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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 7

AASLD 2013 COVERAGE

In this Issue...

The standard of care for treating chronic HCV infection has recently changed for the better with the FDA approval of two new direct-acting antivirals (DAAs) for HCV: an NS3/4 protease inhibitor, simeprevir, and an NS5B inhibitor, sofosbuvir. These approvals came on the heels of the 64th Meeting of the American Association for the Study of Liver Disease, where the data that played a role in these approvals for certain select patient populations (genotype 3 infection, HIV coinfection, and pre- and post-liver transplantation) was presented. In addition, phase II and phase III findings were presented on multiple all-oral DAA regimens that are expected to become the standard of care in less than 12 months. While investigational agents provide much excitement in the field, another area of HCV is coming into its own: HCV testing and linkage to care, which already has shown many similarities to what we have learned from treating HIV infection.

In this issue, we review key data on the phase II and phase III studies of HCV therapies presented at the 64th AASLD meeting, as well as HCV testing and HBV-related abstracts, including the longevity of HBV vaccine-related immunity and hepatocellular screening methods in patients infected with HBV.

LEARNING OBJECTIVES

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

- Describe HCV treatment advances in special populations, including HIV co-infected patients and the pre- and post-liver transplant population.
- Discuss treatment options for HCV genotype 3 infected patients.
- Explain the CDC birth cohort screening recommendations and their application in the clinical setting.

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- Secondary: gastroenterologists, infectious disease specialists, and other clinicians involved in the care of patients at risk for HBV

The target audience for the HCV curriculum includes:

- PCPs, OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians,

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1.0 hour Physicians
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Expiration Date

February 24, 2016

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and others involved in the care of patients with hepatitis.

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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.

Reviewed and Approved by
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Unlabeled/Unapproved Uses

The author has indicated that there will be references to the unlabeled/unapproved uses of sofosbuvir, simeprevir, daclatasvir, asunaprevir, and faldaprevir.

Program Directors' Disclosures

COMMENTARY

On the eve of the FDA approval of simeprevir and sofosbuvir, the 2013 AASLD meeting foreshadowed things to come … very soon. If the meeting had themes, they would have been (1) "2013: The Year Of The Special Population," with the first interferon free data presented in both HIV/HCV coinfection and liver transplantation; (2) "How Low Can You Go," with SVR rates reported for interferon-free regimens as short as six weeks; and (3) "Baby Boomer Birth Cohort Screening: Everybody's Doing It." As always, there were excellent studies across many other disease states including hepatitis B viral infection, cirrhosis, and hepatocellular carcinoma.

AASLD 2013: The Year of the Special Population

The FDA approved both simeprevir and sofosbuvir in December 2013 and data presented at AASLD played a critical role in some of the recommendations. One great advance came in the approval of these agents for the treatment of HCV in patients infected with HIV. Simeprevir was approved for use in the treatment of chronic genotype 1 infection and HIV/HCV co-infection was not identified as a special population. Based on previously presented phase III data from the C212 trial in patients with HIV/HCV coinfection suggesting similar efficacy and safety as reported in the HCV monoinfection phase III trials, the approval does not differentiate treatment in HCV mono-infection from HIV coinfection — with the exception of noting the drug interactions with multiple antiretrovirals that cannot be used concomitantly with simeprevir (including HIV protease inhibitors and efavirenz). Sofosbuvir was approved for treating chronic genotype 1-4 infection, including in two special populations: those with hepatocellular carcinoma awaiting liver transplantation and those with HIV/HCV coinfection. The data supporting the efficacy and safety of sofosbuvir in these special populations was presented at AASLD.

Just as several years ago the scientific community questioned if HCV could be eradicated without interferon (which we would come to learn is "yes"), we then queried if "more difficult to treat" populations could fare as well with interferon-free regimens as has been reported in chronic HCV mono-infection. Could interferon-free regimens provide highly efficacious options for all? The answer was clear at AASLD —in fact, it was a resounding "yes." In a phase III study of sofosbuvir in combination with ribavirin in patients with HIV/HCV coinfection, the rates of SVR were the same as those reported in patients with

HCV monoinfection, providing support for the use of sofosbuvir containing regimens in multiple HCV genotypes including 1, 2, and 3 in this special population. This same drug combination was reported in use before liver transplantation to prevent recurrence after liver transplant and after liver transplant for treating recurrent HCV infection. In both studies the tolerance of the regimen and response rates were excellent. The inclusion of these special populations in the FDA approval will significantly improve the accessibility of these drugs for patients who have been previously denied DAA therapy because of off-label use.

