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VOLUME 4, ISSUE 8: TRANSCRIPT – DR. DAVID L. WYLES

DR. RAYMOND CHUNG: I'm Dr. Ray Chung, Director of Hepatology and the Liver Center at Massachusetts General Hospital. I'm speaking with Dr. David Wyles, Associate Professor of Medicine, Division of Infectious Diseases, at the University of California San Diego about *Sofosbuvir/Velpatasivr Fixed Dose Combination for 12 Weeks in Patients Co-Infected with HCV and HIV-1: The Phase 3 ASTRAL-5 Study* that was presented at the April 2016 EASL meeting.

Dr. Wyles, thank you for joining us today.

DR. DAVID WYLES: Thanks, Dr. Chung. It's a pleasure to be here and talk about the ASTRAL-5 study.

DR. CHUNG: Please explain the study.

DR. WYLES: As you mentioned, is a phase 3 study looking at the fixed dose combination of sofosbuvir plus velpatasvir. For our listeners, here's a brief background about that combination. Many are probably familiar with sofosbuvir, which is an NS5B nucleotide inhibitor that has been approved individually and in other combinations for several years, but now we're looking at a combination with velpatasvir, which we can call a next generation NS5A inhibitor that has pangenotypic activity and a somewhat better resistance profile than currently available NS5A inhibitors.

In this study we looked at 106 patients with HCV/HIV coinfection. All of these patients were treated with 12 weeks and no ribavirin with this combination. The inclusion criteria for this study allowed patients to be any HCV genotype 1 through 6, although only genotypes 1 through 4 were actually enrolled. Patients could be either treatment naïve or treatment experienced, and up to 30% of the population could have cirrhosis.

They had to be on stable HIV therapy with a suppressed HIV viral load for three months, although only study-specific antiretroviral regimens were allowed for the two months before entry in this study. The allowed antiretroviral regimens were a broad representation of different classes. Patients could be on nonnucleoside reverse transcriptase inhibitors, although only rilpivirine from that class. They could be on integrase inhibitors, including boosted elvitregravir or raltegravir. Unique to this study, they also could have been on HIV boosted protease inhibitors, including atazanavir, darunavir, or lopinavir boosted with ritonavir. Almost all the regimens included some type of nucleotide backbone for the HIV therapy.

The enrolled population is fairly representative of an HCV/HIV coinfected population in the United States, although somewhat different than an HCV monoinfected population, so I'll just point out some of those differences.

This coinfected population was predominantly, almost 90% men, and we had a high proportion of patients who identified as black race, in this study approaching 45%, so almost half the study made up that demographic. While 30% of patients with cirrhosis were allowed, only 18% had cirrhosis on enrollment.

The genotype distribution reflected what we have in the United States: predominantly a genotype 1 population, within which 62% of the patients had the genotype 1A subtype. Twelve patients, or 11%, had genotype 3.

Overall response rates were very good. For SVR-4 we had 95% of 106 patients. At the time we presented the study, two patients hadn't completed SVR-12, so only 104 patients were in the SVR-12 analysis; but it was a 95% SVR-12 rate, meaning the patients had

undetectable hepatitis C viral loads three months or 12 weeks after they stopped the study treatment.

Overall, treatment was very well tolerated. Across the genotype subtype distribution, the only two patients who had viral relapse both happened to have genotype 1A. No viral relapses occurred in the 1B subtype or in other genotypes.

Notably, patients with cirrhosis did very well in this study. All 19 patients with cirrhosis achieved SVR-12 in this study.

Another concept that often comes up is baseline resistance. In this study baseline NS5A resistance-associated variance was present in 12% of the patients, or 12 actual patients since only 101 were evaluable for resistance, and all 12 of those patients, 100%, had an SVR-12.

The last thing I'll point out is that since velpatasvir is slightly different than other NS5A inhibitors, this was considering any NS5A class rAAVs. Of those 12 patients, only three would have even been predicted to have potential resistance to velpatasvir, and all three of those patients also achieved SVR-12.

DR. CHUNG: This is a really impressive set of findings, Dr. Wyles. One of the very interesting questions that emerged from the first generation NS5A inhibitors, namely ledipasvir, was the potential for an interaction with boosted HIV protease inhibitors and with tenofovir. Were there any a priori predictions about what would be expected with this NS5A inhibitor, vis-à-vis those interactions coming into the study? And as a corollary to that, were any of those interactions observed to be clinically meaningful?

DR. WYLES: Thanks, Dr. Chung, I think that's a great question and one that's certainly clinically relevant for practitioners. Velpatasvir has a lot of the same characteristics as ledipasvir; it's both a substrate inhibitor of some transporters, and it is probably a little more dependent on cytochrome P450 metabolism. I have a couple of things to mention in regard to that.

You'll notice I alluded rilpivirine being the only NNRTI allowed in the study. That's because in a preliminary drug interaction study, efavirenz, which is also a nonnucleoside reverse transcriptase inhibitor and a significant CYP inducer, lowered velpatasvir levels in a drug interaction study by about 50%. That was more than was seen with ledipasvir, so for that reason, it was excluded from this study.

For the tenofovir interaction, the magnitude of increase in plasma tenofovir levels with exposure following administration of the prodrug, tenofovir disoproxil fumarate, are at least percentagewise the same with sof-velpatasvir as they with sof-ledipasvir. In other words, you see about a 20% to 40% increase in the geometric mean ratio of tenofovir in plasma when it's coadministered with either sof-ledipasvir or sof-velpatasvir.

On the surface it might seem interesting that boosted protease inhibitors were included in this study but not in, say, the companion study in ION-4 that looked at sof-ledipasvir in a population with coinfection.

