Understanding the Impact of HCV and Therapeutic Considerations for the Front-Line Provider

pmiCME Updates
March 10, 2012
George R. Brown Convention Center
Houston, Texas

Education Partner
Session 1: Understanding the Impact of HCV and Therapeutic Considerations for the Front-Line Provider

Learning Objectives
1. Identify and screen patients at risk for hepatitis C virus (HCV) infection and counsel patients accordingly.
2. Illustrate knowledge gained on new triple-combination therapy combinations that include DAAs and collaborate with HCV specialists in the treatment of patients with chronic hepatitis C.
3. Monitor HCV patients on direct-acting antiviral (DAA) therapy for potential adverse events, drug interactions, and issues relating to drug adherence.

Faculty
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Medical Director, Liver Transplantation
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Dr Paul Kwo is currently a professor of medicine and medical director of transplantation at the Indiana University School of Medicine. He joined the faculty in 1995 after receiving gastroenterology and hepatology training at the Mayo Clinic in Rochester, Minnesota. He is currently board certified in internal medicine, gastroenterology, and liver transplant Certificate of Added Qualification (CAQ).

Dr Kwo has distinguished himself in the field of chronic hepatitis C and oversees a large practice devoted to current and novel therapies for the treatment of hepatitis C. He has won multiple awards at the university, local, and national levels. Dr Kwo’s clinical interests include hepatitis B and C, liver transplantation, end-stage liver disease (cirrhosis), liver cancer, and autoimmune liver disease. He is active in clinical research involving therapy for chronic hepatitis B and C, post-transplant viral hepatitis, and liver transplant outcomes.

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Dr Stephen Harrison is a clinical associate professor of medicine in the Division of Gastroenterology at the University of Texas Health Science Center in San Antonio. A lieutenant colonel in the United States Army, he also serves as the chief of hepatology and program director of the Gastrointestinal Fellowship Program at Brooke Army Medical Center, Fort Sam Houston, Texas. He received his medical degree from the University of Mississippi School of Medicine in Jackson. Dr Harrison completed his internship and residency, serving as chief resident, in internal medicine at Brooke Army Medical Center, where he also completed a fellowship in gastroenterology. He pursued an additional fellowship in hepatology at St. Louis University in Missouri.

His numerous honors include the Order of Military Medical Merit, the Research Excellence in GI and Liver (REGAL) Award, and the William Beaumont Clinical Research Award. Dr Harrison has served in various leadership capacities and continues to be a member of the American Association for Study of Liver Diseases (AASLD), the American College of Physicians (ACP), and the American College of Gastroenterology (ACG).

Dr. Harrison has acted as principal investigator of numerous research projects, and lectured extensively on the topics of steatosis and HCV, non-alcoholic fatty liver disease, and hepatitis C.

In addition, Dr Harrison has authored, or contributed to, over 100 publications. A reviewer for 13 journals, he serves on the editorial boards of Gut and Clinical Gastroenterology and Hepatology and was recently selected to a 5-year term as an associate editor of Hepatology.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Dr Kwo reports receiving research support from Vertex, Merck, Bristol-Myers Squibb, Gilead, and Abbott. He serves on the advisory boards of Vertex, Bristol-Myers Squibb, Gilead, Novartis, Johnson & Johnson, Boehringer-Ingelheim, Inhibitex, and Merck; and is a consultant for Bristol-Myers Squibb, Merck, Gilead, Vertex, and Roche.

Dr Harrison serves on the advisory boards of Merck and Vertex, and has served as a speaker for Merck and Bristol-Myers Squibb.

Education Partner Financial Disclosure Statement
The content collaborators at Consensus Medical Communications report the following:
Bill Doutre, PharmD, has no financial relationships to disclose.

Suggested Reading List


**Drug List**

**Generic Name**
- erythropoietin
- boceprevir
- pegylated interferon
- ribavirin
- telaprevir

**Brand Name**
- Procrit
- Victrelis
- Pegasys, Pegintron
- CoPegus, Rebetol
- Incivek

**Understanding the Impact of HCV and Therapeutic Considerations for the Front-Line Provider**

**Learning Objectives**
- Identify and screen patients at risk for HCV infection and counsel patients accordingly
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- Monitor HCV patients on DAA therapy for potential adverse events, drug interactions, and issues relating to drug adherence

