JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW™
eViralHepatitis Review
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

eViralHepatitis Review
VOLUME 3, ISSUE 1

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)/HCV UPDATE

Editor's Note: *As we begin Volume 3, we want to welcome back our returning subscribers and say hello to our newly registered clinicians. In Volume 3, we will continue to provide you with current, clinically relevant data important to helping you improve outcomes in your patients via 6 newsletters and 6 case-based podcasts. Topics scheduled for this volume include: EASL Coverage, AASLD Coverage, HCV Screening and Natural History, HBV Cure, and Non-Invasive Markers.*

In this Issue...

When future physicians pause to reflect on the fight against the global HCV epidemic, there will undoubtedly be some obvious watershed moments to consider: the discovery of the pathogen (1989), treatment with interferon (1992), treatment with interferon/ribavirin (1998), treatment with oral direct acting antivirals (telaprevir or boceprevir) in combination with interferon/ribavirin (2011), and the first interferon-free, HCV treatment regimen, albeit limited to HCV genotype 2/3 (potentially in 2013). While there are more watershed moments to come (ie, oral regimens for genotype 1), the 2013 European Association for the Study of the Liver (EASL) meeting provided critical data illuminating the path toward eradicating HCV infection.

In this issue, we highlight several of the key HCV treatment trials discussed at EASL 2013.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss recent advances for the treatment of HCV genotype 1 infection using peginterferon/ribavirin plus direct acting antivirals (DAAs)
- Describe recent advances for the treatment of HCV genotype 2 and 3 infection using peginterferon/ribavirin plus direct-acting antivirals (DAAs) and interferon-free oral regimens
- Evaluate emerging interferon-free regimens for the treatment of HCV genotype 1 infection

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

ACCREDITATION STATEMENTS
Physicians
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns

STATEMENT OF RESPONSIBILITY
The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Program Information
CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 contact hour Nurses

Launch Date
August 27, 2013

Expiration Date
August 26, 2015

TO ACCESS THE POST-TEST

Step 1.
Review the CE Information and study the educational content.

Step 2.
Click the post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access a post-test.

Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians
eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
eNewsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hour, or a total of 6 contact hours for the six newsletters in this program. To obtain contact hours, you must complete this Education Activity and post-test before August 27, 2015.

Podcast: These paired 0.5 contact hour Educational Activities are provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour, or a total of 3 contact hours for the 6 podcasts in this program. To obtain contact hours, you must complete this Education Activity and post-test

before July 29, 2015.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, then link to The Johns Hopkins University School of Medicine's or The Institute for Johns Hopkins Nursing's website to complete the post-test and evaluation. Once you receive a passing grade, you can access and print your certificate of credit.

NOTE: If you have already registered for other Hopkins CME programs on their prospective websites simply enter the requested information when prompted.

There are no fees or prerequisites for this activity.

This activity is supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

LAUNCH DATE

August 27, 2013; activities expire 2 years from the date of publication.

INTERNET CME POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM CME maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in an Internet-based CME program. Your information will never be given to anyone outside of the Johns Hopkins University School of Medicine's CME program. CME collects only the information necessary to provide you with the services you request.

STATEMENT OF NEED

HCV

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV

- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

INTENDED AUDIENCE

The target audience (clinicians) for this initiative includes: OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence.

PLANNER DISCLOSURE

As a provider approved by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Johns Hopkins University School of Medicine Office of Continuing Medical Education (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control the content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships regardless of their relevance to the content of the activity. Faculty are required to disclose only those relationships that are relevant to their specific presentation. The following relationships have been reported for this activity:

- **Mark S. Sulkowski, MD,** discloses that he has served as a consultant for AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated. He has received grant/research funding from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated, and has served on a steering committee for Pfizer, Inc
- **Raymond T. Chung, MD,** discloses that he has served as a consultant for AbbVie, Inc. and Idenix and has received grant/research funding from Gilead and Mass Biologics.

No other planners have indicated that they have any financial interest or relationships with a commercial entity.

Guest Authors Disclosures

CONFIDENTIALITY DISCLAIMER FOR CONFERENCE ATTENDEES

I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the Privacy

Regulations). Protected health information is information about a person's health or treatment that identifies the person.

