Transcript: New Data Explores Current Treatment Options

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At the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Peter Staley asks Dr. Joe Eron about the good news on a challenging drug – newly-approved Selzentry – and the very potent new protease inhibitor, Prezista. To see the video click here.

PS: This is Peter Staley of AIDSmeds.com, and we're back for part two of our interview with Dr. Joe Eron discussing an important session at the conference this morning at ICAAC that looked at both experimental and approved HIV agents, and right now we're going to talk about the stuff that's already on the market. But two big studies that may change the way people use the current drugs, especially for those who are highly treatment-experienced, I would imagine. And maybe one of them might change people trying treatment for the first time.

JE: Absolutely.

PS: So let's start with Pfizer's CCR5 blocking entry inhibitor. We talked about the experimental entry inhibitors before this. Selzentry, which was recently approved – maraviroc – they came out with 48-week data in a study where we had previously discussed 24-week data. What can you tell us?

JE: Well I actually was very, very encouraged with these data. There were two phase-three studies of maraviroc, or Selzentry: Motivate 1 and Motivate 2. So at this meeting we only saw Motivate 1, the 48-week data of Motivate 1. But what we saw basically is the proportion of patients that were less 50 at 24 weeks really was absolutely sustained at 48 weeks. And I honestly had some concerns that maybe we would see a fading of the activity of this drug over time and we would see a drop off in the proportion of people that were less than 50. But it really was spot-on, in terms of the proportion of patients suppressed. And it was just around 46 to 48 percent, less than 50 copies, with the twice-daily dose. And I just think that- I was impressed and I was encouraged by that information. We also saw that the tolerability essentially held up—very well-tolerated drug. This was a placebo-controlled trial, and you couldn't really see substantial differences from placebo.

PS: There were some concerns at the FDA hearing about liver and cardio.

JE: I'm not as sure about the cardio toxicity. I know that because one of the CCR-5 inhibitors, aplaviroc, which was a GSK compound, had substantial liver toxicity and actually had to have development discontinued. The FDA's very concerned about liver toxicity with this group of drugs

and there've been two cases with maraviroc of hepatotoxicity out of literally thousands of people treated. But if you look at the Motivate study results, the differences in LFT abnormalities between maraviroc-treated patients and placebo is actually very small. In Motivate 1, there was a little bit more of these LFT abnormalities in the maraviroc-treated arms. But in Motivate 2, which we'll see in Madrid, in about two weeks, it actually was flipped the other way. There was actually a little more liver enzyme elevation in the placebo arm. So I think when you put the two together there just really doesn't look like there's much liver toxicity.

PS: Pretty safe drug. Still a complex one to use though- you have to worry about the tropism of your virus, which is very complex. Patients are having a hard time wrapping their head around this. We also heard data on some of the failures that are occurring: 8 percent failed in Motivate 1…?

JE: We'll take this one at a time here. So in order for these CCR5 drugs to be active, at least active virologically, a patient has to have this R5 virus. So you have to have a tropism assay. What we know is, in the Motivate studies, between screening and entry, before anything happened to these patients, 8 percent had a tropism switch. So what that means is the assay's not perfect. So somewhere between 5 and 8 percent of patients are probably going to be misidentified as being someone for whom maraviroc or Selzentry is active. The separate question then is what about people who either don't respond or who rebound. In those patients, about two-thirds of them we see a receptor switch, so we see viruses come up that are no longer using R5, so they're X4 or dual-tropic viruses and in about a third, somehow the virus figures out how to use the receptor with the drug bound, so in effect it gets around the drug not by competing with the drug for binding, but actually using the receptor with the drug bound. Which is a really complicated concept, one we really haven't had to face before.

PS: Sort of resistance, but not.

JE: It's definitely resistance, but it's resistance that's actually dependent on the drug so as soon as you remove the drug, that resistant virus diminishes very quickly. It probably doesn't go away entirely. I think it's very complicated for patients; I think it's even going to be complicated for providers. On top of that, maraviroc has three different doses, so depending on which drugs you pair it with, you're either going to give maraviroc 150 milligrams twice daily, 300 milligrams twice daily, or 600 milligrams twice daily. So we're really going to have to be on our toes using Selzentry or maraviroc.

PS: Are you seeing a lot of patients that need salvage that are trying maraviroc?

JE: Well, I can tell you that in order to use this drug, you have to get the tropism assay. So it's taken us a few weeks in our clinic to actually set up the mechanism to send out the samples to get the tropism assay.

PS: This was just approved last month.

JE: So we have this all worked out, but I would say in my clinic, with my own patients, I probably have 4 or 5 patients right now where I'm going to send the tropism test. Now, how many will end up having R5 only virus, I don't know, because these are pretty advanced patients.

