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TRANSCRIPT - GR 02 14 25 ***"Goal-Directed Therapy for Osteoporosis"*** guest speaker Suzanne Jan De Beur MD, University of Virginia

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Internal Medicine Grand Rounds

- All right. Everyone welcome to Medicine Grand rounds. Special Valentine's Day Edition. We are fortunate to have our division chief for endocrinology. Suzanne John deboer here to speak with us on goal directed therapy for osteoporosis. So I'll take us through our Cme. Accreditation slides our lecture objectives for today and then for faculty claiming Cme. Credit. Grab a photo of this screen
- and I'll turn it over to our chief president, Dr. Hasan, to introduce our speaker.
- So good afternoon. Everyone. It's my pleasure to introduce our grand round speaker for today. Dr. Suzanne John Deboer, Dr. John Deboer, is the Gerald D. Arbach, Professor of Endocrinology, and chief of the division of endocrine and metabolism. Here at Uva, she obtained her medical degree from Cornell Medical College, and went on to complete her Internal Medicine, residency and subsequent endocrinology, fellowship at Johns Hopkins as a physician, scientist and practicing endocrinologist. Her clinical and research work focus on understanding rare and metabolic bone diseases at the basic level, and translating these observations to the bedside she identified and characterized the molecular basis of several disorders of mineral metabolism, including pseudohypoparathyroidism, progressive osseous hydroplasia and tumor induced osteomalacia. Her work has led to important new treatments for x-linked hypophosphatemia. Tumor-induced osteomalacia and osteogenes imperfecta she is an internationally recognized expert in osteoporosis and rare bone diseases, and has contributed to many clinical guidelines for the care of patients. With these disorders we're very excited to have her join us today, so please join me in welcoming her and I think you deserve congratulations for pronouncing my name and all those disorders. I'm very impressed. Well, happy Valentine's day. Everybody. I'm excited to be talking to you today about osteoporosis and about some treatments about think in sequence and about some new goals of therapy.
- So let's start out with a case. So this is a 77 year old woman with a history of Gerd. She had an N. Stemi 7 years ago, and she's had a recent T 11 vertebral compression fracture after falling from a standing hike while gardening.
- She has no known previous fractures, and she's never had any osteoporosis treatment.
- When you ask her further information, her mother suffered a hip fracture when she was 79, and she has no smoking or excessive alcohol intake, no history of fluid porticoid exposure. When you ask her on exam, she has vertebral tenderness around T. 11, and she states that she's lost about an inch and a half of height in 2 years. She was surprised when you measured her in the office. She's a Bmi of 23, so these are her imaging in labs. So when you do a dexa, you find that her lumbar spine T score is minus 2.0 her femoral neck T score is minus 2.3, and her total hip T score is minus 2.2. When you do a secondary evaluation for osteoporosis, you

find that her Cmp is normal, as is her Tsh and her serum protein electrophoresis and uroprotein electrophoresis, and her vitamin d is sufficient at 42.

- So you have a woman who has a recent T. 11. Compression fracture, a family history of a hip fracture and osteopenia on Dexa. So I asked this audience, and then maybe those at home to think about. Would you treat this patient so if I could just ask to show a hands? Because sometimes I think, putting your dime down your nickel down makes you learn better how many people in this audience would not treat this patient so smart. Coming to an osteoporosis lecture. Excellent. How many people would treat this patient? All right.
- My work here is done. Great. So what you do is you recognize this is a 77 year old woman who's had a fracture. But her Dexa is not in the Osteoporosis range, so of course, you want to calculate a frac score. I won't spend a lot of time going through this Frax calculator, because I think a lot of you are familiar with it. But you know, put information in there like height, weight, previous fracture, family history of fracture and also history of past smoking current smoking is the only thing counts, but glucocorticoid exposure. I just wanted to point out that if you've had more than 5 milligrams of prednisone for 3 months straight at any time in your life, this button gets clicked. Yes, it's not just current, it's past as well rheumatoid arthritis. And then, of course, you put in the bone density and the femoral neck, and you find that surprisingly, she has a very high risk of major osteoporotic fracture, about 42% in the next 10 years, and she has a 27% risk of hip fracture in the next 10 years, and we know from many treatment guidelines that if our major osteoporotic fracture risk exceeds 20% or our hip fracture risk exceeds 3% that you're a candidate for treatment. So this woman is at very high risk of fracture. So if you leave this room today and take away. One thing it would be. If you see an older person with a fracture and a bone density that's not in the Osteoporotic range. Please calculate their frax and think about their fracture. Risk not just their absolute bone density. Okay so let's talk a little bit about fracture risk.
- So major drivers of fracture is age is a big one. Previous fracture is a big one. Family history, parental hip fracture is a big one, low body weight current smoking past its current glucocorticoid exposure and rheumatoid arthritis actually is a big risk factor. So when you think about your patient in front of you, think about these risk factors and think about things that might push you to calculate a frac, or think about treating at a lower bone density.
- And then there's this concept of imminent risk after a fracture. So imminent risk of fracture comes from the concept that for the 2 years after you've had a fracture, you are at increased risk of having a fracture. So this shows you that these are the sites of fracture, and this is the one year whoops.
- This is a 1 year risk of recurrent fracture by site. So with spine fracture, you have close to 15% risk of having another fracture in the next 2 years. So this time period where we have a lady with an acute fracture is going to be her highest risk. Time for another fracture. And this is a time for intervention. Okay also, knowing that people that have had multiple prior clinical fractures are also going to be at high risk. So people, multiple clinical fractures or recent fractures are people that you really want to grab and interview.
- And it's just some data from the fit trial. Looking at a number of years of follow up in about 6,000 postmenopausal women, and those that had a clinical fracture. During this fit trial a spine or hip fracture, spine, fracture gave me about an 8.6 fold

