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Optimizing Bone Health in Postmenopausal Post-Fracture Patients

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Dr. Singer:
Osteoporosis can lead to fractures, often accompanied by significant morbidity and economic burden. These patients are at an increased risk for life-altering secondary fractures, but most do not receive evaluation or attention. Today, Dr. Susan Bukata and I address this medical challenge.

This is CME on ReachMD, and I’m Dr. Andrea Singer. I’d like to welcome Dr. Susan Bukata.

Dr. Bukata:
Thank you, Dr. Singer. Glad to be here. Let’s dive right in. Orthopedic specialists are broadly aware that post-fracture patients are at high risk for another fracture, but how great is that risk? And why is secondary fracture prevention and treatment inertia so poor?

Dr. Singer:
Well, as I think all of us know, 1 in 2 women 50 years of age or older will have an osteoporotic fracture in their remaining lifetime. As if that’s not bad enough, as high as 85% of women who’ve had a first or prevalent fracture will have another or subsequent fracture. I often like to say that there aren’t very many osteoporosis emergencies; people don’t become osteoporotic overnight. But if ever there is an osteoporosis emergency or urgency, it’s in the patient who has had that first fracture because the risk of having another fracture is so high.

There have been a number of different studies done. One that I’ll quote from, Balasubramanian and colleagues, that looked at a Medicare database of women and found that the cumulative risk of subsequent fracture was 9.8% at 1 year following the initial fracture, at about 18% at 2 years, and just shy of a third of women had 1 or more fractures by the time they reached 5 years. I think 1 of the questions that always comes up is why do we have this gap? And I think there are a lot of different reasons. What always comes to mind is time, right? There’s not time to undertake care and evaluation. We don’t always do the right handoffs or warm handoffs to our colleagues who might be helpful in terms of managing this post-fracture care. People may have some knowledge gaps or lack of confidence in providing adequate care and dealing with medications, the concerns about potential adverse reactions or side effects, so lots of us work in this arena.

Dr. Bukata:
Absolutely, Andrea, and, you know, as an orthopedic surgeon, I can tell you my colleagues and I are on the frontline of seeing patients with fractures, and while we always talk about the fractures, the endgame here is quality of life and independence and function and staying out of a nursing home, and we really need to address this fragility fracture crisis in order to keep that independence and functions for our patients. People are living longer and longer, and they want to stay active, they want to stay in their homes, and these

fragility fractures are catastrophic for them. So being able to prevent the first fracture is great, but we certainly want to prevent the second fracture, and we're in a position to work as teams to really help patients prevent that second fracture.

Dr. Singer:
I think that when we work in silos and not as teams as you've mentioned, we know that care is substandard. So the Bone Health and Osteoporosis Foundation and the International Osteoporosis Foundation have made secondary fracture prevention and the push for establishment of post-fracture care programs, or what we often refer to as fracture liaison services, a priority, and they're really working to standardize these focused, strategic, and multidisciplinary or collaborative approaches to disease management to make sure that that patient who has a fracture is identified, receives appropriate evaluation, diagnosis, and treatment where appropriate to reduce the risk of those life-altering second fractures.

So, Susan, can you provide us with background or a foundation on bone physiology as well as the pathophysiology of osteoporosis? Specifically, what cells and pathways are involved? And how does our understanding of these pathways inform both the development of therapeutics as well as their use?

Dr. Bukata:
We have to go back to some of our basic biology. Osteoclasts are the bone-cutting cells. Those are the cells that remove bone in remodeling, and they are active at different times of our lives at a higher rate, particularly at menopause or in response to certain medications like steroids. Osteoblasts are the bone-building cells, and osteocytes and the bone-sitting cells. They're in the bone itself, and they're measuring mechanical forces that are coming across the bone. They don't just sit there, though. They send out signals to the osteoblasts and the osteoclasts to allow those cells to know how to balance with one another and to make bone in the areas of highest mechanical stress. It's having bone at those areas of highest mechanical stress which allows us to have bone that is light as well as architecturally and structurally strong, and that's what we need to prevent fractures.

