CME NEWSLETTER

Advances in Chronic Hepatitis C Management and Treatment

Reporting From

THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD) ANNUAL MEETING

(This coverage is not sanctioned by the conference organizers and is not an official part of the conference proceedings.)

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Introduction

This newsletter is based on discussions held during the continuing medical education Internet symposium* Advances in Chronic Hepatitis C Management and Treatment. *This program provided an update on important presentations made during the 62nd American Association for the Study of Liver Diseases (AASLD) Annual Meeting, held November 4-8, 2011, in San Francisco, California.*

Faculty panel and contributors for this program consisted of course director and moderator Mark Sulkowski, MD from the Johns Hopkins University School of Medicine, Baltimore, Maryland, and panelists Nezam Afdhal, MD from the Harvard School of Medicine, Boston, Massachusetts, Fred Poordad, MD from the David Geffen School of Medicine at UCLA, Los Angeles, California, and K. Rajender Reddy, MD from the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Updates on the Current Status of HCV Therapy

Dr. Reddy began by discussing an analysis of a database that recorded causes of mortality between 1999 and 2007 in the US population.[1] The database included data on >20 million deaths. Overall, 73% of HCV-related deaths and 59% of HBV-related deaths were in patients aged 45 to 64 years. HIV-related mortality was stable during this time period, HBV-related mortality decreased, and HCV-related mortality increased and has overtaken HBV-related mortality. Certain factors, such as chronic liver disease, co-infection with other hepatitis viruses, and alcohol-related co-morbidity increased odds of death. This analysis shows that HCV-related mortality is now the major cause of death associated with chronic viral infection.

Discussion: Dr. Afdhal suggested two explanations for increases in hepatitis C–related mortality. The first is that the majority of patients were infected in the 1960s and 1970s and had decades to develop cirrhosis before being diagnosed. The second reason is that many patients with hepatitis C have not been diagnosed. By the time they present with symptoms, they may have advanced liver disease and it is too late for effective treatment. Dr. Poordad emphasized that one of the important reasons for diagnosing people with HCV infection is to counsel them about avoiding alcohol, because it can significantly increase the risk of death in people with HCV infection.

Dr. Reddy then discussed an international survey of 1,400 physicians from the United States, Canada, South America, Europe, Africa and the Middle East, and the Asia-Pacific region.[2] Survey participants treated at least 5 HCV patients per month. A 10-point Likert scale was used to assess barriers to HCV therapy (0 indicated that a factor was not a barrier, 10 indicated it was a major barrier). In the Western world – the United States, Canada, Western Europe, and the Nordic countries – the greatest barriers were at the patient level, and involved fear of side effects, prolonged treatment duration, and medication expense. In the Middle East and Africa, the provider-level barriers were strong and included lack of infrastructure, low reimbursement, and insufficient training. In Central and Eastern Europe, the greatest barriers were government-related, such as insufficient funding and lack of treatment promotion. The strongest barriers in Latin America and in the Middle East and Africa were payer-level barriers, related to lack of coverage and excessive paperwork.

Although there is heterogeneity across different regions, many barriers are common to all parts of the world and only vary in relative frequency. These findings can be used to prioritize efforts and policy changes to remove barriers. The data also suggest that efforts to build infrastructure and train providers for treatment of HCV will be needed in the next 5-10 years, similar to what was done for HIV.

Dr. Reddy discussed retrospective data from 5 large centers in Europe and Canada.[3] The data were from 529 patients who had advanced fibrosis and were treated with interferon (IFN)-based regimens between 1990 to 2003. The median follow-up was 7.7 years and 36.1% achieved sustained virologic response (SVR). In those who had SVR, it had a favorable impact on outcome compared to nonresponders. Specifically, hazard ratios for liver failure, hepatocellular carcinoma (HCC), liver-related death, and overall death were significantly higher in the non-responders compared with sustained responders ($P<0.001$). These data show the benefit of treating chronic HCV in patients with advanced liver disease.

Discussion: Dr. Sulkowski asked if SVR should be considered a cure. Dr. Poordad responded that SVR 6 months after stopping treatment should be considered a cure, and it is now clear that such a response leads to clinical benefit even in patients with advanced fibrosis before starting therapy.