increased risk of having another fracture. So you know, fractures beget fractures, and people that are fractured there. To use a Valentine's day analogy.

- A fracture is a skeletal heart attack, so you would never send someone out of the hospital who's had an mi without a beta blocker without aspirin without a statin. So when you see someone who's had a fracture, especially an acute fracture, that is time to intervene and the outcomes of hip fractures are terrible.
- So there's about 300,000 hip fractures annually. About 25% of people are not alive within a year of their hip fracture. About 50% of them don't return to their prefracture function. So hip fracture is also an emergency, a time for intervention, because the outcomes are terrible.
- All right, let's talk about osteoporosis therapies, and I'm going to focus a little bit more on the anabolic or the bone building therapies. Give you some data about head-to-head trials, so giving you relative efficacy, and then teach you a few things about sequence which are important.
- So this is the bone remodeling cycle, and our bone is being broken down and built up little by little every day in a bunch of different sites. And what's important to note here is that you know osteoclasts come in and resort bone. But then monuclear cells then differentiate into pre-osteoblasts, and then osteoblasts and fill in that bone and then mineralize the matrix and the osteoblasts get, get buried in the bone and become osteocytes. This is a coupled process. So when we're thinking about Osteoporosis therapy, it comes in 2 flavors, it comes into those that are anti-resorptives that primarily decrease bone resorption or osteoclast function and those that are anabolic. They primarily work on increasing osteoblast bone. Production.
- So these are our approved therapies, and I broke them down roughly into antiresorptives and anabolic anabolic.
- What another important thing I want you to take away is the ones that have stars are actually ones that have been shown in clinical trials to reduce the risk of nonvertebral fracture or hip fracture. Okay, so not all of these reduce hip fracture. So if you have someone at high risk for hip fracture, you need to make sure you're selecting an agent that reduces risk of hip fracture. So, for example, Ebandron boniva. Sorry Sally Fields does not reduce hip fracture.
- If vista or raloxifene does not reduce hip fracture piraparatide actually has not been shown to reduce hip fracture.
- So it's important to think about selection of agents when you're thinking about the person in front of you. And what type of fractures they have. So I'm going to focus a little bit on these Osteoanabolics and then head to head data between the antiresorptives and the anabolics.
- So the relative potency of octopus therapies. It's fair to say that anabolics are more effective at reducing fracture and increasing bone density than antiresorptives, and we have this from a few trials, and I'll dig into some of these data. So the Vero trial looked at Teriparatide versus resedronate and resegrenate is a bisphosphonate, and it increased bone density more and reduced fracture more.
- The arch trial looked at Romazosumab, which is an antisclerosity antibody, and we'll talk a little bit more about this against alendronate, which is a bisphosphonate. Again, it was superior, both in reducing fracture and increasing bone density, and then about a peritide versus teriparatide the active trial should they were roughly similar. But when I show you the data you'll see that Aballaparatide seems like it is superior to teriparatide, and both of these are anabolic treatments and then, in a post hoc analysis, a bowelparatitis appeared, or randomly so, generally anabolics

better at reducing fracture, better at increasing bone density than animal resorptives.