Interferon Free Regimens: How Low Can You Go?

Just a few years ago we were asking if chronic HCV could be cured without interferon: today we have the first FDA approved interferon-free regimen (sofosbuvir and weight-based ribavirin) for the treatment of chronic genotype 2 and 3 infection, with options for interferon-free treatments for genotype 1 and 4. However, what we are learning is that the length of treatment required for cure will vary depending on the virus and the host. At EASL 2013 there was great concern about the future treatment options for chronic genotype 3 infections, given the low response rates with 12 weeks of interferon-free treatment reported in the FUSION, POSITRON, and FISSION trials. Although FUSION suggested 16 weeks of treatment improved response rates, the rates were still not high enough to satisfy the expectations we now have for DAA therapies. The VALENCE study presented at AASLD investigated the utility of 24 weeks of sofosbuvir and weight based ribavirin and proved that while 12 weeks might be good for genotype 2, 24 weeks improved response rates by 66% (from 56% to 93% SVR12 in treatment-naïve patients) in patients with genotype 3. This was the regimen approved by the FDA for the treatment of genotype 3 infection.

While a single, highly potent DAA in combination with ribavirin has changed the paradigm of HCV treatment for genotype 2 and 3 infections, this is not true for patients with genotype 1 infection. The ELECTRON study (among others) has confirmed that for genotype 1 infection, a minimum of two DAAs is required to render an interferon-free regimen for this historically more difficult to treat viral infection, especially for patients who have previously failed interferon-based therapies and those with severe fibrosis. AASLD 2013 was a show-and- tell of what the future holds in interferon-free regimens and provided great hope for our patients who hold the not-so-illustrious label "most difficult to treat," null-responder patients with cirrhosis.

Leading off the Presidential Plenary at AASLD 2013, the first interferon- and ribavirin-free regimen likely to be approved in Japan for treating chronic genotype 1b infection reported excellent response rates in the phase III trial of daclatasvir (NS5A inhibitor) and asunaprevir (NS3/4 inhibitor) for Japanese patients who were pegylated interferon-ineligible, naïve/intolerant, and nonresponsive. The phase II COSMOS study reported that a combination of just two highly potent DAAs can achieve excellent SVR rates even in patients with null-response cirrhosis, and in as little as 12 weeks. While the phase II LONESTAR suggested that even eight weeks of two DAAa might be enough in patients without cirrhosis who were treatment-naïve. Meanwhile, the SYNERGY study pushed the limit even further, investigating the recently FDA-approved sofosbuvir in various combinations with several investigational agents including a NS5A inhibitor, NS3/4 protease inhibitor, and nonnucleoside NS5B inhibitor. With a highly potent combination of three DAAs, patients without cirrhosis who were treatment-naïve achieved SVR4 rates of 90-100% after just six weeks of treatment. Multiple dual and triple combinations of DAAs are in phase II-III study, and the first all-oral regimens for chronic genotype 1 infection will likely be approved by the end of 2014.

Birth Cohort Screening: Everybody's Doing It

Last year the Centers for Disease Control and Prevention (CDC) expanded their existing recommendations for HCV testing. In addition to the risk-based testing strategy that previously existed, CDC now recommends a one-time test for HCV without prior ascertainment of HCV risk for all US persons born during 1945-1965. This recommendation is based on epidemiologic data suggesting that this "birth cohort" accounts for more than 75% of the total HCV prevalence in the US. Two US-based cost-effectiveness studies support this expanded testing strategy with estimated cost per QALY gained of $35,700-$39,963. The USPSTF later endorsed this recommendation by giving a Level B recommendation to birth cohort testing. We now have to understand how best to

institute this recommendation and link these newly identified patients to care. Multiple reports at AASLD 2013 explored the logistics of implementing an HCV testing program and of linkage to care after infection is identified.