Dr. Reddy discussed a study designed to address the question of whether ribavirin (RBV) can be dosed once daily rather than twice daily.[4] The study examined 10 patients with HCV genotype 1 who were dosed with RBV once daily. After 12 weeks they were crossed over to twice daily dosing. The conclusion was that the once daily regimen was pharmacokinetically comparable to the twice daily regimen, and no increase in adverse events was observed.

Discussion: Dr. Sulkowski asked why RBV is usually dosed twice daily when it can be dosed once daily. Dr. Afdhal answered that the study described by Dr. Reddy was RBV monotherapy. In contrast, RBV may be hard to tolerate when the patient is also taking IFN, largely because of gastrointestinal side effects. New IFN-free regimens are being developed, but RBV continues to be a part of treatment. So, this study was done to determine if RBV can be dosed once daily in the hope that it will be better tolerated in the newer regimens.

Dr. Reddy reviewed the ENABLE 1 study, which studied eltrombopag, a thrombopoietin agonist, and its role in augmenting platelet counts in HCV patients on pegylated interferon (PegIFN) alfa-2 + RBV therapy.[5] In the first part of the study, HCV patients (N=715) who had platelet counts <75,000/µL received open-label eltrombopag at a starting dose of 25 mg per day and escalated up to 100 mg per day or a platelet count ≥90,000/µL. After patients reached that target, they were randomized to either eltrombopag or placebo. Among enrolled patients, 78% had bridging fibrosis or cirrhosis, and the median platelet count at baseline was 59,000/µL. The primary endpoint was SVR, which was achieved in 23% of eltrombopag patients versus 14% in the placebo group ($P=0.0064$). There was also a longer interval to first HCV therapy dose reduction in the eltrombopag group ($P<0.0001$), and lower proportion of patients who had HCV therapy dose reductions in the eltrombopag group ($P=0.0029$) compared with placebo. Among genotype 1 patients, 18% achieved SVR in the treatment group versus 10% in the placebo group; for genotypes 2 and 3, the corresponding percentages were 35% versus 24%. These findings may provide a way to help patients maintain platelet counts while receiving IFN-based therapy, especially patients with cirrhosis, in whom thrombocytopenia is a problem.

Dr. Afdhal, who had presented the data at the meeting, provided more details on the study, and noted that this is the first large trial in the thrombocytopenic population. Most of the patients had evidence of portal hypertension on Doppler ultrasound, with splenomegaly and lower platelet counts. He noted that, although there was an improvement in SVR, the 23% SVR rate was modest. Drugs like eltrombopag can be associated with adverse events, including increased risk of thrombotic events, although this was not seen ENABLE 1. In ENABLE 2, however, there did appear to be more thrombotic events in the eltrombopag arm. Because of that concern, Dr. Afdhal does not recommend use of eltrombopag at this time.

Discussion: Dr. Sulkowski asked the panel what platelet counts would they require for starting therapy, and how low would they allow counts to fall before discontinuing therapy? Dr. Poordad noted that the package label for PegIFN recommends not starting therapy if the platelet count is <75,000/µL. Dr. Sulkowski noted that patients who have low platelet counts often have substantial portal hypertension and liver dysfunction, and perhaps should be treated at more advanced centers with transplant options.

Dr. Reddy concluded with a study of silymarin, an extract of milk thistle.[6] It is widely used around the world as a botanical treatment for liver disorders, and is a mixture of flavonolignans, with silibinin being the major constituent. Participants (prior nonresponders to IFN-based therapy) were randomized to receive silymarin 700 mg three times a day, 420 mg three times a day, or placebo. The primary endpoint of the study was normalization of ALT after 24 weeks, which showed no effect from treatment. There was also no change in HCV RNA levels. So, this well-conducted study found no benefits of this extract for hepatic well-being in patients with HCV.

