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VOLUME 4, ISSUE 3: TRANSCRIPT – DR. GRAHAM FOSTER

DR. MARK SULKOWSKI: Hello, and thank you for joining us. I'm Dr. Mark Sulkowski, professor of medicine and the medical director of the Viral Hepatitis center at the Johns Hopkins University School of Medicine. I'm speaking today with Dr. Graham Foster, professor of hepatology at Queen Mary University of London. Today we're going to speak about the ASTRAL-3 study which was presented at the November AASLD meeting. Dr. Foster, thank you for joining us today.

DR. GRAHAM FOSTER: It's a real pleasure.

DR. SULKOWSKI: Well great, let's jump right in to the ASTRAL-3 study. Dr. Foster, can you give us a brief summary of the trial?

DR. FOSTER: ASTRAL-3 looked at optimal treatment without interferon for patients with genotype 3. It summarized a large group of patients who received either sofosbuvir or velpatasvir or the current standard of care, sofosbuvir/ribavirin.

The importance of the sofosbuvir/velpatasvir combination is that this was a short, 12 week duration of therapy. It shows for the first time in genotype 3 a high response rate without interferon and without ribavirin. We're all used to seeing sustained response rates well over 90 percent in patients with genotype 1 infection without using the multiple-side-effect-prone ribavirin and interferon. But for genotype 3 we've struggled to hit these high levels until now.

So for me the key features from the sofosbuvir/velpatasvir arm were that over 90 percent of the patients responded to therapy. In fact, patients with cirrhosis who happened to have prior treatment had a 93 percent chance of a sustained response. We haven't seen that rate in patients with genotype 3 before.

The patients with really difficult to treat genotype 3 are those with cirrhosis who previously failed treatment. In this niche group of patients we saw sustained response rates of 89 percent, which is a very significant improvement over what we've seen before, even with interferon, ribavirin and sofosbuvir regimes.

So the take-home message for me from ASTRAL-3 is, we now have a tablet only, ribavirin-free treatment for genotype 3 that works even in tough-to-cure patients.

DR. SULKOWSKI: This certainly is a tremendous advance in the treatment of patients infected with hepatitis C genotype 3. But are there any particular populations where you might want to think about extending the duration of the sofosbuvir/velpatasvir therapy for 24 weeks or perhaps adding ribavirin? In other words, are there still some groups of patients where 12 weeks of this single tablet regimen might not be enough?

DR. FOSTER: We're always looking to cure every single patient we treat, and if you look very hard at the sofosbuvir/velpatasvir data, it's clear that in treatment-experienced patients with cirrhosis there is a little drop-off to 89 percent response. I think in those patients I would be tempted to consider adding ribavirin. I personally wouldn't go for an extended duration of therapy. I think evidence that extending therapy in the presence of ribavirin is necessary, but it's not really there even for genotype 1.

So I would argue that for patients with cirrhosis who are treatment-experienced you might consider adding something extra. I would, however, point out that those patients are now a vanishing breed — we're not treating patients with genotype 3 patients and cirrhosis with pegylated interferon and ribavirin. Just about all the patients who have therapy have already

been retreated. So this is a population that's getting very small, indeed.

I think for treatment-experienced patients who don't have cirrhosis, the sustained response rate of 91 percent is very respectable. I'm not sure that the disadvantages of ribavirin, the added side effect burden, justify treatment additions in this group. I'm also not sure the cost of 24 weeks of sofosbuvir and velpatasvir would justify that. So in my view, the only group where I would think about extending or adding ribavirin would be treatment-experienced patients with cirrhosis.

DR. SULKOWSKI: Well, let's jump into another somewhat challenging topic, and that topic is baseline testing for Resistance Associated Variance (RAV). There was a lot of focus at this year's Liver Meeting on the presence of resistance variance to the NS5A inhibitors, in this case velpatasavir, do you see any role for NS5A resistance testing at baseline before we treat patients with this sofosbuvir/velpatasvir combination?

DR. FOSTER: I think the jury is still out on the value of testing everyone before treatment for variants that might be associated with a small reduction in treatment efficacy. In the sofosbuvir/velpatasvir trial, we did see the patients with the Y93 variant, and 84 percent of them had a sustained virological response. So the impact of the RAV in this particular study was minimal.

The disadvantage of testing for RAV and trying to find the few extra patients who might need a little extra treatment is that it makes treatment much more cumbersome and may have a paradoxical effect of slowing down access to therapy. So in my own practice at the moment I take the view that the response rates are good enough with straightforward 12-week therapy without RAV testing.

However, I think if we have to retreat patients who had an NF5A inhibitor, that's when I would consider adding the RAV testing. I suspect that if RAV testing becomes widely available, and if clinicians get used to the difficult nomenclature and number of RAVs, then we might see it move into mainstream. But at the moment, I'm an advocate for getting out there, treating as many patients as we can, and for those few who fail, then we can start to apply sophisticated molecular diagnostics.

DR. SULKOWSKI: We've really focused on the new data from ASTRAL-3 on velpatasivr but I want to take you back for a minute and talk about interferon. You had previously published in Gastroenterology the BOSON study which looked at the treatment in this genotype 3 population with peginterferon, sofosbuvir and ribavirin. At the time it was presented it really looked like there was major role for peginterferon in the treatment of this patient population group. So here we are with the ASTRAL-3 data. Do you still see any role for interferon in the treatment of this patient population?

DR. FOSTER: I have been a great believer in interferon for many years. We've been old friends, in fact, and I was very pleased to see that it was hanging on for patients with genotype 3 who have cirrhosis; in the BOSON study it did seem to produce some benefit. But I think now even I've got to accept that with sofosbuvir/velpatasvir these sustained response rates are better than those in the BOSON study. We can compare across studies, of course, but when we have response rates that are nearly 90 percent across the board, I don't think there's a role for interferon anymore. There may yet be an opportunity to bring back interferon for patients who have multidrug resistant viruses, and perhaps in patients who fail velpatasvir we may have to consider it, but I think at the moment for most patients, interferon, I'm glad to say, is probably a dead drug.

And I've got to be honest and say if I had hepatitis C, I'd do everything I could to avoid interferon. I think it is a bit of a side effect prone drug and we're much better without it.

DR. SULOWSKI: Well Graham, I see we're just about out of time. I want to thank you for sharing your insights with our listeners and for being a part of this *e*ViralHepatitis Review Special Edition program.

DR. FOSTER: Thanks very much, Mark, it was a pleasure.