Paradigm Shift in HCV Standard of Care Treatment: DAAs
A CME/CE Satellite Symposium

TABLE OF CONTENTS

CME/CE Information ...............................................................................................................................................2
Introduction ....................................................................................................................................................................3
Faculty Biographies .................................................................................................................................................4

AGENDA

7:00 PM  Welcome
         David R. Nelson, MD

7:05 PM  DAAs: A New Standard of Care in the Treatment of HCV ..............................6
         Mark S. Sulkowski, MD

7:25 PM  New and Evolving Perspectives: What the Data Tell Us..............................14
         Robert G. Gish, MD

7:40 PM  Putting DAAs into Practice: Case-Based Discussion with Patient Videos .......20
         Ira M. Jacobson, MD

8:20 PM  Conclusion: HCV—Present and Future ............................................................ 23
         David R. Nelson, MD

Supported through a medical education grant from Vertex Pharmaceuticals Incorporated.
Paradigm Shift in HCV Standard of Care Treatment: DAAs

Ira M. Jacobson, MD, has received grant/research support from Anadys Pharmaceuticals, Inc, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc, Globelmmune, Inc, Human Genome Sciences, Merck & Co, Inc, Schering-Plough, Novartis Pharmaceuticals Corporation, Pharmasset Pharmaceuticals Inc, Roche/Genentech, Tibotec Pharmaceuticals, Vertex Pharmaceuticals Incorporated, and ZymoGenetics Inc; is a consultant for Achillion, Inc, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Globelmmune, Inc, Human Genome Sciences, Merck & Co, Inc, Schering-Plough, Novartis Pharmaceuticals Corporation, Pfizer Inc, Pharmasset Pharmaceuticals Inc, Roche/Genentech, Tibotec Pharmaceuticals, Vertex Pharmaceuticals Incorporated, and ZymoGenetics Inc; is on the speakers bureaus of Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, Irc/Scherling-Plough, and Roche/Genentech. Dr. Jacobson's presentation will include off-label discussion of anti-HCV drugs and growth factors.

David R. Nelson, MD, has received grant/research support from Abbott Laboratories, Bayer/Onyx, Biotech, Bristol-Myers Squibb, Genentech, Inc, Gilead Sciences, Inc, Merck & Co, Inc, Pharmasset Pharmaceuticals Inc, Tibotec/Jul, and Vertex Pharmaceuticals Incorporated; and is a consultant for Bayer/Onyx, Biotech, Bristol-Myers Squibb, Genentech, Inc, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, Pharmasset Pharmaceuticals Inc, and Vertex Pharmaceuticals Incorporated. Dr. Nelson's presentation will include off-label discussion of anti-HCV drugs.

Robert G. Gish, MD, has received grant/research support from Bayer/Onyx, Bristol-Myers Squibb, Genentech, Inc, Gilead Sciences, Inc, Pharmasset Pharmaceuticals Inc, Roche/Genentech, and ZymoGenetics Inc; is a consultant for Abbott Laboratories, Anadys Pharmaceuticals, Inc, Astellas/OSI, Bayer AG, Bristol-Myers Squibb, DURECT Corporation, Gilead Sciences, Inc, GlaxoSmithKline, Globelmmune, Inc, HepaHope, Inc, Human Genome Sciences, Merck & Co, Inc, Metabasis Therapeutics, Pharmasset Pharmaceuticals Inc, Roche/Genentech, Inc, Schering-Plough Corporation, Three Rivers Pharmaceuticals, Vital Therapies, and ZymoGenetics, Inc; is on the speakers bureau of Bayer Corporation, Bristol-Myers Squibb, F. Hoffmann-La Roche, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, Schering-Plough, Onyx Pharmaceuticals, Inc, Saliq Pharmaceuticals, Inc, ScioncePharmaceuticals, and Three Rivers Pharmaceuticals; and is a major stock shareholder and on the Board of Directors of HepaHope, Inc. Dr. Gish's presentation will include off-label discussion of anti-HCV drugs.

Mark S. Sulkowski, MD, has received grant/research support from and is a consultant for Abbott Laboratories, Anadys Pharmaceuticals, Inc, Astellas/OSI, Bayer AG, Bristol-Myers Squibb, Genentech, Inc, Janssen, Merck & Co, Inc, Pharmasset Pharmaceuticals Inc, Roche, and Vertex Pharmaceuticals Incorporated. Dr. Sulkowski's presentation will include no off-label discussion. Peer reviewer has disclosed no significant relationships.

Nancy J. Nordenson, MT (ASCP), MFA, medical writer, has disclosed no significant relationships. Projects In Knowledge staff members have disclosed no significant relationships. Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process. The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge. This CME/CE activity is provided solely as an educational service. Specific patient care decisions are the responsibility of the clinician caring for the patient. There is no fee for this activity. Presented for attendees of the 62nd AASLD Annual Meeting (The Liver Meeting®). This event/function is sponsored by Projects In Knowledge and supported by Vertex Pharmaceuticals Incorporated. This is not an official function/event of the American Association for the Study of Liver Diseases.

Supported through a medical education grant from Vertex Pharmaceuticals Incorporated.

Projects In Knowledge is a registered trademark of Projects In Knowledge, Inc.
Implementing New Models of Care with DAA Therapy

This year, 2011, has seen the approval of two new therapies—boceprevir triple therapy and telaprevir triple therapy—for the treatment of chronic hepatitis C virus (HCV) genotype-1 infection, and the publication of five phase III trials of those therapies. Boceprevir and telaprevir, each in combination with peginterferon alfa plus ribavirin, offer significantly improved sustained virologic response rates for genotype-1 patients: approximately 70% to 75% for treatment-naive patients, 70% to 85% for relapsers, 40% to 60% for partial responders, and 30% for null responders.

Clinicians who treat hepatitis C greeted the May 2011 approvals of boceprevir and telaprevir triple therapy with excitement, yet also recognized the simultaneous challenge. We can now offer our genotype-1 infected patients new treatment options with dramatically improved response rates and shorter durations of therapy for many. The challenge is to apply the myriad of published data to treatment decisions regarding our unique and individual patients and to integrate new and complex protocols recommended in the FDA-approved product labeling and informed by clinical judgment into our clinical practice.