Boceprevir Studies

Dr. Poordad discussed boceprevir (BOC) studies, beginning with several studies analyzing data from the SPRINT-2 and RESPOND-2 studies. In these trials, patients were treated for 4 weeks with PegIFN + RBV before initiating BOC or placebo. The first analysis was an assessment of the difference between 'limit of detection' and 'limit of quantification' at 8 weeks, when clinicians decide between short duration and long duration therapy.[7] In the trials, they used the limit of detection, which was HCV RNA <10 IU/mL. The analysis assessed how SVR

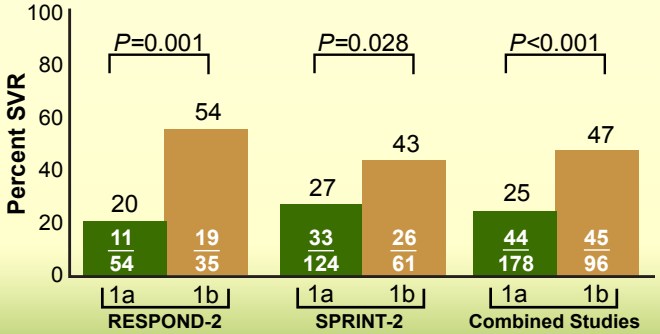
would differ if the threshold was the lower limit of quantification, or <25 IU/mL. The results revealed that as many as 20% more patients achieved SVR if the lower limit of detection was used, so this measurement should be used for response-guided therapy. This result should apply to telaprevir (TVR)-based regimens as well. This finding is important because many clinicians do not get the lower limit of detection.

Discussion: Dr. Sulkowski noted that the FDA clearly indicated in the labels for TVR and BOC that, in order to qualify for shortened therapy, patients must satisfy the criteria for undetectable HCV RNA. But Dr. Afdhal noted that some assays being used in clinics do not have <10 IU/mL as their standard lower limit of detection. Some have a limit of detection as high as 19 IU/mL. Every clinician should strive to use a lab that uses an assay they are familiar with and achieves a lower limit of detection close to 10 IU/mL.

Dr. Poordad then presented additional data from the same study, which showed how the results differed when PCR values were obtained at weeks 7, 8 or 9. At week 7, 47% of patients would have been found to be undetectable, but this percentage increased to 66% at week 9. This result indicates that this time period is a critical one, during which viral activity becomes negative. It looks like the best time to perform the test to determine if patients are eligible for response-guided therapy is just before the 9th IFN injection in patients receiving BOC, and before the 5th IFN injection in patients receiving TVR.

Another analysis discussed by Dr. Poordad focused on patients who had <1 $\log_{10}$ unit decline in HCV RNA after 4 weeks of PegIFN lead-in therapy.[8] As shown previously, among patients who do not have a 1 $\log_{10}$ decline at the end of 4 weeks, the eventual SVR is around 30%. Among patients who do have a 1 $\log_{10}$ decline, the SVR is around 80%. The current analysis looked at patients who had less than 1 $\log_{10}$ decline at the end of week 4 to determine if there were any differences that could be detected. The analysis of this subgroup found that genotype 1b patients were significantly more likely to achieve SVR than genotype 1a patients (47% vs. 25%; P<0.001) (Figure 1).

Figure 1. SPRINT-2 and RESPOND-2: HCV G1 Subtype as a Predictor of SVR in Patients with Poor IFN Response (BOC Arms Combined)



Discussion: Dr. Sulkowski noted that genotype 1a patients are particularly vulnerable when IFN therapy does not work well, and asked why. Dr. Afdhal responded that these patients have a much greater ability to develop mutations that give them resistance to the BOC component of treatment. Patients with genotype 1a have a lower genetic barrier to BOC resistance. Dr. Sulkowski noted that both genotype 1a and 1b patients respond very well to triple therapy that includes BOC or TVR. Dr. Afdhal commented that the genotype might affect how he proceeds in patients who do not achieve 1 $\log_{10}$ reduction in HCV RNA levels after PegIFN lead-in therapy.