- And this is just some data. So this is looking at change in bone density at 24 months in the lumbar spine and total hip. So total. Hip, Bmd, here. Lumbar spine. Bmd. Here, looking at 24 months, so realize that many of these treatments we give beyond 24 months, and they have increased in bone density beyond that. But in a 24 month snapshot, you can see that, you know zoledronic acid is gives better increase in bone, density in the hip and the spine, than allendronate denosumab, more so in the spine teriparatide, more so in the spine than the hip and then Romazosumab, followed by alendronate. And then our biggest gun is Romazosumab, followed by Denosumab. At 24 months almost an 8% increase in hip and about a 17% increase in spine and in bone. In the bone world, 17% increase is huge.
- So I just want to talk about denosumab just really quick to point out something that might that you all might not know. So Denosumab is an antibody that binds rank Ligand.
- So rank ligands are important in that communication from the Osteoblasts to the Osteoclasts. It's secreted by the Osteoblasts, and it increases the maturation and the activity of the Osteoclasts so Denosumab Binds out Rank Ligand. So it shuts down the maturation signal, and it decreases the activity. But what it does is it keeps those osteoclasts in this immature state, where they can become multinucleated.
- So they're arrested. But once the antibody is removed, they then begin to mature and break down bone. So that's 1 of the limitations that we can talk about a little bit later of denosumab. You have to follow it by something, and you can't abruptly stop it.
- So these are just 10 year extension data of denosumab in the freedom trial. And what you see in the white blue is you're seeing a treatment of denosumab for 10 years, and the lumbar spine, the total hip, the femoral neck, and the one-thirdrd radius, and the green is placebo, followed by the dark blue which is crossed over to denosumab.
- And what's surprising here for an anti resorptid agent, because generally you get kind of a plateauing of effect. But you see, in the lumbar spine there's increase in bone density that continues out almost linearly to 10 years, and after 10 years you get about a 20% increase in your spine bone density, which is quite a lot and about a 10% increase in your total hip bone density. And the data on the right are just to show the fracture, reduction significant fracture, reduction. At at 3 years, about a 70% reduction in the vertebral fractures.
- Okay, let's talk about our anabolic therapies.
- All of our anabolic therapies work through this pathway. The wig signaling pathway went signaling pathway is really important for bone formation. Okay? And what what the wind signaling pathway does when when it binds to its coreceptor, frizzled, lrp. 5, 6, it stabilizes beta-catenin and stabilization of beta-catenin increases osteoblastic bone formation. And it and it decreases osteoclastic bone resorption. So it's a nice double whammy there are inhibitors of this pathway. One is made by the Osteocyte called sclerostin inhibits at the level of the receptor. And then there's Dkk one made by the osteoblast that inhibits this pathway.
- So our anabolic therapies. One is a direct antibody that inhibits this inhibitor, therefore increasing, signaling down the wet pathway.

- Then our other anabolics are parathyroid, hormone and parathyroid hormone related protein that work through this pathway, and I'll just show you really quick not to belabor this, but the Pth receptor, both Pth and Pth. Rp. Bind to this Pth receptor. It can work through beta-catenin to also signal down this wnt pathway. So all of our anabolic agents really work through the Wnt pathway.
- And this is just to remind you that both Pth and Pthrp. So this would be, teriparatide. Is Pth. One to 34. That's forteo.
- and then a balaparotype is. It's an analog of Pth. Rp, but they both bind to this Pth receptor.
- So let's look at some of the head-to-head trials that have been performed to give us an idea of what anabolic therapy we might be thinking about selecting. And why
- so this, the active trial is a randomized, controlled comparator trial, where they looked at Valiparatide versus Teriparatide versus placebo, and 18 months, and 2,400 postmenopausal women.
- So the orange is a Ballparatite. The blue is teriparatide, and we're looking at a total hip b femoral neck, C. Lumbar spine. You can see a balloparatide when it comes to bone. Density increases bone density more than a teraparatide does, and both of them are superior to placebo and when we look at fracture, what we see, this is nonvertebral fracture or hip fractures. This is clinical fractures, and this is Major osteoporotic fractures. You can see a boliparatide does better than Teriparatide, the Placebo arm and the Teriparatide group don't start to separate until about 12 months, whereas a Ballparatide group have already separated with lower incidence of nonvertebral fractures. We see that also with clinical fractures and then Major Osteoporotic fractures periparatide seems to take a longer time before it starts to separate from the placebo arm. But a valid paratide works quicker.
- What about teriparatide versus denosumab? So an antiresorptive, a potent antiresorptive against an anabolic.
- So this is the data trial. It's a small trial. But it was important. For a few reasons it'll become apparent. It was open label, randomized, controlled trial for a year, and individuals at high risk for fracture. They had a pretty decent bone density, but they had other risk factors and the outcome was bone, mineral density and bone markers, not fracture.
- So these data, the green is both tera puritide and alzumab together, and we rarely use that combination together because it's expensive and it's not FDA approved.
- But the red by itself is teriparatide by itself, and we're looking at spine femoral neck, 1 3rd radius and total hip.
- You can see Denosumab is blue. Teriparatite is red. They're about the same when it comes to about 12 months at the spine but when you start to look at the hip. Denosumab is improving. Sorry denosumab is improving bone density better than teriparatide at the hip at 18, at 12 months and also at the femoral map. You see, Denosumab is improving abundancy more the entire paratype.
- And this is an important detail as well. When we're looking at the 1 3rd radius. Basically denosumab is maintaining the bone density or increasing a bit. But you're actually losing bone density with treatment with tera peritida in the forearm.
- And you all might realize, too, that when you have hyperparathyroidism and elevated levels of Pth consistently, you also get forearm, bone density, loss. So if someone with a really low bone density in the forearm. Tearparatite and bowel paratite are probably not the best agents. Okay so here's another really important piece of information about sequence of therapy from the same data switch trial.

