Recent Successes and Noteworthy Future Prospects in the Treatment of Chronic Hepatitis C

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Within the last year, the landscape of therapy for genotype 1 chronic hepatitis C virus (HCV) has changed dramatically as 2 much-anticipated protease inhibitors became available for use. These agents, telaprevir and boceprevir, when used in combination with pegylated interferon and ribavirin, offer patients an improved chance of cure and the opportunity for a shorter duration of therapy. Although these medications represent a significant achievement in the battle against HCV, they do not represent the final phase in the evolution of HCV therapy. Many other direct-acting antiviral agents representing several classes, as well as agents that act via host-mediated pathways, are in development. Recent proof of concept studies demonstrating the capacity to eradicate HCV without interferon signal the potential for yet another quantum leap in the field.

Hepatitis C virus (HCV) infection affects approximately 180 million people worldwide, which accounts for roughly 2%–3% of the world’s population [1]. Complications arising from chronic HCV infection include the development of cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Hepatitis C virus remains the leading cause of death from liver disease and is the most common indication for liver transplantation in the United States and Europe. The rates of cirrhosis and HCC in the United States and elsewhere have risen over the past several years and are expected to continue on that trajectory over the next decade unless substantial improvements in treatment are developed [2, 3]. Viral eradication arrests the progression of liver disease and has been shown to result in measurable improvements in clinical outcomes [4, 5].

For years, clinicians have relied on interferon-based regimens. The progression from using standard interferon alpha monotherapy to pegylated interferons in combination with ribavirin resulted in improvements in the rates of sustained virologic response (SVR). Unfortunately, despite these improvements, the rates of cure in genotype 1 infection with the standard combination of pegylated interferon and ribavirin (PR) remained around 40%–50% in treatment-naive individuals, with worse outcomes for African Americans, those with cirrhosis, prior treatment failure, and human immunodeficiency virus (HIV) coinfection, and other groups [6–9].

Extensive research has yielded a deeper understanding of the HCV life cycle and the elucidation of the crystal structures of several of the viral proteins [10–12]. This has enhanced the development of drugs targeted at specific points in the HCV life cycle. Once the virus enters into host hepatocytes, the viral RNA undergoes translation into a viral polyprotein that is ultimately cleaved by viral and cellular proteases into smaller proteins. Some of these smaller proteins constitute structural components of the virion and some are nonstructural (NS) proteins that are required for ongoing viral replication and spread. It is the NS proteins, including the proteases, that have been the
primary targets of drug development. Direct-acting antiviral agents (DAAs) include NS3/4A protease inhibitors (PIs), NS5A (replication complex) inhibitors, and NS5B polymerase inhibitors, the latter including nucleos(t)ide agents that bind to the active site of the polymerase and nonnucleos(t)ides that act via steric inhibition. Interest has also emerged in agents that target host proteins involved in viral replication, such as cyclophilin A antagonists. With the advent of these newer agents our ability to treat HCV is greatly enhanced. Current data also suggest that combining several of these agents may soon allow for the limited use or even omission of interferon from many treatment regimens.

**RECENT SUCCESS: THE ADDITION OF NS3/4A SERINE PIS**

The year 2011 witnessed the landmark approval of the first 2 DAAs for patients with HCV genotype 1 infection: telaprevir and boceprevir. The early clinical programs for these drugs demonstrated potent antiviral activity when these drugs were administered as monotherapy. However, both drugs have a low barrier to resistance, requiring the concomitant administration of pegylated interferon and ribavirin to prevent the emergence of resistant variants. The large phase 3 programs confirmed the attainment of significantly higher rates of SVR for PI-containing regimens over PR alone in treatment-naive as well as treatment-experienced patients and firmly established the role of response-guided therapy (RGT), with the potential to truncate treatment duration in a large number of patients who have a rapid virologic response (RVR).

**TELAPREvir**

PROVE-1 and PROVE-2 were phase 2 studies conducted in the United States and Europe to test the efficacy and safety of telaprevir in treatment-naive genotype 1 HCV infection PR [13, 14]. The SVR rates when telaprevir was combined with PR were superior to standard PR therapy, with >60% attaining SVR. These early studies also provided the first evidence that regimens containing DAAs could be truncated from 48 weeks to 24 weeks based on parameters of viral response. A unique contribution of the PROVE-2 study was to demonstrate the critical role of ribavirin in the regimen, sparking renewed discussion about the elusive mechanism by which ribavirin adds so much to the efficacy of interferon-based therapy.