Even with the tremendous strides forward that this year has witnessed, research continues. Ongoing analyses of the phase III boceprevir and telaprevir triple therapy trials are further refining the data to identify the impact of various host and viral factors on response. New trials of these therapies are assessing their role in different populations, such as HIV/HCV-coinfected individuals. Novel therapies, such as nucleoside inhibitors, NS5A inhibitors, and cyclophilin inhibitors, are currently being studied in early clinical trials to determine whether interferon-free therapies may be possible in the future. These and other trials now reporting data and those still on the horizon suggest that the evolution of anti-HCV therapies away from conventional peginterferon/ribavirin combination therapy will continue to be exciting. The shift to boceprevir or telaprevir triple therapy as the new standard of care marks a first and important step in that evolution.
Co-Chair

Ira M. Jacobson, MD
Vincent Astor Professor of Medicine
Chief, Division of Gastroenterology and Hepatology
Medical Director of the Center for the Study of Hepatitis C
Weill Medical College of Cornell University
New York, New York

Ira M. Jacobson, MD, is chief of the Division of Gastroenterology and Hepatology and Vincent Astor Professor of Medicine at Weill Medical College of Cornell University in New York City, and attending physician at New York-Presbyterian Hospital. He is also medical director of the Center for the Study of Hepatitis C at Weill Cornell and Rockefeller University. After receiving his BS summa cum laude from Yale University in New Haven, Connecticut, and his MD from the Columbia University College of Physicians and Surgeons in New York City, Dr. Jacobson completed an internship and residency in internal medicine at the University of California, San Francisco. He completed a fellowship in gastroenterology at Massachusetts General Hospital and Harvard Medical School. He is board certified in internal medicine and gastroenterology.

In addition to maintaining an active practice with a focus on patients with liver disease, Dr. Jacobson has been an investigator in many trials on antiviral therapy for hepatitis B and C, including most of the pivotal trials on interferon-based therapy since the 1980s, and was the principal investigator of the WIN-R trial, the largest trial performed to date on anti-HCV therapy. At Weill Cornell Medical College, he directs a highly diversified clinical trials program dedicated to novel therapies for hepatitis B and C.

Dr. Jacobson has authored more than 200 papers, chapters, and abstracts, and his papers have appeared in *New England Journal of Medicine*, *Annals of Internal Medicine*, *Hepatology*, *Journal of Hepatology*, *American Journal of Gastroenterology*, *Journal of Viral Hepatitis*, and *Clinical Gastroenterology and Hepatology*, among other journals. He has edited two books, *ERCP: Diagnostic and Therapeutic Applications* and *ERCP and Its Applications*. In addition, he edited a volume on hepatitis B for *Clinics in Liver Disease*, which appeared in 2007. He is a recently named associate editor of *Journal of Hepatology*, and is on the editorial boards of *Alimentary Pharmacology and Therapeutics* and *Digestive Diseases and Sciences*, in addition to being a reviewer for numerous journals. Dr. Jacobson is a Fellow of the American College of Physicians, the American Gastroenterological Association, and the American College of Gastroenterology, and a member of the American Association for the Study of Liver Diseases, the American Society for Gastrointestinal Endoscopy, and the European Association for the Study of the Liver. He is a past president of the New York Society for Gastrointestinal Endoscopy and the New York Gastroenterological Association. In addition, he has served on both the Gastroenterology Board and the Transplant Hepatology Board of the American Board of Internal Medicine.

Co-Chair

David R. Nelson, MD
Professor of Medicine
Associate Dean for Clinical Research
University of Florida College of Medicine
Gainesville, Florida

David R. Nelson, MD, is professor of medicine and associate dean for clinical research at the University of Florida, where he also serves as the director of the Clinical and Translational Science Institute. He completed a residency in internal medicine at the University of Massachusetts, and obtained fellowship training in gastroenterology and hepatology at the University of Florida.

Dr. Nelson's area of clinical expertise is hepatology with an emphasis on the management of viral hepatitis and liver cancer. He also has strong basic research interests, focusing primarily on the immunopathogenesis and treatment of chronic hepatitis C and hepatocellular carcinoma. He currently oversees more than 15 active clinical trials and has a 20-year track record of funding from the National Institutes of Health. Dr. Nelson serves as principal investigator on both basic science and translational research grants, along with mentoring/training grants in gastroenterology and hepatobiliary diseases. Dr. Nelson's record of academic achievement includes more than $20 million in research funding and more than 250 publications in journals such as *Gastroenterology*, *Hepatology*, *New England Journal of Medicine*, *Journal of Hepatology*, and *Liver Transplantation*. He currently is completing his term as associate editor for *Hepatology*. 
Robert G. Gish, MD, began his medical training in 1974 when he was enrolled into the Pharmacy School at the University of Kansas. Dr. Gish transferred to the University of Kansas Medical School in 1977 and completed his medical degree in 1980. Dr. Gish went on to complete a 3-year residency in internal medicine at the University of California San Diego, and a 4-year fellowship in gastroenterology and hepatology at the University of California Los Angeles, during which time he was awarded the NIH Physician Scientist Award to study calcium signaling in liver cells.

After completing his training, Dr. Gish moved to San Francisco and took a position at the California Pacific Medical Center (CPMC), formerly known as Pacific Presbyterian Hospital. He became the co-medical director of the Liver Transplant Program in 1988 and then the medical director of the Liver Transplant Program in 1994. In that role he developed an outreach program with 14 clinics that eventually served more than 35,000 patients in the Northern California and Nevada regions, and made the CPMC a leading liver transplant center in the United States.

Dr. Gish has had and continues to have an active research program in viral hepatitis, liver transplantation, liver cancer, bioartificial liver, and public policy, especially related to liver cancer, liver transplantation, and viral hepatitis. Although his primary research focus is clinical research, he frequently collaborates with basic scientists in his research activities. He has published more than 500 original articles, review articles, abstracts, and book chapters, and more than 100 peer-reviewed publications. Dr. Gish is also actively involved in numerous professional societies, including the American Association for the Study of Liver Diseases and the American Society of Transplant Physicians. He is a Fellow of the American College of Physicians and a long-term member of the American Association for the Study of Liver Diseases. Dr. Gish has served on the editorial boards of the American Journal of Gastroenterology, Journal of Hepatology, Digestive Diseases and Sciences, Gastroenterology, Hepatology, Liver Transplantation and Surgery, and Journal of Viral Hepatitis.

In December 2010, Dr. Gish moved to San Diego to join the faculty of the University of California San Diego as a clinical professor of medicine, section chief of hepatology, and director of the Center for Hepatobiliary Disease and Abdominal Transplantation (C.H.A.T.). Activities in HBV Free San Francisco and San Diego have led to the screening of more than 4000 people for viral hepatitis. Dr. Gish has had a major interest in Vietnam and has helped co-author a public health policy for liver health in that country and is assisting with healthcare policy in the Philippines and Armenia.

