A CME Newsletter

Advances in Chronic Hepatitis C Management and Treatment

Reporting From Digestive Disease Week 2011*

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

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

Introduction

The following newsletter describes discussions held during the Advances in Chronic Hepatitis C Management and Treatment Internet symposium, an update on presentations made during Digestive Disease Week (DDW 2011), held May 7-10, 2011, in Chicago, Illinois. The symposium reviewed and discussed the key studies on chronic hepatitis C management and treatment presented during this conference.

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

Updates on Current Status of HCV Therapy: Dr. K. Rajender Reddy

Dr. Reddy started the symposium by discussing the Extension for Community Health Outcomes (ECHO) study.[1] In this program, primary care clinicians in rural areas and prisons were trained to treat HCV in rural New Mexico. The investigators wanted to demonstrate that such care is as safe and effective as in the university clinic, and that this type of program would improve access to HCV care for minorities. The program used technology-based learning, which cuts down on the amount of resources needed, and focuses on improving outcomes by reducing variation in processes of care and sharing best practices.

The ECHO team conducted a prospective study in which the university served as a control and intervention groups were community-based clinics and the New Mexico Department of Corrections. They used standard inclusion/exclusion criteria for treating patients with pegylated interferon (PegIFN) and ribavirin (RBV). Primary care physicians, who had interactions with the university physicians, provided treatment in the community. 407 HCV patients met inclusion/exclusion criteria. Most of them were men; 65% were minorities and the majority were HCV genotype 1 patients, with average viral loads of about 6 logs IU/mL.

The investigators found the sustained virologic response (SVR) rates were similar at the University of New Mexico clinic and in the rural areas where primary care physicians treated patients. The results for HCV genotypes 2 and 3 were similar, as well. These results suggest that rural primary care physicians can treat patients with HCV with outcomes equal to a university clinic, and that this is an acceptable model for treating patients safely and effectively.

Discussion: Dr. Sulkowski asked, is this a model we can apply? Can we get more patients on treatment with the protease inhibitors using this type of model? Dr. Poordad responded that this is an excellent model and probably the only realistic way that we are going to have enough outreach to get expertise from a medical center to help individuals in rural areas. He said it is groundbreaking and could serve as a prototype for the future. Dr. Sulkowski then asked about urban settings, where there is a high prevalence of HCV – who is going to do the treatment? In ECHO, the interesting thing was that primary care providers were trained. What will happen in urban settings? Dr. Afdhal replied that he and his colleagues are adapting the ECHO project to Boston and New England. Their goal is to expand treatment access to large community care centers within the city

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to involve more infectious disease specialists in treatment and to try to take treatment in a more comfortable way to the patients and treat them at home. He added that they are also attempting to expand treatment into joint care with centers such as methadone clinics. He said that clinicians should take the technology and apply it to different settings and validate the ECHO results in those centers. Dr. Reddy added that for clinicians, this would give a sense of confidence that they can partner with experienced centers and be able to treat patients. Dr. Sulkowski stated that treatment is only effective if we actually get patients into treatment, and we know that we are going to need innovative models to do so.

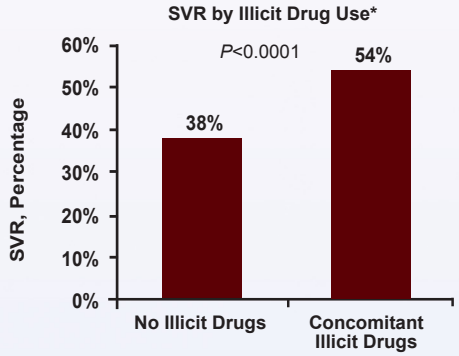
A study that examined whether patients who have achieved SVR have a decreased risk of hepatocellular carcinoma (HCC) was reviewed.[2] This was a large retrospective cohort study of patients with HCV cirrhosis. They examined the impact of treatment on the risk of liver cancer. The study demonstrated that if patients with a background of cirrhosis have SVR, there is a decrease in the risk of cancer by 75%. Patients who were treated but did not achieve SVR also had a decreased risk of cancer of 31%. Patients who had regular screening were often picked up with cancer, and the older patients were also more often diagnosed with cancer.

Discussion: Dr. Sulkowski asked Dr. Afdhal how he screens cirrhotic patients for HCC, how often he screens them and how long did he screen after SVR? Dr. Afdhal responded that American Association for the Study of Liver Diseases (AASLD) guidelines suggest that for screening, clinicians should use a cross-sectional imaging test, either ultrasound or MRI alternating with ultrasound. He said he rarely uses CT, because of the radiation load. In cirrhotic patients, he screens every six months. He always screens cirrhotic patients after SVR, and continues to screen them until they no longer have cirrhosis. Dr. Reddy added that even if patients have achieved an SVR, clinicians should continue to monitor them. If they have cirrhosis, they could come back to the clinic for surveillance. Dr. Sulkowski added that they have been cured of HCV but not necessarily of liver disease.

Next, Dr. Reddy discussed a retrospective analysis of over 6,000 US veterans treated for HCV; of these, about 3,500 had rapid virologic response (RVR).[3] In genotype 1 patients, favorable predictors of RVR were low viral load and low AST. The unfavorable predictors were African American race, LDL <100 mg/dL, elevated ferritin and comorbid conditions such as diabetes and advanced fibrosis/cirrhosis. About 15% of genotype 1 patients had RVR. In those patients, SVR rates were up to 52%. Genotype 2 and 3 patients had a higher SVR. Based on these findings, clinicians can tell their patients that if they have a low viral load, they are more likely to achieve RVR, although this is likely to change with the new drugs.

