Is The HCV Pipeline Heading in the Right Direction?

Hepatitis C (HCV) is a global health concern, with >180 million people infected worldwide. Advances in HCV therapy do not necessarily result in improvement of patient outcomes unless specific patient needs and therapeutic options are incorporated into development plans. In this white paper, we explore the lessons learned from the first generation of direct-acting antivirals (DAAs) and apply this insight to optimize delivery, safety, and efficacy to patients who will receive future generation of DAAs.

Lessons Learned From the First-Generation DAAs

The release of boceprevir and telaprevir in May 2011 marked a new era in HCV therapy. For many patients with genotype 1 HCV, DAA-based therapy has offered a significant improvement from previous standard of care. However, first-generation DAA-based therapy is not a panacea, and to date, many patients remain untreated. Identification of the therapeutic need of at-risk patients will be of increasing importance as new HCV medications are under development.

Access to Care

In an era where a significant proportion of patients can now be cured of HCV, lack of adequate awareness, screening, access to care, and affordability of therapy persist; therefore, many infected patients remain both undiagnosed and untreated. Patients with limited resources, including those from developing countries with limited access to medical care, are among those with the highest prevalence of HCV and are unlikely to benefit from advances in HCV therapy. Reduction of HCV related burden of disease will be realized only if a global infrastructure is in place to allow for cost-effective screening and delivery of HCV care. First, in resource-limited regions, consideration should be given to allocate therapy to patients based on need such as those with more advanced disease. Targeting effective therapy on a global scale is not a “one size fits all” approach. Patients who reside in resource limited regions may not have access to the newest generations of DAA therapy and creative approaches for therapy that control cost should be sought. For example, in East Asian countries with a high prevalence of interleukin (IL)-28b CC genotype, focus on improvements in screening, and treatment with peginterferon alfa/ribavirin (PEG/RBV) may yield more overall benefit than attempting to pay for increasingly expensive DAA regimens that offer relatively small improvements in efficacy. Next, policy promoting effective linkage to care will be needed to ensure access to HCV care for all patients. This type of policy would include increases in mid-level providers specializing in HCV treatment, expansion of HCV treatment into the realm of primary care, and improvement in physician education along with incentivizing HCV care. Finally, ongoing research should prioritize simplified therapeutic algorithms that reduce the cost of initial evaluation and monitoring during therapy.

Currently Underserved Populations

Cirrhosis. Cirrhosis is becoming increasingly common among patients with HCV. Recently reported data from the CUPIC cohort, a French early access program consisting of cirrhotic nonresponders, revealed poor tolerability of telaprevir and boceprevir-based treatment. A 16-week interim analysis reporting data from 292 patients receiving telaprevir and 205 patients receiving boceprevir showed significantly more patients with serious adverse events, including 6 deaths, when compared with published clinical trials (32.7%–45.2% SAE in CUPIC versus 9%–14% in clinical trials). Ongoing development programs should prioritize identification of features predictive of good treatment outcomes as well as development of better tolerated treatment regimens for cirrhotic patients.

HIV coinfection. HIV/HCV coinfection carries increased risk of progression to fibrosis and decompensation compared with the monoinfection. Although small phase II studies have shown improved efficacy and acceptable safety profiles in telaprevir- or boceprevir-based therapy in this population, treatment remains off label in coinfected patients and treatment decisions are currently being based on limited data. Despite these limitations, off-label use will continue to occur to provide therapy to those most in need. Drug development programs should prioritize early and robust study of drug–drug interactions (DDI), ideally in parallel with phase II studies. Efforts should also be made to obtain labeling that extends to the HIV/HCV coinfected population because this will likely be necessary for widespread reimbursement. Rapid development and dissemination of treatment guidelines by specialty societies will also be important in guiding treatment decisions and reimbursement.