Mark S. Sulkowski, MD, is an associate professor of medicine and serves as the medical director of the Viral Hepatitis Center in the Divisions of Infectious Diseases and Gastroenterology/Hepatology at the Johns Hopkins University School of Medicine in Baltimore, Maryland. He received his medical degree from Temple University School of Medicine, Philadelphia, Pennsylvania (1992), and completed his Fellowship in infectious diseases (1998) at the Johns Hopkins University School of Medicine, in Baltimore, Maryland.

Dr. Sulkowski has been the principal investigator for numerous clinical trials related to the management of viral hepatitis, including novel agents. He is the coinvestigator for adult patients at the Johns Hopkins site of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Hepatitis B Clinical Research Network.

Dr. Sulkowski is a member of numerous professional societies, including the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and Infectious Diseases Society of America. He is widely published with works in Annals of Internal Medicine, New England Journal of Medicine, Journal of the American Medical Association, Journal of Infectious Diseases, and Hepatology. As an invited lecturer, he has presented discussions of the management of viral hepatitis at numerous, major national and international medical meetings.
DAAs: A New Standard of Care in the Treatment of HCV

Mark S. Sulkowski, MD

Treatment regimens utilizing new direct-acting antivirals (DAAs)—boceprevir and telaprevir—in combination with peginterferon alfa-2a or -2b and ribavirin dosed according to body weight represent a new standard of care for adults with genotype-1 chronic hepatitis C infection. The regimens, as approved by the FDA and described in product labeling, are based on data that emerged from phase II and III trials.

Treatment-Naive Individuals

For treatment-naive individuals, the duration of therapy is determined by assessment of the HCV RNA level at specific time points, which vary between the two HCV protease inhibitors (ie, “response-guided therapy”).

For the boceprevir-based regimen, treatment-naive individuals should be treated with peginterferon plus ribavirin for 4 weeks (“lead-in”), after which boceprevir 800 mg by mouth thrice daily (every 7–9 hours) is added for 24 weeks’ duration. For most patients, the duration of total therapy is determined by the achievement of a rapid virologic response defined as HCV RNA suppression to below detection by treatment week 8. Patients with suppression by treatment week 8 may be treated for 28 weeks, whereas those with detectable HCV RNA at treatment week 8 and suppression prior to treatment week 24 should be treated for 48 weeks, of which the final 12 weeks include only peginterferon plus ribavirin. Patients with compensated cirrhosis or poor interferon response during the lead-in phase should be treated for 48 weeks (4 weeks of peginterferon plus ribavirin followed by 44 weeks of boceprevir triple therapy).

For the telaprevir-based regimen, treatment-naive individuals should be treated with peginterferon plus ribavirin plus telaprevir 750 mg by mouth thrice daily (every 7–9 hours) for 12 weeks, after which telaprevir should be discontinued and peginterferon plus ribavirin continued for an additional 12 or 36 weeks. For most patients, the duration of total therapy is determined by the achievement of a rapid virologic response defined as HCV RNA suppression to below detection by treatment week 4. Patients with HCV RNA suppression by treatment week 4 may be treated for 24 weeks, of which the final 12 weeks include only peginterferon plus ribavirin. Patients with detectable HCV RNA at treatment week 4 or at week 12 who achieve HCV RNA suppression to undetectable prior to treatment week 24 (“late” responders) should be treated for 48 weeks, of which the final 36 weeks include only peginterferon plus ribavirin.

Treatment-Experienced Individuals

The regimens for treatment-experienced individuals are similar to those for treatment-naive individuals, but the duration of therapy is determined by time to an undetectable HCV RNA and/or by the prior treatment response to peginterferon plus ribavirin.

For boceprevir-based therapy, patients with prior viral relapse and partial response should be treated with response-guided therapy based on the treatment week 8 HCV RNA level (undetectable or detectable). Patients would receive boceprevir triple therapy ending at week 36 but peginterferon/ribavirin continuing through week 48 if detectable. Treatment-experienced patients with cirrhosis or prior null response should be treated for 48 weeks (4 weeks of peginterferon plus ribavirin followed by 44 weeks of boceprevir triple therapy).

For telaprevir-based therapy, patients with prior virologic relapse may be treated with the response-guided therapy paradigm used for treatment-naive patients. In contrast, those with prior partial and null response should be treated for 48 weeks (12 weeks triple therapy followed by 36 weeks of peginterferon plus ribavirin).

Futility (Stopping) Rules

For both regimens, stopping rules for insufficient virologic response should be applied to prevent further selection of resistant variants as well as adverse events and cost associated with futile therapy. For boceprevir-based therapy, all treatment should be discontinued in patients with HCV RNA >100 IU/mL at treatment week 12 or detectable at treatment week 24. For telaprevir-based therapy, all treatment should be discontinued in patients with HCV RNA >1000 IU/mL at treatment week 4 or 12, as well as those with detectable HCV RNA at treatment week 24.

Equipped with a solid understanding of response-guided therapy, dosing and administration instructions, treatment durations, stopping rules, and adverse effect management strategies, clinicians have two highly effective new anti-HCV treatment regimens to offer genotype-1 infected patients.

Suggested Readings


**DAAs: A New Standard of Care in the Treatment of HCV**

Mark S. Sulkowski, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

---

**Overview**

- **Treatment-Naive Data and Regimens**
- **Treatment-Experienced Data and Regimens**
- **Futility Rules**
- **Adverse Effects**

---

**2011—Standard of Care**

- **Genotype 1**
  - Peginterferon (PEG IFN) alfa plus ribavirin (RBV) weight-based PO BID plus
  - Boceprevir PO TID
  - Telaprevir PO TID
  - Variable duration based on regimen and viral kinetics (response-guided therapy)

- **Genotypes 2 and 3**
  - PEG IFN alfa plus RBV 400 mg PO BID
  - 24 weeks

- **Genotype 4**
  - PEG IFN alfa plus RBV weight-based PO BID
  - 48 weeks

---

**Boceprevir and Telaprevir—Indications and Usage**

- Chronic HCV genotype-1 infection
- In combination with PEG IFN/RBV
- Adults with compensated liver disease, including cirrhosis
  - Treatment-naive
  - Failed previous IFN-based therapy
- **Must not be used as monotherapy**

---

**Boceprevir and Telaprevir—Contraindications and Specific Populations**

- All contraindications to PEG IFN/RBV apply
- Drug-drug interactions with drugs that:
  - Are highly dependent on CYP3A for clearance
  - Strongly induce CYP3A
- Safety and efficacy not established
  - Organ transplantation
  - End-stage liver disease
  - HIV or HBV coinfection
  - Pediatrics

---

**Treatment-Naive Patients—Treatment Regimens**

<table>
<thead>
<tr>
<th>Protease Inhibitor (+ PEG IFN/RBV)</th>
<th>Lead-In</th>
<th>RGT</th>
<th>Total Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir without cirrhosis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>28 or 48 weeks</td>
</tr>
<tr>
<td>Boceprevir with cirrhosis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Telaprevir&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No</td>
<td>Yes&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24 or 48 weeks&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Eligibility for RGT with boceprevir triple therapy is determined by HCV RNA response at treatment week 8.
<sup>2</sup> Eligibility for RGT with telaprevir triple therapy is determined by HCV RNA response at treatment week 4.
<sup>3</sup> Cirrhosis with undetectable HCV RNA at treatment weeks 4 and 12 may benefit from 48 weeks treatment.