DISCLAIMER STATEMENT
The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of The Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

"The Office of Continuing Medical Education at The Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only."

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed and Approved by
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS
Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

IN THIS ISSUE

Program Directors

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Associate Professor of Medicine
Harvard Medical School
Director of Hepatology
Vice Chief of Gastroenterology
Massachusetts General Hospital
Boston, Massachusetts

Julie McArthur, MS, CRNP
Adult Nurse Practitioner
Division of Infectious Disease
The Johns Hopkins University School of Medicine
Baltimore, Maryland

GUEST AUTHOR OF THE MONTH

Commentary:

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Guest Faculty Disclosures

Mark S. Sulkowski, MD has disclosed that he has received grants/research support from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated. He has served on consulting/advisory boards for AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated. He has also served on a steering committee for Pfizer, Inc.

Unlabeled/Unapproved Uses

Dr. Sulkowski has indicated that there will be references to interferon, interferon/ribavirin, telaprevir or boceprevir in combination with interferon/ribavirin, sofosbuvir plus peginterferon/ribavirin (currently being reviewed by the FDA, not yet approved), simeprevir or faldaprevir plus peginterferon/ribavirin, and the first interferon-free HCV treatment regimen (limited to HCV genotype 2/3) as experimental anti-HCV drugs.

Program Directors' Disclosures

COMMENTARY

Major milestones achieved in HCV treatment - is the end in sight?

The most important new HCV-treatment data presented at the 2013 EASL meeting can be broadly generalized into three categories:

1. Refinement of "triple therapy" with peginterferon/ribavirin plus a single DAA.

While the currently available first-generation protease inhibitors (telaprevir and boceprevir) have proved to be highly effective agents, their utility has been limited by complicated dosing and clinically significant adverse effects such as anemia and rash. The 12-week regimen of sofosbuvir, 400 mg by mouth daily, plus peginterferon/ribavirin (SOF/RBV), was submitted to the US Food and Drug Administration ahead of the 2013 EASL meeting and, pending regulatory consideration, may be available to patients as early as December 2013. Also discussed were the 24- or 48-week regimens of simeprevir or faldaprevir plus peginterferon/ribavirin, expected to provide highly effective treatment for many patients infected with HCV genotype 1 with fewer side effects and, for the majority, 24 weeks of therapy.

However, these data on safer, more effective "triple therapy" must be considered in the context of emerging interferon-free oral, direct-acting antiviral regimens. Health care providers and their patients will have to carefully consider this treatment option, which

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

appears to be markedly better tolerated, to have less drug-drug interactions, and to be more effective than the current standard of care treatment — telaprevir or boceprevir plus peginterferon/ribavirin for 24/28 weeks or 48 weeks for patients infected with HCV genotype 1.

The second major refinement to "triple therapy" is the extension to treat infection with other HCV genotypes such as genotype 4. Notably, because of the highly conserved active site in the NS5B polymerase, sofosbuvir has been shown to be active both in vitro and in vivo against all HCV genotypes — this sofosbuvir-based regimen represents the first advance treating patients infected with HCV genotypes 4, 5, and 6 since the approval of peginterferon in 2001. In light of the tens of millions of people infected with HCV genotype 4 in Egypt and other parts of the world, the importance of a simpler and more effective DAA regimen for patients with HCV genotype 4 cannot be overstated. Other second-generation HCV protease inhibitors (simeprevir and faldaprevir) are also active against HCV genotype 4 infection; in addition, simeprevir is active against all HCV genotypes except 3. Taken together, these advances in HCV "triple therapy" presented at EASL represent major milestones for treating patients with non-genotype 1 infection.

2. *The first interferon-free, all-oral regimen for treating HCV genotype 2 and 3 infection.*

One fact that has been known since the first trials of interferon alfa to treat non-A, non-B hepatitis is that human beings do not like interferon alfa. Their dislike of interferon alfa is not limited to the patients who may experience side effects such as flu-like symptoms, fatigue, and depression, but also extends to family members who interact with patients under treatment, as well as health care providers who must manage these considerable side effects. The other major problem with interferon alfa is that its antiviral activity depends on patient characteristics, namely the IL28B haplotype. Therefore, the likelihood of SVR varies dramatically according to the patient's genetic polymorphism. Hence, the promise of interferon-free therapy has been that of a more effective, better-tolerated treatment that can be delivered to more people, including those who have contraindications to interferon alfa.