Dr. Reddy then discussed a German study conducted between 2005 to 2010.[4] The investigators studied 1,630 patients with a history of substance abuse. The overall SVR rate was 50%, and about 767 patients were on stable opioid maintenance. The investigators looked at patients who had no illicit drug use, those who abused between one and three drugs, and those who abused four or more drugs. They found that there was a good SVR rate even in those who had concomitant illicit drug use: 54% versus 38% in those who were not using illicit drugs (Figure 1). This study demonstrates that illicit drug use does not compromise SVR.

Figure 1. Concomitant Substance Abuse Did Not Reduce SVR in HCV Treatment



* Drug use consisted of cocaine (4.7%), opiates (7.8%), benzodiazepines (8.3%), amphetamines (1.2%), cannabis (26.1%)

Discussion: Dr. Sulkowski stated that this was an important study, and the data are impressive and reassuring. He asked Dr. Poordad how he manages HCV patients with concomitant drug use. Dr. Poordad stated that he handles each patient on a case-by-case evaluation. He thinks that in many cases it is a life-long process - it is not as simple as them simply stopping drug use one day. They have relapses. Clinicians have to be aware of possible liver disease and treat aggressively. Dr. Sulkowski expressed his view that addiction can be thought of as a disease that calls for addiction specialists working with clinicians treating patients with HCV. Dr. Afdhal noted that one message from this study was that people who are actively using illicit drugs can be very compliant. In this study, patients were in methadone clinics, were seeing their regular general practitioners, and most of this management was done in the community. They were very compliant and were doing well. Dr. Afdhal said a second issue associated with drug abuse is re-infection, although many were abusing non-IV drugs, such as cannabis or cocaine. So, as Dr. Poordad said, we have to individualize our approach to each patient. We should not deny therapy to patients because of their abuse of illicit drugs. It is worth pointing out that the fastest growing group of patients

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with HCV in the United States is young people who have had drug use as their risk factor. Therefore, this study looked at the people that clinicians are diagnosing with HCV today. Dr. Reddy added that with a careful monitoring and good support system, these patients can do well during treatment for HCV.

The final study Dr. Reddy addressed was a presentation from DDW of data from the IDEAL study. Patients were treated with either PegIFN α2b and RBV or PegIFN α2a and RBV.[5] He explained that many clinicians believe that neutrophils are important in the context of infection. But this study suggests that lymphocytes may be more important. In this study, about 36% of HCV patients had infections of any grade, and about 19% had moderate to life-threatening infections. According to the data, predictors of serious infections were minimum on-treatment lymphocytes and female gender – but not neutrophils. As the number of lymphocytes gets progressively smaller and moves toward zero, there is a higher probability of serious infection.

Discussion: Dr. Afdhal said that clinicians may have been looking at the wrong parameter and maybe should be more focused on lymphocyte counts. Dr. Sulkowski asked Dr. Afdhal if he is monitoring lymphocytes during treatment with PegIFN/RBV, and how clinicians should interpret these data? Should they dose reduce for lymphopenia? Dr. Afdhal said that since the data were first presented, he has gone back to his group and discussed this with them and that they have instituted monitoring of the lymphocyte count. They will probably dose reduce the IFN at a lymphocyte count below 0.5 or 0.4. He said the issue is that the probability of infections is high – at a lymphocyte count of 0.4, there was about a 30% infection rate. The concern he had about the study is that we do not know what the infections were, which makes it difficult to determine whether to dose reduce. However, he said this is very important clinical data.

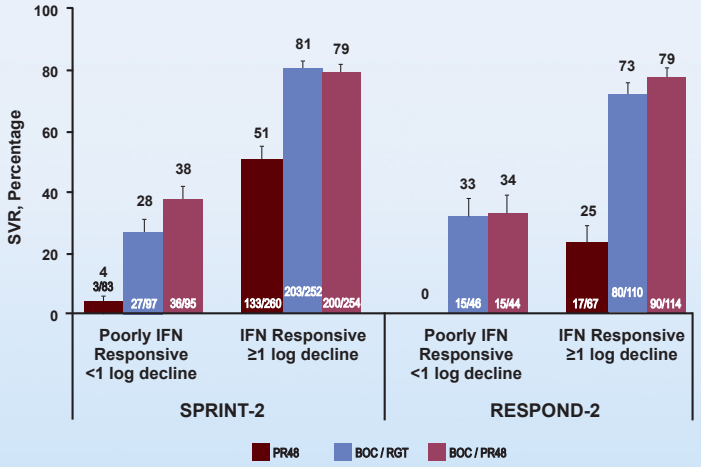
Boceprevir Studies: Dr. Fred Poordad

Dr. Poordad discussed boceprevir (BOC), which shortly after DDW was approved by the FDA. He started by discussing two trial designs for BOC regimens: in a treatment-naïve population (SPRINT-2), investigators compared 48 weeks of PegIFN/RBV with two different regimens of BOC: one was the standard 4-week lead-in (with PegIFN/RBV) followed by 44 weeks of PegIFN/RBV + BOC, while the other was an exploratory arm to assess response guided therapy (RGT), which consisted of a 4-week lead-in, then another 24 weeks of triple regimen (PegIFN/RBV + BOC) with a possible extension of 20 more weeks of PegIFN/RBV alone.[6] The determination of who would get the extended therapy to 48 weeks with the PegIFN/RBV backbone came at the week 8 assessment point. If the virus was undetectable at that point, and remained negative until week 24, those individuals could truncate therapy at week 28; otherwise, they got an extra 20 weeks of therapy.

The RESPOND-2 trial had a similar trial design but with some important differences.[7] It was conducted on a previously treated population. The study excluded null responders – patients who did not achieve a 2-log decline with their initial therapy by twelve weeks – but it did include partial PegIFN responders and relapsers. The control arm was 48 weeks of PegIFN/RBV. It had two treatment arms: a standard 4 + 44 week arm, which was similar to the design used with the treatment-naïve population in SPRINT-2, but the RGT arm was a bit different. In this study, the week 8 time point was the determinant as to who got shorter or longer treatment, but the total duration of therapy was 36 weeks or 48 weeks. So, patients who became negative by week 8 and remained negative were potentially able to end all therapy at week 36. Patients who became negative after week 8, but by week 12, had an extra 12 weeks between weeks 36 and 48 of just PegIFN/RBV. There was a week 12 futility rule: patients who were not undetectable by week 12 had to discontinue all therapy.

