Transcript: The Skinny on Metabolic Complications

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PETER STALEY: This is Peter Staley with AIDSmeds.com and I'm speaking with Dr. Donald Kotler, chief of gastroenterology at St. Luke's Roosevelt Hospital in New York and a longtime researcher of wasting, lipodystrophy, and metabolic problems in people living with HIV. Lipodystrophy and metabolic complications were a frequent theme at the 14th Conference on Retroviruses and Opportunistic Infections in Los Angeles, otherwise known as CROI 2007, and we're going to discuss those now with Dr. Kotler. Thanks for joining us, Donald.

DR. DONALD KOTLER: Hi, everybody.

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STALEY: First let's talk about TH9507 (now known as Egrifta), a growth hormone precursor, being developed by Therotechnologies in Montreal. First, can you briefly explain how this precursor growth hormone is different from the typical growth hormone that we've all heard about, which is Serostim, which is also being studied for lipodystrophy.

KOTLER: Ok. First of all, TH9507 is a releasing factor rather than a precursor. I guess the real first point to make is that growth hormone has something to do with visceral fat. We always thought of growth hormone as a way to make people grow muscle, as an anabolic agent. Because that's how it was used, that's how it's approved, that's its approval in HIV. But the studies that showed that it increased lean mass also showed that it burned fat even in people who were wasting. And in fact, when you look really carefully at the data, the fat that got burned was fat in the trunk, rather than fat in the limbs, in patients who were wasting. More than that, people with growth hormone deficiency increased their visceral fat, and when you replace growth hormone the visceral fat goes away. And if you look at people who start out with a lot of visceral fat, they secrete less growth hormone than normal, and when you give those people growth hormone, the amount of visceral fat decreases, and that was shown in HIV-negatives and it's also shown in HIV-positives. So there

really is some relationship between visceral fat and growth hormone, kind of a mutual antagonist. So, growth hormone has been looked at, and two studies have been done, and it's now with the FDA, and there is safety and efficacy, but there are indeed some side-effects, and that is the FDA's business.

STALEY: And this is Serostim.

KOTLER: Serostim, right. TH9507 actually is related to a hormone in the brain that leads to growth hormone secretion. It comes from a part of the brain called the hypothalamus, and it's been manipulated so it's a little bit more long acting in the 9507. The proposed differences and benefits between 9507 and Serostim, is that when you give the TH9507 it causes pulsed secretion of growth hormone rather than steady levels, which is more like what happens physiologically. And when you give the hormone from the hypothalamus to stimulate the pituitary to make growth hormone, there's actually a preserve feedback mechanism, which prevents there from being too much activity. You also might look at it and say, well, it could actually prevent there from being too much abuse, so you can't just sort of go and take a lot and get buff, if you understand. So the drug has been tried, it appears that the dosage that's being used sort of gives the equivalent of somewhere between one and two milligrams of Serostim. Not super high, but enough to cause about the same kind of effects as what [EMD Serono, Inc.] was seeing in their maintenance Serostim, because they're giving one to two milligrams sort of in a maintenance kind of way.

STALEY: And what did we hear from the study at the conference itself?

KOTLER: This is the second study, the second demonstration of benefit. And as I said, the benefit is like a milligram and a half or a tiny bit more of Serostim. There seems to be a better safety record, especially in terms of glucose. One of the problems with growth hormone is that not only does it decrease visceral fat and lipids in a positive way, it seems to make glucose metabolism worse. The TH9507 helped visceral fat, helped the lipids, and did not make glucose metabolism worse. So it appeared to have a bit of a benefit compared to Serostim.

STALEY: And we didn't see any wasting in the limbs or face?

KOTLER: No there was no wasting in the limbs or face. Again, in Serostim there's not very much of that either. The other worry about Serostim is that a growth factor might possibly make visible tumors, or tumors grow faster. And it's related to another hormone, that growth hormone stimulator that's called IGF-1. It appeared that TH9507 had a little bit less of an effect on the IGF-1, so there may be a little bit less of a concern about tumor genesis. On the other hand, there haven't been a lot of tumors in people taking any of these meds. And the tumors that occur aren't really the HIV tumors. You know what I mean? The few tumors that have been seen in growth hormone are more like skin cancer or anal cancer, things like that, rather than KS or lymphoma, which is what people are really worried about in HIV.

STALEY: Help us quantify the fat loss that we're seeing with TH9507 in the gut. Is it like a belt notch or two?

KOTLER: The first studies of Serostim for visceral fat accumulation, used 6 milligrams, really high doses. And that took two and a half inches off a waistline. Using a 4 or 3 milligram [dose] really only takes off about an inch and a half, and using the Thera product really only takes off an inch or

so from the waist. So if you're huge, you know what I mean? If you are really, really fat accumulated, you know, suddenly you have a waistline of 42 inches when you're used to 34, taking the TH9507's not gonna get you back to 34. If you're 42, it'll get you down to 40, maybe.

STALEY: We're saying, basically there was a 20 percent different between the placebo group and the Thero group?