PS: Now, something came up during this that just went right over my head, and confused the

crowd as well, and that is the people who did break through, the 8 percent, most of them were misidentified. They were the group with higher CD4 counts. What did that mean? Do they know what's going on there? The drug seemed to raise their CD4 counts more than those who were doing well on the drug.

JE: Yeah, I think that might have been a consequence of just small numbers of patients. I don't fully understand that. I think we also saw those slides pretty quickly, and we need to digest them a little bit better. It is true, though, that people that have dual/mixed virus, this virus that can use X4…

PS: As opposed to R5.

JE: R-5. As opposed to R5…We do see that when they get maraviroc, even though they don't have much in the way of antiviral effect, they do tend to have a CD4 cell increase. We don't really understand that. It's kind of a mystery, and I don't think that anybody can give you a perfectly clear explanation yet. But we'll learn.

PS: Now some of the most interesting data came at the end, late-breaker session, on Tibotec's Prezista, which has been on the market for about a year now, and 48-week results from Artemis, which is the name of the study. And this compared Prezista plus Norvir—it's another protease inhibitor, you take it with Norvir—to Kaletra, which has Norvir built into it. But it did it in treatment-naive patients. So this is one of the few protease-inhibitors that's dared to test itself against Kaletra. What did they find?

JE: So this is a very large, head-to-head study. Over 300 patients in each arm. They combined it with Truvada, so kind of the standard of care, and basically the top line, I think, is that Prezista with Norvir, compared to Kaletra was what we call non-inferior. And I think in this case, we can use the word, "equivalent," though I guess if you were a statistician, you would not say that was completely correct. But in fact a greater percentage of patients on Prezista-Norvir achieved a viral load less than 50 copies.

PS: It was 84 percent versus 78 percent.

JE: Exactly right. So actually a greater percentage. Now, you might ask, was Prezista superior to Kaletra? And when they did that analysis, it didn't quite make it as being superior, though in very high viral load patients, it did appear to be superior.

PS: If you started treatment with a viral load of over 100,000, Prezista worked better than Kaletra. Fascinating.

JE: Right. To be fair, we haven't seen that in other studies of Kaletra, like the KLEAN study that we published last summer. Really, Kaletra had the same response in high-viral load patients, greater than 100,000, compared to lower viral loads, less than 100,000. So this is a little different. And what they did show, which I didn't realize, in this Artemis study is that patients were actually given the choice to take Kaletra either twice daily or once daily. And while is wasn't a planned analysis, there was at least a suggestion that perhaps twice daily was a little bit better than once daily with the Kaletra. And in fact, there was an ACTG study presented last summer, that's a year ago now at the Toronto meeting, that also showed that, that perhaps twice daily was a little bit better than once daily, especially in people with higher viral loads, greater than 100,000. So it is kind of

consistent.

PS: And they also compared Prezista once daily to Kaletra once daily, and Prezista looked much better on that sub-analysis as well.

JE: Right, so Prezista was given once daily, in fact it was 800 milligrams with 100 milligrams of Norvir. So all the Prezista doses were once daily. The Kaletra doses were either the standard 400/100 twice daily or 800/200 once daily, and I think clinicians were given a choice—that part I don't quite remember, and we have to check out the data. But the Prezista with ritonavir was definitely given once daily, and they showed some very nice PK curves, suggesting that it's just fine to give it once daily in this population, so I think it's pretty exciting. Kaletra has its advantages. You can't beat having both drugs in one pill. It's tough to beat that.

PS: What about toxicity?

JE: Looked like there were more gastrointestinal toxicities with the Kaletra. But again, not everyone in this study was able to get the tablet formulation of Kaletra. A certain percentage got the old capsule formulation, so we need to sort that out a little bit. They also showed us data on toxicity where the clinician thought it was possibly related, probably related, or definitely related. And my own opinion is in an open-label study, you should show all the toxicity. Don't show clinician attribution, because a clinician will think, "Oh, so-and-so got diarrhea, they're on Kaletra, must be due to the Kaletra," whereas I might say, "They're on Prezista, they got diarrhea, but it must have been what they had for lunch yesterday." So I think you have to be a little bit careful about that. On the flip side there were more rashes in people who got Prezista. And in that case, they weren't very serious rashes, there were very few discontinuations due to rash but that was a difference in the other direction.

PS: Thanks once again for this amazing overview. I've learned a lot from it. It was hard to digest everything this morning.

JE: I'm still digesting.

PS: Hopefully it will help our audience and a lot of people with HIV digest some of this, so we'll be more educated going forward. Thanks again, Joe.

JE: Well, Peter, I'm sure I'll see you again very soon.

PS: In Madrid!

JE: Well, no, I won't be in Madrid. We'll have to wait. Boston.

PS: See you in Boston.