Dr. Poordad than presented a related analysis showing that, among patients who had <1 $\log_{10}$ decline in HCV RNA at week 4 and subsequently had <3 $\log_{10}$ decline at week 8, 0% achieved SVR. He noted that this result may change his practice because the risk-benefit ratio suggests that these patients will not benefit from treatment beyond week 8. Dr. Afdhal takes a different approach; he is less likely to initiate BOC at week 4 in patients who have <1 $\log_{10}$ decline in HCV RNA at that time. The current stopping rule is to treat patients until week 12, however, and both clinicians noted that they have options available to them that other clinicians do not because they are clinical trial investigators.

Dr. Poordad then showed results of another substudy of SPRINT-2 and RESPOND-2. This study showed that with increasing viral load (VL) at baseline, >1 million IU/mL, >5 million IU/mL, and >10 million IU/mL, there is a slight downward trend in efficacy with BOC.[9] Although the trend was not statistically significant, it suggests that patients who have a high viral load are less likely to achieve SVR.

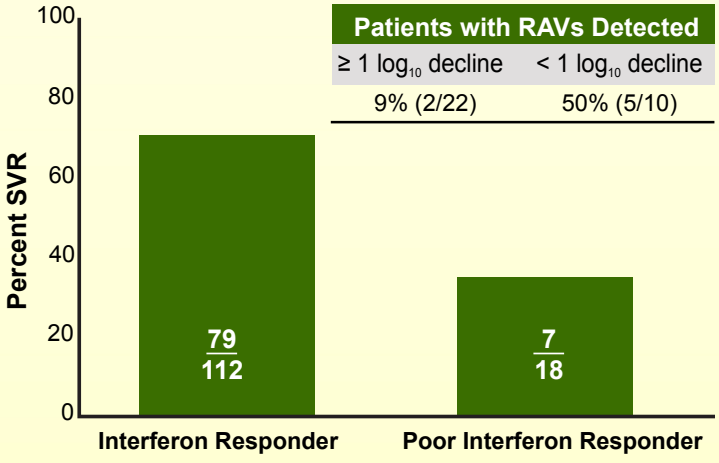
Discussion: Dr. Reddy pointed out that the effect of VL with BOC was substantially weaker than that seen with PegIFN + RBV, and he indicated that he does not consider baseline VL an important factor when using protease inhibitor (PI) therapy.

Dr. Poordad then presented another study that analyzed stopping rules for BOC using data from the SPRINT-2 trial.[10] This study found that the normal stopping rule for BOC (stop therapy if HCV RNA >100 IU/mL at week 12) left no patients untreated who would have achieved an SVR. This stopping rule maximizes the number of patients who can be stopped for futility without depriving any patients of the opportunity to achieve SVR. Another subanalysis looked at the subset of non-cirrhotic, black patients who had an early response (HCV RNA undetectable at week 8-24).[11] These patients had high SVR rates, comparable to white patients. In addition, response-guided therapy for the rapid responders in the black population was as effective as in the non-black population. Dr. Sulkowski pointed out that cirrhotic patients should receive a full 48 weeks of triple therapy. The same subanalysis found that black patients were no more likely than white patients to experience neutropenia or lymphopenia.

Dr. Poordad then discussed studies of drug-drug interactions involving BOC. While TVR is metabolized by cytochrome P450, BOC has dual mechanisms of clearance. The primary pathway is the aldoketoreductase pathway. The other is the CYP3A4 pathway. The clinical ramifications of this are not yet clear. However, the effect of concomitant medication used in the clinical trial, including SSRIs, methadone, and oral contraceptives, was analyzed.[12] There were no differences in SVR rates. Dr. Poordad noted that he generally continues the same dose of these antidepressants or methadone, although clinicians should be vigilant for potential toxicity of methadone, and may need to reduce the dose. With oral contraceptives, a second barrier method of contraception should be used to prevent an unwanted pregnancy.

Another study presented by Dr. Poordad reported that patients who have IFN responsiveness are less likely to have resistance-associated variants than if they are not IFN responsive (Figure 2).[13] Another study found that fewer patients with low ITPA (inosine triphosphatase) activity experienced anemia, yet they had numerically higher SVR rates.[14] Anemia is sometimes thought of as a surrogate for RBV exposure, but there is a subset of patients who do not have much anemia and yet have good SVR rates. At this time, a test for ITPA activity is not widely available.