Patients with HCV genotype 2 or 3 infection are expected to be the first patient group to have the option of taking FDA-approved interferon-free therapy in the form of sofosbuvir/ribavirin (SOF/RBV). The data presented at EASL 2013 demonstrate that more than 90% of patients infected with HCV genotype 2 can be effectively treated with 12 weeks of SOF/RBV with a side-effect profile consistent with that of placebo. These same data also demonstrated conclusively that patients infected with HCV genotype 3 appear to require longer therapy; in these patients, SOF/RBV for 16 weeks was clearly found to be more effective than 12 weeks of treatment. However, even with 16 weeks of treatment, the rate of virologic relapse appeared to be higher than was observed in patients with HCV genotype 2 infections. Therefore, additional strategies for HCV genotype 3 are under investigation, including: SOF/RBV for 24 weeks, SOF + NS5A inhibitor, and SOF/RBV plus peginterferon alfa. Importantly, patients treated with SOF/RBV who experience virologic relapse after stopping therapy have not shown evidence of resistance to SOF by deep sequencing methodologies. This finding raises the possibility that clinicians may elect to treat patients with HCV genotype 3 with 16 weeks of SOF/RBV and reserve the use of "triple therapy" with SOF/RBV + peginterferon for patients who experience virologic relapse; of course, more data will be needed to support this approach. While further refinement of these regimens with novel agents will be forthcoming, a major milestone in treating HCV infection has been achieved in 2013 — the first all-oral, interferon-free HCV treatment.

3. The roadmap for future interferon-free all-oral regimens for treating HCV genotype 1

Although the FDA is not expected to approve all-oral, interferon-free regimens for treating

HCV genotype 1 infection in 2013, the EASL meeting provided an increasingly clear roadmap for developing such regimens. Broadly, these regimens can be categorized by the inclusion (or not) of the nucleotide analogue polymerase inhibitor sofosbuvir. Nucleotide analogue-containing regimens presented at EASL 2013 include SOF/ledipasivir (NS5A), SOF/daclatasvir (NS5A), SOF/simeprevir (PI) and SOF/GS9669 (nonnucleotide polymerase inhibitor). In general, highly potent antiviral activity, once-daily dosing, and an unremarkable adverse effect profile have characterized these regimens. This regimen profile was exemplified by the success of SOF/daclatasvir in 100% of 41 patients with HCV genotype 1 infection who had virologic failure with peginterferon/ribavirin plus telaprevir or boceprevir, including those with persistent resistance to these first generation protease

inhibitors. Additional studies of these regimens, including phase 3 clinical trials of a single tablet fixed dose combination of SOF/ledipasivir with or without RBV for the treatment of HCV genotype 1, patients are underway.

Regimens currently being investigated that do not include the nucleotide analogue polymerase inhibitor sofosbuvir include:

- ABT450/ritonavir (protease inhibitor [PI]) + ABT267 (NS5A) + ABT 333 (non-nucleotide polymerase inhibitor); asunaprevir (PI) + daclatasvir (NS5A)[for HCV genotype 1b only] +/- BMS325 (nonnucleotide polymerase inhibitor) [for HCV genotype 1a/b]
- faldaprevir + BI 7127 (nonnucleotide polymerase inhibitor) + ribavirin [for HCV genotype 1b only]

Of these, phase 3 clinical trials of the regimen of ABT450/ ritonavir + ABT267 (these agents have been co-formulated) + ABT339 (with or without ribavirin) for the treatment of HCV genotype 1 are underway.