One of the challenges we have with osteoporosis is that as we age, we lose bone, and we lose bone in a variety of patterns. People can become osteoporotic because they're big bone losers, they're bad bone builders, or a combination of the 2. And it's not just the quantity of bone that you have. Quality of bone plays a major role in providing strength to the bone and fracture resistance. Things that we measure on a bone density scan, which is a DEXA scan, really only gives us half of the equation. It measures the quantity of mineral we have in that bone, but it doesn't tell us things like the architecture, the porosity, the distribution, how the molecules between the mineral and the collagen are interacting with each other, and all of those things play a role in fracture risk.

There are several medications that we can use to try to help keep our bones strong and to help prevent bone loss. I often describe it to my patients that you're a pile of rocks in a sweater, and as you age, you lose some of the rocks, but also the sweater unwinds. You get holes in the sweater, you get snags, cookie crumbs are in there – all of those things compromise the way the sweater looks compared to what it looked like when it was brand new, and similar things happen to our skeleton as we age that make us more prone to fracture. Gaps, holes, lack of structure, lack of additional mineral – all of those things increase our fracture risk. Some of the medications that we use and we think of commonly – estrogen. We know estrogen helps us to maintain bone mass. It slows down the development and the function of osteoclasts, and it keeps osteoblasts healthy and making bone. Using estrogen at the time of menopause can continue that younger balance that we've had to keep us in balance between losing and making bone, and that helps to maintain not only bone mass but also bone strength.

There are several other medications that are in our toolbox. RANK ligand, for example, is a molecule that osteoblasts produce and they push out into the environment. That is a signal that helps to call in osteoclasts, allows them to mature, and then activates them to take away bone. So it's a way that the osteoblasts can stimulate bone remodeling and the removal of bone in a particular area. There's elements like sclerostin, which are produced predominantly by the osteocytes who are managing that mechanical stress in the bone itself. Sclerostin acts like a stop sign to prevent bone formation in a particular area. When you take away that stop sign, then you're able to make bone in that area and stimulate the osteoblasts in that area to make that new bone. So by using this biology, we're able to make changes for patients as they age and develop osteoporosis in order to maintain bone mass and bone strength.

Dr. Singer:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Andrea Singer, and here with me today is Dr. Susan Bukata. Our focus is on identifying clinical strategies to optimize outcomes for our postmenopausal, post-fracture patients.

Dr. Bukata:
Andrea, let's move on to some of the novel monoclonal antibody approaches to managing osteoporosis. How do these differ in fracture prevention compared to other agents commonly used to treat osteoporosis?

Dr. Singer:

Well, your description previously about some of the pathways lead me to talk about 2 specific medications that are both first- and only-in-class and that are important in the management of osteoporosis. The first is denosumab, which is a RANK ligand inhibitor, so it works primarily to decrease bone breakdown or bone resorption at the level of the osteoclasts. We have a lot of information in terms of the effectiveness of denosumab, which is based on data from the pivotal fracture trial, which enrolled about 7,808 women and compared denosumab to placebo. The endpoints showed significant reductions across a range of sites, both with spine fracture reduction, hip fracture reduction, and non-vertebral fracture reduction at 3 years. And this is important because osteoporosis is a skeletal disease. So we feel confident using an agent when the trials show us that the agent works at all of the sites about which we worry. The results were preplanned 7-year open-label extension trial, which was mainly designed to assess safety and efficacy of denosumab, thinking about if we use a drug longer term, do we have to worry about treatment-emergent adverse events or side effects? Patients will often ask, "Am I going to start to fall apart at the seams?" And what this trial really showed us is that in women who were treated for up to 10 years, there was no increase in side effects or issues seen that hadn't been seen in the first 3 years. There was really long-term safety and tolerability. In addition, I think some important data that comes out in treating what is a chronic disease and is going to require long-term management is that in women who were treated with denosumab for up to 10 years, there is a 21.7% increase in spine bone density and a 9.2% increase in hip bone density at the 10-year mark. Importantly, fracture rates – both spine and non-vertebral fracture rates – also remained low. So we have some very good data in terms of early efficacy as well as long-term safety and efficacy.

