There have been significant changes in the treatment for hepatitis C virus (HCV) this year with the long-anticipated approval of two new direct-acting antiviral agents. Over the past decade, hepatitis C treatment has progressed from interferon (IFN) monotherapy to combination therapy with pegylated interferon and ribavirin (RBV), which has sustained virologic response (SVR) rates of 40 to 50 percent in the more difficult-to-treat genotype 1 patients and more than 80 percent SVR in genotypes 2 and 3. If SVR is achieved, it is considered essentially a cure and long-term viral clearance. Unlike interferon and ribavirin, the protease inhibitors are direct-acting antiviral agents, developed to target specific steps in the viral replication cycle. The two recently approved agents, telaprevir (Incivek™) and boceprevir (Victrelis™), target the NS3/4A serine protease required for RNA replication and virion assembly. These agents were approved for hepatitis C therapy in genotype 1.

Efficacy in the treatment-naïve patient

In making the clinical assessment of treatment for a patient, analysis of the studies and data can be looked at in two ways: treatment for the naïve patient and treatment in the previously treated patient.

Boceprevir

Boceprevir (BOC), the first of the two newly approved agents, is an oral medication given 800 mg (4x200 mg tabs) three times daily with food. The boceprevir clinical trial1 SPRINT-2 was designed with a four-week lead-in with pegylated interferon (PEG IFN) alfa-2b and weight-base dosed ribavirin followed by either:

1. 24 weeks of triple therapy (IFN+RBV+BOC) if the patient responded well to therapy in the first several weeks, an approach called “response-guided therapy”
2. Triple therapy (IFN+RBV+BOC) for 44 weeks
3. PEG IFN+RBV as the standard of care (SOC) control arm

The triple therapy arms resulted in overall SVR rates of 63 to 66 percent compared to SOC (38%). Black patients had SVR rates 42 to 53 percent. Of important note, success with six months of triple therapy was comparable to one year of triple therapy when patients were selected appropriately based on their early weeks of viral response. The best predictor of treatment success is the rapid virologic response (RVR), defined as undetectable virus four weeks into triple therapy. Sixty percent of non-black patients on triple therapy demonstrated RVR, and in these patients, SVR was 88 percent after 24 weeks of treatment. Triple therapy was especially remarkable for its ability to shorten the duration of therapy for those genotype 1 patients who had high response rates.

Telaprevir

The clinical study design for the ADVANCE trial of telaprevir did not include a lead-in phase and incorporated triple therapy immediately.2 Patients were given telaprevir 750 mg (2x375 mg tabs) every eight hours with food+PEG IFN+RBV. Triple therapy was studied for either eight or 12 weeks, then PEG IFN+RBV was continued to complete either 24 or 48 weeks depending on the RVR. In this study, RVR was defined as “extended” RVR (eRVR; negative at four weeks and staying negative through 12 weeks). A control arm with PEG IFN+RBV was also included.

Overall SVR rate was 72 percent for the eight weeks of triple therapy and 79 percent for 12 weeks of triple therapy, compared with 46 percent for PEG IFN+RBV. As with boceprevir, the RVR was the best predictor of response, and 58 percent of patients achieved eRVR with telaprevir triple therapy and 90 percent of these patients went on to achieve SVR with six months of therapy. This treatment paradigm for telaprevir was confirmed in the ILLUMINATE trial,3 which also had an overall SVR rate of 72 percent, and 24 weeks of therapy in those with eRVR yielded a remarkable 92 percent SVR.

Continued on page 2 (see “New Standard”)
Retreatment with triple therapy

For the treatment-experienced patient, trials for both boceprevir and telaprevir achieved higher SVR rates in those who received the triple therapy regimens than in those who received the PEG IFN+RBV alone. In the RESPOND-2 boceprevir retreatment trial, the SVR rates were 59 to 66 percent in the triple therapy arms compared to 21 percent in the control arm. The SVR rates in the telaprevir retreatment trial REALIZE3 were 65 to 67 percent in the triple therapy arms (84% and 88% in relapsers, 61% and 56% in partial responders, and 31% and 33% in null responders) compared to 16 percent in the control arm.