Two studies supported by the CDC Foundation provided useful insight on HCV testing in the birth cohort population. The first study implemented HCV opt-out testing of all patients seen in a large urban hospital center emergency department born between 1945 and 1965 who were medically or surgically stable and able to complete a verbal questionnaire administered by their ED nurse. The investigators reported on their experience after only six weeks of the screening program and identified an anti-HCV prevalence of 12%. The second study implemented the birth cohort screening recommendations in a primary care clinic in Washington, DC and instituted a linkage to care mechanism in collaboration with the infectious diseases and gastroenterology services of the hospital center. The investigators reported an anti-HCV prevalence of 8.9% and successful linkage to care with an evaluation by a provider in 69% of the newly identified cases. One underlying theme to these reports and others at AASLD is that, similar to the patients during the HIV epidemic, the patients newly identified with HCV infection were more likely to have public insurance or to be underinsured, suggesting access to care will remain a challenge for a majority of the patients identified by birth cohort testing.

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ALL-ORAL THERAPY WITH SOFOSBUVIR PLUS RIBAVIRIN FOR THE TREATMENT OF HCV GENOTYPE 1, 2, AND 3 INFECTION IN PATIENTS CO-INFECTED WITH HIV (PHOTON-1)

Sulkowski M, Rodriguez-Torres M, Lalezari J, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2, and 3 infection in patients co-infected with HIV (PHOTON-1). The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 212.

View journal abstract

The PHOTON-1 study was a phase III, open-label trial that enrolled patients with HCV coinfection who were treatment-naïve genotype 1 (N = 114), treatment-naïve genotype 2 and 3 (N = 68), and treatment-experienced genotype 2 and 3 (N = 41) . Patients received sofosbuvir (400 mg once daily) and weight-based ribavirin (1000-1200 mg daily dosed BID) for 12 (treatment-naïve genotype 2 and 3) or 24 weeks (treatment-naïve genotype 1 and treatment-experienced genotype 2 and 3). The interim analysis presented at AASLD included all treatment-naïve patients. The study population was predominantly male (81%) and white (75%). Twenty-seven percent of patients with genotype 1 carried the favorable IL28B genotype and few in the study (6.5%) had cirrhosis. The majority of patients (95%) were on antiretrovirals with excellent baseline CD4 counts (mean 559-636). Because of limited drug interactions all antiretroviral classes were represented, including efavirenz (34%), rilpivirine (6.6%), atazanavir/ritonavir (17%), darunavir/ritonavir (17.5%), or raltegravir (16%) in combination with tenofovir DF/emtricitabine. Ninety percent of patients completed the study treatment, and adverse events were an uncommon reason for discontinuation (3-5%).

Patients exhibited very rapid viral kinetics to the study regimen, with 96-100% achieving a rapid virologic response (HCV RNA < LLOQ at week 4 on therapy). SVR12 was 76%, 88%, and 67% for patients infected genotype 1, 2, and 3, respectively. The only baseline factor with a poorer response to therapy was GT1b subtype; although cirrhosis and black race had a trend toward lower responses, they were not statistically significant. Relapse was the most common reason for treatment failure (N = 37). Two patients (genotype 1 and genotype 2) experienced on-treatment viral breakthrough, but neither had detectable serum levels of the study drug consistent with nonadherence. Deep sequencing (lower limit of detection = 1% prevalence) was performed on all patients following viral relapse, and no S282T mutations were detected. Other NS5B polymorphisms were detected, but none conferred changes in susceptibility to sofosbuvir or ribavirin on phenotypic analysis.

The study regimen was well tolerated with 23 grade 3-4 AEs and 14 serious AEs. AEs leading to discontinuation included weight loss, insomnia/agitation, staphylococcal pneumonia, suicide attempt, foreign body sensation in the throat, increased anxiety, and dyspnea/shortness of breath. There was no significant difference in AEs between the 12 and 24 week arms, with the exception of more insomnia in the 12-week arm (21% vs 13%). Grade 3/4 laboratory abnormalities were more common in the 24-week arm, including indirect hyperbilirubinemia (19% vs 6%), which primarily occurred in patients on concomitant atazanavir, and hemoglobin < 10 mg/dL (19% vs 10%). Two patients experienced transient HIV viral breakthrough (defined as HIV RNA ≥ 400 copies/mL) and both had undetectable serum levels of the antiretrovirals in their regimens consistent with nonadherence. There was a decrease in absolute CD4 T-cell count but not in CD4 T-cell percentage.

