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Managing High-Risk Osteoporosis: Post-Hoc Findings on Abaloparatide

Announcer:

You're listening to *On the Frontlines of Osteoporosis* on ReachMD. And now, here's your host, Dr. Charles Turck.

Dr. Turck:

This is *On the Frontlines of Osteoporosis* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss a post-hoc analysis on the efficacy of abaloparatide in women with osteoporosis who are at high fracture risk is Dr. Bart Clarke. Dr. Clarke is an endocrinologist at Mayo Clinic in Rochester, Minnesota, and he specializes in treating parathyroid and other metabolic bone disorders, osteoporosis, and calcium disorders, and he's also a co-author of the study we'll be discussing today.

Dr. Clarke, welcome to the program.

Dr. Clarke:

Thank you.

Dr. Turck:

Well, to start us off, Dr. Clarke, would you give us a brief overview of the ACTIVE trial?

Dr. Clarke:

So the ACTIVE study, or ACTIVE trial, is a clinical trial that was performed in patients using abaloparatide to a comparator, in terms of recombinant human parathyroid hormone 1-34 compared to placebo, so it's a wide-ranging study with an active comparator. And in this case, these are in women who were at particularly high risk of fracture based on various professional society guidelines. So they go through that in the paper. We can talk more about that if we want. But these were women who would be considered to be at high risk of fracture by different criteria.

And what they evaluated was a total of 2,026 participants who met the fracture risk criteria in the guidelines. About a third were assigned to abaloparatide, a third to placebo, and a third received teriparatide, the recombinant human PTH 1-34. And what they found was that vertebral fracture risk was reduced, as expected, in those who got abaloparatide and teriparatide both compared to placebo, so this was the expected outcome of the study. And then, of course, they started to look at this in more detail.

So the vertebral fracture risk was the main focus. They looked at nonvertebral fracture risk and saw similar results where the abaloparatide and teriparatide both reduced fracture risk compared to placebo. They compared this to clinical fractures, a broader segment of the population with fractures of different types, saw similar results, and in this case, the abaloparatide and teriparatide both worked better than placebo.

And then they also looked at wrist fractures and saw similar results, although the magnitude of the difference was less.

And essentially, after looking at the fracture results, they then went back and looked at bone density changes. They saw abaloparatide was associated with the bone marrow density increases at all time points in the lumbar spine, total hip, and femoral neck, and that common adverse events reported in the participants treated with abaloparatide were as expected: hypercalciuria (high urine calcium), dizziness, lightheadedness, and arthralgia (joint pain). So the conclusion of the paper was that abaloparatide reduced fracture incidence and increased bone density in the participants at highest risk of fracture consistent with the overall ACTIVE study that had evaluated a

slightly larger population of people, most of whom met these same criteria.

Dr. Turck:

Now, what was the rationale behind revisiting data from the trial to focus specifically on women at the highest risk of fracture?

Dr. Clarke:

So the basic study showed these findings, but the concern was, well, maybe there's a subpopulation within that larger population that might also benefit from this where we don't have as widely available therapies. So by going back and looking at those at highest risk of fracture, one of the questions was, would the drug work as well, perhaps, or maybe not work? It's always difficult to know that in advance. But the purpose in this was to see if those who met various national society guidelines that were coming out right around the same time this paper was published also benefited as much as the general population that was used in the clinical trial. Fortunately, for abaloparatide, that did work.

Dr. Turck:

And what criteria did you use to define this highest-risk subgroup?

Dr. Clarke:

So they looked at different societies, like I said. It turned out they had to meet at least one of the following criteria. I'll just read these off from the paper because they're in the paper: fracture within the past 12 months or prevalent vertebral fracture, meaning the patient on x-ray or imaging evidence had the fractures already present. Whether they were known or not, it didn't matter. So these people—once they've had a fracture—are at higher risk.

They also looked at baseline bone density T-scores. Certainly, if they were below -3.0 at any site, that's a high-risk population. They also looked at very high fracture risk probability using FRAX. FRAX estimates the 10-year anticipated fracture risk if treatment is not given, and they set up their criteria for those who had a greater than 30 percent risk for major osteoporotic fracture or for hip fracture risk of greater than 4.5 percent. Just so you know, for comparison, according to FRAX, usually, if the patient has a greater major osteoporotic fracture risk than 30 percent or a hip fracture risk of more than 3.0 percent, that would be a reason for treatment, so in this case they set the bar higher to exclude some of those that would have been treated with something, just not necessarily abaloparatide. And then finally, their last criteria was that if the patient had had multiple prior fractures at baseline since age 45 for reasons not clear otherwise, this was regarded as being a high fracture risk population.