The figure below (Figure 2) shows SPRINT-2 results on the left and RESPOND-2 results on the right, broken down by the 4-week lead-in.[8] Dr. Poordad noted that in BOC-treated patients, those who did not have a 1 log decline, whether they were previous treatment-naïve patients, previous relapsers or non-responders, all had about a 30% SVR, while patients who had some PegIFN/RBV responsiveness – regardless of what their baseline status was – had an SVR that was closer to 80%. This is important because it allows clinicians to look at these patients differently. Classically, we looked at them as treatment naïve, relapsers or non-responders, but this study suggests it is PegIFN/RBV-responsiveness that determines how the patient responds.

Figure 2. SPRINT-2 and RESPOND-2: SVR Rates and Week 4 Lead-in Responses



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Discussion: At this point, Dr. Sulkowski asked the panel about the following scenario. They are treating an HCV patient who has received 4 weeks of PegIFN/RBV. At 4 weeks, they are going to add BOC. Do they wait until the results come back to see which category applies – poor IFN responsiveness or good IFN responsiveness? Dr. Reddy said that because he is not going to be able to measure HCV RNA at the 4-week time point, he has to make a decision. After 4 weeks of treatment, he feels committed to starting the third drug – although he may want them to start and later stop it. But if he follows this paradigm, he feels committed to starting treatment. Dr. Afdhal said that he does not think there is any definite need to start additional therapy at exactly 4 weeks. This approach was not used in these trials. They did not get instant results back at exactly 4 weeks. So, he said it is acceptable to wait until we get results back and then start the treatment once we have 4-week HCV RNA results. But he said he wants to get the RNA result after the fourth shot of IFN, and he does not think it makes any difference if we start BOC at week 4, week 4.5 or week 5. But he said if a patient is poorly IFN responsive, he is not sure he would be interested in starting him on BOC, because the patient might develop resistance. Dr. Poordad agreed, saying that patients who do not achieve SVR eventually develop resistant variants. The clinical significance of that is not known, but he thinks it is something we need to monitor. He said it is clear that not all patients are going to have great SVRs. People who do not respond to IFN, which remains the backbone of therapy, are not going to do that well. Dr. Poordad added that if patients have previously failed IFN (and some patients have failed IFN two or three times) – rather than subjecting them to another course, he may not treat them if there is no urgent reason to treat them. If they have no fibrosis, he may actually withhold therapy. So in those individuals, he would probably wait until he gets the HCV RNA results. Dr. Sulkowski responded that there is a one-in-three chance the IFN poorly responsive patient will obtain a cure. So, he said we have to look at the histology of that patient and include that in the decision, because we do not yet know the impact of resistance.

Next, Dr. Poordad noted that in the SPRINT-2 trial, both the RGT and the 4 + 44 week arm were superior in a subset analysis over the control arm.[9] So, whether the patient was black or non-black, had high or low viral load, was male or female, above or under the age of 40 years, they all benefited from therapy. The same analysis was done for RESPOND-2 and it showed essentially the same thing, that both the RGT arm or the longer duration 48-week arm were both superior to control.[10] If we look at the RGT arm in RESPOND-2, the overall SVR for patients who responded quickly was 89% in the RGT arm and 97% in the longer duration arm. If we remove cirrhotic patients from the analysis, the result is essentially the same number. In other words, cirrhotic patients will probably benefit from longer duration therapy and should not be subjected to response-guided paradigms.

Discussion: Dr. Sulkowski asked Dr. Afdhal to imagine he was treating a patient who took PegIFN/RBV (either a relapser, or partial or null responder), and they sign up for another course, and they have responded. Would he give the patient the full 48 weeks of therapy, or, as Dr. Poordad demonstrated with the data he presented, would he provide RGT therapy, potentially giving the rapid responders 36 weeks of treatment? Dr. Afdhal responded that he did not think there is a clinical difference between 36 weeks and 48 weeks, and most of his patients who are cirrhotic receive 48 weeks of treatment. In non-cirrhotic patients, he thinks the data are pretty good for 36 weeks, especially for relapsers. But the reality is that this includes relapsers and partial responders. And a lot of relapsers are not going to need 48 weeks if they have a good viral response. He said he would use RGT with relapsers. Dr. Poordad noted that just under half of the patients were eligible for potentially shortening the duration of therapy. If they are having difficulty, he would probably suggest stopping therapy at week 36, but in some cases we may want to continue to week 48.

Next, Dr. Poordad described data presented by Dr. Michael Manns, which were an analysis of patients who responded early in the SPRINT-2 study.[11] The analysis demonstrated several points. First, the SVRs were very high: about 90% of patients who became negative by week 8 went on to achieve SVR. They broke this down by various subgroups and found that for the most part, except for cirrhotic patients, these findings hold true. So, it appears that RGT in the treatment-naïve population works well, but cirrhotics probably deserved to be treated for a longer duration. The same analysis was done for RESPOND-2, and the numbers were almost identical: about 90% of patients who became negative by week 8 go on to achieve SVR. Except for the cirrhotics, all of the subgroups had the same results.

Dr. Poordad then reviewed the results of an analysis of anemia from both trials.[12] About half of the patients had a hemoglobin that fell below 10 g/dL. Erythropoietin (EPO) was allowed, and the majority of patients received EPO if they became anemic. The guideline was to use it if the hemoglobin fell below 10 and to stop using it once the hemoglobin reached 12. There appeared to be more response if patients had anemia. In other words, anemia portends a better response, and this may be a reflection of RBV exposure; nonetheless, patients who had anemia had a higher SVR. For patients who developed anemia but did not receive EPO, and who were managed with RBV dose reduction, there was no negative impact on SVR. They achieved the same SVR as those patients who received EPO; in fact, when the analysis included patients who received both EPO and a dose reduction, it was found they essentially had the same SVR.

