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Clinical Setting and Decision-Making

Postmenopausal osteoporosis with vertebral fracture: teriparatide vs romosozumab

Case report:

This is the case of a 66-year-old woman who went to her doctor complaining of lower back pain that appeared right after jumping while playing volleyball on the beach. The X-ray of the dorsal spine reveals the presence of 2 vertebral fractures. The dual-energy X-ray absorptiometry (DXA) showed a T-score of -3 in the femoral neck. The patient had a past medical history of breast cancer 15 years ago, which is why it was decided to prescribe chemotherapy but no local radiation therapy. She has experienced zero relapses since then.

She has a history of smoking 20 packs/year. However, she quit over a year ago when her sister had a myocardial infarction at the age of 50. The patient does not do any exercise but walks daily for an hour. She has hypertension, is not a diabetic, and her blood test results shows show elevated total cholesterol levels (250 mg/dL). Her HDL cholesterol levels are 30 mg/dL.

During the physical examination, the patient's vital signs are stable, her body mass index (BMI - the weight in kilograms divided by the square of the height in meters) is 24.4, and apart from a previous mastectomy scar, no particular findings are reported on her physical examination.

The risk of fracture estimated using the FRAX tool shows a 25 % and 8.6 % rate of suffering major osteoporotic and hip fractures, respectively, within the next 10 years. The patient has not had any cardiovascular events yet. However, the cardiovascular risk estimated using the Systematic Coronary Risk Evaluation (SCORE2) tool shows a 6.8 % risk within the next 10 years.

Treatment options:

You need to decide what the best initial treatment option for osteoporosis in this clinical setting would be taking the balance between the risk of fracture and cardiovascular risk into consideration:

Based on your own clinical experience, the medical literature available, the guidelines published, and other sources of information, which would be your approach with this patient?

1. *Start treatment with romosozumab is advised.*
2. *Start treatment with teriparatide is advised.*

To help in the decision-making process, we have asked 2 experts in the field of mineral bone metabolism to discuss the position held by the editors. At the end, we will also publish a comment from a cardiologist who has studied the patient's cardiovascular profile.

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OPTION #1.
START EARLY TREATMENT WITH ROMOSOZUMAB IS ADVISED

Dr. Serge Ferrari

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This 66-yr-old woman with two recent vertebral fractures is at "imminent" risk of another fragility fracture. Indeed, up to 25% of women with a recent vertebral osteoporotic fracture refracture within 1 year, particularly after 65 years of age (1). In addition, her low BMD at the femoral neck (-3.0 T-scores) indicates a generalized bone fragility also affecting the cortical compartment. Her high fracture risk is confirmed by the FRAX score, namely a 10-year risk of major osteoporotic fracture and a hip fracture at 25 % and 8.6 %, respectively, although in this case it might underestimate her actual fracture risk in the next couple of years since FRAX does not yet take into account the multiplicity nor the recency of the prevalent fractures.

Treatment must therefore be introduced promptly, not only to quickly reduce her risk of a subsequent fracture, but also to improve hip BMD in order to prevent peripheral, and notably hip, fractures. In her case I would prescribe romosozumab as first line therapy for one year, followed by an antiresorptive. Indeed romosozumab has been shown to significantly decrease the incidence of new vertebral and clinical fractures within one year as compared to alendronate (the ARCH trial [2] in women at high risk similar to this patient (i.e. with prevalent vertebral fractures, T-scores around -3.0 and average FRAX scores of 20 %). In addition, romosozumab has been shown to significantly increase hip BMD compared to alendronate (2) and also teriparatide (3,4), which in the case of our patient is a very relevant issue. Regarding her CV risk, the patient is not known for suffering from ischemic disease, which would contra-indicate the use of romosozumab. Her moderate CV risk can be improved by the appropriate use of anti-hypertensive medication, hypocholesterolemic agents, and by maintaining a healthy lifestyle (refraining from smoking). Finally, the history of breast cancer is not a contra-indication for romosozumab either.

I would therefore strongly recommend romosozumab therapy for one year, with a re-evaluation of BMD before switching to an anti-resorptive, either a BP or denosumab (5).

OPTION #2.
START TREATMENT WITH TERIPARATIDE IS ADVISED

Dr. Manuel Muñoz Torres

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The case presented here is representative of an "extremely high risk of fracture". Although this denomination does not have a universally agreed definition, it is included in the most recent clinical practice guidelines. Therefore, the pharmacological treatment of postmenopausal osteoporosis according to the Endocrine Society (6) states that anybody with multiple vertebral fractures and a BMD T-score < -2.5 in the spine or hip meets this criterion. More recently, the latest version of the clinical practice guidelines of the Spanish Society of Bone Research and Mineral Metabolism (SEIOMM) (7) spares this risk category for individuals with 2 or more vertebral fractures, 1 vertebral or hip fracture with a T-score < -3.0 or a T-score < -3.5. In these cases, early treatment with a bone-forming drug followed by an antiresorptive agent is considered the preferred approach (8). Teriparatide and romosozumab are the 2 bone-forming drugs currently available in Spain. To decide which of these 2 drugs is more appropriate for this patient we should take into account which are her most significant comorbidities in addition to the efficacy of each option.