Figure 2. Patients with Poor IFN Response Are More Likely to Have Resistance-Associated Variants (RAVs)



The final study presented by Dr. Poordad was an interim analysis of null responders in the PROVIDE study.[15] Patients in the control arm of BOC clinical trials and who were null responders (failed to achieve 2 $\log_{10}$ decline in HCV RNA at week 12 of PegIFN + RBV) were then given access to BOC, open label. The SVR rate for this group was 38%, confirming that null responders do not respond well to the addition of BOC.

Telaprevir Studies

Dr. Sulkowski then presented studies on TVR, beginning with several subanalyses of the REALIZE trial. The REALIZE trial was a large, international study in people who had failed PegIFN + RBV: relapsers, partial responders, and null responders.[16] They were randomized to TVR or placebo, with all patients receiving PegIFN + RBV. A number of investigators pooled data from the two TVR arms, which included nearly 500 patients, and then performed retrospective analyses to better refine how we treat this patient group. Individuals who were prior relapsers had good SVR rates (87% to 84%) across histological stages (ranging from no fibrosis to cirrhosis, respectively). Prior partial responders had lower SVR rates that declined with more advanced disease (77% to 34%). Among prior null responders, SVR rates were 41% and 42% in patients with non-cirrhotic histology or bridging fibrosis, falling to 14% in patients with cirrhosis.

Discussion: Dr Sulkowski asked the panel how these data impact use of TVR in their clinics. Dr. Afdhal noted that the first thing it impacts is the discussion with patients. Prior relapsers have a good chance of responding, even if they have cirrhosis. Most prior partial responders had an SVR rate above 50%, but prior null responders remain a challenge. Dr. Reddy noted that his approach in patients with cirrhosis is to try the new treatment following the stopping rules, because it is unlikely to hurt them and may provide benefit.

A study presented at AASLD explored reasons why some patients treated with TVR in REALIZE did not achieve SVR.[17] Among 139 cirrhotic patients in the study, 73 (53%) failed to achieve SVR and 47% achieved SVR. One-third (32%) had virologic failure, so likely selected for a resistance variant, and about 12% relapsed. Thus, it is likely that in this group of cirrhotic patients who failed TVR-based therapy, about half had resistant HCV variants.

Dr. Sulkowski then presented several studies on the impact of baseline factors on responses in REALIZE. The first study examined insulin resistance determined by HOMA-IR among 578 patients in the REALIZE trial.[18] As many as 28% of patients had high HOMA scores, suggesting that they were insulin resistant. As insulin resistance scores increased, SVR declined from 72% to 59%. However, after adjusting for factors such as cirrhosis, insulin resistance was not an independent predictor of SVR.

Another study focused on a multivariate model of factors affecting SVR that took into account baseline factors, as well as the addition of extended rapid virologic response (eRVR).[19] In the model that did not include eRVR, factors such as baseline viral load, fibrosis stage, and LDL levels were important predictors of SVR, and the strongest predictor was prior IFN response. However, when the model included eRVR, it was by

far the strongest predictor, although prior IFN response was still significant. This analysis also examined SVR rates among individuals who achieved an RVR, subdivided according to prior IFN response. Even among prior null responders, those who had an eRVR (viral load undetectable at week 4) had a 71% chance of achieving SVR.

This study also looked at predictors of SVR after the 4 weeks of lead-in therapy. Among prior relapsers and prior partial responders, those who had any response at 4 weeks, even a half $\log_{10}$ decline in HCV RNA, had reasonably high SVR rates (60%-67%). Prior null responders did better when they had at least a 1 $\log_{10}$ response at 4 weeks.