The next major milestone for the treatment of HCV infection is anticipated in 2014 with the presentation of data from these pivotal phase 3 trials — so stay tuned!

back to top

THE NEUTRINO STUDY SOFOSBUVIR PLUS PEGINTERFERON/RIBAVIRIN (12 WEEKS) FOR GENOTYPES 1, 4, 5 OR 6

Lawitz E, Wyles D, Davis M, Rodriguez-Torres M, Reddy KR, Kowdley KV, Svarovskaia E, Jiang D, McNally J, Brainard DM, Symonds WT, McHutchison JG, Nyberg L, Younossi Z. Sofosbuvir + peginterferon + ribavirin for 12 weeks achieves 90% SVR12 in genotype 1, 4, 5, or 6 HCV infected patients: The NEUTRINO study. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 1411

Published concurrently with EASL in the New England Journal of Medicine:

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878-1887

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

The NEUTRINO study was a phase 3, single-arm, open label trial that enrolled 327 treatment-naïve patients infected with HCV genotypes 1, 4, 5, or 6, including those with cirrhosis. Regardless of rapid virologic response status, all patients were treated for 12 weeks with the oral nucleotide analogue polymerase inhibitor sofosbuvir (SOF), 400 mg QD, plus peginterferon alfa-2a, 180 mcg weekly, and ribavirin 1000-1200 mg/daily. In

contrast to the current HCV "triple" therapy treatment paradigm with telaprevir or boceprevir, the duration of therapy in this study was not guided by an individual patient's HCV RNA response at treatment week 4; instead, the duration was fixed at 12 weeks for all patients. The study was conducted in the United States, and the enrolled population reflected the population: the mean age was 52 years; 67% were male; 17% were black; 29% had IL28B CC genotype; 89% were infected with HCV genotype 1; and 17% had compensated cirrhosis.

After four weeks of SOF plus peginterferon/ribavirin, 99% (326 of 327) of patients had an HCV RNA level < 25 IU/mL. At 12 weeks post-treatment (sustained virologic response, SVR12), 90% (295 of 327) achieved SVR, including 89% of those with HCV genotype 1

infection, 96% of those with HCV genotype 4 infection, and 100% of those with HCV genotypes 5 or 6 infection. SVR12 rates were slightly lower in patients with cirrhosis (80% SVR12), and in a multivariate model, SVR12 was independently associated with Il28B CC genotype (98% SVR12) and the absence of cirrhosis (92% SVR12 in noncirrhotic patients). Although inclusive of interferon, the regimen was well-tolerated: only five (2%) of patients had early treatment discontinuation due to adverse events. Among those with treatment failure, resistance to SOF was not detected.

back to top

THE FISSION, POSITRON, AND FUSION STUDIES: INTERFERON-FREE SOFOSBUVIR PLUS RIBAVIRIN FOR GENOTYPES 2 AND 3

Gane E, Lawitz E, Rodriguez-Torres M, Gordon S, Dvory-Sobol H, Arterburn S, McNally J, Brainard DM, Symonds WT, McHutchison JG, Sheikh A, Mangia A. Phase 3 randomized controlled trial of all-oral treatment with sofosbuvir + ribavirin for 12 weeks compared to 24 weeks of PEG + ribavirin in treatment naïve GT2/3 HCV-infected patients (FISSION). 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 5

Jacobson I, Yoshida EM, Sulkowski M, Nelson DR, Svarovskaia E, An D, McNally J, Brainard DM, Symonds WT, McHutchison JG, Pianko S, Kowdley KV. Treatment with sofosbuvir + ribavirin for 12 weeks achieves SVR12 of 78% in GT2/3 interferon-ineligible, -intolerant, or unwilling patients: results of the phase 3 POSITRON trial. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 61

Nelson DR, Feld J, Kowdley KV, Al-Assi MT, Lin M, Mo H, McNally J, Brainard DM, Symonds WT, McHutchison JG, Patel K, Gordon SC. All oral therapy with sofosbuvir - ribavirin for 12 or 16 weeks in treatment experienced GT2/3 HCV-infected patients: results of the phase 3 trial. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 6

Published concurrently with EASL in the New England Journal of Medicine:

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867-1877

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View full article

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878-1887

View journal abstract View full article

The treatment of HCV genotypes 2 and 3 infection with sofosbuvir (SOF) plus ribavirin (RBV) was defined by 3 phase 3 clinical trials which evaluated the regimen in different patient populations (treatment naïve, treatment experienced, and treatment ineligible or intolerant or unable). The clinical trials also provided the direct, randomized comparison of SOF plus RBV to the current standard of care (peginterferon/ribavirin [PegIFN/RBV]) as well as to placebo.