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THE OPTION OF ALL ORAL THERAPY FOR THE PREVENTION AND TREATMENT OF HCV INFECTION PRE- AND POST-LIVER TRANSPLANTATION

Reinfection of a liver graft is universal in patients with detectable HCV RNA in the serum at the time of transplantation and is a leading cause of post-transplant complications, including graft failure and cirrhosis, often resulting in the need for retransplantation and risk of death. Two studies reported on the safety and efficacy of an all-oral regimen for preventing and treating HCV infection pre- and post-liver transplantation.

Curry MP, Forns X, Chung R, et al. Pretransplant sofosbuvir and ribavirin to prevent recurrence of HCV infection after liver transplantation. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 213.

View journal abstract

The pre-transplant study is an ongoing, single-arm, open label, multicenter study investigating the prevention of HCV recurrence following orthotopic liver transplant (OLT) with 24-48 weeks of sofosbuvir (400 mg once daily) and weight-based ribavirin (1000-1200 mg daily, dosed BID). The original protocol was written to continue treatment until liver transplant or up to 24 weeks of therapy but was amended to extend the treatment length to 48 weeks. The study population included liver transplant candidates with chronic HCV infection and hepatocellular carcinoma (HCC) meeting MILAN criteria (one lesion smaller than 5 cm, up to 3 lesions smaller than 3 cm, no extrahepatic manifestations, no vascular invasion) with a MELD (Model for End-Stage Liver Disease) exception for HCC, and a Child Pugh (CPT) score of ≤ 7. Exclusion criteria included: (1) living donor liver transplant, (2) planned induction therapy with biologics, (3) signs of decompensated cirrhosis, (4) HBV or HIV coinfection, (5) history of prior solid organ transplantation, (6) evidence of renal impairment (CrCl < 60 mL/min). The study population (N = 61) was predominantly male (80%) and white (90%). The predominant HCV genotype was 1 (39% 1a, 34% 1b, 13% 2, 12% 3a, 2% 4) and a majority of patients carried the unfavorable IL28B polymorphisms (78%). Seventy-five percent of patients had received prior HCV treatment and failed to achieve cure. Forty-one (67%) of the patients received a liver transplant with a suppressed HCV RNA (< LLOQ) and 10 (16%) discontinued treatment. Of the 39 patients who had reached 12 weeks post-liver transplant, 64% had undetectable HCV RNA. The only baseline predictor of HCV recurrence was the number of continuous days with undetectable HCV RNA prior to transplantation. Patients with recurrence had a median of 5.5 days of viral suppression versus 95 days for those who did not suffer recurrence. Severe AEs occurred in 18% of patients, with 3% resulting in study treatment discontinuation. Two patients died before transplant and three died after transplant. The most common grade 3/4 laboratory abnormalities were cytopenias including anemia (15%), lymphopenia (8%), thrombocytopenia (7%).

Charlton C, Gane E, Manns MP, et al. Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis c infection after liver transplantation: preliminary results of

a prospective, multicenter study. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract LB-2.

View journal abstract

The post-transplant treatment study is an ongoing, single-arm, open label, multicenter study investigating the treatment of HCV recurrence after orthotopic liver transplant (OLT) with 24 weeks of sofosbuvir (400 mg once daily) and low, ascending-dose ribavirin (400-1200 mg daily, dosed BID). The study population included patients who had undergone liver transplantation ≥ 6 and ≤ 150 months before enrollment, had CPT score ≤ 7 and MELD ≤ 17 and absence of organ rejection. Patients who had been previously treated for HCV and primary and secondary transplants (liver alone or liver-kidney) were included. Patients with signs of decompensation and/or use of corticosteroids at any dose > 5mg of prednisone equivalent/day were excluded. The study population was predominantly male (78%) and white (85%). The predominant HCV genotype was 1 (55% 1a, 28% 1b, 15% 3, 3% 4), and a majority of patients (73%) carried the unfavorable IL28B polymorphisms. Most patients had severe fibrosis (23% F3, 40% F4). Eighty-eight percent of patients had received HCV treatment and failed to achieve cure. The median time from transplant was 4.3 years. At the time of the presentation 35 patients had reached 4 weeks after the end of 24 weeks of treatment, and 77% remained undetectable (HCV RNA < LLOQ). There were no baseline predictors of relapse. Tacrolimus was the most commonly used immunosuppressant (70% tacrolimus, 35% mycophenolate mofetil, 28% prednisone, 25% cyclosporine, 5% azathioprine). The average daily ribavirin dose achieved was 644 mg. Severe AEs occurred in 15% of patients, and two patients discontinued therapy because of AEs. Grade 3 and 4 laboratory abnormalities were common (25% and 28%, respectively); lymphopenia and anemia were the most common. There were minimal, clinically insignificant fluctuations in serum creatinine over the study.

