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VOLUME 4, ISSUE 3: TRANSCRIPT – DR. VINCENT LEROY

DR. MARK SULKOWSKI: Hello and welcome. 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 in Baltimore, Maryland. Today I'm speaking with Dr. Vincent Leroy, professor of medicine and medical head of the liver transplantation unit at Grenoble University Hospital in Grenoble, France. Dr. Leroy had one of the most impactful presentations at this year's Liver Meeting held in San Francisco, it was known as the ALLY-3+ and focused on patients with advanced liver disease and genotype 3 infection. Dr. Leroy, thank you for joining us, and please tell us a bit about the ALLY-3+ study, what led to it, and how the study was designed.

DR. VINCENT LEROY: The study design and the rationale for the study design came from the ALLY-3 study showing excellent results for patients without cirrhosis, a 96 percent response but only 63 percent response in patients with cirrhosis. The design of the study was two arms, 12 and 16 weeks of treatment with a combination of sofosbuvir and daclatasvir plus ribavirin in each arm. The aim of the study was to compare the efficacy of the two arms of treatment.

DR. SULKOWSKI: Let me ask you about that, because it was a remarkable result of the original ALLY-3 study that the regimen of daclatasvir/sofosbuvir worked very well in the patients without cirrhosis, but what is it about a patient with genotype 3 who has cirrhosis that you think led to that 60 percent or so response without ribavirin in a 12 week treatment?

DR. LEROY: Of the two options, it is clear that 63 percent is clearly not sufficient for this patient population of genotype 3 affected with cirrhosis. So the two options clearly were to extend treatment duration to 16, 24 weeks, and use ribavirin. The problem is that these patients with cirrhosis have a very special natural history, more rapid fibrosis progression and clearly need to be treated very early. This was the rationale to try two treatment durations, 12 weeks and 16 weeks with ribavirin, trying to reduce the rate of relapse.

DR. SULKOWSKI: Certainly the study was performed very quickly. We had the ALLY-3 presentation in publication and a lot of experts and clinicians who read the study in Hepatology said, we need this ALLY-3+ study, and you were able to pull it together relatively quickly. Please take us through the patients you enrolled. How many did you enroll, what type of patients were they?

DR. LEROY: A total of 50 patients were included. I know that is a small number of patients, but again, speed clearly was a priority because we really needed to get the results as soon as possible. We treated 50 patients, 14 of them had advanced fibrosis, METAVIR F3, and 36 patients had cirrhosis using very stringent criteria, FibroScan liver thickness with a cutoff of 14.6 kilopascal. That means the study population clearly had true cirrhosis.

DR. SULKOWSKI: I noticed you also allowed a range of patients with prior treatment. I think about three-quarters of the patients had previously been treated and failed, including individuals who were treated with sofosbuvir. It sounded to me like this patient population was very difficult to treat. Can you tell me about the prior treatment course and what we know about that in these patients?

DR. LEROY: You are perfectly right, the vast majority of patients were treatment experienced. That was the case for 74 percent of patients, and six patients received sofosbuvir/ribavirin combination, so that clearly is a difficult to treat population. All patients have compensated cirrhosis, but some of them had

portal hypertension, so again, it was clearly a very difficult to treat population of experienced patients with genotype 3 and cirrhosis.

DR. SULKOWSKI: These are certainly the types of patients many of us are seeing in our clinical practice. In fact, certainly in the United States where I practice, we are seeing sofosbuvir/ribavirin failures. In the HCV target presentation of patients with genotype 3 and cirrhosis in the US, we only demonstrated a 47 percent SVR rate with sof/ribavirin. So I think this population is really growing and making up a part of our study population.

Take me through how they were treated and then the outcomes.

DR. LEROY: Patients received either 12 or 16 week treatment duration. The main result is that overall, 90 percent of patients achieved SVR. In patients with advanced fibrosis, the rate of SVR was 100 percent. For patients with cirrhosis, the rate of SVR was 86 percent without. The difference between the 12 and 16 week arms, and looking at the cause of failure, four patients relapsed, two in each arm. So overall, in the more difficult to treat population, the cirrhotic patients, the rate of SVR was 86 percent.

DR. SULKOWSKI: That is certainly a considerable improvement over sofosbuvir/daclatasvir without the ribavirin. So it seems, at least in my view, that ribavirin is really doing a lot of help, the patients with cirrhosis respond, and I think you definitively answered the question whether ribavirin is helpful.

But I do want to ask you about the duration. The US treatment guidelines, and actually the use of this regimen in many parts of Europe, have been for 24 weeks, often with ribavirin. Now we're looking at 12 and 16 weeks, and I'm curious is what are you doing in your practice with this population based on the ALLY-3+ data and what we know about how hard it is to cure this population? Are you using 12, 16, 24 weeks; how do you apply this information?

DR. LEROY: Optimal treatment duration is clearly a difficult question. The main result of ALLY-3+ study is that 12 week duration with ribavirin gives excellent results in patients with cirrhosis, but the main limitation of the study is the limited number of patients. In my clinical practice, in patients with advanced fibrosis, F3, and what we could call early cirrhosis, I think that 12 weeks of treatment with ribavirin is sufficient.

For patients with more advanced cirrhosis, it is probably better to go for a longer duration, 24 weeks. The remaining question is whether ribavirin is still necessary in these patients treated over the longer duration. For example, looking at the results from the French Early Access Program, we showed during the same meeting in San Francisco that 24 weeks with ribavirin and without ribavirin get exactly the same SVR results. This is an observational study, it is not a randomized study, and we really need to interpret these results with caution, but maybe using the longer duration we could avoid ribavirin.

DR. SULKOWSKI: That is very helpful information. I think all of us as clinicians are struggling with how to best manage this difficult to treat population, and I must say that the French hepatology researchers led the way, both with the expanded access study you referred to, but also the ALLY-3+ study. I think adding ribavirin and considering a longer therapy really is critical to success in this patient population.

I want to thank you for sharing your insights and the results of this very important study that you presented at the Liver Meeting in San Francisco. Thank you, Dr. Leroy.

DR. LEROY: You're welcome.