Discussion: In discussing this study, Dr. Sulkowski noted that the FDA had shown data that RBV exposures, when they were higher, lead to more anemia. Therefore, it is reasonable

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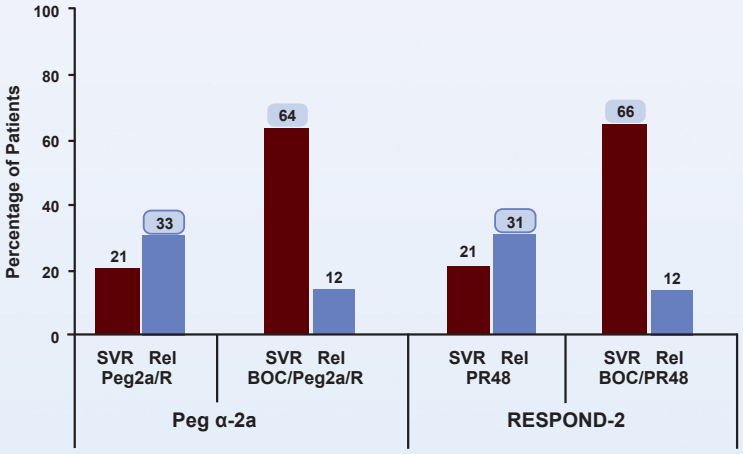
to assume that patients who develop anemia have higher RBV doses. So, when we reduce the RBV dose, it is lowering exposure a bit, but not to low levels. He also pointed out that about 80% of the patients who got anemia took EPO. He asked Dr. Reddy if he is going to use EPO in his practice in patients on protease therapy. Dr. Reddy responded that when a patient has achieved an adequate RBV exposure, he would be willing to drop the dose of RBV a bit, because he wants to try to lower the complexity of the care. Because EPO is a fourth drug, using it increases the complexity. While some clinicians would use EPO, he would be more inclined to go with the small RBV dose reduction rather than EPO use upfront. Dr. Sulkowski stated that Dr. Afdhal published a study a few years ago that showed EPO in a randomized controlled fashion helped patients keep their RBV dose up and feel better. Dr. Afdhal said that clinicians can dose reduce with relative safety and can use EPO with relative safety. EPO has side effects and has a black box warning for use with HCV patients but if patients are symptomatic and have difficulties with anemia – shortness of breath, fatigue – then he would consider the use of EPO. The alternative, not using EPO, runs the risk of worsening the anemia and the need for blood transfusions. So, we have to balance the use of EPO against the risk to the patient and the need for blood transfusion. Dr. Sulkowski said that they looked carefully at this in the IDEAL study, and they found that EPO helped patients who had rapid anemia to stay on therapy. The message he is taking from this is that if a patient is symptomatic, and we are concerned that he or she may stop therapy, then EPO has a role. Dr. Afdhal said it is worth pointing out that there is an ongoing study comparing EPO versus dose reduction in a randomized controlled fashion.

Next, Dr. Poordad discussed data that examined the distribution of IL28B polymorphisms in SPRINT-2 and RESPOND-2 patients.[13] This assessment was done in about two thirds of the patient population. The analysis showed in both the previously treated and untreated groups that 24% to 30% of the patients had the favorable CC polymorphism. The majority of patients, 51% to 61%, had the heterozygote CT, and 15% to 19% had the TT variant. If we combine the lead-in response and knowledge of the patient's IL28B polymorphism, an interesting trend emerges. Patients who were IFN responsive did very well; they achieved SVR rates of about 80% regardless of whether they had the TT, CT or CC genotype. On the other hand, patients who did not have IFN responsiveness did not do as well. In those patients, the longer duration of therapy of 48 weeks was numerically better than RGT, whereas in the patients who had some IFN responsiveness, the RGT arm was as good as the longer duration.

Discussion: Dr. Sulkowski said that very few of the CC patients were IFN unresponsive. So, one could argue that CC is the same as IFN responsive. Dr. Poordad said that he agrees with that view. In the study, there were 4 patients in each arm who did not have a 1-log decline. And even in those individuals, the SVR was still 50% to 67%. Dr. Reddy noted that in patients who were naïve to treatment and IFN sensitive, there was a good SVR, even with just PegIFN/RBV, and about a 60% added benefit with a third drug. The question is, how do we use these data? Dr. Poordad responded that it is important to note that CC patients did very well with PegIFN/RBV alone. However, that is still a 48 week treatment. So, 90% of these patients, who were CC and received BOC, were eligible for 28 weeks of therapy. Dr. Sulkowski said that PegIFN/RBV, even for rapid responders, uses longer therapy, and that this is a key point – these patients qualify for shorter therapy.

Dr. Poordad then discussed a study presented by Dr. Steve Flamm, which looked at previous treatment failure patients using PegIFN α2a with RBV and BOC. This was a two-arm study. One arm was the PegIFN/RBV control, and the other arm was 4 weeks of lead-in plus 44 weeks of 3 drugs.[14] Dr. Poordad compared the RESPOND-2 data with Dr. Flamm's presentation from DDW (Figure 3), and essentially they had identical results. Whether we use PegIFN α2b or PegIFN α2a, the SVR rates were 64% and 66%, and in the control the SVR was 21% for both studies. The relapse rate was also the same. So, BOC can be used with either PegIFN α2a or PegIFN α2b, which reflects what was seen in the IDEAL trial, that these two IFNs behave the same.