Post liver transplantation. HCV treatment with PEG/RBV in the post liver transplant population has yielded suboptimal results owing to low sustained virologic response rates, poor tolerability, and adverse events such as acute rejection. Unfortunately, extensive DDI with commonly used immunosuppressants have hindered the use of first generation DAAs in this population (70-fold increase in tacrolimus concentration.
Table 1. Direct-Acting Antiviral Agents Currently in Phase 3 Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of agent</th>
<th>Interferon-containing regimen</th>
<th>Genotype</th>
<th>Response in phase 2 trials</th>
<th>Anticipated completion of phase 3 trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (TMC 435)¹³</td>
<td>Protease inhibitor</td>
<td>Yes</td>
<td>1</td>
<td>75%-6% SVR 24 in treatment naive</td>
<td>January 2013</td>
</tr>
<tr>
<td>Faldaprevir (BI 201335)¹⁴</td>
<td>Protease inhibitor</td>
<td>Yes</td>
<td>1</td>
<td>71%-83% SVR 24 in treatment naive</td>
<td>February 2014</td>
</tr>
<tr>
<td>BI 207127¹⁵</td>
<td>NS5B inhibitor (given in combination with faldaprevir)</td>
<td>No</td>
<td>1</td>
<td>52%-69% SVR 12 in treatment naive</td>
<td>August 2015</td>
</tr>
<tr>
<td>Daclatasvir (BMS 790052)¹⁶</td>
<td>NS5a inhibitor</td>
<td>Yes</td>
<td>1</td>
<td>64%-65% SVR 12 in treatment naive</td>
<td>January 2014</td>
</tr>
<tr>
<td>Asunaprevir (BMS 650032)¹⁷</td>
<td>Protease inhibitor (given in combination with daclatasvir)</td>
<td>No</td>
<td>1</td>
<td>63%-87% SVR 4 in null responders</td>
<td>July 2014</td>
</tr>
<tr>
<td>Sofosbuvir (GS 7977)¹⁸,¹⁹</td>
<td>Nucleotide polymerase inhibitor</td>
<td>Yes</td>
<td>1</td>
<td>90% SVR 12 in treatment naive</td>
<td>July 2013</td>
</tr>
<tr>
<td>GS 5885²⁰</td>
<td>NS5a inhibitor (given in combination with sofosbuvir)</td>
<td>No</td>
<td>2.3</td>
<td>100% SVR in treatment naive</td>
<td>July 2013</td>
</tr>
<tr>
<td>ABT-450/r, ABT 267, ABT-333</td>
<td>Protease inhibitor, NS5A inhibitor, non-nucleoside polymerase inhibitor</td>
<td>No</td>
<td>1</td>
<td>No SVR data available</td>
<td>Dec 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>SVR 85%-99% in treatment naive/null responders</td>
<td>October 2014</td>
</tr>
</tbody>
</table>

SVR, sustained virologic response.

The Next Generation of HCV Therapy

Ongoing clinical trials hold considerable promise for improvements in HCV therapy. Newer NS3/4A protease inhibitors, NS4B inhibitors, NS5A inhibitors, NS5B polymerase inhibitors, lambda interferon, and cyclophilin inhibitors are currently under development with hopes to deliver effective, safe and shorter duration of therapy when compared with current standard of care (Table 1).¹³-²¹

Agents featuring increased potency that allow for simultaneous targeting of various aspects of HCV replication using multiple agents will likely result in interferon-free therapy.

Anticipated Challenges

Will All Patients Be Able to Be Treated Without Interferon?

Interferon-free HCV therapy will represent a breakthrough in HCV treatment. Trials to date are encouraging, but have begun to reveal important interactions between drug, host, and virus that need to be better understood before interferon-free therapy becomes a mainstay of treatment. Previously unidentified host and viral characteristics may create a requirement for interferon-based therapy for some, raising the possibility that all oral regimens may not be appropriate for all patients. In addition, the cost of newly developed interferon-free regimens may be prohibitive, especially in many resource-limited regions of the world. Enthusiasm over the possibility of an “all-oral” cure for HCV must be balanced with realization that cost of therapy will create a disparity among those who can receive interferon-free therapy and those who do not have access. HCV will and 4.6-fold increase in cyclosporine concentration when administered with telaprevir).¹⁰ Many transplant centers have devised internal protocols using DAA-based treatment by extrapolating data from pharmacokinetic studies in an effort to make treatment as safe as possible. Although investigation to optimize the current treatment regimen is ongoing and of importance, first-generation DAA will not be durable agents in this population, and prospective studies using newer generation DAA, ideally without need for interferon, should be aggressively pursued.

Patients with medical comorbidities. Patients with multiple medical comorbidities are unlikely to be candidates for telaprevir- or boceprevir-based therapy owing to concerns over tolerability and a relative paucity of robust DDI data available for patients on multiple medications. Polypharmacy in the setting of multiple comorbidities is especially prevalent in older patients. These patients are at increased risk of HCV-related morbidity and mortality and have unique therapeutic needs that are not fully addressed by currently available HCV therapy. In addition, HCV has a high prevalence among patients with chronic kidney disease and is an independent risk factor for mortality in patients who are undergoing hemodialysis.¹¹ Currently, there are no published efficacy, pharmacokinetic, or safety data for the use of telaprevir or boceprevir given in combination with PEG/RBV in patients with severe chronic kidney disease.¹² Ribavirin is renally cleared and therefore carries increased risk in this patient population. Consideration should be given to devising dosing schedules based on renal clearance with DAA regimens.
carry an extensive global burden of disease, even in an interferon-free era, if efforts are not made to diminish this disparity.