**In which of the following patients would you test for HCV?**

Patients who:
1. Previously injected illicit drugs
2. Are on dialysis
3. Received a blood transfusion in 1995
4. All of the above
5. 1 and 2 only

**How would you manage a patient who develops anemia while on boceprevir (BOC)/pegylated interferon (PEG-IFN)/ribavirin (RBV) therapy for HCV?**
1. Immediately discontinue boceprevir and refer him to his gastroenterologist
2. Stop all HCV therapy and refer him to his gastroenterologist
3. Don’t stop HCV therapy, refer him to his gastroenterologist
4. Add iron supplementation and follow up in 2 weeks

**A patient receiving triple combination therapy with telaprevir/PEG-IFN/RBV presents to you with a pruritic, diffuse rash. How do you manage this patient?**
1. Do nothing, mild to moderate rashes are common and do not progress to more severe skin reactions
2. Treat with oral antihistamines and/or steroids and refer back to the patient’s gastroenterologist
3. No need to refer, treat with oral antihistamines and/or topical steroids
4. Discontinue telaprevir at the first sign of a rash
HCV: Scope of the Problem, Risk Factors, & Natural History

The Modern Hepatitis C Patient: Evaluation & Management Considerations

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Introduction

• Goals of this CME session:
  – Review the risk factors, diagnostics, transmission, and complications of HCV
  – Discuss appropriate screening strategies to identify patients with HCV in your practice
  – Discuss how to counsel patients with newly diagnosed HCV
  – Discuss the evolution of HCV therapy and which patients are most appropriate for treatment
  – Discuss treatment options, potential adverse events, drug interactions, and issues relating to drug adherence

Introduction

• ~ 3.2 million people in the United States are chronically infected with hepatitis C virus (HCV)
• 1%-5% will die from complications
• HCV accounts for 8000-10,000 deaths/year
  – Forecasted to increase to 35,000 annually by 2030
• In the United States, HCV is the leading indication for liver transplantation
• HCV therapy can cure the disease, decreasing the risk for liver-related complications and liver cancer
• Identifying those that are infected with HCV before advanced disease is imperative

Hepatitis C Information for Health Professionals. Centers for Disease Control and Prevention.

Scope of the Problem

• Most common chronic blood-borne infection
• Leading cause of liver-related morbidity and transplantation
• HCV is under-recognized, as most infections are asymptomatic and universal screening is not recommended


Scope of the Problem

• Overall US prevalence
  – HCV-Ab 1.6%
  – HCV-PCR 1.3%
• 2 times more common in men (2.1%)
• Most prevalent in non-Hispanic blacks (3%)
• Most infected individuals born between 1945-1964

Prevalence of HCV Infection by Age and Gender, US, 1988-1994

Hepatitis C Information for Health Professionals. Centers for Disease Control and Prevention.

Disease Burden

• Incidence has dramatically decreased
  – Screening of blood products
  – Universal precautions
  – Behavior modifications
• Overall disease burden will peak in 2015
  – It takes decades to develop disease complications

Incidence of Acute, Symptomatic Hepatitis C/Non-A, Non-B Hepatitis*
US, 1992-2008

*Until 1986, acute hepatitis C was reported as acute hepatitis non-A, non-B

Hepatitis C Virus Infection
Natural History

- Acute HCV
  - Resolved 15% (15%)
  - Chronically 85% (85%)
- Chronic HCV
  - Stable 80% (88%)
  - Cirrhosis 20% (17%)
- Slowly progressive
  - 75% (13%)
- HCC Liver failure
  - 25% (4%)

HCC: hepatocellular carcinoma

Case
- MJ is a 52-year-old WM identified during a life insurance evaluation to have abnormal liver enzymes
  - Referred to his PCP who orders an acute hepatitis panel
  - HBsAg (negative) HBcAb IgM (neg)
  - HCV-Ab (positive)

Risk Factors
- Transmission through percutaneous contact with infected blood or body fluids
- Linked to viral load and repeated exposure
- Injection Drug Use
  - Currently the most common means of transmission in the United States
  - Highly efficient
  - May involve contaminated drug paraphernalia
  - 1/3 of IV drug users aged 18-30 years are infected
  - Rapidly acquired after regular IVDU
  - 30% prevalence after 3 years
  - >50% after 5 years
  - Older and former drug users prevalence approaches 70% to 90%