It is clear from these retreatment trials that patients treated in the past who were relapers and partial responders will do well with retreatment with triple therapy. Previous null responders (those who did not have a >2 log drop in viral load at 12 weeks) may have an approximately 30 percent chance of null responders (those who did not have a >2 log drop in viral load at 12 weeks) may have an approximately 30 percent chance of SVR with new therapies. However, this treatment response must be balanced against the risk of developing viral resistance, which appears to be higher in these patients.

Side effects

The clinical difficulties with HCV therapy are well-known among both clinicians and patients. Interferon side effects, including flu-like symptoms, anemia and thrombocytopenia, can be challenging—especially in conjunction with ribavirin-associated side effects. The direct-acting agents will only add to the complexity of therapy, in terms of both side effects and the new risk of viral resistance.

In the boceprevir registration trials, anemia and dysgeusia were common side effects. Hemoglobin levels dropping below 10g/dl occurred in more than 50 percent of patients receiving boceprevir compared to 32 percent in those with PEG IFN+RBV alone. Telaprevir, 34 percent had anemia below 10g/dl. Growth factors were permitted in the boceprevir trials but not in the telaprevir trials. Dose reduction of ribavirin with anemia did not appear to affect SVR rates. Therefore, the potential benefits of growth factors must be considered against cost and risk.

Side effects reported in the telaprevir trials included rash, anemia, nausea and diarrhea. A rash (of any severity) was noted in 56 percent of patients who received triple therapy, including telaprevir, compared to 32 percent of those who received only PEG IFN+RBV. The rash appeared eczematous and maculopapular, with a severe drug reaction (involving greater than 50 percent of the body surface area) in one percent of cases. Clinical management with local and topical therapies appeared to help ameliorate symptoms in some cases. Very few patients required discontinuation of the medications. Stevens Johnson syndrome or drug-related eruption with systemic symptoms (DRESS) occurred in less than one percent of patients.

Neither boceprevir nor telaprevir should be dose-reduced for side effects as this may result in viral resistance.

Resistance

One of the most important new considerations in therapy with boceprevir and telaprevir is the development of resistant variants with therapy. Similar variants were observed for both medications, suggesting some degree of cross-resistance. Overall, telaprevir-associated resistant variants were observed in 12 percent of treatment-naive patients and 22 percent of retreated patients. Among treatment-naive patients receiving boceprevir, resistant variants were observed in 16 percent of patients. Patients with a poor response to interferon and those who experienced virological breakthrough or incomplete virological suppression on therapy appear to have a higher risk of resistance. Once resistance develops, it is unclear how long it persists. Resistant variants were detected in 43 percent of patients at two years' follow-up.

In summary, resistance is high if profound viral suppression does not occur. If patients have persistent virus, there are hard stopping rules to prevent resistance. All three therapies, including boceprevir should be stopped at week 12 if viral levels are >1000 IU. Triple therapy including telaprevir should be stopped at either week 4 or 12 if viral levels are >1000 IU/ml. Boceprevir and telaprevir cannot be dose-reduced, as this may result in viral resistance. If interferon and ribavirin are discontinued, the protease inhibitors must also be discontinued.

Drug-drug interactions

Protease inhibitors are inhibitors of CYP3A, resulting in significant drug-drug interactions with many classes of medications. Many commonly used medications will need to be adjusted accordingly while a patient is on boceprevir or telaprevir, and importantly, readjusted once triple therapy is completed. Common medication interactions will be seen with antibiotics, antidepressants, calcium channel blockers, hormonal contraceptives and others. The package inserts have extensive available data on known drug-drug interactions, which all clinicians should familiarize themselves with before initiating therapy.

Conclusions

The era of new therapies with direct-acting antivirals for hepatitis is here and will result in many more successful treatment outcomes for our patients. Excellent rates of viral cure need to be balanced with awareness of side effects, viral resistance and drug-drug interactions. We anticipate that other targets for HCV therapy will come to the approval stage in the next several years, perhaps even multiple combinations that could eliminate interferon. A new era of treatment has really just begun.