Both studies provide evidence for the safety and efficacy of an all-oral regimen in an extremely needy patient population that has a lot to gain by achieving HCV eradication. How this will translate into long-term outcomes is yet to be determined but is expected to have a great impact on the morbidity and mortality of this special population.

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THE VALENCE TRIAL: SOFOSBUVIR + RIBAVIRIN FOR 24 WEEKS FOR PATIENTS WITH HCV GENOTYPE 3 INFECTION

Stefan Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients With HCV Genotype 2 or 3: the VALENCE Trial. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 1085.

View journal abstract

The VALENCE trial is a randomized phase III, multicenter study conducted in Europe that was initially designed to investigate the efficacy and safety of sofosbuvir (400 mg once daily) and weight-based ribavirin (1000-1200mg daily, dosed BID) for 12 weeks in patients with genotype 2 and 3 infection who were treatment-naïve and treatment-experienced. Because of data from the phase III FUSION trial suggesting that patients with genotype 3 infection achieved higher SVR when treatment with this same investigational regimen was extended from 12 to 16 weeks, the VALENCE study was amended to extend treatment to 24 weeks for all patients infected with genotype 3, and patients randomized to the placebo arm were offered treatment in an alternative protocol. Only 11 patients with genotype 3 received the initial 12-week duration of therapy; these patients were included with those with genotype 2 for safety reporting but excluded from the primary outcome analysis. The study enrolled 323 patients who were analyzed as part of the amended protocol: 73

patients with genotype 2 randomized to 12 weeks of treatment and 250 patients with genotype 3 randomized to 24 weeks of treatment. There were no differences across the groups at baseline; the study population was predominantly male (55% vs 62%, respectively) and white (89% vs 94%). Patients primarily carried the less favorable IL28B genotypes (67% vs 65%). A minority of patients had cirrhosis (14% vs 23%) and a majority was treatment experienced (56% vs 58%), primarily prior relapses (68% vs 65%).

Ninety-three percent of patients with genotype 2 and 85% of those with genotype 3patients achieved SVR12. Treatment naïve-patients with genotype 2 had similar response rates, regardless of cirrhosis (97% noncirrhosis vs 100% cirrhosis), while treatment-experienced patients with genotype 2 had slightly lower SVR12 (91% noncirrhosis vs 88% cirrhosis). In patients with genotype 3, the role of cirrhosis was clearer, with significantly lower response rates (60%) in treatment-experienced patients with cirrhosis than treatment-experienced patients without cirrhosis (87%), treatment-naïve patients with cirrhosis (92%), and treatment-naïve patients without cirrhosis (94%). Virologic failure was primarily due to relapse, and no factor was identified that significantly associated with relapse. No S282T mutation was identified at baseline or on relapse. Approximately 96% of patients receiving 12 weeks of therapy and 98% of patients receiving 24 weeks of therapy completed the study, with only one in each group discontinuing because of adverse events. Grade 3/4 AEs occurred in 4% and 7% of the 12-week and 24-week arms, respectively. No SAEs occurred in the 12-week arm, but 4% of patients in the 24-week arm experienced an SAE. Grade 3/4 laboratory abnormalities were similar across groups: 20% in the 12-week arm and 18% in the 24-week arm. Anemia and hyperbilirubinemia were the most commonly reported laboratory abnormalities.

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INTO THE FUTURE: INTERFERON FREE REGIMENS FOR GENOTYPE 1 INFECTION IN 2014

It is worth highlighting several phase II and III studies that provide insight into what the future holds for HCV therapies, especially for patients with genotype 1. In fact, several of these regimens are likely to be approved by regulatory bodies before the end of 2014.

Chayama K, Suzuki Y, Ikeda K, et al. All-Oral Combination of Daclatasvir Plus Asunaprevir in Interferon-Ineligible Naïve/Intolerant and Nonresponder Japanese Patients Chronically Infected With HCV Genotype 1b: Results From a Phase 3 Trial. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 211.

