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Emerging Therapies in Hepatitis C: Dawn of the Era of the Direct-Acting Antivirals

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Infection with hepatitis C virus (HCV) is a worldwide epidemic affecting up to 3% of the world's population.[1,2] Approximately 80% of people infected with HCV will go on to develop chronic disease. Of these individuals, approximately 25% develop cirrhosis and are vulnerable to its complications, including hepatocellular carcinoma.[3] Treatment for HCV can be curative, and successful treatment improves the quality of life of HCV infected individuals as well as prevents progression of liver disease and its associated morbidity and mortality.[4]

For the last decade, the standard of care treatment for HCV has been pegylated interferon-α (pegIFNα) plus ribavirin (RBV) for 24 to 48 weeks depending on viral genotype.[5] Therapy is expensive, difficult to tolerate, and associated with a variety of quality-of-life–limiting side effects. Furthermore, the response rates to treatment are not optimal; only about 40% of genotype 1–infected patients respond to treatment.[6] Patients infected with genotypes 2 and 3 have a higher rate of treatment response, which approximates 80%.[7]

A major goal within the fields of hepatology and infectious diseases is to improve the rate of response to HCV treatment. Novel discoveries over the past few years, such as the finding of a polymorphism near the *IL28B* gene, have helped identify those patients that are most likely to respond to HCV treatment with pegIFNα nd RBV.[8] Additionally, new therapies have been developed, and some of the most promising new drugs are those that act to directly inhibit the virus. These direct-acting antiviral (DAA) drugs are currently in various stages of development, and are described in detail in this review.

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VIRAL STRUCTURE AND LIFE CYCLE

A basic understanding of the viral structure and life cycle (Fig. 1) is important to understand the targets of the new drugs in development. The HCV is a positive single-strand RNA virus with 9.5 kilobases. The virus enters the hepatocyte via a variety of receptors (including glycosaminoglycans, CD81, SR-BI, Claudin-1) by receptor mediated endocytosis. Once in the hepatocyte, the virus is translated into a single long polypeptide on the ribosome then cleaved by both host and viral proteases into 10 functional proteins. A replication complex is formed using viral and host proteins and results in a double-stranded RNA intermediate that includes a positive-strand RNA and a negative-strand RNA. The negative strand serves as a template for the synthesis of positive-strand RNA, which is then packaged and released from the hepatocyte. The synthesis of positive-strand RNA is disproportionate to the negative strand and is transcribed in a 5- to 10-fold excess of negative-strand RNA.[9]

HCV is fairly unique in that there is not a DNA intermediate in the life cycle. Thus, the virus does not incorporate itself into the host DNA. The result is the ability to effectively cure the infection indefinitely. This is in contrast with the hepatitis B virus or HIV, where suppression is the major goal of therapy.[10]

The viral RNA produces 10 functional proteins. These proteins are composed of structural and nonstructural proteins.[9] The nonstructural proteins are involved in viral replication and processing and are the target of most DAAs. These are described in more detail herein.

VIRAL RESISTANCE

An important barrier in the development of antiviral agents is the emergence of virus resistance. There are several qualities of HCV that make it particularly prone to developing drug-resistant strains. The virus has a high rate of replication with 10^{12} virions produced daily.[11] The viral protein that mediates viral replication is NS5B, or RNA-dependent RNA-polymerase. This protein lacks proofreading ability and has a high error rate, thus leading to a variety of genetic strains of virus.[12] In general, viruses that are mutated versions of the wild type have less replication fitness than wild-type virus, and so are present in the blood at lower quantities.[13,14] Some of these mutated viruses result in a change to the viral protein structure; thus, if this occurs at the site where a DAA acts, it may not be effective in inhibiting the action of the protein. Often these drug-resistant strains of virus are present at low levels in the blood at baseline, but when subjected to selection pressure, such as the addition of a DAA, the wild-type virus decreases and the mutated virus increases and ultimately renders the DAA ineffective (Fig. 2).[15]

NS3/4A PROTEASE INHIBITORS

The NS3/4A protease acts to cleave the polyprotein into its various functional proteins.[9] First-generation agents that target this protease—boceprevir and telaprevir— are the furthest along in development. Several phase II and III study results are available and are summarized. The primary end point of HCV clinical trials is achievement of sustained virologic response (SVR), which is absence of HCV RNA in the blood 6 months after the completion of treatment.

Boceprevir

Early phase studies of boceprevir revealed that viral load reductions were greater, and the development of resistance lower, when boceprevir was given in combination with pegIFNα.[15] Subsequent early phase studies showed that the highest rates of viral load reductions were seen in patients who received boceprevir 800 mg 3 times daily in combination with both pegIFNα and RBV and served as the basis for the study designs of phase II and III studies.[16] Boceprevir trials have largely used a lead in phase of 4 weeks of pegIFNα and RBV followed by varying courses of triple therapy with boceprevir, pegIFNα, and RBV.

Boceprevir phase II studies—The goal of the Serine Protease Inhibitor Therapy (SPRINT)-1 trial was to determine the effectiveness of boceprevir in combination with pegIFNα and RBV in genotype 1 treatment-naïve patients, and to determine whether a lead in phase of pegIFNα/RBV for weeks before boceprevir therapy improved response rates. A second part of the study evaluated whether lower dose RBV is as effective as standard dose RBV.[17]

Table 1 details the treatment groups and results, including achievement of SVR and relapse. The highest rates of SVR with the lowest relapse rates were seen in the groups that received a total of 48 weeks of therapy (SVR 75% and 67% in lead in group and 48 week treatment group, respectively). The groups that received a total of 28 weeks of therapy had better rates of SVR than the control group (SVR 54% and 56% vs 38%), but had relatively high relapse rates (30% and 24%). The control group had no viral breakthrough, defined as a persistent 2-$\log_{10}$ or greater increase from nadir and 50,000 IU/mL or higher. The lead-in groups had less viral breakthrough than the groups with no lead in (4% vs 9%), although this did not reach significance ($P = .057$). Phase III studies were designed using a lead in strategy for all boceprevir groups to minimize viral breakthrough.