Figure 3. PegIFN α2a and RESPOND-2: SVR and Relapse



Next, Dr. Poordad discussed a report that highlighted the complexity of resistant variants. The study, by Ogert and associates, showed that at baseline, using a fairly insensitive technique, the investigators could detect resistance-associated variants (RAVs), prior to treatment, in 70% of patients.[15] After therapy, they found an increase in the number of detectable variants. These were in patients who did not respond, because if the patient has an SVR we are not going to find resistant variants.

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So we are on the verge of better understanding resistance in terms of its prevalence but we still do not know what it means clinically. However, regardless of the variants that patients develop, if they are IFN responsive, their SVR is going to be about 80%. Conversely, if they are not IFN responsive, the majority of patients do not achieve SVR, and they develop variants, some of which make the drugs less effective.

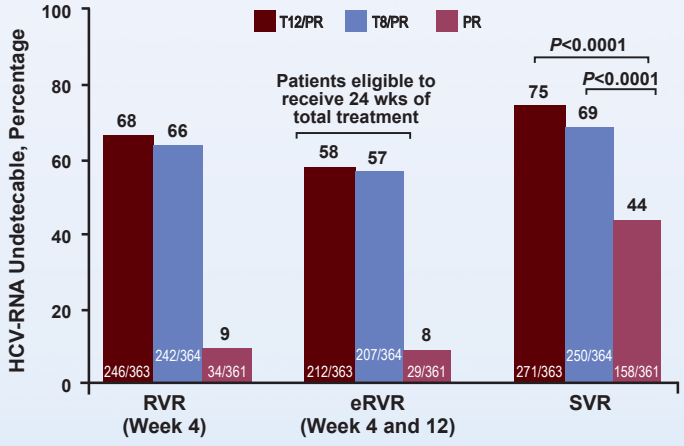
Discussion: Dr. Sulkowski asked, do we need HCV resistance testing in the lab for our clinical practice? Dr. Afdhal said that this type of testing is not yet something we can use in clinical practice. These variants are there, and the level of these does not preclude patient response. But, as we learn more about resistance, and as we perhaps find resistance variants that are highly fit and replicative, we may see changes in disease state. He is not worried that there is resistant virus present – everybody has low levels of it. What he is worried about is that this will have a clinical consequence, and that we will not get reversal to wild type. The consequence could be either poor response to other combinations, or worsening of clinical disease, as is seen with the YMDD mutation in HBV. So, this needs to be studied. For clinicians, at the moment this is not a necessary test, because if we do not clear the virus, the patient is going to get resistance. Dr. Sulkowski expressed the view that this point is very important: the patients that never get resistance are those who are cured. And the best way to prevent resistance is to use these medications effectively – good adherence, adequate dosing of the medications, adequate aggressiveness with side effects. Dr. Sulkowski then brought up the issue of stopping rules – what are they going to look like? Dr. Poordad said that one of the things that clinicians have to focus on and understand with the new antivirals is that stopping rules must be adhered to – more so than previously with PegIFN/RBV. The FDA is currently trying to simplify this and find some common ground. One of the proposals on the table is that patients who have more than 100 IU of HCV at week 12 of therapy should be discontinued because it is unlikely they will achieve an SVR. Perhaps we could continue the PegIFN/RBV but certainly the directly acting antivirals should be discontinued. So, if that stopping rule is in play, and clinicians abide by that, they will see fewer resistant variants. It will not cut them down to zero, but the key is to identify the patient who is going to develop variants and stop the drug. Dr. Sulkowski said that once we know a patient is not going to respond to triple therapy with a protease inhibitor, we should stop the drug to prevent additional selection of variants. That is a major paradigm: we are asking people to go from levels of virus in the millions to less than a hundred in a matter of weeks. Dr. Poordad added that a way to look at it is that these patients are not on their way down, they are on their way back up. The key is that clinicians have to learn these stopping rules.

Telaprevir Studies: Dr. Mark Sulkowski

At this point, Dr. Sulkowski discussed telaprevir (TVR), the other protease inhibitor that shortly after DDW was approved by the FDA. He started with some background on the phase 3 registration trials. The ADVANCE trial was conducted with more than 1,000 genotype 1, treatment-naïve HCV patients. The cohort was randomized into 3 groups with all receiving PegIFN α2a and RBV (PR): (1) PR alone, (2) TVR 750 mg Q8H + PR for 12 weeks. All three drugs were started at the same time, and at 12 weeks the TVR is removed. RGT was applied: If the patient was a rapid responder with a negative viral load at week 4, and it stayed negative, the patient stopped all therapy at 24 weeks. If a slower responder, the patient went up to 48 weeks, (3) TVR 750 mg Q8H plus PR for 8 weeks. This was an attempt to see if cutting the exposure of TVR, and hopefully improving tolerability, might be as effective. These patients also followed the RGT paradigm.

Presenting the overall data, Dr. Sulkowski noted that RVR rates were as high as 68% among those who received triple therapy.[16] The eRVR rate was 58% in those patients who qualified for 24 weeks of treatment. The SVR rate among the TVR + PR RGT arm was 75% (Figure 4). It is worth noting that on a reanalysis of the data set this number was changed to 79% when it took into account patients who were detectable in the post-treatment follow-up period. The results were also a bit better than TVR 8 weeks. So, this suggests the arm that would be most favorable is TVR + PR. However, both TVR arms were better than control.

Figure 4. Higher RVR and SVR Rates with TVR + PegIFN/RBV vs. PegIFN/RBV Alone



Dr. Sulkowski also discussed a confirmatory study with TVR called ILLUMINATE.[17] This study consisted of 450 patients, all of whom received TVR + PegIFN/RBV for 12 weeks, then they were randomized. Rapid responders (eRVR) were randomized to either 48 weeks of PegIFN/RBV or to a response-guided paradigm. The data showed that overall (ITT), 72% had an SVR and in the group that was randomized, those who had an eRVR,

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whether they got the longer therapy or the RGT, the response rate was very similar. In fact, the shorter therapy response rate was 92% and longer therapy rate was 88%.

