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Time Is Bone: Making the Case for Early Anabolic Treatment in Osteoporosis

Announcer:

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Dr. Saag:
Today, we're discussing a critical, underappreciated area of osteoporosis treatment: the use of bone anabolic agents. Despite their proven potential, these are drugs and biologics that are widely underutilized in the management of osteoporosis in fracture risk reduction, and we really thank you for joining us as we further explore this area.

This is CME on ReachMD. I'm Dr. Ken Saag from the University of Alabama, and it's a pleasure to welcome my friend and colleague, Dr. Kendall Moseley from Johns Hopkins. Welcome, Kendall.

Dr. Moseley:
Thanks so much for having me today.

Dr. Saag:
All right, let's get started. Dr. Moseley, could you talk a little bit about changes in osteoporosis and bone architecture for patients that are at high risk for fragility fracture and some of the tools that we use to assess that risk? And maybe you could also comment on how our osteoanabolic agents might be considered differentially in assessing bone with some of the available tools that we have for bone measurement.

Dr. Moseley:
So as we know, bone changes as we get older. We gain bone, or we gain more bone than we lose until we're about 30 years of age, or that third decade of life. And in midlife, there's a steady state that we enter into where we're building up bone, we're breaking it down at approximately the same rate. Women go through menopause where they lose a significant amount of bone, and then a little bit later on, inflection point, maybe around 70. But depending on how much we gain and then eventually lose, we're at increased risk of fracture. And these conditions and these other incidences that may happen to us during our lives really will categorize us into different groups. So we might be at low risk for fracture, moderate risk for fracture, or high or very high risk for fracture, and the higher that risk for fracture becomes, the more necessary medications sometimes become.

And how do we determine this? Well, we do have screening tools in our world, and the gold standard screening tool is a bone density test, or a DEXA scan. And it's in that DEXA scan that we get things like a T-score, which categorizes as osteoporotic when the T-score is less than negative 2.5. From that DEXA scan, we can calculate a FRAX risk, which gives us our overall risk of 10-year fracture and hip fracture at 10 years. We can get a trabecular bone score which is a surrogate measure of bone quality, particularly at the vertebrae, and

even a vertebral fracture assessment, where we can screen for incident and prevalent vertebral compression fractures. And it's really that combination of T-score and FRAX and VFA and TBS that puts together our overall fracture risk and helps us then categorize ourselves as to whether or not we're in that low, moderate, high, or very high fracture risk category and eventually will dictate therapy, particularly when we're considering anabolic agents for that high- and very-high-fracture-risk group.

Dr. Saag:
I wanted to ask you a little bit more about the trabecular bone score. That often comes up. Do you find that differentially helpful in trying to think about the use of anabolics?

Dr. Moseley:
I do find it to be helpful. What you see is not always what you get with the bone density test. This is a 2D representation of bone, kind of a bone quantity. But oftentimes there's bone weakness that kind of lurks beneath the surface of the skeleton, where patients may be fracturing despite fairly normal bone density scores. But you get that TBS sometimes, that bone quality assessment, and oftentimes we're surprised with that superimposed score on the DEXA.

Dr. Saag:
Terrific.

Dr. Moseley:
Yeah. So I've kind of hinted that there's different types of medications, Dr. Saag, but could you please give us a brief overview of the available anabolic agents we have?

Dr. Saag:
Yes, so we really currently have only 3 therapies that are considered bone anabolic. Most of our medicines, the estrogen, bisphosphonates, denosumab, selective estrogen receptor modulators, those are drugs that really are predominately antiresorptive, and of course, bone is in a steady state of remodeling, and so blocking resorption actually does have some effects on rebuilding bone to a lesser degree. But stimulating bone directly is the job of teriparatide, abaloparatide, and, most recently, romosozumab.

Teriparatide has been around the longest. This is a synthetic version of parathyroid hormone, and it's a little bit surprising for many to think, gosh, hyperparathyroidism, that's bad for bone. And it's the continuous exposure to PTH that has this catabolic effect on bone. When you give PTH in a pulsatile way, as a daily shot with teriparatide or abaloparatide – we'll talk more about that in a minute – it actually stimulates the osteoblasts and leads to an increase in markers of bone formation and the rise in bone mineral density, particularly at trabecular bone sites like the spine initially, and eventually at cortical sites, too.