According to a meta-analysis, a 2-year course of teriparatide has shown 65 %, 50 %, and 50 % drops of the risk of vertebral, non-vertebral, and hip fractures, respectively (9). Contraindications for its use include unexplained elevations of alkaline phosphatase levels, patients who have previously been treated with external radiation or localized radiotherapy to the skeleton, and the presence of tumors or bone metastases. There is extensive experience on this drug, and recently, biosimilars have been developed that have reduced costs.

Romosozumab is a monoclonal antibody that inhibits sclerostin with a beneficial effect on bone homeostasis as it stimulates bone formation while inhibiting resorption simultaneously. Romosozumab rapidly and significantly decreases the risk of vertebral fractures and clinical fractures in 12-month courses of monotherapy. In addition, it minimizes the risk of all types of fractures in sequential treatment both with denosumab and long-term alendronate (10). The drug is well-tolerated, but in one of the studies, there was a slight imbalance in the rate of cardiovascular events occurred. Differences were small (1.3 % vs 0.9 % in the control group), and although there is no plausible biological explanation for this finding, it is contrain-

dicated in individuals with a past medical history of myocardial infarction or stroke.

In our case, the patient's significant past medical history is the diagnosis of breast cancer —currently in remission— 15 years ago that was not treated with radiation therapy and no evidence of bone metastasis. Although a complete blood test including alkaline phosphatase levels would be necessary, there is not such a thing as a formal contraindication for the use of teriparatide. On the other hand, no previous cardiovascular events have ever been reported. However, the past medical history does identify several cardiovascular risk factors like smoking until a year ago, dyslipidemia, hypertension, and a family history of early coronary artery disease. Therefore, the cardiovascular risk index (SCORE) showed values of 6.8 %. The National Spanish Health Service has established specific conditions for its funding including, among other, low or moderate cardiovascular risk (SCORE < 5 %).

In conclusion, this patient on an extremely high risk of fracture should receive early treatment with a bone-forming drug as first-line therapy. Considering the comorbidities reported and funding limitations in Spain, the option recommended would be teriparatide after discussion and agreement with the patient.

COMMENTARY ON ASPECTS RELATED TO CARDIOVASCULAR RISK

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The cardiovascular risk profile should be estimated routinely in individuals over 40 years (11) of age during any contacts with their healthcare providers, especially women like the one reported in this case who has a medical history of breast cancer and has received chemotherapy in the past. Therefore, recent data from the Spanish CARDIOTOX Registry (12) indicate that the risk of cardiotoxicity (defined as a reduction of left ventricular ejection fraction < 40 %) or progression into clinical heart failure, is associated, among other factors, with the patients' baseline cardiovascular risk.

In this case, the patient has a SCORE2 cardiovascular risk of 6.8 % that falls into the moderate-risk group. According to the recent European clinical practice guidelines on prevention, interventions on the patient's lifestyle would be advised including smoking cessation, exercise recommendations, and dietary changes. The guidelines also state that LDL cholesterol levels should be < 100 mg/dL and blood pressure kept under 140-130 mmHg. Other factors that should be taken into consideration — spared by the SCORE2 estimate— include the patient's risk profile, her sister's previous history of myocardial infarction at the age of 50, low HDL cholesterol levels, and having been received breast cancer treatment with chemotherapy. Although the specific LDL level is not provided, it is mentioned that her total cholesterol levels were 250 mg/dL with low HDL, indicative that the LDL levels are likely well above the 100 mg/dL mark. Therefore, the patient should receive treatment, at least, with a powerful enough statin to bring LDL down to < 100 mg/dL, and if necessary, consider adding ezetimibe to statin therapy. The patient's blood pressure levels are not described either. If they fall within the hypertension range (> 140 mmHg and/or 90 mmHg), apart from lifestyle recommendations, which should also include reducing salt intake, initiating antihypertensive treatment with an ACE inhibitor, ARB, thiazide or dihydropyridine calcium channel blocker should be considered too. If achieving blood pressure control requires bringing systolic pressure down by > 20 mmHg and/or diastolic pressure down by > 10 mmHg, combined therapy with a low-dose ACE inhibitor or ARB plus a thiazide or calcium channel blocker is advised.

In conclusion, this patient requires cardiovascular risk assessment by the healthcare professional involved in her management. Also, instructions on lifestyle changes and specific therapeutic interventions should be provided.

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