- So when we took teriparatide in blue and switched to denosumab, and this is lumbar spine, you can see, there's a nice increase in bone density.
- However, when you take denosumab and switch to teriparatide, which is a lot of times what we see in clinical practice. People are approved for antiresorptive. You put them on antiresorptive. They have a fracture, or they have reduction of bone density. You want to switch them to an anabolic, and they want you to put them on teriparatide. But the problem is, you lose bone with that sequence, and this is lumbar spine. But look at the look at the femoral neck.
- I mean it plummets, and you don't. It takes a couple of years to get back to the the baseline where you were, and if you look at the total hit, you don't even make it there at 48 months.
- This also shows you the distal radius denosumab. You're increasing, you switch to teriparatide, and it begins to plummet. So the clinical pearl here is when switching from denosumab to teriparatide or bowelparatide. You lose bone. And that is not a great sequence. Okay, so that's not a sequence that I would do if I had to alright. So I always love to put this slide in here, because it shows you the power of looking at at rare conditions. So this is a condition called sclerosteosis, and this is a condition called high bone mass trait. And these individuals have really dense, strong bones. So, for example, these people here, you can see they have larger jaws, and this is the growth in the jaw over time, and you can see how dense the cortices of this femur are. These people came to clinical one of the one of their features when when they came to clinical.
- I it's where I want, I thank you. Clinical attention was that they can't float in a pool.
- Their bones are so heavy that they can't float and pool and this gives you an idea of how dense this person's skull is. This one skull weighs as much as 3 normal skulls. Okay? So these are mutations activating mutations in the wind pathway. These are people that have sclerostin. And there are sclerostin knockouts. So they basically have absence of sclerostin. So they have signaling down that pathway. These are people that have activating mutations in the co-receptor. The lrp. 5, 6.
- So this from these data, from these individuals, academics and pharmaceutical companies developed an antisclerospin antibody. And again, sclerostin inhibits this pathway antibodies inhibit the inhibitor of this pathway, and you get signaling down this pathway. What's nice about this is that sclerosin is bone specific. So wnt is important in a lot of different pathways in cancer pathways. But the sclerosin is bone specific. So this gives us a bone specific enhancement of wnt signaling, and that antibody is called Romazosumab.
- This is just a that's I don't need that.
- And what Romazosumab does because of that wind signaling where it increases bone formation, but decreases bone resorption. It's unlike any other osteoporosis medication. We have. It opens this window where you have increased formation, but decreased resorption, where you can really build bone for these 1st 6 months. Teriparatide. It's coupled bone. Resorption is coupled with bone formation. Alendronate decrease in bone resorption is coupled with decrease in bone formation. So this is the only thing we have that has this dual action.
- So let's look at some of the Romazosumab data. So this is looking at Romo and postmenopausal women. About 7,000 women that were randomized to placebo versus Romo, and then followed by denosumab.
- And you can see this is in the spine really nice increases at 12 months about 13% increase in the lumbar spine bone density you follow with denosumab, and you

continue to have increases the same thing here in the total hip. Let's so about 8% increase. But nonetheless, a nice increase, and also at the femoral neck and reduction in fracture. That's very significant.