References

4. Bacon BR et al. HCV RESPOND-2 final results: high sustained virological rates among genotype 1 previous nonresponders and relapers to peginterferon/ribavirin when treated with boceprevir plus Peginteron (peginterferon alfa-2b)/ribavirin. 61st AASLD; Boston, MA; Oct. 29–Nov. 2, 2010.
Hepatitis C: Beyond the New Standard of Care

Fred Poordad, MD

On the heels of the approval of boceprevir and telaprevir for genotype 1 hepatitis C virus (HCV),1-3 it is clear there remains a great need for other therapies. While these two compounds are great advances in the field, they do not cover many patient groups, including HIV co-infected patients, post-liver transplant patients, dialysis patients and those unable to tolerate interferon or ribavirin. Even in patients with poor interferon response, the outcomes are less than optimal. The ultimate goal is the development of all-oral regimens that are pan-genotypic, well-tolerated and of short duration.

There are many classes of compounds currently under study at Cedars-Sinai and other institutions. These compounds include polymerase inhibitors, NS5A inhibitors and next-generation protease inhibitors. They have different characteristics and many of them have the potential to work well in combination (Fig. 1).4

There are also several combination studies underway, and this approach appears to hold promise as the likely next step beyond the first wave of direct-acting antivirals (DAAs) (Table 1). Combinations of oral regimens with and without interferon have thus far shown good viral suppression. One combination has demonstrated sustained virologic response (SVR) rates and there are undoubtedly more to come. The combination of the Bristol-Myers Squibb protease inhibitor BMS-650032 and the NS5A inhibitor BMS-790052 for 24 weeks led to SVR in four of 11 (36%) null responders. When combined with pegylated interferon and ribavirin, 10 of 10 patients achieved SVR with 24 weeks of therapy.4 This proof-of-concept study has catapulted the field forward in terms of the potential to cure the most difficult patients with only two oral drugs. The foundation is now there to build upon and continue combination studies.

Perhaps the most exciting single class of DAA is the nucleoside polymerase inhibitor, which has broad genotypic coverage, is dosed daily and is well-tolerated. A phase 2 study (PROTON) using the PSI-7977 compound with pegylated interferon and ribavirin for only 12 weeks achieved SVR rates of 96 percent in genotype 2/3 patients. A combination of the PSI-7977 and another similar compound, PSI-938, yielded a 5-log decline in virus in two weeks in genotype 1 patients.4 This apparently well-tolerated combination may be another landmark step in the HCV therapeutic arena.

What is becoming clear is that the next five years will likely see a change in the HCV treatment paradigm. It appears that interferon-based therapies will largely be replaced by oral regimens. It is expected that the next compound to gain FDA approval by 2014/2015 is the TMC-435 protease inhibitor, a once-daily potent compound without rash and anemia. Soon after, however, it is very likely that multi-drug combinations will emerge as the preferred treatment modalities. All-oral regimens will be the focus, and this should allow for much broader application to most patient groups. This rapidly changing field offers patients great hope of having therapies that may make hepatitis C a rare condition in much of the world over the next decade.

References:


Table 1: Combination therapies with two or more DAAs.4 PI=protease inhibitor; NPI=nucleoside polymerase inhibitor; NNPI=non-nucleoside polymerase inhibitor.

<table>
<thead>
<tr>
<th>DRUG COMBINATIONS</th>
<th>CLASS</th>
<th>COMPANY</th>
<th>PHASE</th>
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<tbody>
<tr>
<td>BMS-650032 + BMS-790052</td>
<td>PI+NS5a</td>
<td>Bristol-Myers Squibb</td>
<td>2a</td>
</tr>
<tr>
<td>Danoprevir (RG-7227) + RG-7128</td>
<td>PI+NPI</td>
<td>Genentech</td>
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<tr>
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<td>NPI+NPI</td>
<td>Pharmasset</td>
<td>2a</td>
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Figure 1: Direct-acting antivirals against various protein targets of the HCV genome.

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Cholangiocarcinoma: A Challenging Disease

Steven D. Colquhoun, MD, FACS

Cholangiocarcinoma (CCA) may be the second most common primary hepatic malignancy, but it ranks first as the most difficult and frustrating to both diagnose and treat. In the United States, primary sclerosing cholangitis remains the disease most recognizably associated with the development of CCA, but the vast majority of patients have no such identifiable risk. Early detection obviously remains difficult. Significant advances in diagnostic techniques, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS), have certainly improved the comprehensive characterization and accuracy of diagnosing CCA—but these have likely had more impact on the number of unnecessary surgical explorations than improved outcomes. In recent years, remarkable advances have been made in many areas of oncology, but among patients afflicted with CCA, treatment options remain limited and outcomes still appropriately categorize this as a devastating disease.