Sources of Infection for Persons With Hepatitis C

Injection Drug Use
- Currently the most common means of transmission in the United States
- Highly efficient
- May involve contaminated drug paraphernalia
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Receipt of Donated Blood, Blood Products, and Organs
- 90% of post-transfusion hepatitis (non-A, non-B hepatitis) prior to 1992
- The risk of transmission has decreased to 0.03% per unit transfused from 0.19% in the 1980s


Sexual transmission of HCV occurs, but efficiency is low
- Linked to known contact, multiple partners, early sexual activity, lack of condom use, other STDs, and sex with trauma
- Surveys of spouses and monogamous sexual partners show < 5% infected
- Spread occurs in <1% / year
- Not higher in men who have sex with men
- Transmission is more efficient from HCV-positive men to women
- Parallels viral titers
- No change in sexual practices recommended for monogamous patients
- Avoid sharing personal items potentially contaminated with blood


Birth to an HCV-Infected Mother

- Vertical or maternal-to-infant transmission is not common
  - ~5% of infants born to infected women
  - Associated with high serum viral load, illicit drug use, co-infection with HIV, maternal ALT, blood loss at delivery, prolonged membrane rupture, and invasive procedures
  - However, few of these variables can be modified
  - Avoid invasive fetal monitoring (eg, using scalp electrodes)
  - Avoid breast-feeding if nipples are cracked or bleeding
- C-section has not impacted transmission rates
- Anti-viral therapy contraindicated during pregnancy
- Disease in newborns is usually mild
  - Testing recommended at 18 months

Needlestick Injuries in Health Care Settings, Medical and Dental Procedures

- With standard infection-control practices, medical and dental procedures hold minimal risk
- Avoid sharing injectable medications or intravenous solutions between patients
- Transmission through a needlestick injury is low (0%-10%)
  - Risk increases with a hollow-bore needle
- The prevalence of HCV antibody in health care workers is similar to the general population

In my practice, I refer a patient who has tested positive for the presence of HCV antibody to a gastroenterologist for evaluation.

1. Always
2. Almost always
3. Most of the time
4. Only if they are candidates for treatment
5. I rarely screen for HCV antibody

Why Is HCV Under-Recognized?

- Asymptomatic
  - 40% with normal liver enzymes
- High prevalence in groups with limited access to medical care
- Difficulty in implementing risk-based screening
  - Limited time during primary care appointments
  - Invasive questions may not be asked
  - Patients may not be forthcoming

How Can We Better Identify HCV?

- Increase patient awareness
  - Risk factors and treatment outcomes
  - SVR = cure
- De-stigmatize questions
  - List risk factors with simple “yes / no” choices
- Birth-cohort screening
  - Cost effective
  - Proposal to pare this with colonoscopy
**Milestones in Therapy of HCV: Overall SVR Rates**

- Data from genotype 1 patients

**Impact of Antiviral Treatment on Risk of HCV-Related Complications**

- Patients with compensated cirrhosis treated with IFN monotherapy between 1992 and 1997

**Individuals Who Should Be Screened for HCV**

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organisms before July 1992
- Were ever on chronic hemodialysis
- Have evidence of liver disease (elevated alanine aminotransferase [ALT] levels)
- Are infected with HIV

Testing also should be performed based on the need for exposure management, including:

- Health care, emergency, and public safety workers after needlestick/mucosal exposure to HCV-positive blood
- Children born to HCV-positive women

**Case Continued**

- MJ reports no risk factors. He is confused as to how and when he was exposed
- What is the significance of a positive HCV-Ab?
- What is the chance that this test is falsely positive?
Diagnostic Tests: Screening

- Serologic assays
  - Detect antibody to HCV
  - Very sensitive
  - Cannot differentiate between past, current, and resolved infection
  - False-positive results are most common when testing a low-prevalence region
- Antibodies typically are detectable within 4-10 weeks after infection
- Confirmatory testing with RIBA (recombinant immunoblot assay) has been replaced by nucleic acid testing for HCV RNA

Diagnostic Tests: Diagnosis

- Up to 5 million Americans have been infected with HCV
  - 85% will develop chronic infection
- Nucleic acid (NA) testing
  - All patients with positive anti-HCV should have confirmatory NA testing
    - Positive NA = infection
  - Highly sensitive assay with low limit of detection is essential for both diagnosis and monitoring of therapy
  - Real-time PCR and transcription-mediated amplification (TMA) assays eliminate the need for a qualitative option

Case Continued

- Subsequent labs obtained on MJ show that he has active virus
  - Viral load 1,200,000 IU/mL
  - Genotype 1b
  - ALT 42 IU/L and AST 37 IU/L
  - He is not anemic and platelets are 210,000
- Do these labs assure you that his HCV is indolent?