- What if you do, Romo, against alendronate. So these are people that were randomized to do alendronate versus Romazosumab, followed by alendronate.
- And this was a year treatment followed by the Alendron after that.
- So alendronate, you get about a 5% increase. And that's pretty. That's a pretty good increase most of the time. You won't see that increase with your patients, but about a 14% increase with romazosumab and then, followed by alendronate, basically get a plateauing, whereas with resolve, it continued to go up some, and that happened in the lumbar spine and in the total hip.
- So, and this also looked at the incidence of of fractures of alendronate versus Romazosumab. This is at 12 months, and this is at 24 months. You could see there was a superior reduction in fracture at 12 months, and even more at 24 months.
- Okay, so remember, I told you we didn't want to do denosumab teriparatide or a ballparatite, because we'll lose bone. Well, this is our solution when you have to move from an antiresorptive agent to an anabolic agent when you're talking about denosumab being your antiresorptive.
- So this I This is Romezosumab in green, followed by yeah, followed by denosumab.
- If you treat with Romazosumab, and you do nothing, you lose bone. That's the block. If you treat with denosumab, you continue to gain bone but this is the real upshot. This is lumbar spine, and this is tovap. If you pre-treat with a lendronate you blunt this effect of the Romazosumab in green so elendronate. And this is what we get in clinical practice all the time. Persons on on Alendrony. We need to put them on. An anabolic problem is if you treated them with an antiresorptive you're going to blunt. You'll still get some effect. But you're going to blunt a lot of your anabolic treatment. So when you're in a situation where you have an antiresorptive first, st like alendronate, and you have to go to an anabolic. You're going to lose some potency by bleeding with an anti-resorptive.
- I think the next slide is where I anyway, the upshot and I'll show you this, and it's like, Oh, this is the one I wanted.
- But if you need to transition from Denosimab, which now is in black, so if we go placebo denosumab, and then, romazosumab, you don't lose bone like you do with Rrp type. So if you're on Denosumab, and you have to intensify you want romazosumab. That's the thing that you won't. You won't get as good a bump as if it were naive. But you'll get some bump all right. So this is getting to the end of this part. But this is we just published this paper in the Journal Clinical, the Journal of Bone and Metal research. This is an estimate of when you're trying to select therapy for your patient, and you're looking at their bone density.
- What you need to think about starting with to try to achieve getting them out of the Osteoporosis range.
- So romazosumab denosumab is our most potent lumbar spine, minus 3.7 about 50% of people can get out. The Osteoporosis range of this treatment within the lumbar spine about minus 3.1. The total hip alendronate is going to be our weakest, followed by denosumab. And then the anabolics, followed by antiresorptives.
- So just think about your patient. How low their bone density is if they've had a recent fracture. And this is when we're starting to think about what type of agents we want to start and how what sequence we want to go in.

- So let's talk about a goal directed approach. This is a new concept. Because until recently we haven't had these anabolic agents that have been so potent they can increase bone density to the point where we can actually get people out of osteoporosis. Like I said, with the lender date, we're settling for 5% increase in bone density. And many times that's not getting people out of osteoporosis. So this is a framework that we can think about people that now we have the full armamentarium that we can think about. What are we going to choose first, st to get these people out of osteoporosis?
- This was just. I'd give you the reference there. So you can see this. I was. I'm part of this writing group.
- So what are the goals of therapy? So the goals of therapy are to remain fracture free, 1st and foremost.
- Secondly the most appropriate initial treatment and subsequent treatment is selected for each patient based on their characteristics, their bone density, their fractures and treatment targets are individualized, based on those same things. And then a lot of other things comorbidities cost. There's a lot of things you have to put in the equation and their treatment choices are individualized, based on the treatment goal and the patient preferences.
- So treatment targets.
- Remember, we talked about this imminent risk. People that have fractured especially a spine, pelvis, or hip within the last 2 years. Those people you want on the maximal rapid fracture reduction. So those are the people you want on anabolic treatment. Okay for people with a T score of minus 2.5. So osteoporosis, we would love to get them out of osteoporosis, the lumbar spine and hip, realizing that we can do a lot better at the spine with increasing bone density than we can at the hip just because of the the makeup of those bones and then patients with a T score of better than minus 2.5 that are high risk of fracture. We want to treat them to reduce their risk of fracture and generally that takes about a 3% increase in the total hip or a 6% increase in the spine.
- So this is the algorithm in the paper. And I'm just going to take you down each of the each of these of these columns so imminent fracture risk. This is our patient, recent fractures within 2 years, or multiple fractures.
- And those individuals that they've had vertebral pelvis or hip fracture. We want to lead with osteoanabolic as 1st choice.
- Sometimes we can't get there our 1st choice. It's too expensive. We can't get insurance approval. People can't take injections every day. They can't come and get an injection once a month, so you might need to do bisphosphonates or denosumab as a second choice.
- So we want to. In those imminent risk patients, we need to get their fracture risk down, and we need to get it down fast, and that's going to be the the anabolic agents.
- What about those that have fractures? But it was 2 years or earlier.
- Well, those with low bone density, a T score minus 2.5 or below. This is when you know this, I think this arm takes a lot more clinical nuance. So if it was 10 years ago, and they haven't fractured since. Generally I'm using how low their T score is as a guide for me. If they have a very low T score, minus 3 or lower in the lumbar spine, or minus 2.8 or lower in the hip. I'm going to be thinking about osteoanabolic treatment if it's not that low, and it's been a while since the fracture, or maybe it wasn't a vertebral pelvis or hip fracture, but maybe it was a forearm fracture or

ankle fracture. I probably would be giving antiresorptives, bisphosphonates, or denotimab. So in this situation I'm looking at how many fractures how long ago what other comorbidities that might be increasing the fracture risk. And then I'm also looking at things like how low the T score is to decide. Am I going in resorptive, or am I? Am I going anabolic?