Abbreviation: RGT, response-guided therapy.

Paradigm Shift in HCV Standard of Care Treatment: DAAs

Slides produced as of October 21, 2011 (may not reflect final presentation)

**Slide 7**

**Boceprevir—RGT in Treatment-Naive Patients with No Cirrhosis**

PEG IFN/RBV for 4 weeks, followed by boceprevir 800 mg TID + PEG IFN/RBV

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TW8</td>
<td>Undetectable</td>
</tr>
<tr>
<td>TW24</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Detectable</td>
<td>Administer all 3 drugs through TW28</td>
</tr>
<tr>
<td>Detectable</td>
<td>Administer all 3 drugs through TW36, then administer PEG IFN/RBV through TW48</td>
</tr>
</tbody>
</table>

Abbreviations: RGT, response-guided therapy; TW, treatment week.

**Slide 8**

**SPRINT-2—Overall SVR and Relapse Rate by Cohort and Treatment Arm**

![Graph showing SVR and Relapse rates](image)

Abbreviations: RGT, response-guided therapy; PR4/BPR44, sustained virologic response.

**Slide 9**

**SPRINT-2—SVR Rates Based on HCV RNA at Week 8**

![Graph showing SVR rates](image)

**Slide 10**

**Boceprevir—Treatment-Naive Non-RGT Regimens**

**Poor Interferon Responsiveness**

Consideration should be given to extending treatment for treatment-naive patients with poor interferon responsiveness (<1-log drop<sup>2</sup>) at week 4:
4 weeks of P/R followed by 44 weeks of B + P/R

**Compensated Cirrhosis**

4 weeks of P/R followed by 44 weeks of B + P/R


**Slide 11**

**SPRINT-2—SVR Based on Week 4 Lead-In Response**

![Graph showing SVR based on week 4 lead-in response](image)

**Slide 12**

**SPRINT-2—SVR in Advanced Fibrosis/Cirrhosis**

![Graph showing SVR in advanced fibrosis/cirrhosis](image)

1. Undetectable or ≥2-log decline.
2. <1-log decline.

DAAs: A New Standard of Care in the Treatment of HCV

Mark S. Sulkowski, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

Slide 13: Telaprevir—RGT in Treatment-Naive Patients

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable at TW4 and TW12</td>
<td>Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW24</td>
</tr>
<tr>
<td>Detectable (≤1000 IU/mL) at TW4 and/or TW12</td>
<td>Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW48</td>
</tr>
</tbody>
</table>

Slide 14: ADVANCE—Overall RVR, eRVR, and SVR Rates

- **RVR (Wk 4)**
  - Patients eligible to receive 24 weeks of total treatment
  - P < 0.001
- **eRVR (Wk 4 and 12)**
  - P < 0.001
- **SVR (Wk 24 post-EDT)**
  - T12/PR24
  - T8/PR24
  - PR48

Slide 15: ADVANCE—SVR in Patients with eRVR vs No eRVR

- **SVR (%)**
  - eRVR: 89, 83, 97
  - No eRVR: 54, 50, 39

Slide 16: ILLUMINATE—SVR and Relapse Rates

- **SVR**
  - Overall (ITT): 72, 92, 88
  - T12/PR24: 8, 6, 3
  - T12/PR48: 8, 6, 3
- **Relapse**
  - Overall (ITT): 32, 65, 145
  - T12/PR24: 32, 65, 145
  - T12/PR48: 32, 65, 145

Slide 17: Telaprevir—Treatment-Naive Non-RGT Regimens

- **Compensated Cirrhosis**
- Treatment-naive patients with cirrhosis and undetectable HCV RNA at weeks 4 and 12 may benefit from continuing peginterferon and ribavirin through week 48

Slide 18: ADVANCE—Impact of Host and Viral Factors

- **Results from the T12/PR24 Group**
- Viral Load
- Genotype
- Race
- Fibrosis

* *<800,000 IU/mL, vs ≤800,000 IU/mL*

DAAs: A New Standard of Care in the Treatment of HCV
Mark S. Sulkowski, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

Slide 25

Slide 26

Slide 27

Slide 28

Overview
Treatment-Naive Data and Regimens
Treatment-Experienced Data and Regimens
Futility Rules
Adverse Effects

Boceprevir—Futility (Stopping) Rules

STO rules
STOP ALL DRUGS

Week 12 HCV RNA ≥100 IU/mL
OR
Week 24 HCV RNA confirmed detectable
Decreased drug exposure and cost

Paradigm Shift in HCV Standard of Care Treatment: DAAs

Slides produced as of October 21, 2011 (may not reflect final presentation)

Slide 31: Telaprevir—Futility (Stopping) Rules

STOP ALL DRUGS

Week 4 and 12 HCV RNA >1000 IU/mL
OR
Week 24 HCV RNA confirmed detectable
Decreased drug exposure and cost


Slide 32: Overview

Treatment-Naive Data and Regimens
Treatment-Experienced Data and Regimens
Futility Rules
Adverse Effects

Slide 33: Boceprevir Triple Therapy—Adverse Effects

Pooled Data from Treatment-Naive Population (SPRINT-1, SPRINT-2)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Boceprevir + PEG IFN/RBV (n = 1225)</th>
<th>PEG IFN/ RBV (n = 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia*</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*Anemia was managed with erythropoiesis-stimulating agents, with or without RBV dose reduction (boceprevir + PEG IFN/RBV 43%, PEG IFN/RBV 24%)


Slide 34: Boceprevir—SVR According to ESA Use and Ribavirin Dose Reduction

Treatment-Naive (SPRINT-2) Boceprevir Arms Only

Boceprevir—Rash Summary from Pooled Safety Database

- In most subjects, rash was mild to moderate
  - Severe rash in 4%
- Occurred early, usually first 4 weeks but can occur at any time during telaprevir exposure
- Led to discontinuation of telaprevir in 6%
- Serious skin reaction in <1%, including Stevens-Johnson syndrome or DRESS
- Treat with oral antihistamines and/or topical corticosteroids
  - No data available on effectiveness
  - Systemic steroids are not recommended

Abbildung: DRESS, Drug Rash with Eosinophilia and Systemic Symptoms
DAAs: A New Standard of Care in the Treatment of HCV
Mark S. Sulkowski, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

**ILLUMINATE and ADVANCE—SVR Rates According to RBV Dose Reduction**

![Graph showing SVR rates according to RBV dose reduction.]

