Transcript: Simple Test Eliminates Abacavir Risk

October 18, 2007

In this videocast interview from the International AIDS Society Conference in Sydney, Peter Staley asks Professor Simon Mallal from the Royal Perth Hospital about a simple new genetic test that accurately predicts if a patient is at risk for an allergic reaction to abacavir (an NRTI known by its brand name Ziagen, and one of the drugs in Epzicom and Trizivir). To see the video, click here.

PS: This is Peter Staley with AIDSmeds.com, and we're here with Dr. Simon Mallal from Australia, the first doctor we've talked to that actually lives in the country that we've been reporting from all week. You're from the Royal Perth Hospital, is that correct?

SM: Yes.

PS: Well, thanks for joining us.

SM: Well, thank you for asking me.

PS: You presented a late-breaker session at the conference today that really had some exciting news. A drug that's been kind of a very good backbone drug as far as the nukes, but it's always had kind of a scary toxicity.

SM: Had an issue...

PS: Yeah, had an issue. And we're talking about abacavir or Ziagen from GlaxoSmithKline. It's been on the market for many years, but a very dangerous hypersensitivity reaction in a small number of people that if you had it and then you actually took the drug again, it could be fatal.

SM: Right. Well, yes, it was potentially very dangerous. I'm happy to say that patients and clinicians got pretty familiar with hypersensitivity and patients, being so sophisticated and well informed, knew what to look out for. So we've always been out to manage it clinically. But the big breakthrough has been the ability to do a genetic test to individualize the choice of therapy based on the genetic makeup of the patient. In this case, a gene, an allele, called HLA-B*5701.

PS: We need a catchy name for that! It's very hard to remember.

SM: Yeah, B*5701 is, you know, it is an important allele that also, in fact, turns out to be associated with a very good immune response to HIV. And so it's generally associated with strong responses. In the same way people with this allele make a strong response and control their HIV well, unfortunately they also make a very strong response to abacavir and feel very unwell in the

first 1-3 weeks after going on therapy if they're predisposed genetically.

PS: So what was the great news that came out of this late-breaker about this genetic test and hypersensitivity to abacavir?

SM: Well, we reported in 2002 this association between B*5701 and abacavir hypersensitivity. And that was actually independently found by the GSK team in case control, that included US patients. In fact we introduced screening in Perth and effectively eliminated the side effect from our own population. But that was open screening. And really to justify taking personalized medicine at the clinic for the first time, this is a world first, needed really the top level of evidence. What we call Level 1A evidence. A randomized clinical trial, blinded, all the bells and whistles. And that was a major exercise. This study involved 265 centers all around Europe and Australia and nearly 2,000 patients that were randomized to either receive the genetic test or not to receive the genetic test. Those that received the B*5701 testing, if they had the allele, didn't go on abacavir. And so when we looked at the results, we had this phenomenal result that none of the patients that had the screening developed abacavir hypersensitivity and we confirmed the diagnosis with patch testing. That's another important part of the study. That abacavir hypersensitivity, understandably, is not very specific in its symptoms. And immune restoration disease, rashes with efavirenz, the flu, may be confused with abacavir hypersensitivity. And it needed the patch test to work out who really did or didn't have HSR.

PS: Now the patch test is not something that we're going to start using in practice. But it's what helped you confirm that the genetic test actually worked. And what we mean by this patch test is that it's actually this patch that they stick on your back or somewhere and it creates some immune bumps like you do with other immune tests. And that actually confirmed whether you were having an abacavir hypersensitivity reaction. And what I found interesting is it showed that the actual abacavir hypersensitivity reaction rate among patients was lower than what the clinical trials of abacavir and its label actually says.

SM: Right. So it's certainly no greater than 3 percent. And in fact we did already know that from randomized clinical trials. In that in trials in which the patient and the doctor didn't know whether they were getting abacavir or the non-abacavir arm, we saw rates of supposed abacavir hypersensitivity, over diagnosis, if you like, of 2-7 percent. Se we've really actually always known that true HSR was at a lower rate. But until we had patch testing we couldn't find our way to the real cases, and therefore we couldn't really nail the genetic association between B*5701 and real patch test confirmed hypersensitivity. And I should mention that in addition to the Predict 1 study done in Europe and Australia, another very important study, the SHAPE study, I'm not sure if you're aware of this, was conducted in parallel in the US.

PS: So bottom line, now that we have these results, this basically means people who want to consider taking this drug can have this genetic test first and they can be almost 100 percent certain whether they can take this drug or not. If they show up positive they should avoid abacavir, and if they're negative, they should feel confident that they can take this without having a reaction.

SM: Right. So, we'll always still be vigilant clinically. We're always going to still warn people and give people the warning card and look out for it. But if someone gets it, they'll certainly get written

up in the literature. Because we've yet to find a case of patch test confirmed HSR in a patient without B*5701. But nevertheless, you're absolutely right. We need to maintain clinical vigilance and make sure that something doesn't slip through the net that we're not yet aware of. But at this stage, it looks very promising. The nice thing is, for the 94 out of 100 people that have a negative test, they go on the drug, that they can really be confident that they're unlikely to get immune-mediated hypersensitivity. And if they do get symptoms in the first few weeks, the doctor and patient can look for what it really is. Is it efavirenz rash? Is it fever from immune restoration disease? And so there will be less misdiagnosis in general.

PS: So tell us. Is the test available now? So you can ask your doctor for it? What kind of a test is it?

SM: Right. So typically, most groups are taking blood. As most new people with HIV, when they receive their diagnosis, get their hepatitis and other serology done. And when that initial workup is done, the groups that have adopted genetic screening, the blood test is taken, the DNA is examined for the presence of that HLA-B*5701. And then if the patient's informed that they're negative, they know that abacavir is a good option. So it provides them that early certainty. And the nice thing about abacavir is we've been using it, certainly in trials, for 10 years. There's over a million patient years of experience with it. So the long-term safety profile is very well established. So there's a nice combination of long-term certainty and short-term certainty now. And it's going to mean there are more options for patients, which is great.

PS: And you can test for this in a variety of ways. Blood and also swabbing the mouth?

SM: Yeah, there is a test. Lab/Cor offers a test, which just involves a mouth swab. Most people do test by blood test. It's also becoming available by flow cytometry with the CD4 count, which is a neat way of doing it and making sure it gets a quick result.

PS: Most of the time the result takes about 7 to 10 days?

SM: Yeah. Most results would take 7 to 10 days. They often should come back within a week. And with the flow test of course, like the CD4 count, it's only one or two days. And that's good.

PS: For our audience, this is not a test that changes over time.

SM: Right.

PS: You're born this way, so you can have this test when you're one year old and the result would be the same right before you die. So you only need to take the test once and then you'll know whether can take abacavir at some point.

SM: Right. And a very important point is if you do find out that you have B*5701, really take that result seriously. Write it down, and make sure everyone treats it as though you're allergic to abacavir. You don't want to see one molecule of that drug if you have B*5701. So pay attention if you do have a positive standing result.

PS: Well thank you very much. That was an excellent explanation of some pretty exciting news. And thanks for welcoming us to this beautiful country.

SM: It's a beautiful place. And I'm very proud of being Australian, but you're very lucky to live where you are too.

PS: [laughs] Thanks.