In the second part of the trial, a “low-dose” RBV group (400–1000 mg) was compared with a “standard dose” RBV group (800–1400 mg). The low-dose RBV group had lower SVR (36% vs 67%) and higher relapse (22% vs 7%) than the standard dose RBV group. Rates of viral breakthrough were high in both of these groups (27% in low dose and 25% in standard dose). The results of SPRINT-1 suggest that low-dose RBV is not an adequate treatment option.

Boceprevir phase III studies—Table 1 details the treatment groups studied in phase III trials and summarizes the results. The goal of SPRINT-2 was to evaluate the effectiveness of response-guided treatment (RGT) with boceprevir in genotype 1, treatment-naïve patients in 2 cohorts: Non-black patients and black patients.[18] In the RGT group, patients who achieved undetectable HCV RNA by week 8 and remained negative for HCV RNA at week 24 completed 28 weeks of therapy. Those who did not achieve undetectable HCV RNA by week 8 received a total of 48 weeks of therapy. This group was compared with a group that received the full 48 weeks of therapy. All patients received a 4-week lead-in period with pegIFNα and RBV alone.

The RGT group had similar SVR rates as the group that received 44 weeks of boceprevir (67% vs 68% in the non-black cohort and 42% vs 53% in the black cohort). All boceprevir groups had significantly higher SVR rates than the standard therapy groups. Of the nonblack patients in the RGT group, 47% were eligible to receive a shortened course of therapy (28 weeks). The patients who received 28 weeks of therapy had an SVR rate of 97% and the patients who received 48 weeks of therapy had an SVR rate of 98%. Thus, SPRINT 2 provided the data to support 28 weeks of combination therapy in patients that achieve undetectable viral loads at weeks 8 through 24.

The goal of RESPOND-2 was to assess the response of boceprevir therapy in genotype 1 patients who had prior relapse (undetectable HCV RNA at the end of prior therapy without subsequent attainment of SVR) or partial response (decrease in HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but detectable HCV RNA level throughout the course of therapy, without achievement of SVR) to standard treatment.[19] Patients with prior null response (lack of 2-$\log_{10}$ reduction in HCV RNA at week 12) were excluded from this study. Patient groups were similar to those in SPRINT-2 and included an RGT group in which patients who achieved a negative viral load at week 8 received only 36 weeks of therapy. The RGT group and the group that received 48 weeks of triple therapy had similar results and were both superior to the control group (SVR 59% and 66% vs 21%). Better response rates were seen in patients with prior relapse to treatment than prior partial response. In the RGT group, 46% of patients were eligible to receive a shorter course of therapy, and these patients had similar rates of SVR when they received a total of 36 weeks of treatment compared with those that received a total of 48 weeks of treatment. Thus, RESPOND-2 supports the use of a shorter course of treatment (36 weeks) for patients with prior relapse and partial response if they achieve a negative viral load at week 8 of treatment.

Adverse events with boceprevir—In general, boceprevir is well-tolerated. However, there is a higher rate of treatment discontinuation and dose reductions in patients that receive boceprevir in combination with pegIFNα and RBV than those that receive standard therapy alone (treatment discontinuation 8%–16% vs 3%–16% and dose reduction 29%–40% vs 14%– 26%).[17–19] The most common side effects experienced by patients are typical pegIFNα and RBV related side effects such as flu-like symptoms, fatigue, and nausea. Effects that are more prevalent in those who receive boceprevir are anemia and dysgeusia. Anemia developed in 43% to 56% of patients who received boceprevir in combination with pegIFNα nd RBV in phase II and III trials. In SPRINT-2, erythropoietin was administered in 24% of the controls and 43% of boceprevir recipients. Another side effect with boceprevir combination therapy is dysgeusia, which occurred in 37% to 43% of patients.

Telaprevir

Telaprevir monotherapy was also determined to have high rates of viral load reduction, but also resistance development in early phase studies; therefore, its development proceeded with concurrent pegIFNα and RBV. The treatment regimens with telaprevir differ from those described for boceprevir. Early phase studies supported using combination therapy for the first 12 weeks followed by pegIFNα and RBV for 12 to 36 additional weeks. This is opposed to boceprevir, where a lead-in with pegIFNα and RBV was followed by use of the

combination therapy. The dose of telaprevir studied in phase II and III trials was 750 mg every 8 hours.

Phase II studies—Multiple phase II studies have been reported with telaprevir, including Protease inhibition for Viral Evaluation (PROVE)-1, -2, and -3. Table 2 details the treatment groups and results for telaprevir phase II studies.

PROVE-1 studied the effectiveness of telaprevir in genotype 1, treatment-naïve patients.[20] All treatment groups in PROVE-1 received telaprevir in addition to pegIFNα/RBV for 12 weeks, but differed in subsequent duration of pegIFNα-2a/RBV (0, 12, or 36 weeks). The lowest rates of SVR were seen in the group that received only 12 weeks of combination therapy (35%). SVR for standard therapy in this study was 41%. The groups that received combination therapy followed by pegIFNα-2a/RBV for 12 and 36 weeks had the highest rates of SVR (61% and 67%, respectively). Among the telaprevir-containing groups, 7% had viral breakthrough (an increase of > 1 $\log_{10}$ unit of HCV RNA compared with the lowest value during the treatment period or HCV RNA value of > 100 IU/mL in a patient who had become undetectable). Thus, PROVE-1 showed that telaprevir in combination with pegIFNα/RBV is effective, but must be followed by an additional 12 to 36 weeks of pegIFNα/RBV therapy.