Next, Dr. Sulkowski discussed the advantages of stopping therapy after 24 weeks. Dr. Andrew Muir addressed this issue in a presentation at DDW. Fatigue is shortened dramatically when one stops treatment at 24 weeks. Dr. Muir's data showed that many patients who were treated for 24 weeks felt better sooner than people who were treated for 48 weeks. This indicates that patients are getting clinical benefit in terms of reduced side effects and exposure to PegIFN/RBV.

There were also some analyses of factors that influenced response in ADVANCE presented at DDW.[19,20] Both genotype 1 subtype a and b patients were found to respond well, although there was a numerically higher response rate among the 1b patients. In high viral load patients, 74% responded, compared to 78% of those with low viral loads. Cirrhotic patients (F3-F4) responded a little less than F0-2 patients. In addition, all triple-treatment groups did substantially better than the control group.

Discussion: Dr. Sulkowski asked the panel if HCV subtype is important with triple therapy. Dr. Afdhal responded that the importance of subtype is the fact that the virological changes necessary for resistance to develop in the 1a subtype is only one mutation, as opposed to two for the 1b subtype. So, the numbers are quite high for genotype 1a and 1b in terms of overall number, but it did not reach statistical significance. It is something we should be aware of. He said the fibrosis issue is more clinically relevant, and he believes it is under-represented in trials. As is shown for PegIFN/RBV, cirrhosis is an independent parameter of difficulty in response. Dr. Sulkowski said that subtype is not something we have been selecting patients based on. He noted that for patients with a high viral load, a 74% SVR is a good response. The cirrhotic patient remains a challenge: these are the patients who need treatment and, with a 62% SVR, we are going to treat this patient group.

Next, Dr. Sulkowski discussed findings from ADVANCE and ILLUMINATE that examined viral response in black and non-black patients.[21,22] There was a slightly decreased response among black patients compared with non-black patients, but it was better than the control group. So, we are seeing that the PegIFN/RBV response parameters still play a role but not as much of a role when one adds TVR or BOC to the equation.

Another study presented at DDW was on IL28B data from the ADVANCE study of treatment-naïve patients.[23] The investigators reported that among the TVR-based regimen CC patients, between 87% and 90% had SVR, and 78% to 80% qualified for the shorter therapy of 24 weeks. There was also a favorable response with TVR in the CT and TT patients. In the control group, the response was only 23% and 25%, compared with the T12 paradigm, 71% and 73%.

Discussion: Dr. Poordad said he does IL28B testing in his practice, because the majority of the patients who are CC qualified for shorter duration therapy both with BOC and TVR. This is an important thing for the patient to know going into therapy. It is a motivational tool, and some people who might be sitting on the fence about therapy will jump at it if they know that they have a high likelihood of response with a short duration of therapy. The other thing that we can probably figure out from this and other studies is that the patients who are less likely to respond are going to develop resistant variants. It is important for the clinician to know which patients to monitor more carefully and certainly those stopping rules come back into play. Dr. Afdhal said that we have learned from PegIFN/RBV treatment that there are multiple parameters that are important in response. These parameters are still important today. IL28B is also important. So what we see in this study is the unfavorable genotype did less well than CC and they required longer treatment, and we are seeing a big delta over control. The idea of trying to personalize treatment is going to be very important. This is an important piece of information to know and to discuss with the patient before starting treatment, especially for the treatment-naïve patients.

Dr. Sulkowski next discussed an analysis of some data with respect to RBV dose reduction in the TVR studies.[24] Unlike the BOC trials, in this clinical paradigm, TVR + PegIFN/RBV dose reduction was the strategy used to manage anemia. No EPO use was permitted. Anemia was more common with TVR; similar to BOC, it causes a decline in hemoglobin. When patients stop taking it, after 12 weeks the hemoglobin comes back a bit. So the question is, does RBV dose reduction impair the likelihood of achieving SVR? Data presented at DDW suggest the answer is no. Patients who reduced RBV had an SVR rate of 76% and those who did not had an SVR of 72%. In the placebo group, the rate was 54% (dose reduction) and 41% (no dose reduction). So RBV dose reduction did not impair response. In this analysis, patients who dropped their hemoglobin more than 3 g while they were taking TVR actually had a better SVR rate. So, if patients dropped their hemoglobin between 1 g and 2 g, SVR was 42%; if they got above 3 g, it was >70%. The same delta was seen with PegIFN/RBV. A little bit of anemia may be a good thing, because it means the patient was exposed to a sufficient level of drug. An analysis by the FDA showed that as RBV concentrations go up, there is more anemia. So anemia may be a marker of getting enough medicine into these patients.

Discussion: Dr. Sulkowski made a comment about the magnitude of the delta. If there is a big drop in hemoglobin, the clinician should reduce the RBV dose to 600 mg. Dr. Poordad agreed. While we have defined anemia as a hemoglobin of 10, the FDA has pointed out that it is only the delta from baseline that is important. This is because if someone starts with a hemoglobin

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of 17 and they fall to hemoglobin of 11, they are not anemic, by definition, but they may be very symptomatic. So, Dr. Poordad said the important message to take home is that a small drop in hemoglobin appears to be a good indication and we should not overly dose reduce the patient. It is also important to note that RBV is required with both TVR and BOC therapy. So, dose reductions are OK, but discontinuation of RBV is not recommended.