Part of that is some comfort in the accumulated experience that those increases in tenofovir plasma levels are probably on the borderline of where you may see some effects, but we're giving it for a short duration, and I think at least in clinical experience there hasn't been a large signal of interaction. So I think it was important to analyze that in the controlled study setting. We didn't have a placebo arm in this study, so it is not definitive in terms of safety, but it certainly looked good.

Finally, I just suggested that there were no significant adverse events or safety signals, but we can speak directly to the renal safety. There was no significant change in any of the groups, whether patients were on tenofovir, boosted or unboosted. During the coadministration we didn't see any difference in changes in creatinine with coadministration over the study. However, specific laboratory abnormalities were of interest, and one was whether any patients would have a creatinine increase of 0.4 mg/dL over the study.

Four patients experienced that, and they were all on a tenofovir-based regimen. Three of those four were even on a boosted tenofovir-based regimen. But when you look at them individually, all of them had coexistent comorbidities that may also predispose patients to renal issues — diabetes, hypertension, several of those patients were African-American. But during the study, none had to stop therapy and all

continued on their tenofovir-based therapy without significant problems.

DR. CHUNG: In those patients, Dr. Wyles, did those patients' creatinines come back down to baseline?

DR. WYLES: Yes, they did. The one patient who had the largest increase turns out to have had a history of CKD. The entry criteria for the study were a creatinine clearance greater than 60 ml/min, and he was right there at the border, but during the study his creatinine clearance did drop and was associated with an increase in serum creatinine. However, that was also in the setting of being on other medications, ACE inhibitors or angiotensin blockers. Nephrology felt his renal disease was most likely related to diabetic nephropathy, not CKD.

But to your point, his serum creatinine rose to about as high as 2.6 mg/dL during the study and did come back down, even during the study, and then dropped further after the study.

DR. CHUNG: Great. Terrific. So for ultimate recommendations for antiretroviral regimens headed into an HCV treatment course using sofosbuvir-velpatasvir, would you recommend that patients need not switch their HIV regimens when they head into treatment?

DR. WYLES: Another great question. I think, yes, given this phase 3 study and the data we have in patients. Although as our listeners may know, even currently you can use sof-ledipasvir, sofosbuvir-ledipasvir with ritonavir-boosted protease inhibitors as an HIV regimen if you have to, with close renal monitoring. This study gives us some confidence that it looks safe to do that. With the 100 or so patients in this study, not all being on tenofovir, personally I would do it, but I would still probably monitor renal function until I had a little more experience with it in the clinic if I do coadminister these.

DR. CHUNG: You mentioned African-Americans earlier. In the discussion of the demography of this study, would you comment on the potential slight diminution in their response rates observed in prior trials of DAAs in coinfection, or even in monoinfection, and whether we saw or could comment on any such lag in this study?

DR. WYLES: That's been a key question going forward from the ION-4 study, where all 10 of the viral failures in that study happened to be African-American, and eight of those 10 happened to be on efavirenz, as well. Interestingly, you pick up on something here in that we had two virologic failures in this study, and both happened to be African-American women in their 60s. With just two virologic failures in this study I don't know that we can say much else, and about half of the overall study population was African-American.

It still does make you wonder. A lot has been done to look at those failures with sof-ledipasvir. It doesn't clearly appear to be a drug interaction related to the efavirenz that each of the 10 were on, and the genome-wide association study didn't seem to identify anything specific in an African-American population that might account for these failures.

In the overall experience with monoinfected patients using that same regimen, sofosbuvir-ledipasvir, there did not appear to be a signal of African-American patients faring worse.

I think it's still really up in the air and something that should continue to be looked at. Maybe we'll get some more insights from one of these phase 4, real world experiences like TARGET or TRIO in that respect.

DR. CHUNG: One final question, Dr. Wyles. Much has been said about NS5A resistance-associated variance, and many questions are swirling around about how to use them effectively and judiciously in clinical practice. From the data from the ASTRAL-5 study, would you therefore conclude that rAAV testing has no role in this group of patients with HCV/HIV coinfection, heading into a regimen of sofosbuvir-velpatasvir?

DR. WYLES: With just this study it probably would be premature and difficult to answer that question, given the numbers. One of the groups I'm specifically interested in having more data about would be genotype 3. In this study we just didn't have enough genotype 3 patients to really be able to assess adequately whether baseline resistance has an impact with sof-velpatasvir in genome type 3. If I cheat a little and look at ASTRAL-1 or ASTRAL-3 studies — I think the ASTRAL-1 study was this same regimen in monoinfected patients — at least in my mind pretty definitively points out that baseline NSA5 resistance is not going to have a major impact for genotypes 1, 2, 4, 5, and 6. There were almost no virologic failures in that large study, so it's really hard to envision much of an impact there.

A variant or rAAV, there was a lower response rate, I think it was 84%, and there were just over 20 patients who had that in ASTRAL-3, so genotype 3 patients.

I think that's probably the one place where there's still some question about whether there might be some utility in resistance testing.

DR. CHUNG: This group certainly continues to reinforce the adage that the rising tide has lifted all boats, including those with HIV coinfection.

Dr. Wyles, I want to thank you for being part of the *e*ViralHepatitis Review. I also want to tell our listeners that this podcast is not available for CME or CE credit.

Finally, Dr. Wyles has disclosed that he has received research and grant support and served as a consultant or advisor for AbbVie, Bristol-Myers Squibb, Gilead, and Merck.

Thank you once again, Dr. Wyles.

DR. WYLES: Thank you very much.