Rapid Fingerstick Testing and Home Testing Kits Are Available

Simple Testing Procedure

1. Collect sample.
2. Press the device onto the finger to collect a small drop of blood.
3. Read the results in 10 minutes.

HCV Genotype

- HCV is classified by genomic sequence heterogeneity
- 3 major genotypes are highly prevalent
  - 1a and 1b are responsible for about 60% of infections worldwide (75% in the United States)
- Genotype does not impact pathogenesis or prognosis, but predicts therapeutic response
  - Performing testing in all patients being considered for anti-viral therapy

Liver Enzymes

- Most patients with HCV have abnormal ALT or AST
  - Normal ALT for women: <20 IU/L
  - Normal ALT for men: <30 IU/L
- Up to 40% of chronically infected patients have normal ALT
  - ALT does not offer reliable information regarding prognosis or degree of fibrosis
  - 5%-30% will have advanced fibrosis
  - 1.3% will have cirrhosis

Other Tests

- Careful evaluation of blood work can reveal signs of cirrhosis
  - Thrombocytopenia (platelets < 150 K/microliter)
  - Low albumin
  - Low cholesterol
  - Increased INR
  - Increased bilirubin
  - Increased AST to ALT ratio

Counseling Patients with HCV

What should be discussed?

- Low but present risk for transmission with sex partners
- To not share personal items that might have blood on them
- Keep open wounds covered
- HCV is not spread by casual contact
  - Sneezing, hugging, holding hands, coughing, sharing eating utensils or drinking glasses, or through food or water
- Treatment can result in cure


Counseling Patients with HCV

- Protect the liver from further harm
- Avoid alcohol
- Check before taking any new medications
- Control other factors that can increase hepatic fibrosis
  - Diabetes, hyperlipidemia
  - Maintain a healthy weight
- Stop smoking
  - Tobacco use is associated with depression, fatigue, difficulty sleeping, and loss of interest in sex in HCV patients and increases the risk of liver cancer
  - Cannabis use independent predictor of fibrosis and steatosis


Case Continued

- MJ takes a statin for hyperlipidemia and has a family history of early heart disease
- He is now afraid to take his medications

Statins and HCV

- Statins can cause liver test abnormalities and liver damage
- Some statins lower HCV replication
- Statins are effective in reducing LDL levels in HCV+ subjects
- Statin therapy is not associated with a higher risk of severe hepatotoxicity in patients with chronic hepatitis C


Case Continued

- MJ is very interested in HCV therapy
- What factors would impact his eligibility for therapy?
Assessment for Contraindications to HCV Treatment

- Goal of therapy is viral eradication (SVR)
- There are few absolute contraindications to HCV therapy
- All HCV therapy requires pegylated interferon (PEG-IFN) in combination with ribavirin (RBV)
  - The addition of a protease inhibitor (PI) improves efficacy in genotype 1 patients
  - PIs have several drug interactions that need to be addressed prior to initiating treatment

Absolute Contraindications

- PEG-IFN
  - Hypersensitivity
  - Autoimmune hepatitis
  - Decompensated liver disease
- RBV
  - Pregnancy (or desiring pregnancy)
  - Hemoglobinopathies
  - Combination with didanosine

Characteristics of Persons for Whom Therapy is Currently Contraindicated

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by PEG-IFN and RBV
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease, such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, and chronic obstructive pulmonary disease
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

Progression is Probably Not Linear: Importance of Duration and Aging

Successful Navigation & New Therapies—Direct Acting Antivirals (DAAs)

Successful Navigation and Impact of New HCV Therapies

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2 Protease Inhibitors Approved for Genotype 1 HCV Infection

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Additional Regimen Components</th>
<th>Considerations</th>
</tr>
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<tbody>
<tr>
<td>Boceprevir 800 mg TID (q7-8hrs)</td>
<td>PEG-IFN alfa + weight-based RBV</td>
<td>Naive to previous therapy + Previous treatment failure + Compensated cirrhosis + RGT</td>
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<td>PEG-IFN alfa + weight-based RBV</td>
<td>Naive to previous therapy + Previous treatment failure + Compensated cirrhosis + RGT</td>
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</table>

For patients with genotype 2/3 infection, HCV therapy with PEG-IFN/RBV remains the standard of care.

