was the universal attainment of viral suppression in all patients at week 12, with all virologic failures attributable to relapse and no resistant variants detected in samples from any relapsers. Adverse events of SOF/RBV were similar to those seen with RBV (eg, anemia). Studies assessing longer durations of treatment or the addition of a third agent to SOF/RBV in genotype 3 patients are ongoing. Finally, in the NEUTRINO study of 12 weeks of SOF/PR in genotype 1, 4, 5, and 6 patients demonstrated an overall SVR12 rate was 90% (80% in cirrhotic patients) with only 2% of patients discontinuing for adverse events, setting a new standard for IFN-based therapy.[7]

Several well-tolerated DAA combination regimens expanded upon the theme reviewed in this article of remarkably high SVR rates with IFN-free therapy. Moreover, the difference in response to DAA regimens between treatment-naive patients and those who had failed previous interferon therapy noted in earlier phase 2 studies appears to be overcome by sufficiently potent antiviral regimens. For example, the results of a 24-week course of daclatasvir combined with sofosbuvir with or without RBV were as dramatic in noncirrhotic genotype 1 telaprevir/boceprevir prior treatment failures as this combination had been in treatment-naive patients given 12–24 weeks of the same regimens (see review above). One hundred percent of a group of 41 patients who had failed protease inhibitor therapy had SVR12 (1 missing at week 12 had SVR24).[8] Another NS5A inhibitor, ledipasvir, was combined with SOF and RBV and yielded SVR12 rates of 100% in 25 treatment-naive and 9 null-responder patients, respectively.[9]

An IFN-free regimen of ritonavir-boosted ABT-450, ABT-333, ABT-267 and RBV for 12 or 24 weeks resulted in SVR24 rates of 90–96% (ITT) in genotype 1 patients who were treatment naive or prior null responders to PR.[10] An IFN- and RBV-free regimen of daclatasvir, asunaprevir, and the non-nucleoside NS5B inhibitor, BMS-791325 at 75 mg BID achieved SVR12 of 94% (ITT) when given for 12 or 24 weeks to treatment-naive genotype 1 noncirrhotic patients.[11] Interim SVR4 rates in patients given BMS-791325 150 mg BID were similarly high.

Appendix References

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