The phase 3 trials of telaprevir for treatment-naive chronic HCV confirmed the superiority of telaprevir-based therapy over PR alone and firmly established the foundation for RGT. In the ADVANCE trial, standard PR was compared with 2 different telaprevir-containing response-guided arms [15]. In arm 1, telaprevir (750 mg every 8 hours) was given with PR for 8 weeks, followed by continued PR (T8PR). In arm 2, telaprevir was given along with PR for 12 weeks, followed by continued PR (T12PR). The third arm of the study was PR given for 48 weeks (PR48). A key element in this trial was the ability to tailor treatment duration based upon the attainment of extended RVR (eRVR), defined as undetectable HCV RNA at weeks 4 and 12. If eRVR occurred, the duration of added therapy with pegylated interferon α 2a and ribavirin was only 12 additional weeks (for a total of 24 weeks), as opposed to 36 additional weeks of therapy. Both the T8PR and T12PR groups achieved higher rates of SVR compared with the standard-of-care PR48 group (69%, 75%, and 44%, respectively; < .0001). Relapse rates were significantly lower in the telaprevir groups. Patients with eRVR had an SVR rate of 83% and 89%, respectively, in the T8 and T12 arms. A supportive phase 3 trial, ILLUMINATE, confirmed the role of RGT by showing equivalent rates of SVR in patients attaining eRVR who were randomized to 24 vs 48 weeks of total therapy (92% vs 88%) [16].

The REALIZE study was a phase 3 trial with >600 previously treated genotype 1 HCV patients who had failed to attain SVR [17]. After treatment with telaprevir in addition to PR, SVR rates were much improved compared to retreatment with PR. Responses were best for those who had previously been relapers (>86% achieved SVR), followed by prior partial responders (54%–59%), whereas SVR rates were lowest for those prior null responders, with up to a 31% SVR rate. In the subgroup of null responders with cirrhosis, however, the SVR rate was only 7/50 (14%). The results of the REALIZE trial demonstrated that there is clearly a role for retreatment of genotype 1 patients—especially prior relapers or partial responders. Although the REALIZE study contained no option for RGT, RGT was approved by the US Food and Drug Administration for prior relapers, whereas patients in whom HCV RNA never became undetectable with prior therapy should receive 48 weeks of total therapy.

**BOCEPREvir**

Boceprevir, like telaprevir, is an orally administered protease inhibitor (PI) that complexes with the NS3 protein. The early boceprevir trial, SPRINT-1, demonstrated the safety and efficacy of boceprevir given in combination with PR in genotype 1 treatment-naive patients [18]. SPRINT-1 introduced the concept of a peginterferon and ribavirin lead-in period of 4 weeks, during which no PI was administered. The rationale for this approach was to reduce the risk of emergent resistance by lowering the HCV load prior to introducing the PIs. Subjects in SPRINT-1 received a combination of 3 drugs for 28 weeks or 48 weeks or for 24 or 44 weeks with a 4-week PR lead-in. The control arm received the standard-of-care PR for
which can result in severe anemia in some patients. Telaprevir hemoglobin decline relative to PR alone of 1 to 1.5 gm/dL, a variety of side effects, including an incremental degree of addition, both approved PIs have been associated with a considered eligible for RGT, regardless of response pattern. In counterparts. Moreover, cirrhotics are not currently considered eligible for RGT, regardless of response pattern. In addition, both approved PIs have been associated with a variety of side effects, including an incremental degree of hemoglobin decline relative to PR alone of 1 to 1.5 gm/dL, which can result in severe anemia in some patients. Telaprevir