Medicines That Are Contraindicated With Boceprevir and Telaprevir*

- Contraindicated may inhibit or induce various metabolic pathways (eg, CYP3A, P-gp)
- Solutions may be found for virtually all potential drug interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC</th>
<th>Contraindicated With TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenergic antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimyocardinergic</td>
<td>Verapamil</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>G1 motility agents</td>
<td>Cleasipine</td>
<td>Cleasipine</td>
</tr>
</tbody>
</table>

*Studies of drug-drug interactions incomplete.

Medicines That Are Contraindicated With Boceprevir and Telaprevir (Cont.)*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC</th>
<th>Contraindicated With TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal products</td>
<td>Hypericum perforatum (St John’s wort)</td>
<td>Hypericum perforatum</td>
</tr>
<tr>
<td>NMG CoA-reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drospirenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial HTN</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial HTN</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam, orally administered midazolam</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

*Studies of drug-drug interactions incomplete.

Telaprevir/Boceprevir in Combination with PEG-IFN/RBV in Genotype 1 HCV Treatment

- Helpful data prior to referring for treatment:
  - HCV genotype 1a/1b (1b predominates in Asia)
  - Quantitative viral level
  - IL-28 genotype (treatment-naive, IL-28B CC with high cure)
  - Previous viral kinetics if non-responder
  - IL-28 is not as helpful with accurate viral kinetics
  - Fibrosis assessment for advanced liver disease (cirrhosis)
  - Concomitant medicines/drug-drug interaction query
  - Management plan for side effects
    - Rash, anemia, GI side effects
    - Set expectations with patients
    - Time for approval, compliance

Telaprevir + PEG-IFN/RBV in G1 Tx-Naive Patients Important Futility Milestones: Weeks 4, 12, 24

- Treatment duration: Patients with extended RVR (eRVR, undetectable* HCV-RNA at week 4 and week 12) receive 24 weeks of therapy
- Patients without eRVR continue on PEG-IFN and RBV for a total of 48 weeks

Pre-existing Resistant Variants During Exposure to Telaprevir/Boceprevir
Resistance-Associated Variants Develop When SVR Is Not Achieved

- Recommendation: Patients with virologic failure on one PI should not be retreated with the other
- Similar mutations selected in resistance-associated variants detectable in patients failing BOC or TVR
- Clinical significance of resistance-associated variants is unknown
- Predominant strain returns to wild type in majority within 2 years
  - Slower process in subtype 1a
- Recommendation: Follow stopping rules strictly to minimize selection of resistance-associated variants


What Can You Tell Your Patients?

Significantly Higher SVR Rates Are Seen in Telaprevir-Treated Patients Compared to PEG-IFN / RBV (PR) Alone

<table>
<thead>
<tr>
<th></th>
<th>T12PR (n = 363)</th>
<th>T8PR (n = 364)</th>
<th>PR48 (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients with SVR</td>
<td>75</td>
<td>44</td>
<td>*P &lt; 0.0001</td>
</tr>
</tbody>
</table>

*Genotype 1 Patients


REALIZE: SVR in Prior Relapers, Prior Partial Responders and Prior Null Responders

Telaprevir: Most Common Adverse Events (AEs) (≥25%) and Discontinuation Rates from Advance

<table>
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<th>% of Patients With</th>
<th>T12PR (n = 383)</th>
<th>T8PR (n = 364)</th>
<th>PR48 (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE*</td>
<td>99</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Pruritus</td>
<td>50</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>43</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Rash</td>
<td>37</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>37</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Insomnia</td>
<td>32</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>28</td>
<td>29</td>
<td>28</td>
</tr>
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*7% of T12PR, 8% of T8PR, and 4% of PR48 patients discontinued all drugs due to AEs during TVR/placebo phase.

