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VOLUME 4, ISSUE 3: TRANSCRIPT – DR. GREGORY DORE

DR. MARK SULKOWSKI: Hello, and thanks for joining us. I'm Dr. Mark Sulkowski, medical director of the Viral Hepatitis Center and professor of medicine at the Johns Hopkins University School of Medicine. I'm speaking today with professor Gregory Dore, who is the program head for viral hepatitis clinical research at the Kirby Institute at the University of New South Wales in Australia. He's also an infectious disease physician at St. Vincent's Hospital in Sydney. Today we're going to discuss an important study called C-EDGE CO-STAR. This study focused on hepatitis C infection and its treatment among persons who inject drugs and was presented at the November SSLT meeting in San Francisco. Dr. Dore, thanks for joining us today.

DR GREGORY DORE: You're welcome, Mark. It really was a pivotal study. It was the first study to target a population that had generally been excluded from phase 2 and phase 3 clinical trials for interferon-free antiviral regimens. The population was different in that, even though other studies included small numbers of people who had been on stable methadone or buprenorphine — people with substitution treatment, as we call it — studies had almost universally excluded people who had ongoing illicit drug use. So for the first time we have a study that is looking at outcomes in this specific population.

This study was evaluating a regimen of grazoprevir and elbasvir in combination with a protease inhibitor, an NS5A inhibitor which is a coformulated, fixed dose, once daily regimen to 12 weeks in this treatment naïve population. The overall outcomes are incredibly favorable. The first thing that was encouraging was the high adherence to therapy. I presented that data at the International Symposium on Hepatitis Care for Drug Users in Sydney earlier than the San Francisco meeting, but the adherence showed that only about 3 percent of the study population missed more than three doses of their 84 day regimen, which is incredibly high adherence, 95 percent. That level was achieved by the vast majority of the study population. We were very encouraged that the adherence data would translate into favorable treatment outcomes. And, in fact, it clearly did.

Further, the sustained virological response rate in the study population was 92 percent. The study was designed as an immediate versus preferred study, so the outcomes we presented in San Francisco were from the first 200 individuals in the immediate treatment arm. There was a placebo controlled arm, around 100 participants, who then had preferred treatment after a four week period after the initial 12 weeks of placebo.

The outcomes for the initial 200 were incredibly encouraging, with a 92 percent SVR12 rate. There were five cases of reinfection. Importantly, the study looks at the incidence of reinfection in this population of people who may be continuing injection drug use, and we identified five cases of probable reinfection in the study population. The 92 percent SVR12 rate includes those cases as failure. To look at what we term "treatment efficacy" in suppressing the virus and probably clearance of the initial infecting virus, the SVR12 rate increases to around 95 percent. So I think it's important to concentrate on that 92 percent mark, because what we're really trying to achieve is clearance and ongoing clearance.

DR. SULKOWSKI: Greg, let me stop you there. Thank you for that overview, and you've raised what I think are several critical points that really affect how we're going to use these highly effective hep C treatments in this important population. I say important population because, number one, this is where hepatitis C transmission is ongoing, and as you know, in the United States we're actually seeing a substantial

increase in hepatitis C transmission among young adults who are using injection heroin. So this is critical data at really a critical time when we have the opportunity to control the infection.

You've hit on two things I want to come back to. One was the issue of adherence. We have heard over the years that this is a group of human beings who would be hard to treat because they can't adhere. What were the keys to success in your study — was it the fact they were on opiate substitution therapy, or what did the sites do to achieve that high rate of adherence?

DR. DORE: I think it's probably a combination of those two, and there are probably some other factors, as well. We should state that one of the eligibility criteria was to be stable on methadone or buprenorphine. In fact, participants had to adhere to more than 80 percent of their visits to receive OST therapy over the recent months. So we're not taking a population who are very unstable in their opioid substitution therapy; that's the first thing to say. The second thing is, as you know, in clinical trials it's a very sort of intensive period when patient oversight is built into the trial itself. Patients received an electronic diary that reminded them with a daily alarm that it's the time to take your medication. They also had to record the date and the time they took the medication. That wasn't specific for this trial; the same adherence monitoring tool that was used in the rest of the phase 3 programs are used in this regimen. I think it's important to say that it was the same sort of monitoring tool, so the adherence is very similar across the other studies, but the tool itself may have been an adherence intervention.

So to have that sort of device that alarms every day may be very helpful for all patients, but particularly this patient population, in reminding them to take their medication.

And the third thing is that for all clinical trials you generally enroll a highly motivated patient population who are obviously very keen to cure themselves of hepatitis C. What we need to do now is look at outcomes in a broader population beyond the phase 2 and phase 3 trial populations that we enroll.