View journal abstract

The first all-oral regimen to be submitted for regulatory approval for the treatment of genotype 1 infection is the combination of daclatasvir (a NS5A inhibitor) and asunaprevir (a NS3/4 protease inhibitor); this regimen was submitted for regulatory review in Japan for treating genotype 1b in November 2013. The phase III study to support the submission was presented at the Presidential Plenary at AASLD 2013. This open-label, parallel-group study (AI447-026) investigated daclatasvir (60mg once daily) and asunaprevir (100mg twice daily) for 24 weeks in Japanese patients with HCV genotype 1b who were interferon-ineligible-naïve, interferon intolerant (N = 135), and had prior interferon/ribavirin nonresponse (N = 87). The study population was quite different from that we generally see in US- and European-based studies: the patients were significantly older, with a median age of 62.5 years, and 40% ≥ 65 years. The population was predominantly female (65%) and 50% carried the favorable IL28B genotype. Ten percent of the study population had cirrhosis and of those with previous nonresponses, 55% had null responses. In the modified intention to treat analysis, approximately 85% of patients met the primary endpoint of SVR24 (87% for interferon-ineligible/intolerant, 80.5% nonresponse). Eight-seven percent of patients completed treatment, with 6.8% discontinuing for lack of efficacy and 5% for adverse events. Seventeen patients experienced either virologic breakthrough or had a detectable HCV RNA at the end of treatment; failures of therapy were associated with emergence of both NS5A and NS3 resistance-associated variants. These two investigational agents are currently in phase II study in combination with a nonnucleoside polymerase inhibitor for treating patients with genotypes 1a and 1b.

Lawitz E, Hezod C, Varunok P, et al. Interferon- and ribavirin-free regimen of ABT-450/r + ABT-267 in HCV genotype 1b-infected treatment-naïve patients and prior null responders. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 75.

View journal abstract

The PEARL-I is a phase II trial investigating the efficacy and safety of a dual-DAA, interferon- and ribavirin-free regimen for the treatment of chronic HCV genotype 1b infection. Similarly to the AI447-026 trial, this study provides the insight that the number of active DAA and the length of treatment required to achieve viral eradication depends on the virus, the host, and the potency of the drugs used in combination. This interim analysis was presented on two of eight study groups, which included patients with chronic genotype 1b infection without cirrhosis, who were treatment-naïve (N = 42) or had previous nonresponse to interferon/ribavirin (N = 40). Patients were allocated to 12 weeks of ABT-450 (a NS3/4 protease inhibitor that requires ritonavir boosting for once-daily dosing) and ABT-267 (a once-daily dosed NS5A inhibitor). As expected, the baseline characteristics of the two groups were different, with treatment-naïve patients more likely to be male (59.5% vs 37.5%) and more likely to be black race (26.2% vs 2.5%). The treatment-naïve patients were more likely to carry the favorable IL28B genotype (32% vs 5%) and more likely to have moderate to severe fibrosis (F2-F4) (50% vs 25%). In the intention-to-treat analysis, 95% and 90% of patients achieved SVR12 in the treatment-naïve and the null responder groups, respectively. The only virologic treatment failures occurred in the null responder group, with one virologic breakthrough and three relapses; all four patients had resistance-associated variants at the time of failure and two of these patients had resistant variants in the NS5A gene at baseline. These two investigational agents are currently in phase III study in combination with a nonnucleoside polymerase inhibitor for treating genotype 1a and 1b infected patients and is likely to be one of the first all oral regimens approved for use in genotype 1 patients in the US.

While these first two studies focused on using a dual DAA, interferon and ribavirin-free regimen for genotype 1b infection, the next two studies attempted to provide insight on shortening the treatment of genotype 1 infection with both dual and triple DAAs and interferon-free regimens and explored the efficacy in more difficult-to-treat patients with cirrhosis who previously failed NS3/4 protease inhibitor triple therapy.

Lawitz L, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C: The LONESTAR Study. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 215.