**SHORTCOMINGS OF THE CURRENT STANDARD OF CARE**

The addition of telaprevir and boceprevir to the standard PR regimen has provided a major advance in the treatment of treatment-naive and –experienced genotype 1 patients. Although there are subtle differences in the published virologic response rates between the 2 PIs, the increments in the active treatment groups are fairly close and there have been no head-to-head trials, making comparisons difficult. African Americans, persons with interleukin 28B (IL-28B) CT or TT genotypes at the rs12979860 locus, and persons with advanced fibrosis or cirrhosis have a major increment in efficacy with these agents but still do not completely catch up to their counterparts. Moreover, cirrhotics are not currently considered eligible for RGT, regardless of response pattern. In addition, both approved PIs have been associated with a variety of side effects, including an incremental degree of hemoglobin decline relative to PR alone of 1 to 1.5 gm/dL, which can result in severe anemia in some patients. Telaprevir is associated with a high frequency of rash, with discontinuation of telaprevir for severe rash necessary in about 5% of patients. Anorectal discomfort of unclear pathogenesis may also occur with telaprevir. Boceprevir is associated with an increased frequency of dysgeusia, although this is rarely if ever treatment limiting. A slightly increased frequency of neutropenia occurs with boceprevir, but the clinical significance of this is unclear.

An additional feature of the PIs is a low barrier to resistance is manifested by the rapid emergence of resistant variants with exposure to monotherapy. Although peginterferon and ribavirin suppress these variants and sharply reduce the emergence of resistance, greater than half of patients who fail to have SVR with these agents are left, at least in the short term, with detectable variants. The frequency of this occurrence is highest in patients with the lowest likelihood of SVR (ie, null responders to prior PR therapy). Reassuring data have emerged from long-term observational studies in patients who have failed treatment and been left with resistant variants with either drug that show that these variants wane in frequency over time, becoming undetectable in most after 2 years [17, 21]. Nevertheless, future trials with novel regimens, with or without PIs, will be necessary to establish the ultimate impact of resistance. Overall, substantial optimism prevails on this issue, such that concerns about resistance, although warranting discussion with patients, should not be a categorically prohibitive consideration in any group of patients. Clinicians must be aware of the stopping rules, designed to minimize resistance, associated with these drugs: an HCV RNA of >1000 IU/mL at week 4 or 12 or detectable HCV RNA at week 24 mandate discontinuation of the entire regimen with telaprevir, as do HCV RNA ≥100 IU/mL at week 12 and detectable HCV RNA at week 24 for boceprevir.

A final concern with the PIs is the potential for drug-drug interactions (DDIs) because of the inhibition effect of both available PIs by CYP34A, and the capacity for either the PI or the other drug to be affected by CYP3A4 induction. This leads to the labeled interdiction against the use of drugs such as certain statins (lovastatin, simvastatin, and, for telaprevir, atorvastatin), ergot compounds, PDE5 drugs for pulmonary hypertension, alfuzosin, St John’s Wort, and others. Clinicians must be aware of the far more extensive list of potential DDIs in the package inserts.

**PARADIGMS OF HCV DRUG DEVELOPMENT**

Simultaneous with the rapid expansion in experience with telaprevir and boceprevir, a large number of additional investigational agents are being evaluated along 2 distinct lines: (1) a DAA combined with PR; (ii) 2 DAs combined with PR to form a quadruple regimen; and (3) interferon-free regimens,
for which long-awaited proof-of-concept data for the curability of HCV infection without interferon have recently emerged. Protease, polymerase, and NSSA inhibitors are all being studied as single agents with PR, as is alisporovir, which inhibits the augmentation of HCV RNA replication by a host factor, cyclophilin A. Still other classes of agents, such as MiR-122 inhibitors, are earlier in development but are candidates for incorporation into the same development pathways.

PEGINTERFERON + RIBAVIRIN + A SINGLE DAA

Several classes of agents are being studied in this context. Essentially all PIs studied thus far have demonstrated potent virologic suppression as monotherapy and, in combination with PR, much higher rates of rapid and SVR (when available) than PR alone in genotype 1 patients [22–24]. Those currently in phase 3 are TMC435 and BI 201335, once-daily drugs demonstrating significant increments in SVR above PR control in completed phase 2 studies.

The PILLAR study was a phase 2b randomized trial of TMC435 in 386 treatment-naive genotype 1 HCV patients who were assigned to variable doses (35 or 150 mg daily) and durations (12 vs 24 weeks of triple therapy, with total treatment duration 24 weeks for those with unquantifiable HCV RNA at week 4 and undetectable HCV RNA at week 12 with PR [22]). Patients in the TMC435 arms had significantly higher early response rates than those in the control arm. The rates of SVR 24 weeks after completion of treatment ranged 75%–86% in those receiving the study drug, as compared to an atypically high rate of 65% in the control group. The RGT paradigm appeared highly effective in rapid responders in this study. TMC435 was generally safe and well tolerated, and 3.6% of those in TMC435 arms discontinued treatment early due to adverse events, compared with 5.2% in the control arm. The 150-mg dose was chosen as the dose for further development based on the findings in this trial. In a preliminary report from a phase 2 study for those who have previously failed therapy, [25] SVR for relapers ranged 77%–89%, 65%–86% for partial responders, and 41%–59% for null responders.