Slide 37

**Conclusion**

- New standard of care for HCV genotype-1 infection
  - Higher SVR rates observed across all patient groups, including “difficult to treat” with peginterferon/ribavirin
- Response-guided therapy allows for shorter duration of therapy for patients with rapid virologic response
- Regimen complexity related to TID dosing and additional adverse effects
  - Patient education and adherence is critical

Slide 38
New and Evolving Perspectives: What the Data Tell Us

Robert G. Gish, MD

Since the publication of the phase III registration trials for boceprevir (SPRINT-2 and RESPOND-2) and telaprevir (ADVANCE and REALIZE), important additional information has surfaced from post-hoc analysis of the phase III data.

Boceprevir: SVR in Poor Interferon Responders

With boceprevir, the incidence of poor interferon response (<1-log drop HCV RNA at week 4) was 20% to 25% in treatment-naive patients (SPRINT-2) and 15% to 28% in treatment-experienced patients (RESPOND-2). In poor interferon responders, a sustained virologic response (SVR) was achieved in 28% to 34% of those on boceprevir triple therapy compared with 0% to 4% in those on peginterferon/ribavirin only. In poor interferon responders, the predictive value of HCV genotype 1a and 1b subtypes was variable, depending on whether patients were treatment-naive or -experienced. The level of advanced fibrosis (F3–4 versus F0–2) was strongly associated with nonresponse. In addition, a <3-log drop in HCV RNA at week 8 had a 100% negative predictive value.

Boceprevir: Stopping Rules

The current boceprevir stopping rules for both treatment-naive and -experienced patients are HCV RNA ≥100 IU/mL at week 12 and detectable HCV RNA at week 24. An analysis of SPRINT-2 and RESPOND-2 data shows that the stopping rules are robust overall with few, if any, patients who could have achieved SVR subjected to discontinuation of therapy by application of these stopping rules. Specifically, the data show that for treatment-naive patients, an SVR occurred with significant frequency with HCV RNA that is detectable but <100 IU/mL at week 12, while no SVR is associated with HCV RNA ≥100 IU/mL at week 12. For treatment-experienced patients, some patients with HCV RNA that is detectable but ≥25 IU/mL at week 12 will achieve SVR. Patients who are quantitatively negative but qualitatively positive have a possible chance of SVR. Larger studies would be needed, however, to define the threshold for continued treatment.

Boceprevir: SVR in Prior Null Responders

In the PROVIDE rollover prospective study of null responders from the control arms of SPRINT-2 and RESPOND-2, 48% of prior null responders achieved undetectable HCV RNA by week 12, with 41% undetectable at end of treatment. Thus, a substantial SVR rate with boceprevir triple therapy may be achievable in this difficult-to-treat population.

Boceprevir: Adverse Effects with Concomitant Medications

Using data from phase II and III trials, an analysis was done of adverse events in patients who received both boceprevir and concomitant CYP3A4/5 substrates, inhibitors, and/or inducers, including antidepressants, azole antifungals, macrolide antibiotics, methadone, and oral contraceptives. Overall, adverse effects related to concomitant medication use during boceprevir triple therapy appear to be modest and manageable.

Telaprevir: SVR Predictors in Treatment-Experienced Patients

The REALIZE study assessed the impact of baseline host and viral factors in patients with prior treatment failure. The strongest predictor of SVR was extended rapid virologic response (eRVR). Both prior on-treatment virologic response and baseline higher low-density lipoproteins (LDL) were significant predictors overall in patients receiving telaprevir or control. The impact of a higher fibrosis stage was greater in patients receiving telaprevir or control. The impact of a higher fibrosis stage was greater in patients receiving telaprevir or control. The impact of a higher fibrosis stage was greater in patients receiving telaprevir or control.

Telaprevir: Impact of Anemia and Ribavirin Dose Reduction in Treatment-Experienced Patients

Anemia with ribavirin dose reduction does not appear to be a significant predictor of lower SVR with telaprevir triple therapy in previously treated patients. Factors significantly associated with anemia on telaprevir triple therapy include: older age, lower body mass index, and lower baseline hemoglobin level (P < .0001); more advanced fibrosis (P = .0369); and genotype 1b versus 1a (P = .0119).

Telaprevir: Subanalysis of Treatment-Experienced Patients with Cirrhosis

In patients with cirrhosis, the univariate predictors of SVR with telaprevir triple therapy were high baseline LDL, high baseline alanine aminotransferase or aspartate aminotransferase, and prior response to peginterferon/ribavirin. In patients with cirrhosis failing triple therapy, the presence or level of telaprevir resistance was not associated with fibrosis stage. Overall, the SVR of 49% in patients with cirrhosis is favorable and encourages us to consider telaprevir triple therapy in compensated cirrhotic patients.

Telaprevir: HCV/HIV Coinfection

Interim 24-week results from an ongoing two-part trial of HCV/HIV-coinfected patients show higher on-treatment responses in patients given telaprevir triple therapy compared with those on peginterferon/ribavirin alone, with undetectable HCV RNA achieved at week 24 in 74% of those given triple therapy compared with 55% of those given peginterferon/ribavirin only. Adverse effects that were at least 10% more frequent in the triple-therapy group compared with the peginterferon/ribavirin group included abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, and pruritis. Although bilirubin adverse events were higher in patients receiving telaprevir triple therapy combined with an atazanavir/ritonavir-based regimen, the safety and tolerability was comparable to that previously seen in HCV-monoinfected patients.
New and Evolving Perspectives: What the Data Tell Us

Robert G. Gish, MD

Suggested Readings


New and Evolving Perspectives: What the Data Tell Us

Slides produced as of October 21, 2011 (may not reflect final presentation)