Switching gears a little bit to talk about romosozumab, which is a monoclonal antibody to sclerostin. If you block the inhibitor of bone formation, you're going to get more bone formation. And indeed, this is an interesting agent because it's actually a dual mechanism of action. Romosozumab works primarily to increase bone formation, but to a lesser degree, it also decreases bone resorption, all through sclerostin inhibition. Wide experience from a clinical standpoint across 3 major clinical trials that enrolled about 12,000 women, so we can be confident, I think, in terms of the number of women who were investigated. There was a placebo-controlled trial, which really gave us a lot of information in terms of early spine fracture reduction with a relative risk reduction of 73% at 1 year and 75% at 2 years when actually both groups had been transitioned to denosumab, so both groups were on a really good agent. Importantly, there was a head-to-head fracture trial, which we call ARCH, where romosozumab was compared head-to-head with alendronate, right, an oral bisphosphonate that is our standard or has been our standard of care for many years. And in this head-to-head comparison, romosozumab demonstrated superiority with a 50% relative risk reduction in new vertebral fractures at the end of 24 months, 19% relative risk reduction in the incidents of non-vertebral fractures at the time of the primary analysis, which was about 33 months, and also hip fracture reduction as well. I mentioned that this works primarily to build new bone, so I should mention that in both trials there was about a 13% increase in spine bone density and a 6% increase in hip bone density seen at the end of just 1 year. So different medications but that work in different ways, both of which have an important place in the management of post-fracture patients and patients with osteoporosis.

Dr. Bukata:
Andrea, this is great that we have tools like this in our toolbox to help our patients.

Dr. Singer:
I think you're right, and what I'd like to do now, building on that, is to have you try to help us put all of this together for our learners. Importantly, how do we match the correct patient with the most efficacious and safe treatment? And at what point do we need to consider moving on to perhaps another agent or one with a different mechanism of action with the goal of optimizing patient outcomes?

Dr. Bukata:
Well, Andrea, the most important thing is that we get patients on a medication that they'll actually take and that they'll continue to take. Certainly, we have, really, 2 different groups of patients that often present to us: those that are at very high risk for fracture and have had a primary fracture and those who have not had a fracture yet.

For patients who've already had a primary fracture, they really are in an emergency situation. As you said before, 20% of them will have another fracture within 2 years, and a third of them will have had another fracture within 5 years. We really need to build bone quickly and get them out of trouble. That is often when we go to an anabolic agent like romosozumab first, where we can make some big gains within a year and then start to stabilize bone and continue to make slower gains over time with denosumab. Both agents really help to strengthen bone and prevent fractures, but we're allowed to make a big jump by putting the anabolic first.

Patients who are at high risk for fracture but maybe haven't had a fracture yet, well, they have risk factors. Maybe they have genetics, a parent who's had a fracture already. As we age, we have tissue degeneration. Things, you know, start to unravel on us, and our tissues are not as strong and fracture resistant. Does someone have a high fall risk? Do they have autoimmune or inflammatory disorders? Do they need to take steroids or immunosuppressants? This is where we can use things like the FRAX score to really help us determine if we need to start a patient onto treatment and to get them onto a whole variety of treatments, including things like denosumab or romosozumab.

Dr. Singer:
Well, I think you bring up a couple of very good points, and what all of our new guidelines, our updated guidelines emphasize is, as you've discussed, this whole idea of baseline risk stratification, and based on somebody's risk for a future fracture, deciding whether to start with an anabolic or osteoanabolic agent and then follow with an antiresorptive, or for those who may not be in the highest risk category, consider perhaps starting with an antiresorptive agent, and we've discussed examples of both of them today.

I think this has really been a great discussion and I'm so happy that you were able to join me. Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Susan, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Bukata:
Always great speaking with you, Andrea. Goodbye.

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