BI-201335 is an oral NS3/4A PI that is in phase 3 trials. The SILEN-C trials tested the efficacy of variable doses of BI-201335 used in combination with variable durations of PR. In SILEN-C1, BI 201335 was given to genotype 1 treatment-naive subjects with or without a 3-day PR lead-in period at varied doses (120 mg daily or 240 mg daily) in combination with PR for 24 weeks, with RGT determining an additional 24 weeks of PR consolidation [23]. Extended rapid virologic response rates ranged 78%–87%. The highest SVR rate observed was 83%, seen in the group receiving no PR lead in with 240 mg of BI-201335.

Danoprevir is another PI tested in combination with PR for efficacy in genotype 1 HCV. Data from the ATLAS trial showed that those in the danoprevir arms were significantly more likely to experience virologic response than those on standard therapy, with SVR of 68%–83%, compared with 42% with PR [24]. Other promising PIs include ABT-450, ACH-1625, GS-9456, BMS-600232, and MK-5172 (Table 1), the last of which appears to have pan-genotypic activity [26–29].

BMS-790052 is a first-in-class NS5A inhibitor, now considered a "replication complex" inhibitor, active against HCV. A phase 2 study consisted of 4 treatment arms, 1 placebo, and variable doses of the study drug (3 mg, 10 mg, and 60 mg). BMS-790052 plus PR achieved higher rates of SVR at 24 weeks compared with PR alone across all BMS-790052 treatment groups (BMS-790052 once daily: 60 mg: 83% [n = 10 of 12]; 10 mg: 83% [10 of 12]; 3 mg: 42% [5 of 12]; control: 25% [3 of 12]). BMS-790052 was well tolerated with an adverse event occurrence in the active arms that was comparable to PR alone. These results have fueled interest in this class, positioned the drug for additional studies with PR, and made it an attractive component of interferon-free regimens.

Nucleos(t)ide polymerase inhibitors have been a major focus of interest because they combine the merits of high potency with a high barrier to resistance, once-daily dosing, and, thus far for those in active trials, an attractive safety profile despite adverse experiences with earlier members of this class. The phase 2b PROTON study was a double-blind, placebo-controlled, randomized trial of 121 genotype 1 treatment-naive subjects treated with an HCV-specific potent nucleotide polymerase inhibitor, PSI-7977 200 mg or 400 mg once daily with pegylated interferon and ribavirin [30]. All groups received 12 weeks of combination therapy followed by 12 weeks of PR. If the HCV load was undetectable from weeks 4 through 12, treatment was complete after 24 weeks. Ninety-eight percent of subjects receiving the study drug at either dose had an RVR, in contrast to only 19% receiving placebo. The SVR rates 12 weeks after therapy were 88%–91%. The drug was well tolerated without discontinuations related to PSI-7977. Even in the absence of any data on interferon-free regimens, the results of this trial would place PSI-7977 at the top tier of potential candidates for a major role in future HCV therapy.

QUADRUPLE REGIMENS: PEGINTERFERON + RIBAVIRIN + 2 DAAs

Quadruple regimens, the combination of 2 potent DAAs with PR, have invariably demonstrated high rates of virologic response in studies thus far. This is likely owing to the differing mechanisms of action having a synergistic effect on viral eradication. The ZENITH trial was a phase 2 study of treatment-naive genotype 1 patients who were treated with the
A combination of telaprevir, VX-222 (a nonnucleoside NS5B polymerase inhibitor), and PR [31] or with dual oral therapy. Treatment with the 4-drug regimen continued for 12 weeks, and patients were eligible for discontinuation of therapy if they had undetectable virus at weeks 2 and 8. Patients not eligible for a shortened course received a total of 24 weeks of quadruple therapy. Fifty percent (15 of 30) of subjects were eligible for a short course of therapy, and of those, 14 (93%) achieved a sustained response at 12 weeks post-therapy. In those who were not eligible for a shortened course of treatment, 100% had undetectable viral load at the end of treatment (24 weeks). High rates of viral breakthrough were seen in the dual arm.