Abaloparatide is a cousin of teriparatide. It actually is an analog of PTH-related peptide. These drugs are really much more similar than they are different. I think probably the 2 differences to note is that teriparatide, on average, increases calcium about a milligram per deciliter, so people that are running a high calcium, they may be at a little bit more risk of getting into trouble with teriparatide. Abaloparatide does not tend to increase calcium as much, but in contrast to teriparatide, there may be just a little more vasodilation, so patients often like to take it later in the day.

Now, what's really great about these drugs is they've been shown to increase bone density, and to reduce fractures, so that was really encouraging information.

The newest addition is romosozumab. This is a monoclonal antibody to sclerostin. Sclerostin is an inhibitor of bone formation. So think about it this way: you're inhibiting an inhibitor, and that has an effect on increasing bone formation. And interestingly, romosozumab also has some antiresorptive properties. It's also given parenterally like teriparatide and abaloparatide, although the shots for that are given every month instead of every day.

So, Dr. Moseley, with this information, this background, let's move on to our next topic. And where should we start?

Dr. Moseley:
I alluded to the fact that there's sometimes some health conditions which may accelerate bone loss or make us more susceptible to fracture. Speak a little bit more to those health conditions of where we might want to consider an anabolic agent.

Dr. Saag:
Yeah. And so when do we think about anabolics, I think, is really the question. And one of the things that we should point out right away, and this is maybe the most important thing, is that anabolics work best when they're used first. The problem is, is that they got to be given as shots, and so that's been an issue. They've been branded compared to generic drugs like alendronate. And so they haven't been historically used as first-line therapy. But if you're trying to get the most benefit, particularly in a high-risk patient, you're going to get it if you give the anabolic first. And whenever you give an anabolic first, you follow it with an antiresorptive later. And particularly with teriparatide, abaloparatide, and also as well with romosozumab, some of the bone that's formed is not fully mineralized. And by following it with an antiresorptive via a bisphosphonate or denosumab, you actually fill in that new remodeling space that's been created.

So as a rheumatologist, another topic that's really exciting to me is glucocorticoid-induced osteoporosis. Unfortunately, we're involved in causing a lot of it, but it is a condition. It's the most common form of drug-induced osteoporosis, and it's important to note that the new American College of Rheumatology guidelines, for the first time ever, highlight the use of bone anabolic drugs as potential first-line therapy for people at high risk. And this makes sense because one of the big problems with glucocorticoids is that they inhibit bone formation, and so by giving a drug that actually stimulates bone formation, we see some benefit there as well.

So I'm going to turn it back to you, Kendall. Maybe you want to talk a little bit about some of the guidelines that are out there besides the ACR.

Dr. Moseley:
Very important guidelines in the ACR, but obviously, lots of other guidelines, too. And I think there's actually been a big effort ongoing to try to unify some of these guidelines so that there's a little bit more cohesiveness and consistency with how we approach treatment for osteoporosis, particularly with these high-risk or very-high-risk patients. I would say that is even one of the biggest differences amongst the guidelines, is how we define these high- and very-high-risk patients. And we need clarity so that we can learn for ourselves but also for our colleagues, maybe on the front lines of primary care, as to how to think about their patients.

But in general, when we think about higher- and, in particular, very-high-risk patients, most of the guidelines would agree that those with a recent fracture, so a fracture that's osteoporotic or fragile, in the last 12 months – so things like the forearm, the spine, the hip, the pelvis – would be included in that group.

They're at high risk for fracture, in a high-risk category. Fractures while on osteoporosis treatment – so again, if someone is on a treatment and then they have then broken a bone, that's considered treatment failure, so you might need to turn up the dial a little bit in terms of treatment intensity. Or multiple fractures while on drugs. A very low T-score – so again, that DEXA may give us some data showing a T-score less than negative 3, which would put someone into a very-high-risk category. Multiple falls. We know that bones usually break in the context of a fall, so someone might not have the worst bone density, but if they're falling on a regular basis, you would worry about that particular patient. And then pulling out that FRAX calculator that I mentioned earlier. If there's a major osteoporosis fracture risk greater than about 30% at 10 years or a hip fracture risk greater than 4.5% at 10 years, in those situations, too, you might want to consider an anabolic drug. And these are just a few things. I think we all have to use our clinical intuition, too, to decide who we would categorize as a high-risk patient. And there are things that I have not mentioned here, but maybe other medical conditions, for example, about to start high-dose steroids, in whom we might want to preemptively get ahead of some of that bone loss anticipated.