View journal abstract

The LONESTAR study is a randomized, open-label, single center study investigating the recently approved NS5B nucleotide analogue, sofosbuvir, in combination with an investigational NS5A inhibitor, ledipasvir, with or without ribavirin for treatment in two study populations: treatment-naïve patients without cirrhosis (cohort 1) and patients who had failed prior triple therapy (cohort 2, 50% of whom had cirrhosis). In cohort 1, patients were randomized to dual DAA therapy with or without weight-based ribavirin for eight weeks (N = 21 and 20, respectively) or dual DAA therapy alone for 12 weeks (N &equal; 19). In cohort 2, patients were randomized to dual DAA therapy with or without ribavirin for 12 weeks (N = 21 and 19, respectively). The study population was predominantly male (66%) and white (91%). Most patients were infected with genotype 1a (87%) and few carried the favorable IL28B genotype (15%). All groups achieved SVR12 ≥ 95%. Two relapses occurred in the ribavirin-free arms and one patient was lost to follow-up after SVR8. One of the patients with relapse developed the S282T mutation and multiple NS5A resistance-associated variants at the time of relapse; this patient was retreated with the same dual therapy in combination with weight-based ribavirin for 24 weeks and has now achieved SVR12.

Kohli A, Sims Z, Marti M, et al. Combination oral, ribavirin free, antiviral therapy to optimize treatment outcomes for hepatitis C Treatment naïve patients: Interim results from the NIAID SYNERGY Trial (6 & 12 weeks therapy). The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract LB-8.

View journal abstract

The SYNERGY study is an open-label, NIAID-led trial investigating multiple DAA combinations in an attempt to shorten treatment duration in a difficult-to-treat Washington, DC population. The study combined sofosbuvir with ledipasvir (NS5A inhibitor) as a once daily, fixed- dose combination (FDC) for 12 weeks in patients with HCV genotype 1 who were treatment-naive at all stages of liver disease or combined the FDC with an additional investigational agent, either GS-9669 (a once- daily dosed nonnucleoside NS5B inhibitor) or GS-9451 (a once-daily dosed NS3/4 protease inhibitor), for six weeks in treatment-naïve patients with HCV genotype 1 without cirrhosis. The study population was primarily black race (88%) and male (72%). The population comprised a difficult-to-treat population including 80% with the unfavorable IL28B genotype, 70% with HCV genotype 1a, and 28% with stage F3/4 fibrosis. This interim analysis presented SVR4 data for all treatment arms with response rates of 100% (20/20), 90% (18/20), and 100% (20/20) for the FDC, FDC+GS-9669, and FDC+GS-9451 arms, respectively. There were no treatment discontinuations and two grade 3/4 events including elevated ALT and hypophosphatemia. These data suggest the addition of a third agent to a potent DAA combination regimen could shorten the length of treatment even in difficult-to-treatment populations, but larger studies are needed to show that this in fact holds true with larger numbers.

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OPT-OUT HCV TESTING AMONG BABY BOOMERS IN THE EMERGENCY DEPARTMENT CONFIRMS THIS IS A HIGH RISK POPULATION

Galbraith JW, Franco R, Rodgers J, et al. Screening in the emergency department identifies a large cohort of unrecognized chronic HCV infection among baby boomers. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract LB-6.

View journal abstract

In one of the first reports of HCV testing in an emergency department (ED), this study set out to describe the experience of integrated, opt-out HCV screening of baby boomers presenting for care to an urban academic medical center. This ED already has a routine, integrated opt-out HIV screening program which screens > 20,000 individuals per year and has reported a prevalence of new HIV diagnoses of 0.25%. Medically and/or surgically stable patients born between 1945 and 1965 who were able to complete a verbal questionnaire were included. The Abbott ARCHITECT anti-HCV assay was used for all testing and had a turn-around time of 29 minutes. A positive anti-HCV resulted in a reflex HCV quantitative RNA test. All HCV testing results were recorded in the medical record, and the ED providers disclosed the results to the patients and provided care linkage information for those patients who tested anti-HCV positive. This interim analysis reported six weeks of testing and a 90.8% (N = 1,148) acceptance rate for testing. Of the 984 anti-HCV tests performed, 12% were anti-HCV positive and of those, 72.5% (N = 71) had quantifiable HCV RNA consistent with active HCV infection (overall 8.7% prevalence). Men, African Americans, and patients on public or federally funded insurance plans or patients who were uninsured had higher anti-HCV prevalence rates (16.5%, 13%, 17.2%, and 16.7%, respectively). Linkage-to-care rates were not reported. These data confirm what has been previously reported by NHANES data: uninsured people who are anti-HCV positive are more likely to use emergency departments for their health care than other venues of care. The investigators argue that the ED may be an important venue for HCV testing in the baby boomer population; however, whether emergency departments and hospitals have the resources to implement such testing is yet to be determined

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HEPATITIS B VIRUS: HOW DO WE PROTECT OUR PATIENTS FROM THE INFECTION AND SCREEN THEM FOR HEPATOCELLULAR CARCINOMA ONCE INFECTED?