Similar success was seen in a trial that combined tegobuvir, a nonnucleoside NS5B polymerase inhibitor, with GS9256, a PI with PR. Of the 46 subjects treated on this particular quadruple regimen, 100% achieved an RVR at 4 weeks, compared with only 38% who received tegobuvir, GS9256, and ribavirin and 7% who received tegobuvir and GS 9256 [32]. At weeks 12 and 24, those receiving the quadruple therapy continued to maintain a 100% viral suppression rate.

The efficacy of quadruple therapy has also been evaluated in a more difficult-to-treat patient group—those with prior null response to PR. In this setting, 2 investigational DAAs, BMS 790052 (a NS5A polymerase inhibitor) and BMS 650032...
developing SVR after stopping therapy prematurely [37]. Remarkably, 10 of 10 subjects achieved an SVR at 12 weeks post–treatment completion and 9 of 10 achieved an SVR at 24 weeks after treatment discontinuation. The tenth patient had detectable but unquantifiable HCV RNA, which then cleared. The potential of quadruple therapy to serve as a reliable and efficient salvage regimen for those failing prior therapy, or a pathway toward highly abbreviated regimens even in treatment-naive patients, particularly those with lower SVR rates, represents a major advance.

**TOWARD AN INTERFERON-FREE FUTURE?**

Early studies of the serine PIs showed that when given as monotherapy, there was a rapid and effective virologic response. Unfortunately, this response was tempered by the fairly rapid development of resistant variants [33, 34]. As has been demonstrated most effectively with the treatment of HIV, combination antiviral therapy using drugs with differing mechanisms of action may be a more effective approach to defend against resistance and subsequent viral breakthrough. Drugs with a higher genetic barrier to resistance are attractive candidates as backbone drugs for such regimens, although combining potent drugs with a low barrier to resistance may also be effective, perhaps assisted by adjunctive ribavirin.

INFORM-1 was the interferon-free study that ushered in a new era of interferon-free therapy studies by showing potent viral suppression without viral breakthrough when a PI and polymerase inhibitor were combined for 2 weeks [35]. The message taken from the INFORM-1 study was that an interferon-free regimen was a possibility, and subsequent studies continued to support this notion. The efficacy of BMS-790052 (NS5A inhibitor) and BMS-650032 (an NS3/4A PI) was tested in 21 genotype 1 null responders to PR [36]. The first group received the 2 study drugs alone, and the second group received the study drugs in combination with PR; 4 of 11 (36%) in the dual arm had SVR at 12 and 24 weeks post-treatment, six experienced viral breakthrough with documented resistance identified, and 1 patient had relapse after initial viral clearance. The SVR rate in the genotype 1a patients was 2 of 9, compared with 2 of 2 genotype 1b patients. A subsequent study from Japan demonstrated SVR in 9 of 10 genotype 1b null responders, with the tenth patient actually also developing SVR after stopping therapy prematurely [37]. These collective findings suggest that the genotype 1 subtype may be of increasing importance with some interferon-free regimens, perhaps depending upon the resistance barrier of the individual components of the regimen. It is also possible that some regimens will require ribavirin, which was not tested in these studies, in patients with 1 subtype but not another.

Zeezem and colleagues recently presented interim results from the SOUND-C2 trial, a large interferon-free trial composed of a cohort of 362 treatment-naive genotype 1 patients [38]. Patients in this trial received oral regimens of variable duration containing BI 201335, a PI plus BI 207127, a nonnucleoside polymerase inhibitor, with or without ribavirin. Those receiving BI 207127 2 or 3 times daily with BI 201335 and ribavirin had comparable viral responses at 4 (87% and 88%, respectively) and 12 weeks (76% and 70%, respectively). Those who received the 2 study drugs without ribavirin fared worse, with 4- and 12-week viral negativity achieved in 72% and 57%. The SVR12 rates are available for the 16-week treatment group. Those with genotype 1b had higher SVR12 rates compared with their genotype 1a counterparts (69% vs 43%, respectively), and among those with genotype 1a, those with a T allele at the IL-28B locus fared worse than CC patients. The latter observation raises the intriguing possibility that host pathways involved in interferon response may still play in role in mediating response to pure antiviral regimens. Alternatively, however, an optimal antiviral regimen containing high-potency drugs with at least 1 component having a high resistance barrier may overcome such obstacles.