KOTLER: Yeah, 20 percent difference in the area of visceral fat on a single slice of a CT scan taken at the navel. If you were to change that to volume, it would probably be more like 25 to 28 percent. You'd lose about a quarter of it. But if it's really huge, µ is still a lot.

STALEY: Well, it's been a hard nut to crack and it still sounds a little promising.

KOTLER: It's absolutely there, there's absolutely an effect. It is not a panacea. The question for the FDA for both Serostim and for 9507: is the benefit going to be worth the cost? Is the benefit going to be worth the toxicity? How much can you push these drugs to get more and more of an effect? Because they're hormones. The more you use, the more you get. How much can you use before the price or the side effects become limiting?

STALEY: And many of our members know this, the cost of Serostim is kind of through the roof. And we don't know what the Thero drug will be, but it's gotta be…

KOTLER: It's gotta be in the same general category.

STALEY: Right.

KOTLER: So they really do have a ways to go. And certainly for Serostim, it's clear that there needs to be a maintenance [dose]. I can't help but believe it will be the same for TH9507. That it's not going to be a single therapy, then stop it.

STALEY: Right you won't be able to just start it and stop it.

KOTLER: Right.

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STALEY: Another metabolic problem that was mentioned in CROI was bone loss, meaning osteopenia and osteoporosis. And I should mention that I suffer from a bit of that myself, I've been diagnosed with osteopenia. There were some encouraging data from a study involving Fosamax, combined with calcium and vitamin D supplementation. What did the study find, and what do you think the implications are for HIV positive folks with low bone mineral density.

KOTLER: We're gonna take a step back. It turns out that osteopenia and osteoporosis are pretty common in HIV and they are especially common in people that you wouldn't expect to have osteopenia, like, you know, white men. Middle-aged white men have very little osteopenia, but the HIV-infected do, and it was found very early that it's not just drug related because it occurs prior to people starting drugs even, or at least prior to HAART therapy.

It seems to be related to an inflammatory condition, at least in part, and in studies by Alessandra Viganò, presented at CROI, it appeared to be related to cytokines that are pro-inflammatory cytokines. Something called a RANK ligand, which is kind of like TMS, being elevated. And it acts at the level of the bone breakdown cell called the osteoclast. And there may be a cytokine tone

between something called osteoprotegerin, which obviously protects bone, and RANK ligands. And that relationship is altered early on which tends to lead to greater bone breakdown. And in fact very early in therapy it might even get a bit worse until there's full immune reconstitution.

In any case, there's a lot of osteopenia at the start, and at least in men who work out, there's even bone fractures. The most common probably being the metatarsals in the foot in people who spend time on the treadmill. But others as well. Now, even though osteopenia is not considered a reason to give therapy, there certainly is a worry in the long term that this would be allowed to continue.

Grace McComsey from Cleveland presented data using the drug Fosamax which blocks osteoblast activity, so she blocked bone breakdown, and it has been an approved drug for the use of osteoporosis. [She] did a study, in the presence of calcium and vitamin D to make sure there would not be that kind of deficiency, and compared the data to calcium and vitamin D plus a Fosamax placebo. And in essence showed that Fosamax in this condition kind of works about the same as Fosamax in any other condition. Calcium and vitamin D had some minor effect, and when you added the Fosamax to it, you actually had much greater effect – 3 to 4 percent, I believe over a year, in terms of increasing bone density.

STALEY: This is in people obviously with HIV, so the results are similar to what they had seen with Fosamax in the HIV negative population?

KOTLER: Right, and they were used in people with osteopenia and osteoporosis. So it seems that if this were to become a standard of care, it would be used for osteoporosis, but it probably wouldn't be used for osteopenia. For osteopenia there would be the recommendation to continue to follow. And that actually brings up a different point about measurements and about the ability of making measurements. Certainly DEXA scanning is done in middle-aged pre-menopausal women, not so much done in HIV-infected men. I would hope that there will be coverage so those kinds of studies could be done. So you could even figure out whether or not there is osteopenia. And while you're at it, since those same machines can be used to measure lean and fat, it would be very nice if there was the opportunity of doing a nutritional assessment to look at fat content, fat distribution, as well as lean tissue mass at the same time. In general, that's not reimbursed. So the average patient going to an average doc just doesn't have that kind of information being generated.

STALEY: And it would be great for almost anybody with HIV to go out and get a baseline at least of how their bones are doing given the prevalence that we're seeing. I mean that's how I caught it. I went to a new doctor and he just said "this is what we're doing" right off the bat. But there's probably a lot more of it out there that people don't know about. And everybody should get it tested.

KOTLER: And you're not going to get it done through a clinic. I mean, I guess if you're a 45-year-old woman it's easier, but for just a sort of a general guy going to a clinic, it's like…

STALEY: I went to a bone expert and everything. And as you said, the advice was, since it was still just osteopenia, I started calcium and vitamin D supplementation and was just told that we'll look at it every year and see if it gets worse, but I'm holding off on the Fosamax, and there's even a newer generation of bone density drugs I believe, but both of those are really for the osteoporosis.