Investigators from the Alaska Native Tribal Health Consortium presented two abstracts investigating important topics related to hepatitis B infection: prevention and hepatocellular carcinoma (HCC) screening.

Bruce M, Bruden DJ, Hurlburt D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 30 year follow-up study and response to a booster dose. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 187.

View journal abstract

This study aimed to understand the duration of protection of the hepatitis B vaccination series in an immunocompetent population. In 1981 a vaccination campaign of Alaska Native adults and children from 15 Alaska villages led to the immunization (three-dose series of plasma-derived HBV vaccine) of almost 1,600 Native Alaskans. Annual serologic testing was performed for the first 11 years and then at 15 years; at 22 years, serologic testing was completed on individuals in seven villages and a booster was administered to those with anti-HBs levels < 10 mIU/mL. At 30 years, Alaska Native persons who had received the plasma-derived HBV vaccine were tested for anti-HBs levels to assess long-term protection. Four hundred and thirty-three people participated in the study, 63 (14%) had received a booster dose at 22 years (group 1), 129 (30%) did not require a booster dose at 22 years because of an adequate anti-HBs titer (group 2), and 241 (56%) did not participate in the 22-year study (group 3). At 30 years anti-HBs levels were > 10 mIU/mL in 9 (14%), 85 (66%), and 123 (51%) persons from groups 1, 2, and 3, respectively. A booster dose was administered to persons from groups 2 and 3 who had anti-HBs levels < 10 mIU/mL and 33/36 (92%) and 75/85 (88%) responded with levels > 10 mIU/mL, respectively. This finding suggests excellent protection is provided by the primary vaccination series, and with the excellent booster response it is unlikely that a booster is required in an immunocompetent population.

Gounder P, Bulkow L, Bruce M, et al. Comparing the cost of screening for hepatocellular carcinoma in person with chronic hepatitis B Infection by ultrasound alone versus a two-step approach using alpha-fetoprotein followed by ultrasound. The 64th Meeting of the American Association for the Study of Liver Disease, November 1-5, 2013, Washington, DC; Abstract 370.

View journal abstract

The current AASLD guideline recommendations for HCC screening in patients with chronic HBV infection is to complete regular ultrasound-based (US) surveillance every 6 months in patients with an estimated annual prevalence of disease of > 0.2%. This includes Asian male carriers over age 40, Asian female carriers over age 50, any carrier with a family history of HCC, African American patients with active infection, and HBV carriers with cirrhosis. Alpha-fetoprotein (AFP) testing was removed from the recommendations because of rates of false positive testing and the added cost. The Alaska Native health system has screened persons with chronic HBV infection (CHB) using a two staged approach: serum AFP every 6 months and persons with AFP > 10 ng/nL received an ultrasound (AFP→US).

Using data from the Alaska Native health system, the investigators conducted a cost effectiveness analysis comparing this two stage approach to the AASLD recommendation of semiannual US testing. The data including 839 patients who were followed for 10,405 person-years (median: 11 years/person) and performed 10,931 AFP measurements

(median: measurements/person). During the follow-up period 21 patients developed HCC, 16 were detectable by screening (12 US alone, 6 AFP → US or US). US alone as recommended by the AASLD guidelines would have resulted in 78 years of life gained compared with 33 years of life gained with the two-step AFP → US approach. US alone would have cost $1.2 million ($15,300/year of life gained) and AFP → US would have cost $422,000 ($12,700/year of life gained). Although less expensive, the two-step approached would have failed to identify a majority of the cases at an earlier stage of disease when HCC is better treated. Outside of the resource-limited setting, this surveillance method is not recommended.

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COMPLETE THE POST-TEST

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PHYSICIAN POST-TEST

NURSE POST-TEST