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## VOLUME 4, ISSUE 8: TRANSCRIPT – DR. ERIC LAWITZ

**DR. RAYMOND CHUNG:** I'm Dr. Ray Chung, Director of Hepatology and the Liver Center at Massachusetts General Hospital. I'm speaking with Dr. Eric Lawitz, Clinical Professor of Medicine at the University of Texas Health Science Center in San Antonio, Texas, about his presentation: *High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 for 12 Weeks in Treatment-Experienced Genotype 1-6 HCV-Infected Patients, Including Those Previously Treated with Direct-Acting Antivirals* presented at the April 2016 EASL meeting.

Dr. Lawitz, thank you for joining us today.

**DR. ERIC LAWITZ:** Thanks, Dr. Chung, for having me.

**DR. CHUNG:** Would you mind explaining the study?

**DR. LAWITZ:** Sure, happy to. As we all know, we're currently in the era of highly effective, direct acting antivirals for chronic hepatitis C. As we also know, despite these regimens with high success rates, small percentages of patients don't respond. As we treat more and more patients, this small percentage of nonresponders will grow into a large number of patients. Up to this point we've had no effective retreatment strategy for patients who failed DAA therapy, so the idea for this study was to look at the combination of three antivirals with different mechanisms of action and nonoverlapping resistance profiles to see if these three agents in combination could create a rescue strategy or retreatment strategy for DAA failures.

These three antivirals have three things in common: they are all pangenotypic, they all have a high barrier to resistance, and they're all given once daily. In this study, sofosbuvir and velpatasvir was given as a single, fixed dose combination pill, and GS9857 was also given as a single daily tablet.

This was a phase 2 open label trial with 128 treatment experienced patients who had genotypes 1 through 6. In any retreatment trial, it's important to define what they had failed in the past or what we're retreating. Genotype 1 patients were required to have either NS5A exposure or two classes of DAA exposure in the past. For genotypes 2 through 6, not as many DAAs are available, so they could have failed peg-riba or any DAA.

The primary endpoint was the usual one: SVR-12. The study demographics were what would be expected in a retreatment group of patients — they're a little older, in their upper 50s, and half have cirrhosis, which is a risk factor for nonresponse. Half of them have genotype 1, a quarter genotype 3, and the rest were a mixture of genotypes 2 through 6. The group had variable exposure to DAAs; a quarter had NS5A exposure, either alone or in combination with other DAAs; and half didn't have NS5A exposure but did have exposure to other classes including NS5B and NS3. About 20% had no DAA exposure, but those were the genotypes 2 through 6 who had failed peg-riba.

Importantly, the overall results showed a 99% SVR-12 — 127 of 128 — so all but one patient was successfully cured. Comparing the genotypes, there was universal success in genotypes 1, 2, 4, and 6, with a 100% response rate; the single failure was a patient with genotype 3. In genotype 3 it was 34%, 35%, or 97%, whereas all the other genotypes had 100% response retreating these DAA failures. So this was really a successful trial.

When everybody responds, looking at subgroups doesn't really tell you much. But it's important to note that cirrhosis didn't have an impact on outcomes; neither did the presence or absence of NS5A exposure or multiple DAAs. None of these baseline factors

predicted nonresponse; all the patients responded despite those three factors.

Most of these patients had baseline recombinant adeno-associated viruses (rAAV), which wouldn't be unexpected, since they all had DAA exposures; but the presence of those rAAVs didn't affect outcome.

From a safety standpoint, as we see in the era of DAAs, safety is remarkably good, and although many patients had adverse events, they were all mild to moderate, with the exception of 2% of people who had more serious adverse events. There was one death, but it was 14 weeks after stopping therapy, deemed not related to the study drug by the investigator, and was presumably a sudden cardiac death.

The most frequent adverse events were those most typical to DAAs — headache, fatigue, and diarrhea — but all occurred in less than 20% and were primarily mild to moderate.

What we learned from this study was that we now have results that show an effective retreatment strategy for patients who failed DAAs. That is, the combination of sofosbuvir-velpatasvir and GS9857 for 12 weeks, showing a 98% SVR-12 in these DAA-experienced patients, which is a great result.

We also learned that baseline presence of rAAVs had no impact. This combination of three DAAs was well tolerated, and four phase 3 trials are going on with the same three combination regimen. The phase 3 trials use a one-tablet regimen, with the three antivirals in a single tablet. We certainly look forward to the results of the phase 3 trials being presented at future meetings and continue to lay the results of this three-DAA regimen on the field and learn how we'll use it to optimize care for our patients.