AASLD 2011

- What do we know now that we didn't know when the phase III registration trials were published?
  - March 2011: phase III boceprevir trials (SPRINT-2 and RESPOND-2) published
  - June 2011: phase III telaprevir trials (ADVANCE and REALIZE) published
- More than 40 abstracts and posters on boceprevir and telaprevir scheduled at AASLD 2011

Boceprevir

Telaprevir
Paradigm Shift in HCV Standard of Care Treatment: DAAs

Boceprevir—SVR Predictors in Poor IFN Responders

- Post-hoc analysis of phase III data
  - Incidence of poor interferon (IFN) response (<1-log drop HCV RNA at week 4)
    - SPRINT-2 (treatment-naive) 20%–25%
    - RESPOND-2 (treatment-experienced) 15%–28%
  - Sustained virologic response (SVR) in poor IFN responders
    - Boceprevir triple therapy 28%–34%
    - PR control 0%–4%
- Baseline characteristics and treatment week 8 response were evaluated in poor IFN responders who achieved SVR vs those patients who did not achieve SVR

Boceprevir—Impact of Genotype and Fibrosis Level on SVR in Poor IFN Responders

- % of Poor IFN Responders* by Genotype and Fibrosis

Boceprevir—Predictive Value of Genotype and Fibrosis Level in Poor IFN Responders

Conclusions
- Predictive value of HCV genotype-1a and -1b subtypes was variable, depending on whether patients were treatment-naive or -experienced
- Fibrosis level (F3–4 vs F0–2) was strongly associated with nonresponse
- HCV RNA decline at treatment week 8 also predictive in this patient group
  - <3-log drop HCV RNA at week 8 had a 100% negative predictive value

Boceprevir—Stopping Rule Analysis of SPRINT-2 AND RESPOND-2

- Treatment-naive patients
  - SVR: Associated with HCV RNA detectable <100 IU/mL at week 12
  - No SVR: Associated with HCV RNA ≥100 IU/mL at week 12
- Treatment-experienced patients
  - Some patients with HCV RNA detectable ≤25 IU/mL at week 12 achieve SVR
  - Current stopping rules for both patient groups from product information
    - HCV RNA ≥100 IU/mL at week 12 and detectable at week 24

Boceprevir—Characteristics of Considered Futility Rules

- Combined boceprevir arms
  
New and Evolving Perspectives: What the Data Tell Us
Robert G. Gish, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

Slide 9

SPRINT-2 and RESPOND-2—Stopping Rule Analysis
Conclusions
- Patients who are quantitatively negative but qualitatively positive have a possible chance of SVR
  - But larger studies are needed to define this threshold to continue treatment
- Overall, stopping rules are robust with few patients missed who could reach SVR


Slide 10

PROVIDE—Efficacy of Boceprevir in Null Responders
- Rollover prospective study of null responders from control arms of SPRINT-2 and RESPOND-2
  - Null response = <2-log HCV RNA drop at week 12 of PEG IFN/RBV alone
  - 46 patients enrolled
- Boceprevir + PEG IFN/RBV given for up to 44 weeks
  - Lead-in repeated if >2 weeks elapsed since previous treatment


Slide 11

PROVIDE—Prior Null Responders with Undetectable HCV RNA
Total Patients with Null Response in Control Arms of SPRINT-2 and RESPOND-2

<table>
<thead>
<tr>
<th>Weeks of Boceprevir Treatment</th>
<th>Undetectable HCV RNA %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>24</td>
</tr>
<tr>
<td>Week 12</td>
<td>48</td>
</tr>
<tr>
<td>Week 24</td>
<td>45</td>
</tr>
<tr>
<td>Week 44 (EDT)</td>
<td>41</td>
</tr>
</tbody>
</table>

Rate of undetectable HCV RNA at end of treatment is comparable to rate in poor IFN responders; relapse rate in this historical group was 19%.


Slide 12

PROVIDE—Efficacy of Boceprevir in Null Responders
Conclusion
Boceprevir triple therapy is predicted to have substantial SVR rates in this difficult-to-treat population


Slide 13

Concomitant Medication Use with Boceprevir
- Patients who received concomitant CYP3A4/5 substrates, inhibitors, and/or inducers in phase II and III trials were evaluated for adverse effects
- Boceprevir is metabolized by
  - Aldo-keto reductase – primary
  - CYP3A4/5
- Boceprevir strongly inhibits CYP3A4/5
  - May increase levels of coadministered drugs that are metabolized by CYP, most importantly 3A4/5


Slide 14

Adverse Effects in Patients Treated with Boceprevir and Concomitant Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants*</td>
<td>Adverse effects (AEs) similar to overall population</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Dysgeusia: boceprevir 43% vs control 37%</td>
</tr>
<tr>
<td></td>
<td>Paresthesia: boceprevir 13% vs control 4%</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Anemia: boceprevir 66% vs control 49%</td>
</tr>
<tr>
<td>Methadone</td>
<td>No dose reduction for psychiatric AEs or recurrence of intravenous drug use</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Anemia: boceprevir 67% vs control 48%</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux: boceprevir 11% vs control 6%</td>
</tr>
</tbody>
</table>

*Most commonly used concomitant medications of interest.
Paradigm Shift in HCV Standard of Care Treatment: DAAs

REALIZE—SVR Predictors with Telaprevir in Treatment-Experienced Patients

- Post-hoc analysis of patients with prior treatment failure
- Multiple logistic regression analyses to assess impact of baseline host and viral factors
- Data available for 578/662 randomized patients

Boceprevir

Telaprevir

REALIZE—Impact of Anemia and RBV Dose Reduction on SVR in Telaprevir Triple Therapy

- No erythropoiesis-stimulating agents allowed
- Data pooled from 2 telaprevir arms

REALIZE—Impact of RBV Dose Reduction on SVR

- Anemia with ribavirin dose reduction does not appear to be a significant predictor of lower SVR with telaprevir triple therapy in previously treated patients
- Factors significantly associated with anemia on telaprevir triple therapy include
  - Older age, lower body mass index, and lower baseline hemoglobin (P < .0001)
  - More advanced fibrosis (P = .0369)
  - Genotype 1b vs 1a (P = .0119)

REALIZE—Impact of Anemia on SVR

- No erythropoiesis-stimulating agents allowed
- Data pooled from 2 telaprevir arms

REALIZE—SVR Predictors with Telaprevir in Treatment-Experienced Patients

- Post-hoc analysis of patients with prior treatment failure
- Multiple logistic regression analyses to assess impact of baseline host and viral factors
- Data available for 578/662 randomized patients

Boceprevir

Telaprevir

REALIZE—Impact of Anemia and RBV Dose Reduction on SVR in Telaprevir Triple Therapy