We do have multiple approved agents to reduce risk of fracture, but as you've already said, those at very high risk for fracture, that's when we want to think about our anabolic drugs. Denosumab does make it into that category as well, but again, I think that reaching for that anabolic first. If there's anything to be taken from this chitchat today, it's the fact that our high-risk patients, in terms of drug sequence, would benefit from an anabolic drug first with the primary goal to treatment is to reduce that fracture risk. And oftentimes in those very-high-risk patients, you want to reduce that fracture risk as quickly as possible in that 1 year from romosozumab, in those 2 years of abaloparatide or teriparatide, ultimately to prevent fracture. And so we have to take all of these things into consideration.

Dr. Saag:
You know, one of the other things that has been a topic of some interest in the bone world is this idea of treat to target, and there was a really nice paper out from a consensus panel. Felicia Cosman was the first author. And they looked at at what T-score you should think about initiating which kind of therapy, based on a goal of trying to get the BMD T-score at minus 2.5 or better. And as you pointed out,

people that get down in the low 2s, and into the 3s, those are people that really should go on a bone osteoanabolic drug first to really try to get to target faster.

So I think the next thing we want to really talk about is important, and that is the issue of cost, and cost varies. It varies a bit with all these drugs.

It really just depends on what health plans they have. And so it's got to be looked at at a patient level in terms of what you can get. Access is really varied, widely. And we have some people that get it through patient assistance programs, so that's been helpful, as well.

So let's go on to the next topic, and I'm going to turn it back to you, Kendall.

Dr. Moseley:
I think that we really should talk about how we feel that these drugs are being taken up by the community, by patients. And I think we'd all agree that there are some challenges that we have out there with patients starting on anabolics, starting with how we diagnose osteoporosis and making that official diagnosis, how we treat it, and then picking the right medication, I think, is really critical. And we see through the data that oftentimes we have lots of patients who are fracturing, which would effectively be a diagnosis of osteoporosis, but they're not formally given that diagnosis. And more importantly, those who fall into a high-risk fracture category aren't given anabolics as first line. There was one trial in which greater than 10 million individuals with osteoporosis were looked at. And sadly, in those 10 million individuals, only about 17% of the high-risk eligible fracture patients were treated for osteoporosis. And of those 17%, only 20% got an anabolic agent. So again, we're not diagnosing people with osteoporosis; we're not treating them. And it starts with making that diagnosis. But then once you make it, figuring out who's in that worrisome category where they may benefit from an anabolic drug.

Dr. Saag:
Yeah, as a rheumatologist, I mentioned steroid-induced osteoporosis, but I see a lot of these people that have had multiple fractures and really low bone mass, and they're the ones I really want to try to get osteoanabolics for first.

So I guess we better close this out. I'll turn it back to you, Kendall, and we'll kind of wrap it up.

Dr. Moseley:
I think if I had some parting thoughts, it would be that it's not enough in our little bone circles that we have these discussions. I think that a lot of what we're doing now is trying to educate not only the lay public but also our colleagues who truly are on those front lines, who not only recognize and diagnose osteoporosis but think about the anabolic agents. Why don't we use more of them? Well, it's kind of complicated, right? It's not just a prescription for alendronate anymore. We have all these other great therapies, but unless we're using them, unless we're prescribing them in the right patients, unfortunately, we're not going to reduce the fractures like we might want to. So I'm thrilled to be able to do these chats to be able to get some of this information out there.

Dr. Saag:
That's all we have time for today, so I want to thank our audience for listening in. I want to thank you, Dr. Kendall Moseley, for sharing your expertise and insights, and it was really great speaking with you all today. Thanks so much.

Dr. Moseley:
Thank you.

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