Dr. Sulkowski then discussed the REALIZE study.[25] This study included previously treated patients who were non-responders, partial responders and relapsers, who were retreated with TVR + PegIFN/RBV; there was no RGT. Patients received 48 weeks of treatment. There were 3 groups – Group A: 12 weeks of TVR + PegIFN/RBV, then 36 weeks of PegIFN/RBV; Group B: PegIFN/RBV 4 week lead-in, then 12 weeks of TVR + PegIFN/RBV, then 36 weeks of PegIFN/RBV; and Group C: placebo + PegIFN/RBV for 16 weeks, then 36 weeks of PegIFN/RBV. The response rates were prior relapsers: 88% and 83% (for TVR-based therapy) vs. 24% (for control); prior partial responders were 54% to 59% vs. 15% (for control); and for prior null responders, 29% and 33% (TVR) vs. 5% (control). Based on these findings, Dr. Sulkowski concluded that prior treatment did matter, in terms of how patients responded. Also, each TVR group did better than the PegIFN/RBV control and there was no benefit of lead-in for this treatment-experienced population.

Dr. Sulkowski also discussed an analysis of SVR in REALIZE based on prior response and by bridging fibrosis, cirrhosis or minimal disease.[26] In this analysis, relapser-cirrhotics had an SVR of 84%, while in partial responders, bridging fibrosis was 56% and cirrhotics were 34%. But in the TVR-treated null responders, bridging fibrosis and cirrhotic patients had SVR rates of only 39% and 14%, respectively.

Discussion: Dr. Afdhal said that the concern he has about these data is that if we look at patients that we most want to treat, the prior partial and null responders with cirrhosis, the response rate was low. He said we need to better define which of the cirrhotics are going to respond. With a SVR of 34% in cirrhotics, he believes that the risk-benefit ratio favors treatment. However, in a group of patients with a 14% response rate, clinicians will begin to worry if they should be treating the patient, or if he or she should be in a clinical trial. Dr. Sulkowski asked Dr. Poordad if he was treating HCV patients who were prior null or partial responders with advanced fibrosis, would he give a lead-in to determine the likelihood of an SVR? Dr. Poordad said he thought it would be useful to know this information, especially if he was able to offer alternatives in the form of clinical research trials. Plus, there are promising treatments on the horizon for this difficult to treat population. So, our enthusiasm has to be tempered somewhat, as we are beginning a new era in HCV treatment. He said if he had a patient who has been treated multiple times, rather than subjecting him or her to another 48 weeks of therapy, he would make an assessment and consider all the options.

Dr. Sulkowski also discussed SVR in REALIZE patients based on their responsiveness to 4 weeks of PegIFN/RBV lead-in.[27] If the patient was a relapser and poorly responsive (<1 log decline in HCV RNA), the SVR rate was 62% versus 94% in those with a ≥1 log decline in HCV RNA. For partials responders, the response rate was 56% vs. 59% – virtually the same. But the SVR for null-responders who failed to drop 1 log was 15%, vs. 54% for those with ≥1 log decline. So there appeared to be the potential additive information from lead-in, in the null-responder group.

Another issue examined in REALIZE was resistance. A report provided information on the time to a resistant variant not being detected by population sequencing. This finding does not mean that the variant is gone, but at the start of follow-up, the variant was, in most cases, the entire population. For genotype 1 subtype b, within about 6 months after stopping, the probability of a patient having a resistant variant had decreased to 8%. For subtype 1a, a similar response took longer, but by 18 months, the probably was 26%.[28] So there is evidence that over time, the population will return to wild type, although the significance of this remains unclear.

Novel Therapies and Strategies: Dr. Nezam Afdhal

Dr. Afdhal discussed a number of new drugs and strategies that are being developed for patients with HCV infection. These new drugs aim to increase SVR rates in all groups of patients, including non-responders and cirrhotic patients. New drugs also aim to simplify treatment, reduce side effects and use IFN-free strategies. The first drug that Dr. Afdhal discussed was the polymerase inhibitor PSI-7977, which was studied in the PROTON study.[29] PROTON looked at both genotype 1 and genotype 2-3 patients. The genotype 2-3 arm in PROTON was once a day PSI-7977 400 mg + PegIFN/RBV for 12 weeks, then stop all three drugs and measure SVR. Genotype 1 patients received one of two doses of PSI-7977 in combination with PegIFN/RBV for 12 weeks. Then, the study instituted a response-guided paradigm for either 24 weeks of treatment if they were negative at 4 weeks, or a full 48 weeks with PegIFN/RBV for those who failed to have an RVR. There was also a standard of care (SOC) control arm.

In genotype 2 and 3 patients, there was a 96% response at 12 weeks. At week 2, HCV RNA was less than the limit of detection (<LOD) in 21 of 24 patients. For patients with genotype 1, there were limited data reported, but for the first 12 weeks, when the patients were receiving all three drugs, there is evidence of patients becoming undetectable, <LOD over time. What was striking was the rapidity with which HCV RNA negativity

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occurred with these drugs – at the 2 week time point, 70% to 80% of patients were undetectable; at 4 weeks, it was close to 100%; and, at 12 weeks, apart from dropouts, they all stayed this way. There were no breakthroughs reported with these drugs in the small studies that have been done; this drug has a very high genetic barrier to resistance.

There is also a strategy that is being developed to move away from an IFN-based regimen. But before we can do this, research has to demonstrate that the combinations of the drugs that we want to study are able to suppress the virus effectively and that suppression can occur without a significant degree of breakthrough. This approach was demonstrated in the NUCLEAR study.[30] This study consisted of a combination of a purine and a pyrimidine nucleotide inhibitor: PSI-7977 and PSI-938. They were studied in a relatively small cohort of patients. The study consisted of treatment-naïve, non-cirrhotic patients. The investigators looked at the response after 14 days in 40 genotype 1 patients using four arms: PSI-938 alone, PSI-938 and then adding in PSI-7977, starting with PSI-7977 and then adding PSI-938, and an arm combining the two together throughout the trial.

The investigators reported 4.5 to 5 log reductions by day 14, which are at the protease inhibitor level of viral load reduction. When they combined the two drugs – whether they did one first and then the other, or both together – we see suppression rates in nearly all patients. So, this study demonstrated rapid viral suppression and it is continued for the 2 week total. While this study only lasted for a short period of time, it tells us that these drugs have potentially a very good profile to be part of combination regimens.