Off-Label Prescribing

First-generation DAAs are already being used off label to treat HIV coinfected patients and post liver transplant patients with significant HCV recurrence. Future availability of multiple DAAs with unique antiviral mechanisms may lead to “mixing and matching” therapeutic combinations that have yet to be thoroughly investigated. Off-label interferon-free combinations with limited supporting data may lead to unintended adverse events, emergence of viral resistance, and missed opportunities to treat with available therapy that is known to be highly effective and safe. Patients with decompensated cirrhosis and/or renal insufficiency are examples of patients with significant need for therapy; however, physiologic response to exposure of new DAAs with or without interferon is unpredictable. Treatment with future DAA regimens off label, without appropriate pharmacokinetic and dosing studies, may pose a significant risk to patients. Despite these risks, off-label prescribing will likely occur; therefore, it should be acknowledged and efforts be made to reduce risk to patients. First, education of patients and providers is essential to gain an understanding of the risks of off-label prescribing. Next, for patients with no other options except off-label treatment, efforts should be made to collaborate and report experience of safety and outcomes. Finally, marketing concerns may dictate access to optimal combination therapy. Even if off-label regimens are promising, payers may not be willing to offer reimbursement. Public–private research partnerships to facilitate development of best-in-class regimens from different sponsors should be considered to encourage clinical collaboration between pharmaceutical companies.

Focusing Drug Development on Patients in Need

Clinical trials focusing on patients with few comorbidities are important to show efficacy and safety; however, because sustained virologic response rates using newer agents approach and exceed 90% in younger, healthy patients with no cirrhosis, we risk creating an oversaturated market for these patients while struggling to treat patients with limited resources and with more extensive liver disease and comorbidities. This disparity has already emerged since approval of the first-generation of DAAs and is at risk of further propagation unless specific attention is given to these underserved populations. Small, open-label studies should be conducted in parallel with phase III, for sicker patients who are ineligible for clinical trials. These trials would offer potentially life-saving treatment and would begin to characterize risks and benefits of different treatment regimens in currently underserved populations. In addition, the robust HCV pipeline comes at a cost. Money spent on research and development will ultimately be passed on to patients and our health care system overall. Payers may not cover costs of incremental improvements of medical therapy once standard of care treatment reaches an acceptable safety and efficacy profile. We should be conscious of reaching a point of diminishing returns in patients with high potential of cure and redirect research effort and funding to benefit those in need including those without access to any DAAs.

Hopes and Expectations: Overcoming Disparities in HCV Therapy

What can be done to ensure the HCV pipeline is heading in the right direction? Focus on appropriate allocation of therapy and accessibility to these resources is key. Large, multicenter, prospective, observational studies such as PEGBase, HCV TARGET, CUPIC, and ANRS CO13-HEPAVIH, all of which aim to gather data from thousands of patients treated with triple therapy since the approval of telaprevir and boceprevir, are already underway and will be crucial in capturing data that is missing from published clinical trials. Because these observational registries obtain data from many providers from multiple sites, the quality of data should be carefully assessed. Standardization of data entry and judicious quality assurance monitoring, preferably though a centralized site, should be employed to ensure reliable and useful data are available. Continued involvement of key stakeholders such as advocacy and patient groups is essential to ensure that vulnerable and underserved populations have appropriate representation. In addition, both the need and potential danger of off-label prescribing of HCV therapy should be acknowledged with steps taken to allow for the safest possible outcomes. Finally, we should not assume that in upcoming years all patients will have access to HCV treatment. HCV is a global epidemic and many patients in resource-limited countries will not have access to DAA-based therapy. Efforts to develop a cost-effective treatment strategy for these populations is essential.

Advances in HCV therapy will bring new challenges. Success of the upcoming generations of DAAs will not be measured in incremental improvements of sustained virologic response, but rather by the availability of treatment options and accessibility to care for all patients infected with HCV.

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References


Acknowledgments

The authors thank Tracy Swan and members of the National Viral Hepatitis Roundtable for assistance with this manuscript.

Conflicts of interest

The authors disclose the following: A.A. serves as a consultant for Vertex, Merck, and Novartis; and has received grants from Merck. A.M. serves as a consultant for Achillion, BMS, Gilead, GSK, Merck, Scynexis, and Vertex; and has received grants from Abbott, Achillion, BMS, Gilead, Medtronic, Merck, Pfizer, Scynexis, and Vertex. D.J. serves as a consultant for Abbott, Astex, BMS, Boehringer-Ingelheim, Genentech, Gilead, Merck, and Vertex; and has received grants from Abbott, BMS, Boehringer-Ingelheim, Genentech, and Gilead.