PROVE-2 evaluated the necessity of RBV in the treatment regimen.[21] Patients were genotype 1 and treatment naïve. The lowest rates of SVR were seen in patients with telaprevir and pegIFNα alone (36%). The SVR for standard therapy was 46%. Treatment groups that received triple therapy alone for 12 weeks, and triple therapy followed by pegIFNα-2a/RBV for 12 weeks had the highest rates of SVR (60% and 69%, respectively). Not only were SVR rates the lowest in the group that received telaprevir with pegIFNα alone, but relapse rates and viral breakthrough were the highest as well (relapse 48%, breakthrough 24%). This is in comparison with standard therapy, with a relapse rate of 22% and breakthrough rate of 1%. The group that received a total of 12 weeks of triple therapy alone had a relapse rate of 30% and breakthrough of 1% compared with the group that received 12 weeks of triple therapy followed by 12 additional weeks of pegIFNα and RBV (relapse 14%, breakthrough 5%). In summary, PROVE-2 demonstrated that RBV is important to achieve higher SVR rates and lower relapse and breakthrough rates, and triple therapy for 12 weeks alone had unacceptable relapse rates.

PROVE-3 studied the effectiveness of telaprevir in genotype 1 patients with prior treatment failure, including those with prior partial response and relapse.[22] The standard therapy group had the lowest rates of SVR in this study (14%). The patient group that did not receive RBV had low rates of SVR as well (24%). The group that received 24 weeks of triple therapy followed by 24 more weeks of pegIFNα and RBV had an SVR rate of 53%. The group that received triple therapy for 12 weeks followed by 12 additional weeks of pegIFNα and RBV had an SVR rate of 51%. Higher rates of response in the triple therapy groups were seen in those patients that had previously relapsed compared with those that had prior partial response (SVR of 69% and 75% vs 39% and 38%). Relapse rates were highest in the standard therapy and telaprevir with pegIFNα alone groups (53% each), followed by the group that received a total of 24 weeks of treatment (30%) and the group that received 48

weeks of treatment (13%). Viral breakthrough was highest in the group that received telaprevir and pegIFNα alone (32%), followed by the groups that received 24 weeks and 48 weeks of therapy (13% and 12%, respectively). The standard therapy group had a breakthrough rate of 3%.

Phase III studies—Table 3 outlines the treatment groups and results from telaprevir phase III trials. All studies were performed using a telaprevir dose of 750 mg every 8 hours. The ADVANCE study evaluated the effectiveness of a shorter course of telaprevir combination therapy.[23] This trial evaluated a type of response guided therapy using the extended rapid virologic response (eRVR, negative viral load at 4 and 12 weeks). Patients who achieved eRVR could shorten the duration of subsequent pegIFNα/RBV from 36 to 12 weeks. Those who did not achieve an eRVR received an additional 36 weeks of pegIFNα/RBV. SVR rates were similar in patients that received 8 and 12 weeks of telaprevir (69% and 75%), and both were significantly higher than the standard therapy group (44%). However, virologic failure occurred in 13% of the patients who received 8 weeks of telaprevir versus 8% in the patients that received 12 weeks of telaprevir, suggesting that a longer duration of telaprevir is important to minimize virologic failure.

ILLUMINATE was an open-label study with no placebo control arm that studied genotype 1, treatment-naïve patients and also evaluated whether patients that achieved an eRVR could complete a shorter course of therapy (24 vs 48 weeks).[24] All patients received 12 weeks of telaprevir in combination with pegIFNα/RBV for 12 weeks. At week 20, patients who achieved an eRVR were randomized to continue receiving PR for 24 or 48 weeks of total treatment. Patients who did not achieve an eRVR received 48 weeks of treatment. In this study, of those patients who achieved an eRVR, 92% of patients treated with a total of 24 weeks of treatment achieved an SVR compared with 88% of patients in the group that received 48 weeks. Additionally, more patients discontinued treatment in the group that was randomized to 48 weeks of treatment than those that received 24 weeks of treatment (12.5% vs 0.6%, respectively). Therefore, in patients who achieve an eRVR, treatment with 24 weeks of therapy is similar to treatment with 48 weeks and is associated with fewer treatment-limiting adverse events.

The REALIZE study investigated telaprevir therapy in genotype 1 patients with prior relapse, partial response, or null response.[25] One distinction from the boceprevir phase III study (RESPOND-2) is the inclusion of null responders (failure to achieve a 2-log reduction in viral load by week 12). SVR was higher for all telaprevir groups compared with standard therapy. Patients with prior relapse had the highest rates of SVR (83% in group that received 48 weeks of treatment and 88% in lead-in group vs 24% in standard therapy). Prior nonresponders had SVR rates of 41% in both telaprevir treatment groups versus 9% in the standard therapy group. One major finding of this study was that prior null responders, a notoriously hard patient group to treat, achieved SVR in 29% and 33% of patients, compared with 5% in the standard therapy arm. Thus, telaprevir therapy for 12 weeks followed by pegIFNα/RBV to complete a total of 48 weeks therapy is effective in patients with prior treatment nonresponse and relapse. The lead-in period did not seem to be significantly more effective.