DR. SULKOWSKI: I think you made some really good points there. I would also point out that we can add some of those adherence type tools to our clinical practice. They can be and indeed have been adopted for things like TB and HIV therapy, so it's encouraging.

Now I want to come back to the issue of ongoing drug use during the treatment by some of these study participants. You know, a lot of the criteria for treatment, at least in the United States, require people to abstain from drug or alcohol use for six months prior to treatment, but at least my understanding of the data is that some of your study participants did, indeed, continue to use. Did that have an impact on adherence or how did they do?

DR. DORE: In fact, not just some of the participants, more than half of the participants had ongoing drug use. Drug use was detected by urinary drug screen performed at day one and throughout the treatment period. The patients were aware that was going to be part of the protocol.

The types of drugs that were detected were amphetamines, cocaine, opiates other than methadone and buprenorphine, and cannabinoids and benzodiazepines were detected as well. But even if you put aside cannabinoids, which have been allowed in many of the studies, the other classes of drugs were detected in around 50 percent of participants during the treatment period.

The one gap in our study data is that we don't know the route of administration of those drugs, so we don't know whether they're taken orally, intranasally, or injected. The study is going to be extended for another three years to follow people for reinfection and also, importantly, collect self reported injection drug use risk behavior. I think that will be really crucial to see what the patterns of drug use are and, in particular, what proportion of people are actually injecting or using other routes of administration for their ongoing drug use.

But if we look just at the drug use detected by urinary drug screen, there was absolutely no difference in the SVR12 rate between those who had detection of drugs during treatment and those that did not have detection.

DR. SULKOWSKI: To me that's a critical finding because it tells us that there is really no medical or scientific justification for using a period of abstinence when talking about the likelihood these treatments will be successful in curing the hepatitis C infection.

To me that was one of the major contributions of this study.

I want to finish by talking about this issue of reinfection because when I talk to people about treating persons who inject drugs, the other concern, as we already talked about, is adherence and success. But the other concern is reinfection. What are the take-home messages and what do we need to do when we're approaching patients who may be at risk of reinfection to prevent that? Talk me through what this study means for you in terms of prevention of reinfection.

DR. DORE: I think the first point is to reiterate the ongoing drug use issues. I think the study very clearly shows that ongoing drug use does not affect treatment adherence and it does not affect treatment efficacy. And that's a very, very strong message, because, as we mentioned, a lot of people are restricted in access to these therapies, not just of injection drug use, but also on ongoing illicit drug use.

So if we think about reinfection, obviously that is related to ongoing injecting drug use. I think sometimes we have to separate illicit drug use between ongoing noninjection drug use and injection drug use. Obviously with injecting drug use there are specific issues around the potential for reinfection.

We've done quite a lot of work in characterizing reinfection incidence in people who inject drugs with ongoing injection, and reinfection clearly occurs. We believe that the incidence is around about five per 100 person use. That's about a 5 percent annual risk of reinfection in someone with ongoing injection drug use.

That is lower than the infection risk of initial infection, and that's probably because people who go through a treatment program are somewhat motivated and probably have better harm reduction strategies in place to reduce their risk of reexposure. But we can always do better in terms of reducing risk of re-exposure, and I think there are a few cases that we need to deal with. One is that when we're starting someone on therapy, one of the key aspects we need to cover is ongoing drug use and whether there's injection drug use, not only the question of whether you have ongoing injecting drug use, but who are you injecting with I think is really crucial.

For example, if someone who is about to go through therapy has ongoing injection drug use and they're injecting regularly with their sexual partner, for example, it makes a lot of sense to try and get both of those people into a treatment program at the same time. Obviously, if you treat one person in that injecting partnership and they have ongoing use together, there will be a higher risk of reinfection. So I think that characterization, the social injection network through an individual, will be one of the key elements to optimizing harm reduction and reduce the reinfection risk going forward. That can be done, but I think as clinicians we just need to be more aware of that and talk to patients more about it.

I think the more we talk to patients, the more comfortable they will be in giving us that sort of information. It's really important to create a space in which patients feel it's an environment where they're not going to be judged and can pass on really important information about their lifestyle and their injecting practices that have relevance to their individual health.

DR. SULKOWSKI: I think we've about run out of time. Greg, I want to thank you for, number one, presenting this important study and sharing your insights with our audience. I believe that this study, known as C-EDGE CO-STAR, has moved the field forward in an important way and informs us on how to treat persons who are using drugs, persons at risk for reinfection. I think the study will have immediate impacts on how we treat this patient population.

So again, thank you for joining us, and thanks for your time, Dr. Dore.

DR. DORE: A pleasure, Mark.