Discussion: Dr. Sulkowski asked how do these nucleotide analogues fit in with future combination therapy? Dr. Poordad responded that they look very promising in these small trials. What we do not have is a larger trial combining them for a significant period of time with other classes of drugs. While these two drugs combined may not be the ultimate ideal regimen, he said that collecting safety data and making sure that these two can be used together is the beginning of a very long process of finding an ideal combination.

Dr. Afdhal also discussed the ZENITH study, which examined the effects of four drug combinations using the non-nucleoside polymerase inhibitor VX-222.[31] This new drug is a potent inhibitor and is a non-nucleotide. In this study, patients received PegIFN/RBV + two drugs (VX-222 and TVR), both of which in monotherapy would have a potentially high rate of resistance. The study had 4 arms. Two of the arms (A and B) combined the two oral agents (VX-222 and TVR), using different doses of VX-222 in a BID regimen. If the patient was undetectable, that was considered a good result; if not, the investigators would stop treatment. In the C and D arms, patients received VX-222 and TVR with PegIFN/RBV, again using different doses of VX-222. And the treatment design was similar; if the patient became negative, there was an early stop, if not negative at week 2 or week 8, then they continued to receive PegIFN/RBV until week 24.

Discussing the results, Dr. Afdhal said that in Arms A and B, there was some viral suppression, and that there were some patients whose HCV RNA was undetectable at week 2. But at week 4, we can see patients starting to break through, and the viral breakthrough was between 17% and 31%, which was above what was acceptable to continue the study based on pre-defined rules. So, all oral arms were stopped because of breakthrough.

Discussion: Dr. Sulkowski said that this is an important point – that not all combinations are equal. The nucleotide and nucleoside analogues are not the same as the non-nucleotides. Dr. Poordad said that the quad therapy looks promising, but as we move forward there are going to be many options, and the nucleotides and the nucleosides appear to be probably favorable in many regards. So, the good news is that quad therapy can increase SVR rates. The question is, will there be other regimens that can give us the same SVR rates without quad and without Interferon?

Continuing his review of ZENITH, Dr. Afdhal said the C and D arms showed very high rates of complete early viral response (cEVR), so these are patients than can potentially shorten duration of therapy to 24 weeks. He interprets these results as indicating that quad therapy is taking that 60% of triple therapy, and pushing it up toward 90% higher for shorter duration of therapy.

While ZENITH was a trial with treatment-naïve patients, ASPIRE was a non-responder treatment failure study.[32] The protease inhibitor TMC435 was used in the ASPIRE trial. It is a large trial, with 7 arms of 60 patients each and multiple regimens. Essentially what they are doing in ASPIRE is looking at different combinations of TMC435 with PegIFN/RBV and then continuation of PegIFN/RBV without TMC435. There are some arms that continuously provided TMC435 at different doses with PegIFN/RBV.

Dr. Afdhal presented the results from ASPIRE, broken down by prior response into relapser, partial responder and null responder groups. He focused on the null responder population, which was the most difficult to treat in the TVR and BOC trials. In the ASPIRE trial, at week 24, responses were ≥70% in null responders in each of the TMC435-containing regimens. These findings suggest that with newer drugs, we can start to target more of the people who we are not targeting well with BOC or TVR. Dr. Afdhal noted that with the new drugs, relapse seems to be relatively unusual.

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Dr. Afdhal reviewed two final studies in his presentation. The first study was with alisporivir (DEB025), a cyclophilin inhibitor. He presented SVR data in treatment-naïve genotype 1 patients.[33] This drug was studied in a four-arm study: three combining alisporivir with PegIFN/RBV and a control arm with PegIFN/RBV alone. In Arm A (alisporivir + PegIFN/RBV for 48 weeks), there was a 79% SVR. Arm B (alisporivir + PegIFN/RBV for 24 weeks) had a 53% SVR. In Arm C (alisporivir + PegIFN/RBV with RGT), there was an SVR of 69%, and in the PegIFN/RBV arm, there was a surprising SVR of 55%.

Discussion: Dr. Sulkowski asked Dr. Poordad how he sees alisporivir being used to treat HCV. Dr. Poordad responded that it is potentially a good partner drug, although in a triple drug regimen he does not think its impact will be impressive. Dr. Sulkowski also asked if alisporivir has activity against genotypes 2 and 3 HCV. Dr. Poordad replied that it does, but it has a different resistance profile, which makes it a good partner drug.

Finally, Dr. Afdhal discussed a study that measured the effect of combining BMS-790052, an NS5A inhibitor and the protease inhibitor BMS-650032 in a small phase 2 study with null responders.[34] The study was designed to give patients either the two oral agents alone, or the two oral agents + PegIFN/RBV for a 24-week treatment period. Presenting the results from the quad therapy group first, Dr. Afdhal said that PegIFN/RBV + these two drugs resulted in a 100% SVR. This was an excellent result, but he stressed the study involved only a small number of patients. However, with the two oral agents alone, there were 4 out of 11 patients who had an SVR24. What this shows is that with 24 weeks of treatment, in prior IFN null-responders, it is possible to suppress virus and provide an SVR. This was a very exciting proof of concept study.

Discussion: Dr. Sulkowski said these are the first data of a cure for HCV without PegIFN. Dr. Poordad stated that the two-drug regimen – with no IFN or RBV – showed a cure rate higher than 48 weeks of triple therapy. Dr. Afdhal said that this may not have been the right combination of agents, but it is the beginning of the future. While we cannot say which drug combinations are going to be the right ones, which patients will be in it, or how many drugs we will need in the combination, we can say that the future is very exciting. Dr. Sulkowski said that we are in an incredible time in HCV therapeutics. We have a major advance with higher SVR rates with TVR and BOC + PegIFN/RBV that will offer patients a higher likelihood of cure. In addition, there are many drugs in development. It has been a very exciting DDW.

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