Adverse events/side effects of telaprevir—Telaprevir is well-tolerated overall. However, discontinuation rates were higher in the telaprevir containing groups than standard therapy in phase II studies (9%–26% vs 4%–7%).[20–22] As with boceprevir, the major treatment-limiting side effects were those that are common to interferon-α–based therapy, such as fever, malaise, and fatigue. However, rash, pruritus, nausea, and diarrhea were more common in telaprevir-receiving groups. The rash that occurs with telaprevir therapy is maculopapular and led to treatment discontinuation more frequently in telaprevir groups (5%–7%) than standard therapy groups (0%–1%). This became apparent in PROVE-1 and rash management plans were subsequently implemented in later studies. The implementation of the rash management plans, which included the use of topical anti-allergic agents and topical or systemic antipruritic agents and discontinuation of telaprevir if progression occurred, led to decreased overall treatment discontinuation in phase III studies. Anemia is another significant adverse event with telaprevir therapy and the average hemoglobin decrease is 0.5 to 1 g/dL higher than that seen with standard therapy alone.

Protease Inhibitor Resistance

Protease inhibitors bind to the active site of the NS3/4A enzyme, mimicking the N-terminal side of the viral substrate. Most of the drug-resistance mutations occur around the protease active site. When the drugs do not fit well into the binding site and protrude from the substrate envelope, they interact with the virus, leading to mutations. Molecular changes then occur that weaken inhibitor binding but do not change the binding of viral substrate.[26] Therefore, the ability of the drug to inhibit the action of the enzyme is impaired, whereas the ability of the protease to cleave the viral proteins and continue its life cycle is preserved.

In early trials of telaprevir and boceprevir, viral resistance rapidly occurred with monotherapy. When telaprevir and boceprevir are used in combination with pegIFNα and RBV, the development of resistance is less frequent, although it still occurs and is reflected in the rates of viral breakthrough. Once telaprevir and boceprevir are stopped, the number of wild-type variants increase and resistant variant decrease, resistant variants are less fit in the absence of selection pressure.[27,28] By 3 to 7 months after telaprevir monotherapy, the majority of virus is wild type, although low levels of resistant variants are still present many months after cessation of therapy. [27,29,30] The cross-resistance profile of boceprevir and telaprevir largely overlap, which suggests that the one protease inhibitor cannot be used when resistant variants have developed to the other.

Clinical use of protease inhibitors—Telaprevir and boceprevir will soon be available for use in clinical practice. As described in detail, treatment with protease inhibitors is complex, and best managed by knowledgeable and experienced specialists. Telaprevir and boceprevir were studied using different treatment regimens. Boceprevir was given for 24 to 44 weeks, in combination with pegIFNα and RBV after a lead-in period of 4 weeks of pegIFNα and RBV. Telaprevir was given for 12 weeks in combination with pegIFNα and RBV, followed by 0, 12, or 36 weeks of pegIFNα and RBV alone. The US Food and Drug Administration has not yet described the appropriate dosing regimen of the protease inhibitors, but we summarize potential treatment regimens, based on the clinical trial designs and results.

Treatment-naïve patients who achieve an RVR with boceprevir, which in this case is determined at week 4 of boceprevir therapy, or week 8 of the full treatment course, can likely complete a total of 28 weeks of treatment. Those who do not achieve an RVR will likely require a full 48 weeks of therapy. Patients with prior nonresponse or relapse who achieve an RVR may be able to complete a shorter course of a total of 36 weeks of therapy, whereas those who do not achieve an RVR will likely require a full 48 weeks of treatment. Clinicians should carefully monitor for the development of anemia in boceprevir-treated patients as well. A side effect that is quite common is dysgeusia, and although this did not lead to treatment discontinuation in the majority of patients, patients should be counseled about this side effect.

Treatment-naïve patients who achieve an eRVR with telaprevir may complete a shorter course of pegIFNα and RBV, for a total of 24 weeks. Others require a total of 48 weeks of treatment. Patients with prior relapse, partial response, or null response likely require a full 48 weeks of treatment (12 weeks of triple therapy followed by 36 weeks of pegIFNα/RBV). Clinicians should monitor closely for the development of anemia, and may need to reduce the RBV dose or add erythropoietin. Additionally, because pruritus and rash are common developments with telaprevir, the treating physician should be familiar with the rash management plan. Dermatologists may also be required to diagnose the severity of the rash to guide plans to discontinue therapy.

The need for 3 times daily dosing may be difficult for patients to comply with. Further studies need to be performed to determine whether these therapies can be administered less frequently, and whether patient compliance becomes an issue in clinical practice.

Protease inhibitor effectiveness by IL28B genotype—Patient samples from ADVANCE, REALIZE, SPRINT-2, and RESPOND-2 have been analyzed for *IL28B* genotype. The number of patients evaluated ranged from 42% in the ADVANCE study to 80% in REALIZE. In general, the CC genotype was most favorable for treatment response, but protease inhibitors are more effective than standard therapy across all *IL28B* genotypes.[31–33] Based on this, it is unlikely that testing for *IL28B* genotype will provide much additional data in the decision to initiate treatment; however, *IL28B* genotype may have a role in determining those patients who can receive shorter courses of therapy.

NS5B RNA POLYMERASE INHIBITORS

The nonstructural protein NS5B, or RNA-dependent RNA polymerase, is a protein that mediates viral replication.[9] NS5B has emerged as another important target of therapy and NS5B inhibitors have been developed in 2 forms: Nucleoside inhibitors and non-nucleoside inhibitors. Polymerase inhibitors are considered to have a high genetic barrier to resistance; thus, the development of resistant variants and clinical viral breakthrough is much less common than what is seen with protease inhibitors. There have been polymerase inhibitors isolated in vitro, however.[34]

Nucleoside Inhibitors

Nucleoside analog inhibitors mimic the natural substrate of the polymerase and become incorporated into the growing RNA chain, terminating replication. The nucleoside inhibitor with the most data supporting its use is mericitabine (R7128). Early phase studies showed significant viral load reductions with mericitabine with no resistance development supporting its use in future studies.[35,36] As with the protease inhibitors, mericitabine was studied in combination with pegIFNα/RBV in phase II studies.