Discussion: Dr. Sulkowski noted that these data give us two metrics to predict SVR: week 4 on-treatment response and week 4 lead-in response. Dr. Poordad noted that the sample sizes for some of these studies were very small. He continues to look for IFN responsiveness in patients who have a low likelihood of achieving SVR. One of the reasons for this is that he has the option of putting those patients in a clinical trial. In his practice, it may not be worth starting a PI in patients who have only 15%-20% chance of achieving SVR. Dr. Sulkowski noted that a 1.5 to 2 $\log_{10}$ decrease in HCV RNA after lead-in treatment appears to be enough to increase the odds of SVR in many patients

Another subanalysis of the REALIZE study looked at patients who became anemic (Hb <10 g/dL), while receiving triple therapy.[20] Anemia was more common among those receiving TVR-based triple therapy (41%) compared to PegIFN + RBV (22%). It was linked to older age–which is not a surprise because renal function begins to decline causing RBV to accumulate–lower BMI, and more advanced fibrosis. The dose of RBV was reduced because of anemia in 25% of patients (versus 12% on control patients). Although there was a lot of concern about reducing RBV dose in these hard-to-treat patients, the analysis found that SVR rates were actually somewhat better in patients who had RBV dose reductions. For example, among the prior null responders, SVR was achieved in 39% who had RBV dose reduction and 30% of those who did not. Dr. Poordad noted that this may be expected because hemoglobin decline confers a higher likelihood of response. Dr. Sulkowski emphasized the importance of monitoring hemoglobin, especially in cirrhotic patients, and intervening early with RBV dose reductions before hemoglobin levels fall too severely.

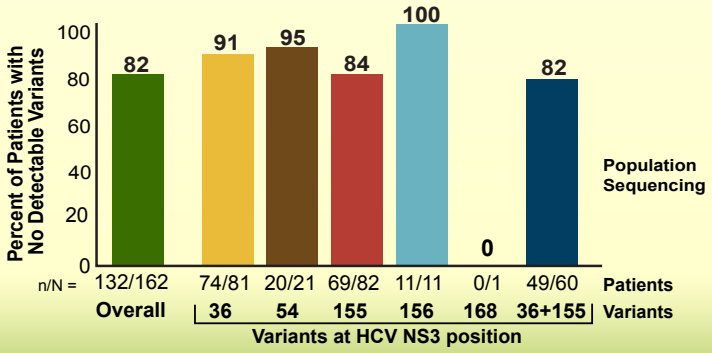
The next study discussed was a 24-week interim analysis of TVR-based triple therapy in patients with HCV-HIV co-infection.[21] This was a controlled trial that enrolled patients with HIV either on no antiretroviral therapy or on antiretroviral therapy that included efavirenz (EFV), tenofovir (TDF)/emtricitabine (FTC), or atazanavir boosted by ritonavir (ATV/r) plus the same backbone. Overall response data at 24 weeks were presented according to HIV regimen. Because of drug-drug interactions, patients on EFV were given higher doses of TVR. At 24 weeks (12 weeks of triple therapy and 12 additional weeks of PegIFN + RBV), about 70% of patients had undetectable HCV RNA. The adverse event (AE) profile was consistent with that seen in HCV mono-infected patients, with one exception: ATV patients had higher bilirubin, probably because of ATV's well-known association with hyperbilirubinemia.

Discussion: Dr. Sulkowski asked the panel if they are treating HIV-HCV co-infected patients? Dr. Afdhal replied that he does not treat them because he believes an HIV expert should be involved. Dr. Reddy asked about the patients not receiving antiretroviral therapy for HIV during part of this trial. Dr. Sulkowski replied that the patients in this study had very high CD4 cell counts and very low HIV RNA levels. In general, he recommended treating HIV with the highest priority and switching to a regimen that is compatible: raltegravir (RAL), EFV or ATV. He is concerned about taking patients off of their HIV therapy.

Dr. Sulkowski then discussed data about resistance and durability from the EXTEND study.[22] The analysis included individuals who took TVR and PegIFN + RBV and achieved SVR. The results showed that 99% of those responses were durable, out to an average of 21 months. One patient who was treated for only 10 weeks in the PROVE-2 study had a late relapse. These data indicate that a TVR response is likely to be as durable as a PegIFN + RBV response. Looking at liver-related clinical events, none of the 223 SVR patients had an event during the short-term follow-up, compared to 4 of 185 patients who did not achieve SVR (two cancers, one encephalopathy, and one liver decompensation). These results indicate that clinical benefits are already appearing.