So those are the different criteria selected. As we said earlier, patients in this analysis had to have at least one of those fracture criteria met, and as you might anticipate, many of these people had multiple fracture criteria met.

Dr. Turck:

For those just tuning in, you're listening to *On the Frontlines of Osteoporosis* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Bart Clarke about abaloparatide for women with osteoporosis who are at high risk of fracture.

So, Dr. Clarke, you provided a bit of an overview earlier, but let's dig a little bit further into the results of the analysis. Just how effective was abaloparatide in reducing vertebral fractures in this subgroup?

Dr. Clarke:

Yeah. So again, given this population, the severity of the osteoporosis they had, and these various criteria that they had to meet, the question was, well, how well did it work? And so, for example, as we just said, looking at new vertebral fracture risk—which was the main endpoint that was evaluated—they found that both abaloparatide and teriparatide had reduced fracture risk, so they worked well together. And again, if I look at the tables here to look at the number of fractures that we're seeing or how much reduction in fracture there was—because that's how they present the data; you could look back at the paper later—but figure one talks about the absolute reduction in fracture. 4.05 percent was the absolute reduction in fracture with abaloparatide. And then compared to placebo—there was no reduction compared to placebo because placebo was the comparator standard. And then teriparatide, for example, reduced absolute fracture risk by 3.78 percent.

So small differences, but in this kind of population where fracture risk is very high, any benefit we get is viewed as being positive and obviously would be a motivation to use the strongest thing we have. In this population, as you might expect, many of the other choices for therapy wouldn't work very well. So we're dealing with sort of the worst case scenario and trying to do the best we can. And of course, even a small difference between abaloparatide and teriparatide would make a big difference for these patients. So that was the major outcome.

They also looked at cumulative incidence rate of nonvertebral clinical major osteoporotic and wrist fractures and saw varying percentages between these, comparing the abaloparatide to placebo or abaloparatide to teriparatide, so that's the difference between these. But similar results were seen not just at the new vertebral fracture sites but also the other more classical sites that we evaluate patients with osteoporosis for.

Dr. Turck:

And what did you find in terms of bone mineral density improvements?

Dr. Clarke:

Yeah. So for the bone density improvements, as you would expect, the abaloparatide and teriparatide are both anabolic agents and they stimulate bone formation, and certainly, compared to placebo, which doesn't do anything, the two drugs, abaloparatide and teriparatide, showed significant increases. So, for example, if you said lumbar spine, it looks like about, on average, the increase seen over the 18 months of duration of the study was about 8 to 10 percent, so a significant improvement. Total hip went up about 2 to 3 percent in that range, and then for femoral neck, abaloparatide and teriparatide both increased by 2 percent to 3 percent range. In terms of the lumbar spine, there was less difference between abaloparatide and teriparatide, whereas those differences were larger looking at total hip and femur neck. Although, at the end of the study, my recollection is the significance of the change seen at the total hip and femoral neck was not great.

Dr. Turck:

Now, before we come to the end of our program, Dr. Clarke, how should these data influence the way we treat patients with osteoporosis who are at a very high risk of fracture?

Dr. Clarke:

So I think, you know, when we look at these patients that are at very high risk, the first thing to say is that we would think in this day and age about anabolic agents first and the antiresorptive agents second. The reason is the anabolic agents stimulate bone formation, they raise the bone density more, and they reduce fracture risk better than the antiresorptive agents. And this is a bit of change in the paradigm or the way this has been since 1995, when the initial antiresorptive agent, alendronate, came out. That's the way we have been practicing for the last 25 years. But now that we have anabolic agents that are more effective, the question is, should a patient at particularly high fracture risk being given an anabolic agent prior to, then saving the anti-resorptive agent for later? And I think this paper, among other papers, is evidence that would suggest that. The suggestion is that the anabolic agents do work better in this case, certainly more than placebo, and there are small differences between the anabolic agents, as we've noted, but they're all better as a group than the previous antiresorptive agents, and there are certain nuances in that difference between even abaloparatide and teriparatide.

Dr. Turck:

Well, with those insights in mind, I want to thank my guest, Dr. Bart Clarke, for joining me to discuss how abaloparatide may improve outcomes in women with osteoporosis who are at a high risk of fracture.

Dr. Clarke, it was great having you on the program.

Dr. Clarke:

Thank you.

Announcer:

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