The ELECTRON study attracted great attention recently by showing that the combination of PSI-7977 and ribavirin produced 100% SVR in 10 treatment-naive individuals with genotype 2 or 3 infection [39]. In contrast, PSI-7977 alone resulted in 6 of 10 SVRs, with the other 4 patients responding but relapsing. By week 4 of treatment, 100% of subjects achieved viral undetectability. Data from genotype 1 patients in this trial are pending. In addition to ongoing phase 2 trials, a phase 3 program centering on the further exploration of interferon-free therapy has been initiated with this drug.

**CYCLOPHILIN INHIBITION**

The cyclophilins are a group of enzymes that are active at the cellular level and aid in the processing of proteins. In the case of HCV, cyclophilins are thought to bind to HCV NS5A and NS5B to modulate the folding and processing of viral proteins. Inhibition of cyclophilin activity interrupts this important step in HCV replication and therefore represents a potentially important class of medications. Alisporivir is the most-studied drug in this class, and in a study to evaluate its efficacy when given with PR to genotype 1 treatment-naive patients, up to 76% achieved an SVR [40]. Hyperbilirubinemia related to effects on transporters, and therefore unaccompanied by hepatic cellular injury, is a recognized side effect of alisporivir, and a serum bilirubin of >5 times the upper limit of normal was seen in up to 6.8% of patients. Further studies with this medication are in progress.
MIR-122 INHIBITORS

Micro RNAs are single-stranded short RNA molecules that serve to regulate viral replication. Mir-122 is a liver-specific micro RNA that, when bound to HCV RNA, stimulates replication. Inhibitors of Mir-122 therefore would block the ability of Mir-122 to bind to HCV and inhibit function. Early phase trials to establish the efficacy of this concept have been promising, and additional studies are anticipated [41].

PRESENT APPROACH TO TREATMENT

The extraordinary pace of drug development in HCV leads to a continued requirement for individualized decision making by clinicians, set against a backdrop of significantly higher SVR rates with the presently available PI-based regimens. The ongoing reliance upon interferon, protracted period of treatment (though capable of truncation to 6 months in many more patients than previously possible), and adverse effects temper any purported adage that “every patient should be treated” in the absence of contraindications to interferon. All patients deserve a thorough explanation of the opportunity for treatment, but the maximum level of proactivity seems appropriate to apply to treatment-naive patients with moderate or advanced liver disease.

Liver histology, as judged either by liver biopsy, which continues to be a foundation for decision making by many hepatologists, especially in patients with genotype 1, or non-invasive markers like serum fibrosis markers or elastography, remains a critical ingredient in the decision-making process. In the United States, tissue elastography is not approved in early 2012 and liver biopsy remains the gold standard. With the hoped for introduction of increasingly effective and well-tolerated therapies in the future, there will likely be less emphasis on liver biopsy to define patients’ histologic status and more of an all-inclusive approach to treatment. Interleukin 28B testing can be helpful in wavering treatment-naive patients because it still provides some differentiating predictive value for SVR and for the likelihood of the ability to truncate therapy. However, it must be recognized that the historically disadvantaged patients with a T allele at the IL-28B rs12979860 locus have the greatest increase in SVR when treated with PI regimens.

Relapsers who have completed a prior course of therapy are very attractive candidates for retreatment because of their presumed tolerance to interferon and their very high chances of SVR with PI-based therapy. Partial responders, too, have a 50%-60% chance of success with retreatment. The approach to null responders, especially cirrhotics, warrants circumspection in light of the lower rates of SVR and the higher rates of emergent resistance. The data on clearance of resistant variants after a failed treatment course are reassuring but not yet definitive evidence, pending actual trials, that resistance will be a minor issue in HCV therapy. The ongoing development of drugs in multiple classes lacking cross-resistance to PIs provides additional reassurance that regimens highly effective even in patients with residual resistant variants following prior PI therapy will be capable of being treated effectively.

For clinical investigators, the increasing number and diversity of clinical trials for patients in various treatment groups, including null responders, offers intriguing options, including interferon-free regimens. The exclusion of patients with a history of PI failure from nearly all such trials will hopefully soon be ameliorated by the introduction of trials intended for these populations.