The JUMP-C trial evaluated the effectiveness of response-guided therapy with mericitabine at a dose of 1000 mg in combination with pegIFNα/RBV.[37] Patients who achieved an eRVR received a total of 24 weeks of mericitabine/pegIFNα/RBV and those who did not achieve an eRVR received an additional 24 weeks of pegIFNα/RBV. These groups were compared with a standard therapy arm of pegIFNα/RBV for 48 weeks. A week 36 interim analysis showed that in the mericitabine treatment groups, 60% of patients achieved an eRVR. At 12 weeks after treatment completion (SVR12) 76% of the patients in the 24-week arm had achieved an SVR and 24% relapsed. There was no difference in safety and tolerability of mericitabine compared with standard therapy.

OTHER VIRAL TARGETS OF DRUG DEVELOPMENT

A number of drugs that target other viral proteins are in development, but this review is focused on the therapies expected to impact clinical practice in the near future. Non-nucleoside polymerase inhibitors are in development, and these drugs bind to the polymerase enzyme itself to induce a conformational change and render it ineffective. The NS5A viral protein and cyclophilin host protein are also important components of the viral replication complex, and agents that target these proteins are also in development in early stages.[9]

ORAL COMBINATION THERAPY

Although telaprevir and boceprevir have provided huge steps forward in improving the response rates of treatment for HCV, there remains significantly high adverse events and treatment discontinuation. Also, patients who are not candidates for treatment with pegIFNα and RBV are still not candidates for treatment in this new wave of therapy. The ultimate goal for HCV is to create a shorter, more effective treatment regimen of oral medications with a better side effect profile than pegIFNα/RBV. Similar to the treatment paradigm for HIV, targeting multiple viral replication sites will help to reduce resistance and increase efficacy of treatment.

The INFORM-1 study evaluated the effectiveness of protease inhibitor danoprevir in combination with polymerase inhibitor R7128 (mericitabine) in treatment of both treatment-naïve patients and prior nonresponders with genotype 1 HCV.[38] Patients were treated for 2 weeks, and viral load reductions with combination therapy ranged from 3.9 to 5.3 $\log_{10}$ IU/mL. HCV RNA values were undetectable in 88% of treatment-naïve patients at 2 weeks. All patients were then treated with standard of care, because they had only received 2 weeks of therapy. Final SVR results are pending, but preliminary reports showed markedly

improved rates of RVR, early virologic response, and end of treatment response (ETR). In fact, the patient group that received the highest doses of each DAA achieved 100% ETR.

The first report of a successful all-oral combination regimen was reported at the EASL meeting in April 2011. The patient population studied was genotype 1 prior treatment null-responders, the most difficult group to treat. The study evaluated the safety and efficacy of a NS5A replication complex inhibitor BMS-790052 and an NS3 protease inhibitor BMS-650032 alone and in combination with pegIFNα/RBV.[39] Of the 11 patients who received the BMS-790052 and BMS-650032 alone, 7 (64%) had undetectable HCV RNA at week 4, 5 remained undetectable at the end of treatment, and 4 achieved an SVR 12 weeks after treatment completion (SVR12). All patients that received the 2 oral medications in combination with pegIFNα/RBV achieved SVR12.

More research is required to evaluate the safety and efficacy of oral combination therapy, but early results are promising. However, it will be another several years before we can expect to use all-oral combination therapy.

SUMMARY

The HCV viral life cycle provides targets for drug development at virtually every step, and many new drugs aimed at these targets are currently being developed. Clinical practice takes a major step forward this year with the arrival of telaprevir and boceprevir, which will be added to the current standard of care of pegIFNα/RBV. Patients will need to be monitored closely and counseled extensively, and clinicians will need to learn the new response-guided therapy algorithms with these therapies. Although there remains work to be done in the field of HCV, these therapies will allow many more patients the opportunity to eradicate HCV infection.

REFERENCES

1. World Health Organization. [Accessed June 7, 2011] Hepatitis C, WHO fact sheet no. 164, revised 2000. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/
2. Alter M. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007; 13:2436–2441. [PubMed: 17552026]
3. Seeff L. Natural history of chronic hepatitis C. Hepatology. 2002; 36(Suppl 1):S35–S46. [PubMed: 12407575]
4. Younossi Z, Singer M, McHutchison J, et al. Cost effectiveness of interferon alpha2b combined with ribavirin for the treatment of chronic hepatitis C. Hepatology. 1999; 30:1318–1324. [PubMed: 10534357]
5. Ghany M, Strader D, Thomas D, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49:1335–1374. [PubMed: 19330875]
6. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009; 361:580–593. [PubMed: 19625712]
7. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol. 2004; 40:993–999. [PubMed: 15158341]
8. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009; 461:399–401. [PubMed: 19684573]