The FISSION study enrolled 499 treatment-naïve patients infected with HCV genotype 2 (28% of patients) or 3 (72% of patients) who were randomly assigned to treatment with 12 weeks of SOF, 400 mg by mouth daily, plus RBV 1000/1200 mg/daily (n = 256) or 24 weeks of peginterferon alfa-2a 180 mcg SC weekly, plus RBV 800 mg/daily (n = 243). Overall, the SVR12 rate was 67% in both treatment groups; however, for both regimens, the SVR12 rate varied significantly according the HCV genotype (2 or 3) and the patients' liver disease stage (cirrhosis or no cirrhosis). For HCV genotype 2 infection, treatment with 12 weeks of SOF/RBV led to SVR12 in 97% and treatment with 24 weeks of PegIFN/RBV

led to SVR12 in 78%. In contrast, for HCV genotype 3 infection, treatment with 12 weeks of SOF/RBV led to SVR12 in 56% and treatment with 24 weeks of PegIFN/RBV led to SVR12 in 63%. The lowest SVR12 rates were observed in cirrhotic patients infected with HCV genotype 3: 34% with SOF/RBV and 30% with PegIFN/RBV. Of note, at the end-of-treatment, all patients treated with SOF/RBV had an HCV RNA < 25 IU/mL, and treatment failure following this regimen represented virologic relapse; importantly, no SOF resistance was detected in of these patients. Compared to 24 weeks of treatment with PegIFN/RBV, SOF/RBV was well tolerated, with lower rates of fatigue, depression, and anemia. Discontinuation of treatment because of adverse effects was significantly lower in SOF-treated patients (1%) compared to PegIFN/RBV-treated patients (11%).

The POSITRON study randomized patients infected with HCV genotype 2 or 3 (n = 278) who were determined to be interferon ineligible/intolerant/unwilling to 12-week treatment with SOF/RBV or placebo (3:1 ratio). Overall, 78% of the patients treated with SOF/RBV achieved SVR12 compared to none of the patients who received placebo. Similar to the finding in the FISSION study, patients infected with HCV genotype 2 91% SVR12) were more likely to have viral eradication than those infected with HCV genotype 3 (61% SVR12). All treatment failures represented virologic relapse after stopping SOF/RBV and occurred in the absence of resistance to SOF. Patients in both the placebo and SOF/RBV arms reported fatigue, headache, nausea, and insomnia; while these symptoms were more frequent in the active treatment group, they were generally mild to moderate in severity. Interestingly, discontinuation because of adverse events was more common among the patients treated with placebo (4%) than in the SOF/RBV treated patients (2%).

The final study, the FUSION trial, evaluated 12 or 16 weeks of treatment with sofosbuvir/ribavirin in treatment-experienced patients with HCV genotype 2 or 3 infection. Overall, 201 patients were enrolled; of those, 63% had HCV genotype 3 infection, 34% had cirrhosis, and 75% had experienced prior virologic relapse or breakthrough with peginterferon/ribavirin. Overall, the SVR12 rates were higher among patients treated for 16 weeks (73%) compared to those treated for 12 week (50%) ($P < .001$). This difference in efficacy was driven solely by virologic relapse, which was observed in 50% of those randomized to 12 weeks of treatment and 27% of those randomized to 24 weeks of treatment. Importantly, the effect of longer treatment differed according to HCV genotype. For patients infected with HCV genotype 2, the SVR12 rates were similar for both SOF/RBV treatment durations: 12 weeks, 86% and 16 weeks, 94%. In contrast, for patients infected with HCV genotype 3, the SVR12 rate was markedly higher in the longer treatment arm: 12 weeks, 30% and 16 weeks, 62%. The safety and tolerability of SOF/RBV did not change with the additional four weeks of therapy, and no treatment discontinuations because of adverse events were reported. As in the other trials, deep sequencing of HCV samples from patients who failed to achieve SVR12 did not reveal evidence of resistance to SOF.