An analysis of EXTEND focused on patients who had resistant variants detected by population sequencing at the time of failure. However, at their last visit, the investigators found that 82% no longer had the resistant variant detected, suggesting that they returned toward a wild-type state. This finding was consistent across many variants, including the 155 variant (Figure 3).

Figure 3. EXTEND: Patients with No Detectable Resistant Variants by Last Visit



The final study presented by Dr. Sulkowski looked at 9 patients who were treated with TVR monotherapy in phase I clinical trials, and were retreated with triple therapy in a C219 rollover study.[23] Six of these 9 were genotype 1a and 8 had resistance variants detected at the time they failed monotherapy. A lot of time went by before they were offered retreatment, and deep sequencing was done prior to retreatment. None of these resistant variants were detected at that time. When the patients were treated with triple therapy, all but one achieved undetectable HCV DNA levels. One emerged with resistance.

Discussion: Dr. Sulkowski asked the panel about the implications of these findings for the belief that triple therapy can induce resistance. Dr. Poordad responded that the patients in this study were initially treated with a regimen that did not include IFN, which is very different than developing resistance in a setting where they are receiving triple therapy. It should be noted that, in general, when patients fail a PI, we cannot expect a different outcome by retreating with the same PI. The lack of IFN was a key difference in this study. Dr. Reddy also emphasized that stopping rules should be adhered to carefully to avoid harming patients.

Novel Therapies and Strategies

Dr. Afdhal discussed novel therapies and strategies, beginning with a focus on combination regimens. The goal of this research is to combine agents that inhibit HCV to obtain regimens that profoundly suppress a broad range of viral variants, including pre-existing and emergent variants. There are numerous drugs in the HCV pipeline at the moment, and they work through many different mechanisms.[24] In the last 6 months, the first two PIs have been approved, but the pipeline also includes drugs targeting host factors and agents that can affect the ability of the virus to infect the cell. When some of these are approved, the issue will be to combine them to get simple, safe, and effective regimens. There are a lot of challenges to achieving these goals, including defining baseline predictors of response for defining whom to treat and how to tailor therapies and durations. New therapies will be associated with new kinetics of viral suppression, requiring new rules for predicting response. Resistance issues include baseline variants and cross-resistance. We may also need to redefine markers of complete viral eradication, and identify and balance additional toxicities. Finally, cost is a significant issue. We have to be cognizant that there is a price per cure, as with HIV.

Dr. Afdhal discussed studies of newer PIs in combination with PegIFN + RBV. The PILLAR study examined TMC435 in different groups of patients at different doses, using a response-guided therapy strategy.[25] Patients who had negative HCV RNA levels at week 4 and week 12 had their duration of therapy shortened to 24 weeks, otherwise patients received a full 48 weeks of treatment. In patients receiving 150 mg TMC435 using response-guided therapy, SVR rates were 80.5%. TMC435 is a once-daily medication with a favorable side effect profile. Danoprevir, another PI, was studied in the ATLAS study in combination with IFN and RBV.[26] Among patients receiving the higher dose (600 mg twice daily), 80% were eligible for shortened duration of therapy. Among those who had the shortened duration of therapy, 95% achieved SVR. Because we are always trying to shorten duration of therapy, we have to try to achieve negative HCV RNA status earlier. This study showed that improvements can be made over TVR and BOC, which had 50%-60% of patients eligible for shortened therapy in clinical trials.

