CLINICAL VIGNETTE

New Anabolic Treatment of Osteoporosis

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Patient's History

An 81-year-old female with past medical history of polymyositis on chronic prednisone treatment for 15 years presented to the endocrinology clinic for evaluation of osteoporosis. She had a prior humerus fracture at the age of 49. Her mother also had a history of severe osteoporosis. She notes that she has lost about 2 inches of her height over the past 5 years. Her medical history is also complicated by a stroke four years prior which led to approximately one month of immobility and a 25 pound weight loss. She went into menopause in her late 40s with normal menses since menarche at age 12. She takes approximately 1200 mg of calcium from diet and supplements and 2000 IU of vitamin D daily. She does two days per week of physical therapy but no weight bearing exercise other days of the week. Her chronic prednisone treatment varies from 1 to 7 mg per day. She has no significant alcohol, tobacco, or recreational drug use.

On physical exam, she had normal vital signs with a BMI of 22. Otherwise, her physical exam was within normal limits. Her labs demonstrated normal calcium, phosphorus, intact parathyroid hormone, thyroid function tests, vitamin d, celiac antibody panel, bone specific alkaline phosphatase, and SPEP/UPEP. Her bone density test demonstrated a T-score of -3.2 in the total hip, -2.9 in femoral neck, and -2.4 in lumbar spine.

After initial evaluation, she was started on zoledronic acid 5 mg IV annually for fracture prevention. She was encouraged to remain compliant with her calcium and vitamin D and to increase her weight bearing exercise to thirty minutes per day approximately five days per week. She tolerated her infusion without any side effects. However, approximately eleven months after her zoledronic acid infusion, she had a flare of her polymyositis symptoms and her prednisone dose was significantly increased to 20 mg per day. After approximately four weeks of treatment, she suffered an acute T12 spine fracture and required treatment with kyphoplasty. Due to the vertebral fracture and continued requirement for higher dose steroids, her treatment was switched from zoledronic acid to abaloparatide. Her fracture pain subsequently resolved within approximately 2 weeks of initiating treatment.

Discussion

This patient's osteoporosis has multiple factors including genetic history, long term steroid use, prolonged period of immobility, and significant weight loss. Her fracture after treatment with zoledronic acid does not necessarily mean treatment failure as she had only one infusion. However, given her high dose steroid requirement and acute fracture, she was a good candidate for anabolic treatment.

There have been several recent developments in anabolic treatments. Until 2017, teriparatide was the only available anabolic treatment of osteoporosis. This has been followed by abaloparatide with is a hybrid of parathyroid hormone and parathyroid hormone related peptide. Its binding to the parathyroid hormone receptor leads to the R^g conformation as opposed to the R^o conformation by teriparatide. The R^G conformation leads to a more transient cyclic AMP release. A study by Miller [1] randomized patients in a double blinded fashion to abaloparatide, teriparatide, and placebo. The bone mineral density (BMD) was significantly higher in the abaloparatide group for total hip and femoral neck compared to teriparatide and placebo. The lumbar BMD was similar in the teriparatide and abaloparatide groups. The abaloparatide group was superior to placebo and teriparatide groups in terms of major osteoporotic fractures (includes spine, hip, upper arm, and wrist). Vertebral fractures were similar in the abaloparatide and teriparatide groups but fewer compared to the placebo group. In terms of adverse events, there were fewer cases of hypercalcemia in the abaloparatide group compared to the teriparatide group. It is thought that the decreased duration of cyclic AMP release may account for the differences observed between abaloparatide and teriparatide.[2]

Another drug awaiting FDA approval is romosozumab. This is an antisclerostin antibody. Sclerostin is a protein secreted by osteocytes. It is encoded by the SOST gene on chromosome 17.[3] Sclerostin is an Wnt antagonist leading to decreased osteoblast activity. Inhibition of sclerostin during exercise may be the mechanism by which weight bearing exercise improves bone strength. This was initially discovered though studying a human double knockout model of the SOST gene. An autosomal recessive condition, sclerosteosis, is characterized by thickening of the bone leading to BMDs upwards of 14.[4] However, these patients do have complications including increased intracranial pressure, cranial nerve compression, and hearing loss. The hope is that romosozumab will mimic the

heterozygous phenotype which is characterized by higher BMD without other health complications. A phase III study [5] has demonstrated that romosozumab has both antiresorptive and anabolic effects based on bone turnover markers which would theoretically allow for accrual of more bone mass. There were fewer vertebral fractures seen within six months of treatment compared to placebo demonstrating rapid antifracture efficacy. In terms of adverse events, there was one atypical fracture and two cases of osteonecrosis of the jaw.

Based on these results, we should consider using these anabolic treatments in patients with low BMD or those with immediate high fracture risk (such as those started on steroids or had a recent fracture). Our patient will be continued on abaloparatide for 18 months and then transitioned to denosumab. Further research is needed comparing the antifracture efficacy and adverse events of these newer agents to our current treatment options.

REFERENCES

1. **Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C; ACTIVE Study Investigators.** Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. *JAMA*. 2016 Aug 16;316(7):722-33. doi: 10.1001/jama.2016.11136. Erratum in: JAMA. 2017 Jan 24;317(4):442. PubMed PMID: 27533157.
2. **Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ.** Binding Selectivity of Abaloparatide for PTH-Type-1-Receptor Conformations and Effects on Downstream Signaling. *Endocrinology*. 2016 Jan;157(1):141-9. doi: 10.1210/en.2015-1726. Epub 2015 Nov 12. PubMed PMID: 26562265; PubMed Central PMCID: PMC4701881.
3. **Krishnan V, Bryant HU, Macdougald OA.** Regulation of bone mass by Wnt signaling. *J Clin Invest*. 2006 May;116(5):1202-9. Review. PubMed PMID: 16670761; PubMed Central PMCID: PMC1451219.
4. **Gardner JC, van Bezooijen RL, Mervis B, Hamdy NA, Löwik CW, Hamersma H, Beighton P, Papapoulos SE.** Bone mineral density in sclerosteosis; affected individuals and gene carriers. *J Clin Endocrinol Metab*. 2005 Dec;90(12):6392-5. Epub 2005 Sep 27. PubMed PMID: 16189254.
5. **Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A.** Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med*. 2016 Oct 20;375(16):1532-1543. Epub 2016 Sep 18. PubMed PMID: 27641143.

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