CONCLUSION

In the last year, DAAs against chronic HCV infection have changed the way practitioners manage chronic genotype 1 HCV infection. Improved SVR has been observed with the addition of the 2 highly anticipated and recently approved NS3/4A serine PIs. Several agents directed at specific HCV replication targets are under investigation in large phase 3 trials and should be available for commercial use within the next few years. These agents, when paired with peginterferon and ribavirin, may offer superior outcomes to our current standard of care. Varied combinations of the DAAs may also allow for shorter therapy durations, more tolerable therapies, and even the avoidance of interferon. The advent of interferon-free regimens would represent the fulfillment of an enormous unmet need in interferon-incapable or -intolerant patients, but many experts are predicting and hoping that such regimens will ultimately supplant interferon-based therapy for most or all HCV patients, perhaps sooner than any would have anticipated a short time ago.

Data presented at the European Association for the Study of the Liver (EASL) Meeting in April 2012 have expanded dramatically upon the proof of the concept that HCV infection can be cured without interferon by demonstrating that a cure can be attained in a remarkably high proportion of patients with such regimens. For example, a combination of daclatasvir, an NSSA inhibitor, and the nucleotide polymerase inhibitor GS-7977, given with or without ribavirin, and with or without a lead-in of the polymerase inhibitor for 7 days, was associated with undetectable HCV RNA 4 weeks after end of treatment in 44 of 44 genotype 1 treatment-naive patients with 24 weeks of total therapy [42]. A ritonavir-boosted protease inhibitor, ABT-450, when combined with one of two non-nucleoside polymerase inhibitors, ABT-333 or ABT-072 combined with ribavirin in over 40 patients, induced SVR 12 exceeding 90% over 40 genotype 1 treatment-naive patients.
prior interferon nonresponse and/or genotype 1a (vs 1b) in-
content of the manuscript have been disclosed. [43, 44]. The study of the latter non-nucleoside consisted of 11
type 1 treatment-naive patients induced SVR-4 in 22/25 (88%)
of patients [45].

Emerging themes include the intriguing observation that prior interferon nonresponse and/or genotype 1a (vs 1b) in-
fection appear to adversely influence the likelihood of successful response to these [43, 45] or other [46, 47] interferon-free
regimens. A major focus in the next 1–2 years will be (1) the
degree to which these regimens can be optimized in order to
combine a high level of potency with a high barrier to resistance,
(2) determination of the adjunctive role of ribavirin, and
(3) overcoming host-virus factors that adversely impact upon
response. As two final points, the high SVR rates associated
with quadruple regimens even in difficult-to-cure patients such
as null responders continue to be borne out [48], and there is a
pressing need for additional studies in cirrhotics, in which very
preliminary data on interferon-free treatment are promising [46].

Notes

Financial support. This work was supported by the Viral Hepatitis Action Coalition (VHAC) of the Centers for Disease Control and Prevention (CDC) Foundation, which receives support from the following corporate sponsors: Abbott Laboratories; Boehringer Ingelheim; Bristol-Myers Squibb; Genentech (Roche); Gilead Sciences, Inc.; GlaxoSmithKline; Janssen Therapeutics; Merck Sharp & Dohme; OraSure Technologies, Inc.; and Vertex Pharmaceuticals.

Supplement sponsorship. This article was published as part of a supplement entitled “The Evolving Paradigm of Hepatitis C,” sponsored by an unrestricted grant from the Viral Hepatitis Action Coalition of the CDC Foundation.

Potential conflicts of interest. I. M. J. has received consultancy fees from Bristol-Myers Squibb, Novartis, Gilead, Merck, Vertex, Boehringer-Ingelheim, Pharmasset, Tibotec/Janssen, Abbott, Roche/Genentech; Achillion, and GlaxoSmithKline; has grants/grants pending from Merck, Tibotec/Janssen,Achillion, Roche/Genentech, Pharmasset, Boehringer Ingelheim, Novartis, Gilead, Vertex, Pfizer, and Bristol Myers Squibb; and has received payment for lectures including service on speaker bureaus from Merck, Vertex, Gilead, Bristol Myers Squibb, and Roche/Genentech. A. N. F. certifies no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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