Telaprevir Rash

- Patients treated with telaprevir
  - Rash reported in 56% of subjects (vs 34% with PR48); 4% severe
  - Typically eczematous, maculopapular, and papular/lichenoid
  - In most subjects, the rash was mild-moderate
  - Rash events resulted in discontinuation of TVR in 6% of subjects
  - Occurred early, usually within first 4 weeks, but can occur at any time
  - < 1% Stevens Johnson Syndrome or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
  - Mechanism of rash remains unknown; however, pyrazinoic acid is a major metabolite of TVR & may contribute to rash/pruritus
  - Structural analog of nicotinic acid
  - Improvement occurs after discontinuation of TVR/placebo or D/C; may take weeks for complete resolution

Telaprevir Rash

- Oral antihistamines early!
- Topical steroid creams (prescription)
- Avoid sun exposure
- Continue telaprevir with PEG-IFN/RBV
**Telaprevir: Severe Rash**

- Generalized rash, or rash with vesicles, bullae, or ulcerations
- No Stevens-Johnson Syndrome/DRESS
- Stop telaprevir, if no improvement in 7 days, stop PEG-IFN/RBV
- Do not reintroduce telaprevir
- If no improvement, refer to dermatologist

**Stevens-Johnson Syndrome (SJS)/DRESS**

- SJS: Fever, target lesions, mucosal erosions/ulcerations
- Drug rash with eosinophilia and systemic symptoms
  - Rash, fever, facial edema, internal organ involvement
  - ± eosinophilia
- Stop all medicines
- Urgent dermatology referral

**Gastrointestinal Side Effects**

- Nausea: promethazine, ondansetron
- Telaprevir should be taken with 20 grams of fat to help with absorption
- Perianal symptoms
  - Anal pruritus with telaprevir: antihistamines
  - Topical therapies: Witch hazel topical, hydrocortisone cream, mesalamine suppositories, lidocaine
- Diarrhea: loperamide, bulk/fiber supplement

**Telaprevir: Anemia**

- Mechanism of anemia thought to be result of bone marrow suppressive effects associated with telaprevir, not RBC hemolysis
- Patients treated with telaprevir had:
  - A higher frequency of anemia—hemoglobin levels < 10 g/dL (36% vs 17%)
  - A higher frequency of hemoglobin reductions to Grade 3 or higher toxicity (7.0 to < 9.9 g/dL or any decrease > 4.5 m/dL) levels (55% vs 25%)
  - A higher frequency of hemoglobin level < 8.5 g/dL (14% vs 5%)
  - More anemia-related severe AEs (2.5% vs < 1%)
  - A higher frequency of anemia-related discontinuations (4% vs < 1%)

**Boceprevir for Genotype 1 Naïve HCV Milestones: Weeks 8, 12, 24**

- Week 4
  - PR lead-in
  - Week 8
  - PR + BOC (24 weeks) Non-cirrhotic
  - Week 28
  - PR + BOC (24 weeks) Undetectable
  - Week 48
  - PR + BOC (24 weeks) Undetectable
  - Week 72
  - PR + BOC (44 weeks) poorly responsive patients

**Boceprevir: Lead-in Strategy**

- 4 weeks of PEG-IFN and RBV lead-in prior to boceprevir
- Lower HCV burden
- May identify rapid responders who may not need DAA
- Allows assessment of interferon responsiveness
  - May provide useful information regarding likelihood of SVR with addition of DAA
  - In non-responders, may help reduce likelihood of generating resistant-associated variants

*Assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL, and limit of HCV-RNA detection of approximately 10-15 IU/mL


SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing or not reported to the protocol. A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39%, 66% and 68%, respectively and in Cohort 2 were 21%, 42% and 51%, respectively. Non-Black Patients: *P < 0.0001 Black Patients: *P = 0.044 SVR Relapse Rate


What Can You Tell Your Patients? Significantly Higher SVR rates in Boceprevir-Treated Patients Compared to PEG-IFN / RBV Alone

Sprint-2 SVR: Influence of Patient and Virus Factors on SVR with Boceprevir + PEG-IFN/RBV


Boceprevir for Genotype 1 Non-Responders: HCV: Key Time Points 8, 12, 24

SVR by Historical Response Non-responders and Relapsers*

Arm 1: 48 P/R N = 80 Arm 2: BOC RGT N = 162 Arm 3: BOC/PR48 N = 161

Non-responder – n / n (%)

2/29 (6.9) 23/57 (40.4) 30/58 (51.7)

Relapser – n / n (%)

15/51 (29.4) 72/105 (68.6) 77/103 (74.8)

Non-responders had a decrease in plasma HCV-RNA of at least 2-log10 by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapsers had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response. Adapted from: Bacon BR, et al. N Engl J Med. 2011;364(13):1207-1217.