- So in this sentence we want to get them out of osteoporosis, if we can. If people have prior fracture, advanced age or falls, you might want to get them a little bit better than minus 2.5, instead of just keeping them on the cusp. Or if you have people that you're going to give a medication holiday that they're going to lose some during that medication holiday, you might want to increase their bone density. A little bit more.
- Okay and some caveat to keep in mind, we really like to get these targets within 3 years. So like a 10 year. Timeline might be too long timeline. But 3 years is a reasonable timeline to think about achieving these targets.
- Okay so this is just another way of looking at the table that I gave you. So this here is a total hip but then see! And this is the baseline T score. It goes from minus 4 to minus 2.5. And this is the baseline lumbar spine T. Score.
- And this is looking at yellow romazosumab, followed by denosumab. That's our biggest gun we've got in blue. We've got romazosabum, followed by alendronate and in red. We've got a landronate alone, and this just gives you the probability. So probably this is 100%.
- This is 20% 0% of achieving a T score of better than minus 2.5 based on how low the T score is, so you can see if you have a minus 4 T. Score, you are never going to achieve a T score minus 2.5 the same thing with the lumbar spine.
- But you know, if you start with a T score minus 2.8, then you have a really good, I mean, minus 2.7. You have a really good chance of achieving T score better than minus 2.5 with lender need. So the lower the T score. The probability of achieving it with an antiresorptive is lower than with an anabolic. So how low your T. Score is, I think really matters in your initial choice, and remember, your initial choice can really affect the efficacy of your layer choices.
- Okay, so again, this is just the same the same thing that I showed you before.
- So selecting subsequent treatments, so say you treat with an anabolic agent, and they and they are, you know, a T score of minus 2.5, you might say great. They're at target, so I don't need to put them on denosumab after I could put them on reclass or elendrony, and they can coast for a while. So how? Where you end up after your anabolic treatment is kind of.
- If you decide where you're going to go next with your subsequent treatment, because everything but alendronate, reclass, bandronate anything but the bisphosphonates has to be followed by something, or you're going to lose bone density. Okay? So bisphosphonates are things that we use to lock in our gains.
- Okay, no history of fracture.
- So you have no history of fracture, but you have a low T score. So in those instances I think that bisphosphonates dinosab are great choices. There. You lower the risk of fracture, you know you don't have to go to the expense of having anabolic therapy or the bother of having anabolic therapy. But again, if you're very, very low, then you might consider anabolic. First, st because anaresorptive is going to limit your efficacy of your anabolic leader.
- All right, I'm gonna that's why I already said, okay, so monitoring your progress.