back to top

THE QUEST-1 AND QUEST-2 STUDIES: SIMEPREVIR PLUS PEGINTERFERON/RIBAVIRIN FOR HCV GENOTYPE 1 TREATMENT-NAÏVE PATIENTS

Jacobson I, Dore GJ, Foster GR, Fried MW, Radu M, Rafalskiy VV, Moroz L, Craxì A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Kalmeijer R, Beumont-Mauviel M. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection n treatment-naïve patients: results from QUEST-1, a phase III trial. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 1425

Manns M, Marcellin P, Poordad FP, Stanislau Affonso de Araujo E, Buti M, Horsmans Y, Janczewska E, Villamil F, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Kalmeijer R, Beumont-Mauviel M. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection n treatment-naïve patients: results from QUEST-2, a phase III trial. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 1413

Simeprevir is a second-generation HCV protease inhibitor that was evaluated in two phase 3 clinical trials in combination with peginterferon/ribavirin (PR). The trials, QUEST-1 and QUEST-2, both evaluated response-guided therapy with simeprevir, 150 mg by mouth

daily + PR versus placebo + PR in persons infected with HCV genotype 1 infection. Overall, the regimen was more effective than placebo, leading to SVR in ~ 80% of patients treated with simeprevir/PR compared to only ~ 50% of those treated with PR alone; many of the simprevir/PR patients were eligible for only 24 weeks of response-guided therapy (RGT). The most important finding in these studies was that the safety profile of simeprevir was similar to that of placebo, with no rash or excess anemia observed. Adverse events led to treatment discontinuation in QUEST-1 of only 3% of simeprevir-treated patients in QUEST-1, and of 1.6% of simeprevir-treated patients in QUEST-2. While patients treated with simprevir experienced an increase in serum total bilirubin, that increase was not characterized by liver injury but rather was the result of interactions of the drug with bile transporters (OATP1B1/MRP2) in the hepatocyte. The data from these phase 3 clinical trials are currently under evaluation by the FDA.

back to top

DACLATASVIR PLUS SOFOSBUVIR FOR PATIENTS WHO FAILED TELAPREVIR OR BOCEPREVIR PLUS PEGINTERFERON/RIBAVIRIN

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, McPhee F, Hernandez D, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM, AI444040 Study Group. Sustained virological response with daclatasvir plus sofosbuvir ± ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or boceprevir (BOC). 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 1417

In the era of telaprevir and boceprevir "triple therapy," we've had to reconsider the type of patient that we consider to be "hard to treat." Some patient characteristics have carried forward from the era of peginterferon/ribavirin – IL28B CT or TT genotype, cirrhosis, and poor response to interferon; whereas other characteristics related to the virus have emerged: genotype 1/subtype A and resistance to telaprevir or boceprevir. In this context, the study of daclatasvir (DCV) and sofosbuvir (SOF) is highly informative since the study enrolled well-characterized, telaprevir and boceprevir triple therapy virologic failures (failures from side effects were excluded). These patients were largely hard to treat on a number of levels: 98% had IL28 CT/TT genotype and 46% had detectable resistance to telaprevir or boceprevir. Despite this profile, all 41 patients achieved SVR12 after 24 weeks of SOF/DCV with or without ribavirin. The side-effect profile was benign.

Although this was a small study, these data provide an important proof of concept that patients who are hard to treat patients can be effectively treated with regimens of SOF + NS5A inhibitors. Indeed, after the EASL meeting, additional information was reported on the fixed-dose combination of SOF/ledipasivir with or without RBV. In the LONESTAR study, this combination was evaluated in patients with HCV genotype 1 infection, including those with cirrhosis and those who had failed triple therapy with telaprevir and boceprevir.

In treatment-naïve patients, treatment durations as short as eight weeks were also evaluated. While these data have not yet been presented at a scientific meeting, the initial reports indicated that ~95% of patients achieved SVR.

Apparently the combination of DCV + SOF is so potent that it even works without additional ribavirin. These findings are very helpful, as they help envision potent salvage regimens, even in patients who failed previous DAA therapy and developed resistance.

back to top