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Let me ask you one more question about a study that came out at CROI, something we *can* all do something about, and that was the one at Massachusetts General Hospital looking at the amount of fat in the diets of people living with HIV. The study seemed to suggest that while we're looking at ways to get around lipid increases caused by HIV medications and other things, we might also benefit from diets low in calories made up of fat. So why don't you summarize what this study told us and what we should take home from it.

KOTLER: You're trying to make me into a dietician [Laughs]. This was actually a review of studies and clinical data, I believe from Mass. General Hospital looking at diet composition, especially the composition of dietary fat, in relationship to lipids. And just what you would expect, saturated fats and trans fats, those people had a greater number of dyslipidemia than did those who did not.

STALEY: The HIV-negative.

KOTLER: It was looking at HIV-positives and HIV-negatives and the HIV-positives had 10 percent more saturated fats, 10 percent more trans fats, 10 percent more cholesterol, etc, than the others. I don't know what to make of it. Because it is true saying that the worse your diet, the worse your lipids. And in general the HIV-positive people have worse diets than the HIV-negative people. It really depends on who the HIV-negative people are, and that wasn't necessarily so well explained.

STALEY: What was interesting to me is it said the HIV-positive group was actually ingesting slightly fewer calories and therefore slightly fewer fat calories. But the percentage of fat in our diet was higher. So it just was not as balanced as the HIV-negative group.

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There was also data I think from Kaiser, in Northern California, Kaiser Permanente, showing that the lipid lowering drugs that we have available to us right now don't seem to produce the same level of reductions in people with HIV than they do in people without HIV.

KOTLER: Once again, a couple of limitations in that study. The major limitation being that, first of all, HIV-positive people had their lipids checked way more often than HIV-negatives, interestingly enough. But when they were treated, well, the treatment that is given to HIV-positives and HIV-negatives is different. So that HIV-negatives are much more likely to take things like simvastatin, and HIV-positives will more likely take something like pravastatin.

STALEY: And what are the brand names of those?

KOTLER: Simvastatin, I think, is Zocor, and pravastatin is Pravachol. So it's unclear whether the difference is HIV-positive versus negative, or whether the difference is Zocor versus Pravachol. So it's either the patients or the drugs. And this study didn't really tell you. I think the more important lesson for treating people is that you set your target and you fight to get there no matter what it takes. So that if it takes more pharmacy, well it's pharmacy. If it's diet, well it's diet. If it's fish oil for the lipids, we'll take the fish oil for the lipids. You don't really want to stop until you get where you want to be.

STALEY: I've been throwing everything at it, personally. I'm on Crestor, which is probably the most potent of the lipid drugs, I'm taking a high dose of that. I'm taking the fish oil. The one thing I

don’t do is look at my diet really closely, so that other study’s kind of pushed me that way. Yeah, it’s hard. And I’ve gotten it to around 200 total on the cholesterol but obviously it could be lower.

KOTLER: One thing that’s interesting that’s come up several times in the meeting, whereas we tend to look at total cholesterol, or we tend to look at LDL cholesterol, or non-HDL cholesterol, and it may be that the most important number to look at is the HDL cholesterol.

STALEY: That’s the good cholesterol.

KOTLER: Yeah, the good cholesterol. The good/bad drug. The good/bad measurement. HDL cholesterol seems to be behind much of the benefit of the antiviral therapies, especially NNRTIs in the DAD study. And in much of what people are looking at, it seems like HDL cholesterol is more and more standing out as the important factor. And that’s interesting because a lot of what we do doesn’t really relate so much to HDL cholesterol. We don’t tend to use a whole lot of niacin, which tends to bring HDL cholesterol up. And, one major difference between the metabolic profiles of NNRTIs and PIs is the effect of NNRTIs on HDL, which is much stronger than with the…

STALEY: The non-nukes.

KOTLER: Yeah. So it may be that with a total cholesterol of 200, or an LDL of 140, if you have a really nice HDL that you’re able to keep up somehow, genetically or otherwise, that may be an okay target for you. The other part about that, which is I guess the bad news, is that people who like to use anabolic agents, one of the real bad effects of anabolic agents is that it really does drive down the HDL.

STALEY: Testosterone, stuff like that.

KOTLER: Testosterone, deca, things like that. Oxandrin has been shown to lower the HDL cholesterol. Cecilia Shikuma last year did a study that said that testosterone does not affect [visceral fat]. So if you decide that you’re gonna go on anabolics to trim your abdomen, it’s probably not going to work, and in addition you may drop the HDL cholesterol. So that’s not a good response.

STALEY: There’s a lot of guys juicing that just don’t know the long-term side-effects of this, it’s a big question mark. Don, thank you so much. Once again this was a fascinating interview. We’re definitely keeping our eyes open for additional news regarding lipodystrophy and metabolic problems, and are glad that you’re still playing a major role in this ongoing research. So thanks very much.

KOTLER: You’re welcome.