9. Pawlotsky J, Chevaliez S, McHutchison J. The hepatitis C virus life cycle as a target for new antiviral therapies. Gastroenterology. 2007; 132:1979–1998. [PubMed: 17484890]
10. Monto A, Schooley R, Lai J, et al. Lessons from HIV therapy applied to viral hepatitis therapy: summary of a workshop. Am J Gastroenterol. 2010; 105:989–1004. [PubMed: 20087331]
11. Neumann A, Lam N, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science. 1998; 282:103–107. [PubMed: 9756471]
12. Ogata N, Alter H, Miller R, et al. Nucleotide sequence and mutation rate of the H strain of hepatitis C virus. Proc Natl Acad Sci U S A. 1991; 88:3392–3396. [PubMed: 1849654]
13. Yi M, Tong X, Skelton A, et al. Mutations conferring resistance to SCH6, a novel hepatitis C virus NS3/4A protease inhibitor. Reduced RNA replication fitness and partial rescue by second-site mutations. J Biol Chem. 2006; 281:8205–8215. [PubMed: 16352601]
14. Keiffer T, Kwong A, Picchio G. Viral resistance to specifically targeted antiviral therapies for hepatitis C (STAT-Cs). J Antimicrob Chemother. 2010; 65:202–212. [PubMed: 19903720]
15. Sarrazin C, Rouzier R, Wagner F, et al. SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. Gastroenterology. 2007; 132:1270–1278. [PubMed: 17408662]
16. Schiff E, Poordad FF, Jacobson I, et al. Role of interferon response during RE-treatment of null responders with boceprevir combination therapy: results of phase II trial. Gastroenterology. 2008; 134:A755.
17. Kwo P, Lawitz E, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT 1): an open-label, randomized, multicentre phase 2 trial. Lancet. 2010; 376:705–716. [PubMed: 20692693]
18. Poordad F, McCone J, Bacon B, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195–1206. [PubMed: 21449783]
19. Bacon B, Gordon S, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1207–1217. [PubMed: 21449784]
20. McHutchison J, Everson G, Gordon S, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009; 360:1827–1838. [PubMed: 19403902]
21. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009; 360:1839–1850. [PubMed: 19403903]
22. McHutchison J, Manns M, Muir A, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010; 362:1292–1303. [PubMed: 20375406]
23. Jacobson I, McHutchison J, Dusheiko G, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naïve patients: final results of the phase 3 ADVANCE study. Hepatology. 2010; 52(Suppl):427A.
24. Sherman K, Flamm S, Adfal N, et al. Telaprevir in combination with peginterferon alfa 2a and ribavirin for 24 or 48 weeks in treatment-naïve genotype 1 HCV patients who achieved an extended rapid virologic response: final results of phase 3 ILLUMINATE study. Hepatology. 2010; 52(Suppl):401A. [PubMed: 20229587]
25. Zeuzem S, Andreone P, Pol S, et al. REALIZE trial final results: telaprevir based regimen for genotype 1 hepatitis C virus infection in patients with prior null response, partial response, or relapse to peginterferon/ribavirin. J Hepatol. 2011; 54(Suppl 1):S3.
26. Romano K, Ali A, Royer W, et al. Drug Resistance against HCV NS3/4A inhibitors is defined by the balance of substrate recognition versus inhibitor binding. Proc Natl Acad Sci U S A. 2010; 107:20986–20991. [PubMed: 21084633]
27. Sarrazin C, Kieffer T, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology. 2007; 132:1767–1777. [PubMed: 17484874]
28. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology. 2009; 50:1709–1718. [PubMed: 19787809]
29. Forestier N, Susser S, Welker M, et al. Long term follow up of patients previously treated with telaprevir. Hepatology. 2008; 48(Suppl):1135A–1136A.

30. Susser S, Forestier N, Welker N, et al. Detection of resistant variants in the hepatitis C virus NS3 protease gene by clonal sequencing at long-term follow up in patients treated with boceprevir. J Hepatol. 2009; 50:S7.

31. Poordad F, Bronowicki J, Gordon S, et al. IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treatment with boceprevir (BOC) combination therapy. J Hepatol. 2011; 54(Suppl 1):S6.

32. Jacobson I, Catlett I, Marcellin P, et al. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial. J Hepatol. 2011; 54(Suppl 1):S542.

33. Pol S, Aerssens J, Zeuzem S, et al. Similar SVR rates in IL28B CC, CT, or TT prior relapse, partial- or null-responder patients treated with telaprevir/peginterferon/ribavirin: retrospective analysis of the REALIZE study. J Hepatol. 2011; 54(Suppl 1):S6.

34. Ali S, Leveque V, Le Pogam S, et al. Selected replicon variants with low level in vitro resistance to hepatitis C virus NS5B polymerase inhibitor PSI-6130 lack cross-resistance with R1479. Antimicrob Agents Chemother. 2008; 52:4356–4369. [PubMed: 18838588]

35. Lalezari J, Rodriguez-Torres M, et al. Potent Antiviral activity of the HCV nucleoside polymerase inhibitor R7128 with peg-IFN and ribavirin: interim results of R7128 500 mg bid for 28 days. J Hepatol. 2008; 48(Suppl):S29.

36. Le Pogam S, Kosaka A, et al. No evidence of R7128 drug resistance after up to 4 weeks treatment of GT 1, 2, and 3 hepatitis C virus infected individuals. J Hepatol. 2009; 50(Suppl):S348.

37. Pockros P, Jensen D, Tsai N. First SVR data with the nucleoside analogue polymerase inhibitor mericitabine (RG7128) combined with peginterferon/ribavirin in treatment-naïve HCV G 1 and 4 patients: interim analysis from the JUMP-C trial. J Hepatol. 2011; 54(Suppl 1):S538.

38. Gane E, Rouzier R, Stedman C, et al. Antiviral activity, safety, and pharmacokinetics of danoprevir/ritonavir plus pegIFN alpha-2a/RBV in hepatitis C patients. J Hepatol. 2011 Feb 24. [Epub ahead of print].

39. Lok A, Gardiner D, Lawitz E, et al. Quadruple therapy with BMS-790052, BMS-650032 and peg-IFN/RBV for 2 weeks results in 100% SVR12 in HCV genotype 1 null responders. J Hepatol. 2011; 54(Suppl 1):S536.