- No erythropoiesis-stimulating agents allowed
- Data pooled from 2 telaprevir arms

REALIZE—Impact of RBV Dose Reduction on SVR

- Anemia with ribavirin dose reduction does not appear to be a significant predictor of lower SVR with telaprevir triple therapy in previously treated patients
- Factors significantly associated with anemia on telaprevir triple therapy include
  - Older age, lower body mass index, and lower baseline hemoglobin (P < .0001)
  - More advanced fibrosis (P = .0369)
  - Genotype 1b vs 1a (P = .0119)
New and Evolving Perspectives: What the Data Tell Us
Robert G. Gish, MD

Slides produced as of October 21, 2011 (may not reflect final presentation)

REALIZE—Subanalysis of Patients with Cirrhosis on Telaprevir Triple Therapy

Patient Demographics

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Prior Response n (%)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 143)</td>
<td>Null 51 (36)</td>
<td>104 (73)</td>
</tr>
<tr>
<td></td>
<td>Partial 29 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relapsers 63 (44)</td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 435)</td>
<td>113 (26)</td>
<td>294 (68)</td>
</tr>
<tr>
<td></td>
<td>79 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>243 (56)</td>
<td></td>
</tr>
</tbody>
</table>

- Mean age: Cirrhotics 54 years; noncirrhotics 50 years
- Mean log viral load: Cirrhotics 6.57; noncirrhotics 6.56

REALIZE—Efficacy in Patients with Cirrhosis

Univariate Predictors of SVR with Telaprevir Triple Therapy in Patients with Cirrhosis

- High baseline LDL
- High baseline ALT or AST
- Prior PR response
- In patients failing telaprevir triple therapy, the presence or level of telaprevir resistance was not associated with fibrosis stage.

Telaprevir Triple Therapy in HCV/HIV-Coinfected Patients Treatment-Naive for HCV

<table>
<thead>
<tr>
<th>Weeks</th>
<th>N = 60</th>
<th>T12/PR48</th>
<th>PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>T + P + R</td>
<td>P + R</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>T12/PR48</td>
<td>PR48</td>
<td>T + P + R</td>
</tr>
</tbody>
</table>

- 2-part trial
  - Part A: No concurrent antiretroviral therapy (ART)
  - Part B: Stable on efavirenz- or atazanavir/ritonavir-based regimen
- Telaprevir dose = 750 mg q8h; 1125 q8h with efavirenz
- Primary outcomes: Adverse effects and HCV RNA at wk 12

Telaprevir Triple Therapy in HCV/HIV Coinfection—24-Wk Interim Analysis

<table>
<thead>
<tr>
<th>Part/Regimen</th>
<th>n</th>
<th>Wk 12 Undetectable (%)</th>
<th>Wk 24 Undetectable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – No ART</td>
<td>13</td>
<td>86</td>
<td>33</td>
</tr>
<tr>
<td>B – EFV regimen</td>
<td>24</td>
<td>88</td>
<td>25</td>
</tr>
<tr>
<td>B – ATV/r regimen</td>
<td>23</td>
<td>73</td>
<td>38</td>
</tr>
</tbody>
</table>

- AEs ≥10% more frequent in T/PR vs PR include
  - Abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, and pruritis
  - Bilirubin AEs more frequent with ATV/r (27% vs 0%)

Conclusion—Boceprevir

- HCV RNA decline at week 8 and HCV fibrosis level predict response in poor IFN responders
  - Predictive value of genotype subtype was variable depending on whether patients were treatment-naive or -experienced
- Stopping rules for boceprevir are robust
- In response to boceprevir triple therapy, prior null responders appear to have favorable EOT rates and possibly SVR
- Adverse effects of concomitant medications during boceprevir triple therapy appear to be modest and manageable

Conclusion—Telaprevir

- eVRV remains the strongest predictor of success or failure with telaprevir triple therapy
- In HIV/HCV-coinfected patients, treatment with triple therapy results in improved response at week 12 and modest adverse effects and drug-drug interactions
- Anemia and ribavirin dose reduction do not appear to affect SVR rates with telaprevir triple therapy in treatment-experienced patients
- 49% SVR in treatment-experienced patients with compensated cirrhosis is favorable and encourages us to consider telaprevir triple therapy in this patient group
Putting DAAs into Practice: Case-Based Discussion with Patient Videos

Ira M. Jacobson, MD
Vincent Astor Professor of Medicine
Chief, Division of Gastroenterology and Hepatology
Medical Director of the Center for the Study of Hepatitis C
Weill Medical College of Cornell University
New York, New York

Case 1—Treatment-Naive Patient

Case 1—Mr. L
- 42-year-old black male supervisor
- HCV genotype-1a infection
  - Has risk factors dating back 20 years
- Presents with his spouse, 33-year-old professional
- Stage 2 fibrosis

Case 1—Discussion Point 1
Would you order an IL28B test? If so, what is your rationale?

Case 1—Discussion Point 2
This patient is started on boceprevir and has an extended rapid virologic response

Would you apply response-guided therapy (RGT)? Do the data satisfy you that RGT applies to blacks?

Case 2—Cirrhotic Relapser
**Case 2—Mr. C**
- 62-year-old white male, active executive who often travels for his job
- Cirrhotic
- Prior relapser to PEG IFN/RBV
  - 3 months after prior treatment ended, he was told his HCV RNA levels were back to baseline
  - Experienced anemia with prior treatment (9.8 g/dL)
- Patient had been following HCV research and made an appointment as soon as the new direct-acting antivirals (DAAs) were approved
- Started on telaprevir
  - Undetectable at 4 weeks
- Patient returned for appointment at 8 weeks

**Case 2—Discussion Point 1**
How long would you treat a cirrhotic HCV relapser who has a rapid virologic response?

**Case 2—Discussion Point 2**
The patient’s hemoglobin level at week 8 = 8.6 g/dL
In light of this patient’s hemoglobin level, rapid virologic response, and remaining 4 weeks of telaprevir therapy, how should his anemia be addressed?

**Case 3—Ms. H**
- 58-year-old Hispanic female high school teacher
- Presents at the start of the school year, on simvastatin
- Partial responder to prior PEG IFN/RBV therapy
  - Baseline HCV RNA 4.5 million IU/mL
  - Week 12: 18,000 IU/mL; week 24: 6500 IU/mL
  - Moderate pruritic rash; hemoglobin 10.1 g/dL
- Metavir 2 with rare focal bridges
- Started on PEG IFN/RBV for 4 weeks, then boceprevir added
  - HCV RNA 70 IU/mL at week 8
  - Hemoglobin drops from 13.2 g/dL to 8.8 g/dL at week 8
  - Develops mild rash and moderate depression
- Presents for 12-week visit

**Case 3—Discussion Point 1**
What would you tell this patient about the anticipated duration of therapy?
Case 3—Discussion Point 2

How would you address this patient's anemia and depression?