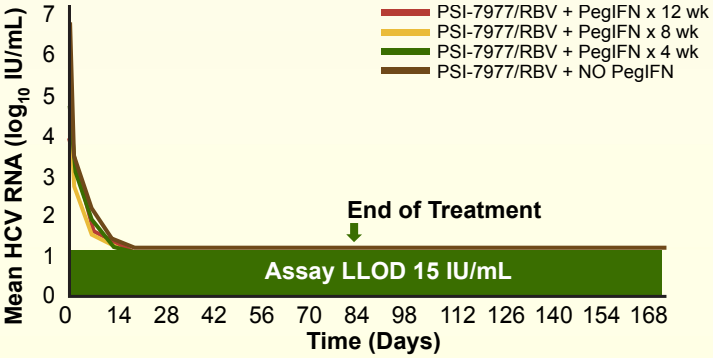
Dr. Afdhal then discussed research with PSI-7977, a polymerase inhibitor. In the PROTON study, patients received different treatment regimens according to HCV genotype.[27] In the genotype 1 arm, patients were randomized to one of two doses of PSI-7977 plus PegIFN and RBV, or control. Standard response-guided therapy rules were used: patients who were HCV RNA negative at weeks 4 and 12 got 24 weeks of treatment. They were able to use response-guided therapy in the majority of patients, and they had SVR rates above 90%. Patients who had RVR or eRVR also had >90% SVR rates, indicating that those patients may be eligible for only 24 weeks of treatment. The SVR 12 was also above 90%. PSI-7977 had a favorable toxicity profile and was administered once daily.

In naïve, difficult-to-treat patients with IFN-insensitive genotypes, there was a rapid reduction in viral load among all 13 patients. They were treated with a 12+12 protocol and all 13 achieved SVR. These findings suggest that as the potency of treatments improves, established predictors of response, such as nonresponse to IFN, may become less important.

Dr. Afdhal then presented results of the ELECTRON study, which enrolled patients at a single site in New Zealand.[28] There were 4 treatment cohorts with 10 patients per cohort. Patients were treatment naïve, non-cirrhotic, and had genotype 2 or 3 HCV. Three treatment regimens contained IFN and one was IFN-free. The IFN-containing regimens were designed to be 1) 12 weeks of triple therapy with PSI-7977and PegIFN + RBV, 2) triple therapy for 8 weeks followed by PSI-7977 + RBV for 4 weeks, or 3) triple therapy for 4 weeks followed by PSI-7977 + RBV for 8 weeks. The IFN-free regimen was PSI-7977 + RBV for 12 weeks.

At 2 weeks, a significant proportion of patients (>80% in each group) were already below the limit of detection. By week 4, 100% of patients across every group were below the lower limit of detection, and this was maintained through weeks 8 and 12. SVR rates were 100% in all groups. Furthermore, the kinetics of viral suppression were similar across the 4 groups, and there were no patients who did not respond or who responded less well (Figure 4).

Figure 4. Mean HCV RNA Levels in ELECTRON



This study included another group of patients (N=10) who received only PSI-7977 monotherapy. Six of these patients achieved viral suppression, but 4 had viral recurrence at week 12. This result supports the continued use of RBV. The side effect profile of PSI-7977 was favorable, with most AEs occurring while patients were receiving IFN.

Discussion: Dr. Poordad reiterated the value of RBV, and also pointed out that the patients in this study were genotype 2/3 and non-cirrhotic. He noted that he would like to see a longer SVR (24 weeks after stopping therapy) to be assured that there were no late relapsers. He also noted that IFN seemed to be doing something in the preceding studies of genotype 1 patients, in which SVR rates were below 100%. It was noted that an IFN-free regimen was being studied in a phase 3 trial, but only in genotype 2/3 patients at this time.

The last study presented by Dr. Afdhal was a small study of an all-oral combination therapy being developed for genotype 1 patients. Previous research has shown that combination of an NS5A inhibitor (BMS-790052) with a PI (BMS-650032) gave a 36% SVR in prior null responders. Analysis of genotypes showed that 2 of 2 genotype 1b patients responded, compared to 2 of 9 genotype 1a patients. The remaining genotype 1a patients had breakthrough with multiple resistance mutations to both drugs. In the more recent study from Japan presented as a late breaker at AASLD, the exact same two drugs were used, albeit at somewhat higher doses, in genotype 1b patients who were non-cirrhotic and prior null responders.[29] Patients (N=10) initially received a 600 mg, twice daily dose of the PI, but that was reduced in response to ALT elevations seen in a different trial. Patients were treated for six months. At week 4, 40% were HCV RNA negative, which increased to 90% by week 12 and remained at 90%. The one patient who did not achieve negative HCV RNA dropped out at week 2 because of an unusual constellation of symptoms. This study is another confirmation of very high SVR rates among patients treated with new IFN-free regimens in development.

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