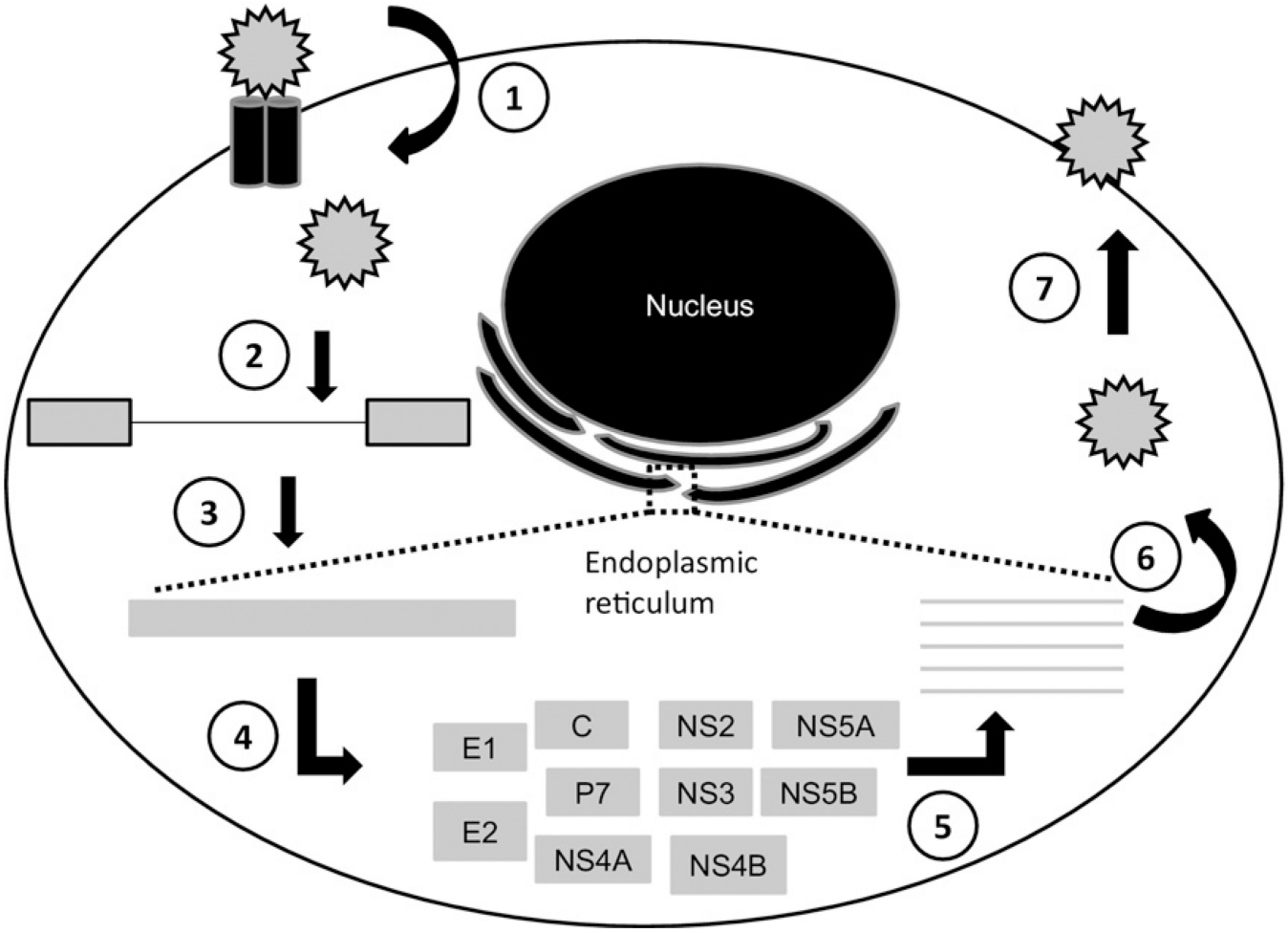

Fig. 1.

Viral life cycle. (*1*) The HCV virus attaches to receptors at the cell surface and enters the cell via receptor-mediated endocytosis. (*2*) Positive-strand RNA is released into the cytoplasm and (*3*) translated into a single polypeptide on the ribosome. (*4*) Polypeptide cleaving occurs in the endoplasmic reticulum resulting in 10 viral proteins that form the structural components of the virus and participate in viral replication and other viral functions. (*5*) A replication complex forms on the membrane of the endoplasmic reticulum and RNA replication then occurs. A negative-strand RNA intermediate generates many copies of positive strand RNA. (*6*) Viral RNA is then packaged into a particle and (*7*) released from the hepatocyte.