- So when you once your major parts, you need to take your interval fracture history, because if they're fracturing on therapy, that's failure, right? You need to measure their their bone density.
- And if people come with back pain, or you know some acute thing you need to do vertebral imaging, because, again. Sometimes people don't know that they've broken a vertebra that they have so low threshold for vertebral imaging.
- And then you're monitoring treatment targets. So people could not achieve a target of minus 2.5 or better, but have a 10% increase in their bone density. So they're responding to therapy. But they're just not able to achieve the treatment target. And sometimes we just can't achieve the treatment target. Because again, we're kind of like we were 10 years ago when we don't have potent enough stuff to take a minus 4 minus 4 and get it into minus 2.5.
- So if the target is has been achieved. We want to maintain our bone density. Want to continue treatment, or you can pause treatment, or you can change treatment, just depend on which treatment you're on. Okay.
- So I'm coming to the end here, and then we'll get back to the patient. So the overall goal is, we want to prevent fractures.
- The secondary goal is, we want to get people out of the Osteoporosis range and what your patient presents with the T score, the fractures, the family history, the other medications they're taking on really help you decide what you want to lead with.
- Sometimes it's anabolic, sometimes it's antiresorptive, imminent fracture. If you take away. Well, I mean, now, I'm going to take away 2 things. Imminent fracture is really, you know, the skeletal heart attack that you really need to intervene with your biggest guns when you can.
- And then also a T score of greater than minus 2.5 is our minimum target. So let's go back to our case. So we all agree. New T. 11. Fracture, family history of hip fracture, height, loss t score in the Osteopenia range, but very high fracture risk.
- We all agreed that we wanted to treat her.
- But what do we want to treat her with knowing that? Knowing? Sorry I'm trying to go back here knowing what knowing this about her. So we know that she has Gerd. She has a history of an N. Stemi, and we know that she needs both hip and spine fracture reduction, and she needs. And and she and she's at imminent risk.
- So we're going to be in the anabolic category, right. So you know, she's had this N 77 years prior. You know, Romazosumab has this black box label about recent cardiovascular events so been within a year, so she doesn't technically need that. But you know I'm not too excited about moving forward, that if I have other options, so what about teriparatide and Baloparatide. Well, we showed you some data looking at Baloparatide being better at the hip than Teriparatide. So Baloparatide might be a good option here.
- So what I decided to do was do a ballot hair tie for 2 years, and because she doesn't need she doesn't have very low bone density and provided that she doesn't fracture during that time. After that time I probably lock it in with zoledronic acid. She has bird, so I don't want to use a lender need, but zoladronic acid, I thought would be a good choice.
- So I went with a balaparatide for 2 years, followed by zoladronic acid because it offered rapid fracture reduction. I didn't have to worry about the black box warning on Romazosumab, and also I could follow it with a couple of the year zoladronic acid, and then we could coast for a few years.

- So with that. I want to thank everybody for their attention through this whirlwind of data and and clinical decision making and open it up for questions.
- Thank you so much for that talk. So I wanted to open up the questions asking something. If you could speak to the residents in the room, especially for those of us who are in the primary care clinic. And we see these patients. And you know, if we were to go down this pathway, and we see that they're a candidate for anabolic therapy. Should we feel empowered to like order that ourselves? What would be the process versus reaching out to endocrine and asking for help with ordering some of these medications that are more cost prohibitive.
- I think that's a great a great question. So a ballparatide and teriparatide you, you write a prescription for, and these are daily injections under the skin, and it's like an insulin PIN. So that would be going through, you know, a pharmacy benefit.
- You might get pushback, they would say, like, Well, why does this patient need this expensive medication? And I think you should feel very empowered to pull this paper, pull paper from the Endocrine society guidelines. This person is at imminent risk of fracture, a high risk of fracture. These are people that are recommended for anabolic therapy. So that would be, if you're going to go, a bowel paratite or terraparatite. A patient barrier might mean, you know, that they don't want to inject themselves every day. I have to say that I've not had one person not be able to do it after being shown the pen and walked through it.
- It's a very small needle. It's a 31 gauge needle. It's very short a lot of times. People tell me they have to look to make sure it's in their skin, because it's so painless. So usually with handholding people can do well with that.
- If you're going to go the Romazosumab route that needs to be ordered, and they need to know that you talk to someone about ordering that we give it at Fontaine, and I think that's the only place that it's given here at Uva. I think that there are some other infusion centers that may be outside Uva system that also give it. It is a once a month injection. It's 2 injections once a month and so they come to the clinic to get the injection, and that's billed actually under medicare part D, so that is like a facility administered medication. So these 2 medications come under different different insurance guidelines.
- So the Infusion Center will be helping you get approval for the romazosumab. So as long as in your note, you know this is imminent risk of fracture. You might want to put a reference in there. You know, that helps the people trying to get authorization to get authorization.
- Thank you for your talk. So my question is more about just care coordination around these patients. So you know, I liked your framing of the issue sort of a skeletal heart attack, and you know it made me sort of think about, you know, in our cardiology service, when people do come in for Mis, like, you know, we have order sets, and nurse coordinators that help us with arranging appropriate, outpatient follow-up. So what do you see? Are sort of opportunities for improvement within our system, either from the outpatient or the inpatient side, at identifying these patients that are at high risk? Or maybe they already came in with a fracture. And how do we follow up on sort of the care that they need? What are your thoughts around? What we could be doing better? Yeah, thank you so much for that insightful question. You know the sad reality of it is even people that are admitted to the hospital for hip fracture, and I showed you how awful those outcomes are. Right. Like 25% of people dead, 50% of people not achieving their pre-fracture function.