**DR. CHUNG:** That's a truly remarkable set of findings that you've described, Dr Lawitz, and this is really good news for patients, albeit a small percentage of them, but those patients who have failed prior DAA regimens.

As we look at this application of a triple DAA or triple class strategy, can you envision the success of this regimen being parlayed into a primary upfront first-line approach, perhaps looking at shaving the duration from 12 weeks downward, as a frontline strategy that would be viable, say, compared to existing strategies?

**DR. LAWITZ:** That's a great question. The treatment-naïve portion of this study was presented by Dr. Gane at EASL, looking at six versus eight weeks and then eight weeks with or without ribavirin. He showed very nice results, particularly in the eight week group. The six week group had a little lower SVR. But it really comes to the question of what's the right frontline strategy. At AASLD we saw the sofosbuvir-velpatasvir data, which generated results in excess of 98% in a lot of the groups. That regimen produced equally high results in treatment-naïve patients.

Ultimately the question is, do you want to use a three-DAA regimen as a primary regimen or reserve it for those few patients fail a two-DAA regimen? I think, given the ASTRAL results, a very logical approach is to use the two-DAA regimen and then still have a plan B for those few patients who don't respond. The two-DAA regimen, as you'll remember, is sofosbuvir with velpatasvir, so in the worst case scenario you would have NS5A resistance, and here with this three-class regimen you would still have the protease inhibitors as a third agent.

One approach is using a two-drug regimen and saving the three-drug regimen as a retreatment strategy. It's certainly not an unreasonable approach to shorten duration and use three drugs up front. But I think if it were a patient in my clinic, I would rather give them two drugs and have one class resistance for those few who fail with other regimens, then potentially have a retreatment option. That would be how I would use it in my clinic. Obviously we need to wait for the large, phase 3 randomized trials to make sure these datasets hold, and defining how to use these drugs will come as a result of the findings of the phase 3 trials.

**DR. CHUNG:** One last question, Dr. Lawitz. Can you envision the potential use of such a triple regimen in groups of patients we've been describing who have less than perfect response rates? By this I might mean some of our decompensated patients who have more advanced stages of cirrhosis, whose response rates, while not awful by any means, certainly may fall somewhat short of the terrific response rates we're now getting accustomed to seeing. Can we envision a triple strategy being used up front in that type of a scenario, and do we know that perhaps this regimen could be used safely under those circumstances?

**DR. LAWITZ:** The triple regimens always have a protease inhibitor involved, and I also presented the hepatic impairment data, the results for 9857 — so two for one here on the review. That showed a two- to three-fold increased exposure with protease inhibitors in patients with decompensated liver disease. So certainly we have concern about protease inhibitors with increasing levels of hepatic dysfunction, and for those patients the safest therapy is probably non-PI, with the nucleotide NS5A combination certainly being an ideal combination for decompensated patients.

At AASLD I presented the IMPACT study with simeprevir, sofosbuvir and daclatasvir in patients with Child-Pugh B showing a 100% response rate. So there's proof of principle that a three-drug combination can provide high SVRs in decompensated patients, but I remember the limitations with a small subset of 20 patients in a single center study at my site. We did have some safety measures to not allow patients with very high bilirubins in relatively stable Child-Pugh B patients.

It's an interesting question, and for the most part we would as a field prefer to avoid protease inhibitors in decompensated patients and instead use nucleotides and NS5A inhibitors. In special situations, in specific patient populations, it may be viable in the right situation. It's one of those areas where you have to be careful to know and understand the patients, their liver function, and the impact of a protease inhibitor in that level of liver dysfunction.

**DR. CHUNG:** Dr. Lawitz, thank you for being part of eViralHepatitis Review. We've appreciated your time today.

Please note that this podcast is not available for CME/CE credit.

I also want to note that Dr. Lawitz disclosed that he's received research or grant support from AbbVie, Achillion, Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix, Intercept, Janssen, Medtronic, Merck, Novartis, Nexidia, Presidio, Roche, Sinteris, and Vertex Pharmaceuticals. He has served as a speaker for Gilead, Kadmon, Merck, and Vertex and has participated on advisory boards for AbbVie, Achillion, BioCryst, Biotica, Enanta, Idenix, Janssen, Merck, Novartis, Santaris, Theravance, and Vertex Pharmaceuticals.

Thank you very much again, Dr. Lawitz.

**DR. LAWITZ:** Thanks for the invitation to visit with you today.