The majority of patients with CCA present with lesions classified as Hilar or Klatskin-type (>50%), while less than 10 percent present as intrahepatic. The remainder present as disease in the distal bile duct and are generally treated as other tumors of the pancreatic head. The annual incidence of this disease in the United States is in the range of two out of every 100,000 (or an estimated 3,000 to 4,000 annually). Worldwide, there is significant variation. Whether a true increase or a diagnostic bias, the incidence of CCA worldwide appears to be on the rise. The histology of CCA most often includes both lymphovascular and perineural invasion, accounting for the low rate of tumors amenable to surgical resection and high incidence of local recurrence. Unfortunately, fewer than 20 percent of patients present as surgical candidates and among those who do, resection with histologically negative margins is feasible in only a small minority. Nevertheless, surgery remains the first and best treatment option for patients with CCA.

Surgical intervention

Although rare, CCA is a disease frequently treated at Cedars-Sinai, and our experience is illustrative (Fig. 1). In a recent review of our experience, a total of 61 patients with this disease were evaluated for resection. The majority were men (37) with a mean age of 67. Based on imaging alone, 31 percent were found to be clearly unresectable. The remaining 69 percent underwent surgery, at which time resection was found to be infeasible in an additional 25 percent (for an overall 56 percent unresectable). While all resection specimens in this study had grossly negative margins, 63 percent were truly negative (R0) margins, while the remainder were found to be microscopically positive (R1). Not surprisingly, those patients undergoing resection fared best. At a follow-up of 13 months, five-year actuarial survival for patients undergoing resection was 42.9 percent, while the survival for patients deemed unresectable (on imaging and exploration) was 10.37 percent (29 v. 19 months, p = 0.05). Surprisingly, among the patients undergoing resection, there was no apparent difference in survival between patients with R0 margins compared to those with R1 margins. We concluded that despite advances in diagnostic imaging, more than half of patients with CCA presenting for surgical evaluation are ultimately found to be unresectable, but that the final determination can still only be made at the time of exploration. Even in the presence of microscopic residual disease, surgical intervention results in improved survivals and that an aggressive stance toward surgical intervention in patients with CCA remains justified.

Liver transplantation

Although not new, utilizing liver transplantation for the treatment of CCA has long held some intuitive appeal, especially in light of the issue of lymphatic and neural spread. Unfortunately, the requisite immunosuppression can have an obviously negative impact on any undetected residual disease. In addition, stewardship of the scarce organs available for transplantation dictates that patients with CCA should have outcomes no worse than those transplanted without a malignancy. Clearly, patient selection is the key. After some pioneering work at select centers, strict inclusion and exclusion criteria have been developed. In conjunction with external beam radiation, brachytherapy, capetabine systemic therapy and pre-transplant staging laparotomy, outcomes now appear acceptable. When criteria are met, one- and three-year survivals in the range of 90 percent and 80 percent can be expected. Indeed, as of 2010, the United Network for Organ Sharing has sanctioned individual liver transplant programs in the United States to list patients with CCA provided they are treated under an institution-defined protocol. Cedars-Sinai has such a protocol in place, and a number of patients who qualify have now been listed for transplantation.

Systemic chemotherapy

While there appears to have been no major recent advances in systemic therapeutic options for CCA, increased response rates have been noted with gemcitabine/platinum combinations compared to other regimens. Neoadjuvant gemcitabine protocols have also been reported, with some successes in making it possible for a small percentage of patients to become surgical candidates. The study of systemic chemotherapeutic combinations are ongoing and may provide some hope in a neoadjuvant setting. The best option for any patient with suspected or proven CCA is referral to a comprehensive program offering an advanced multidisciplinary approach, including experienced hepatobiliary surgery and liver transplantation.

Figure 1: Survival curve of Cedars-Sinai patients with unresectable versus R1 and R0 resections.