Adverse Event Arm 1 (PR48); n=363 (%) Arm 2 (RGT); n=368 (%) Arm 3 (BOC/PR48); n=366 (%)

Fatigue 59 52 57
Headache 42 45 43
Nausea 40 46 42
Anemia 29 49 49
Dysgeusia 18 37 43
Chills 28 36 33
Pyrexia 32 33 30
Insomnia 32 31 32
Alopecia 27 20 28
Decreased Appetite 25 26 24
Pruritus 26 23 25
Neutropenia 21 25 25
Influenza Like Illness 25 23 22
Myalgia 26 21 24
Rash 22 24 23
Irritability 24 22 22
Depression 21 23 19
Diarrhea 19 19 23
Dry Skin 18 18 22
Dyspnea 16 18 22
Dizziness 15 21 17

Most Common Treatment-Related Adverse Events*

*Reported in >20% of patients in any treatment arm and listed by decreasing overall frequency

Boceprevir: Anemia

• Mechanism of anemia thought to be result of bone marrow suppressive effects associated with boceprevir, not due to RBC hemolysis
• Patients treated with boceprevir had:
  – Average additional decrease of Hgb of approximately 1 g/dL
  – Anemia reported as a serious AE (1% vs none with PR)
  – A higher frequency of hemoglobin reductions to Grade 3 or higher toxicity

Case Continued

• MJ is initiated on PEG-IFN, RBV, and telaprevir and told he has a 65% to 75% chance of a cure (SVR) with triple therapy. Potential adverse reactions are discussed and follow-up visits and labs are planned.

Management of Anemia With Boceprevir- or Telaprevir-Based Therapies

• RBV dose reduction
• Addition of erythropoietin*
  – BOC studies allowed for use of erythropoietin
  – TVR studies did not allow for use of erythropoietin in first 12 weeks
    • It has been used in small trials
  – Patients with advanced fibrosis, low normal Hgb levels, and marginal renal function may require erythropoietin support
• Large randomized trial fully enrolled to compare RBV dose reduction vs EPO in boceprevir-treated patients

*EPO products are not FDA approved for this indication

Case Continued

• MJ responds well to TVR/PEG-IFN/RBV with undetectable HCV at week 4 (RVR); however, at week 6 he complains of decreased energy and fatigue. Lab work reveals a 4 gm decrease in Hgb from his baseline of 14 g/dL to 10 g/dL.

• How should his anemia be managed?

Summary

• Both telaprevir and boceprevir added to PEG-IFN/RBV improve SVR rates
• Now at least half of individuals can be treated for 6 months
  – IL-28 CC predicts 6-month duration of treatment
• Telaprevir: Rash, GI side effects, anemia
• Boceprevir: Anemia, dysgeusia
• Careful monitoring, especially in those with advanced fibrosis of hemoglobin
• Identify consultants prior to initiating therapy
  – Dermatologist
• Drug-drug interactions must be assessed while being treated with telaprevir/boceprevir
  – Virtually all interactions can be addressed

Treatment of Chronic Hepatitis C

[Graph not provided]

[References provided]
<table>
<thead>
<tr>
<th>In which of the following patients would you test for HCV?</th>
<th>How would you manage a patient who develops anemia while on boceprevir (BOC)/pegylated interferon (PEG-IFN)/ribavirin (RBV) therapy for HCV?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who:</td>
<td></td>
</tr>
<tr>
<td>1. Previously injected illicit drugs</td>
<td>1. Immediately discontinue boceprevir and refer him to his gastroenterologist</td>
</tr>
<tr>
<td>2. Are on dialysis</td>
<td>2. Stop all HCV therapy and refer him to his gastroenterologist</td>
</tr>
<tr>
<td>3. Received a blood transfusion in 1995</td>
<td>3. Don’t stop HCV therapy, refer him to his gastroenterologist</td>
</tr>
<tr>
<td>4. All of the above</td>
<td>4. Add iron supplementation and follow up in 2 weeks</td>
</tr>
<tr>
<td>5. 1 and 2 only</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A patient receiving triple combination therapy with telaprevir/PEG-IFN/RBV presents to you with a pruritic, diffuse rash. How do you manage this patient?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do nothing, mild to moderate rashes are common and do not progress to more severe skin reactions</td>
</tr>
<tr>
<td>2. Treat with oral antihistamines and/or steroids and refer back to the patient’s gastroenterologist</td>
</tr>
<tr>
<td>3. No need to refer, treat with oral antihistamines and/or topical steroids</td>
</tr>
<tr>
<td>4. Discontinue telaprevir at the first sign of a rash</td>
</tr>
</tbody>
</table>