Case 4—Null Responder

Case 4—Mr. S

- 68-year-old white male, recently retired mechanic
  - Acquired infection likely with drug use at 18 years old, otherwise healthy
  - Worried about HCV disease
- Null response to prior PEG IFN/RBV
  - Tolerated prior treatment well
- Current liver biopsy – bridging fibrosis with architectural distortion and nodule formation: “stage 4”
- Albumin 3.6 g/dL, platelets 94,000 mm$^3$

Case 4—Discussion Point 1

What is this patient’s chance of SVR with PI-based therapy?

What would you advise this patient to do?

Case 4—Discussion Point 2

The decision is made to treat with telaprevir triple therapy

Would you use a lead-in regimen?
Conclusion: HCV—Present and Future

David R. Nelson, MD

Professor of Medicine
Associate Dean for Clinical Research
University of Florida College of Medicine
Gainesville, Florida

The New Standard of Care
SVR in Treatment-Naive HCV
Genotype-1 Infection

Boceprevir—Improved SVR for All Genotype-1 Patients
SPRINT-2 and RESPOND-2 Phase III Trials

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir triple therapy*</th>
<th>PEG IFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naive</td>
<td>67</td>
<td>52</td>
</tr>
<tr>
<td>Relapsers</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Partial Responders</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

*Based on RT-0 arm in SPRINT-2 and P144/PBR44 arm in RESPOND-2

Telaprevir—Improved SVR for All Genotype-1 Patients
ADVANCE and REALIZE Phase III Trials

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir triple therapy*</th>
<th>PEG IFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naive</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>Relapsers</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>Partial Responders</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

*Based on T12/J2R74 arm in ADVANCE and T12/J2R48 arm in REALIZE

Identifying Candidates for Triple Therapy

Factors to Consider in Treatment Decisions

Disease Features: Fibrosis, steatosis, coinfection (HBV, HIV)

Viral Factors: Genotype/subtype, resistance, viral load

Host Factors: Age, gender, race, obesity, comorbidities

Generic factors: IL28B and JTPA

Anti-HCV Treatment Decisions for Protease Inhibitors

PROs
- Protease inhibitors substantially increase chance of SVR across all genotype-1 patient groups
- Protease inhibitors shorten duration of therapy in many
- Successful treatment improves morbidity and mortality

CONs
- Suboptimal response rates in many populations
- Complicated regimens, challenging adverse events, and drug-drug interactions
- Risk of resistance if therapy fails: impact on future options?
**Antiviral Targets and Approaches for the Future**

- IFN
- Immuno-modulators
- Antiviral agents
- Therapeutic vaccines
- Host target

  **Entry**
  - IFN-α
  - IFN-α

  **Replication and assembly**
  - Cyclophilin inhibitors
  - NS5B Polymerase
  - NS3 Protease
  - NS5A Replication complex

Graphic courtesy of Dr. David R. Nelson.

**IFN-Free Regimens—AASLD 2011**

1. **BMS-790052 (NS5A) + BMS-650032 (PI)**
   - 24 weeks treatment in genotype-1b null responders
   - SVR12 = (9/10) 90%

2. **BI-201335 (PI) + BI-207127 (NNI) + RBV**
   - Up to 40 weeks treatment in naive, genotype-1a/1b patients
   - cEVR at week 12: PI + NNI + RBV = 76%; PI + NNI = 57%

*Abbreviations: NNI, non-nucleoside inhibitor; PI, protease inhibitor; RBV, ribavirin*

**IFN-Free Regimens—AASLD 2011**

- **Alisporivir (cyclophilin inhibitor)**
  - Alisporivir monotherapy + RBV in genotype-2 and -3 naive patients
  - 33% alisporivir mono and 48%–51% alisporivir + RBV on-treatment viral response (HCV <25 IU by week 6)

- **Miravirsen (antisense oligo targeting miR-122)**
  - Given sq weekly to genotype-1 naive patients
  - Week 10 decline in HCV RNA: mean 2.2 log


**Towards a Future of Personalized Medicine**

- PEG IFN + RBV + PI
- IL28B CC
- DAA Combination (N + PI + NS5A + CI)
- DAAs + RBV
- PEG IFN + DAAs
- PEG IFN + RBV + DAAs

*Abbreviations: CI, cyclophilin inhibitor; DAA, direct-acting antiviral; N, nucleoside inhibitor; PEG IFN, peginterferon; PI, protease inhibitor; RBV, ribavirin. Graphic courtesy of Dr. David R. Nelson.*
CONTRACT FOR MUTUAL RESPONSIBILITY IN CME/CE

PROJECTS IN KNOWLEDGE WILL PROVIDE:

1. A trusting learning environment free of commercial bias.
2. An activity that has been peer-reviewed, by an expert in the field who is not a member of the faculty, to ensure that the information presented is independent, objective, scientifically rigorous, fair, balanced, accurate, timely, relevant, and beneficial to patients.
3. An activity that is free of any conflicts of interest, as identified through the faculty disclosure process and resolved through our Trust In Knowledge peer review process.
4. Faculty that embrace and support our efforts.
5. Acknowledgment of off-label uses of pharmaceutical products discussed.
6. Content that will positively impact on your ability to manage your patients.
7. Ample opportunity for questions from the participants to add to the scientific rigor and real-life clinical appropriateness of information provided.
8. Access to a "Content Ombudsman" (via e-mail at ombudsman@projectsinknowledge.com) who will handle questions on enduring materials that are not answered by this activity.
9. A dynamic learning and implementation process that meets our rigorous obligations to multiple accreditation/regulatory bodies, and that shows that Projects In Knowledge will be forever evolving and striving to do the right thing.

CLINICIANS’ RESPONSIBILITIES:

1. Be an active participant in the activity.
2. Ask questions relevant to patient care concerns.
3. Commit yourself to the entire activity time frame, because it is only then that the total learning can be experienced, utilized, and measured.
4. Allow this activity to be only a part of your total learning experience.
5. Aid in developing future activities by being a strong participant. The evaluation form assists us in this process; please give it careful professional consideration when filling it out.
6. Return to your practice and mentor the learning experience with your colleagues. Projects In Knowledge will provide extra material for this effort.

Sincerely,
Robert S. Stern
President
Projects In Knowledge, Inc.