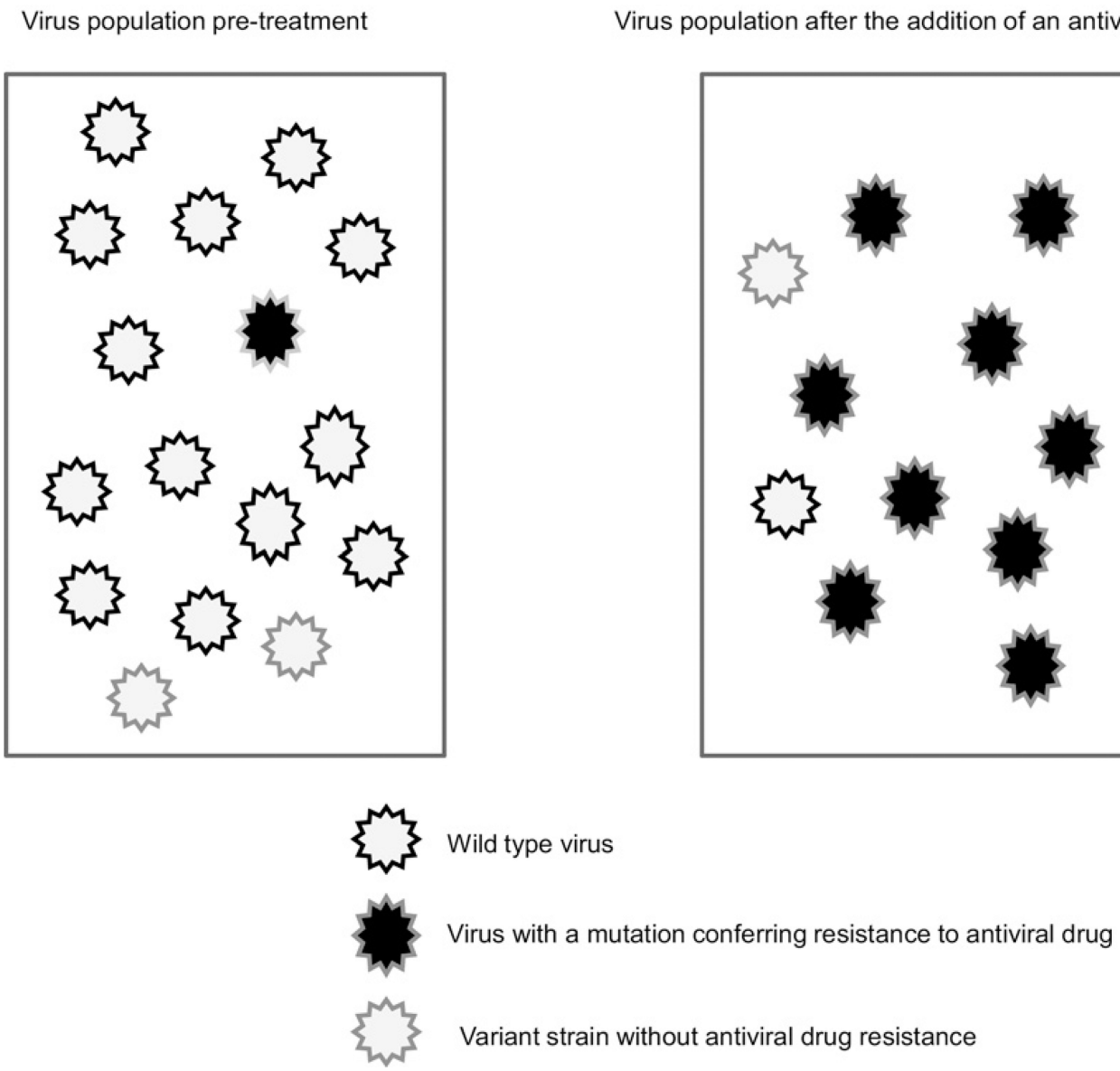

Fig. 2.

Viral resistance. In an HCV-infected individual, there are multiple variants of the virus present at baseline. The wild-type virus predominates and has high replicative fitness. Often, variants are present that confer resistance to the action of an antiviral drug; other variants are present that do not confer resistance to antiviral drugs. These variants generally have lower replicative fitness. When selection pressure is applied by adding an antiviral drug, wild-type viruses and viruses with mutations that do not affect antiviral drug action decrease in response to the drug. However, those viral particles that had resistance to the protease inhibitor now have improved replicative fitness and become the dominant strain.

Table 1

Boceprevir phase II and III trials

Study/Treatment Group	SVR (%)			Relapse (%)	
SPRINT-1					
B/P/R 28w	54			30	
B/P/R 48w	67			7	
P/R 4w, B/P/R 24w	56			24	
P/R 4w, B/P/R 44w	75			3	
P/R 48w	38			24	
B/P/R 48w – Standard dose R	67			7	
B/P/R 48w – Low dose R	36			22	
	Nonblack	**Black**		**Nonblack**	**Black**
SPRINT-2					
P/R 4w, RGT	67	42		23	14
P/R 4w, B/P/R 44w	68	53		8	17
P/R 48w	40	23		23	14
	Overall	**Prior Relapse**	**Prior Partial Response**	**Overall**	
RESPOND-2					
P/R 4w, RGT	59	69	40	32	
P/R 4w, B/P/R 44w	66	75	52	12	
P/R 48w	21	29	7	32	

Abbreviations: B, boceprevir; P, pegylated interferon-α; R, ribavirin; RGT, response-guided therapy.

Table 2

Telaprevir phase II trials

Study/Treatment Group	SVR (%)			Relapse (%)		
PROVE-1						
T/P/R 12w	35			33		
T/P/R 12w, PR 12w	61			2		
T/P/R 12w, PR 36w	67			6		
P/R 48w	41			23		
PROVE-2						
T/P 12w	36			48		
T/P/R 12w	60			30		
T/P/R 12w, P/R 12w	69			14		
P/R 48w	46			22		
	Overall	**Prior Relapse**	**Prior Partial Response**	**Overall**	**Prior Relapse**	**Prior Partial Response**
PROVE-3						
T/P/R 12w, P/R 12w	51	69	39	30	18	37
T/P/R 24w, P/R 24w	53	75	38	13	0	4
T/P 24w	24	42	11	53	46	68
P/R 48w	14	20	9	53	62	40

Abbreviations: P, pegylated interferon-α; R, ribavirin; T, telaprevir.

Table 3

Telaprevir phase III trials

Study/Treatment Group	SVR (%)			Relapse (%)	
ADVANCE					
T/P/R 8w	69			9	
T/P/R 12w	75			9	
P/R 48w	44			28	
ILLUMINATE					
eRVR T/P/R 12w, P/R 12w	92			6	
eRVR T/P/R 12w, P/R 36w	88			3	
T/P/R 12w, P/R 36w	64				
	Prior Relapse	**Prior Partial Response**	**Prior Null Response**	**Prior Relapse**	**Prior Partial Response**
REALIZE					
T/P/R 12w, P/R 36w	83	41	29	7	23
P/R 4w, T/P/R 12w, P/R 32w	88	41	33	7	25
P/R 48w	24	9	5	65	33

Abbreviations: eRVR, extended rapid virologic response (negative viral load at week 4 that persists through week 12); P, pegylated interferon-α; R, ribavirin; T, telaprevir.

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