- Only 16% of those people even get a vitamin DA vitamin d calcium or dexa prescription. So like this is a real problem.
- There are something called fracture liaison services where there's case finding that goes on. So, for example, David Weiss is one of our orthopedists here, and he and his nurse practitioner, Laura Myers.
- What they try to do is they try to case find people that are in the hospital and capture them. To come back, for you know, for an outpatient appointment to get treatment for osteoporosis, but on the inpatient side you could start them on vitamin D. If they need to be started on calcium. You can do that you can send a lab to make sure they're not vitamin d insufficient. They have done studies of doing an effusion of zoladronic acid while they're in the hospital to treat them the the down it's effective. The downside is that you know most people are vitamin d deficient, and you can get hypocalcemic. So that makes me a little worry a little bit. I like to make sure that I've got a vitamin d level and make sure they're vitamin d replete.
- But they actually did a study looking at zoledronic acid or reclass, and it actually improved mortality after hip fracture. So secondary prevention of hip fracture, improved mortality with reclass. So there's a lot we can do to improve the outcomes of these patients, but it's that it's you've got to grab them while they're inpatient and make sure they get plugged in because they might be going to an intermediate care facility. And it's hard to get them back. But you have to make sure that they close the loop, that they have an appointment with endocrine, or they have an appointment with Laura Myers and Ortho to make sure that they're getting getting follow-up care and getting treatment because it can reduce their mortality.
- Thanks for that entitled question. We also have a couple questions in the chat. So this is from Dr. Wolf. Fantastic presentation. The Uspstf. Doesn't offer guidance on. When to repeat screening Dexa. How often should we be repeating Dexa scan in women whose 1st screening Dexa is normal when person's 1st training decks is normal. I probably wouldn't do it for 5 years.
- If you have osteopenia, I would do it in 2 years. So if they said, they are osteopenia, and they didn't meet criteria. So you calculated, Frax. They're below Frax. I would do it in 2 years. If it's stone cold, normal, I do it in 5 years.
- And then last question in the chat, is there a case for bone density screen appointment at perimenopause to screen for individuals at higher risk of osteoporosis.
- Yeah, there's no guideline that says that. But I think it's a good. I think personally, if I have, you know, a lot of my patients, tell me about their their daughters or whatnot. They clearly have osteoporosis, and I think it's a good idea to know your bone density, because you're about ready to head into a time where you're going to have rapid bone loss, and so that might make people consider hormone replacement therapy, or you know, or something to reduce that. Reduce that bone loss and sorry it looks like I missed another question. It says, thanks for a great presentation. Can you clarify if alendronate slash bisphosphonate alone, as 1st choices ever indicated, the graph seems to show it blunts later response to anabolics.
- Yeah. So you know, if you have someone that you know has osteoporosis, but no fractures, not on leukocorticoids, you know, doesn't have a family history of hip fracture. That would be a situation, and you didn't have any Gi side effects. That might be a person that I would start, you know, a bisphosphonate. Start alendronate on. I think that that's especially in a younger person. But if you have a person, you know, that's coming to you with a minus 3, and, you know, on

glucocorticoids I would be leading with the anabolicia. Because you're just. You're just. You're stealing your thunder. You're you know. You're robbing yourself of the gains that you could have. I recognize that it's expensive.

- But you know that's something you're never going to get back.
- So that's just my 5 min. So kind of alluded to it with your last answer. But special population, younger patients that may have been on chronic glucocorticoids for other issues do recommendations change for those patients if they get a dexa, and they're on the osteopenic osteoporosis side.
- Yeah. So if they're not fracturing, and they're younger. So you know at any. So at any given bone density so say you have a T score minus 2.2, and you're 59. Your risk of fracture is going to be way lower than if you're 79, with a T score of minus 2.2 same bone density over life, and sometimes I'll be doing tracks with my patients. I was like this year. You don't meet criteria, but we'll make you one year older. Oh, you met criteria, you know, like age just increases your risk. Right? So younger people on glucocorticoids. It depends on how long they've been on glucocorticoids. Certainly there's a role to using teriparatide and the rheumatology societies have guidelines. That American.
- A. RE. Don't tell Janet have guidelines about using teriparatite, but in someone that has low bone density that's younger I tend to sometimes, especially if they're not on series. I tend to treat for a period of time with the Bisphosphonate, and then give them a long break, and then think about retreating later. We don't know, you know, looking at these data, looking at blunting of animals. I don't know if I use bisphosphonate for 5 years, and they were off of bisphosphonate for 5 years, and then I treated with anabolic if I would be wanting them. I know, if I treat them for 5 years, and then did an anabolic if I'd be wanting them. So if I give them a long enough holiday, I don't know if I would be completely blunting them. So in younger people, with lower bone density I tend to go with the Bisphosphonates for a shorter period of time. Give them a holiday. Reassess them when they're a little older.
- Thank you. All. Been a fantastic audience. I really appreciate all the all the timing never cool. I love your residents. They are fantastic. They I mean, they are really remarkable.