North America. J Clin Microbiol 2005; 43: 991–2.
15. Lee H, Chuang Y, Yu W, Lee N, Chang C, Ko N, Wang L, Ko W. Clinical implications of hypermucoviscosity phenotype in Klebsiella pneumoniae isolates: association with invasive syndrome in patients with community-acquired bacteremia. J Int Med; 259:606-614.

Denosumab-Induced Severe Hypocalcemia in a Patient with Crohn's Disease.

October 6, 2014 Case Reports, Issues, October-December 2014 Issue:Volume 6 Issue 4
Keywords Crohn's disease, Denosumab, Hypocalcemia

Michelle C Spiegel[1], Tonya Tidwell PA[2], Rajasekhar Mulyala MD[2], Natraj Katta MD, FACP[2]

[1] University of Missouri School of Medicine, Columbia, MO

[2] Division of Hospital Medicine, Department of Medicine, University of Missouri School of Medicine, Columbia, MO

Address correspondence to: Michelle C Spiegel

Citation: M C *Spiegel, T Tidwell, R Mulyala, N Katta, Denosumab-Induced Severe Hypocalcemia in a Patient with Crohn's Disease. Journal of Academic Hospital Medicine 2014, Volume 6, Issue 4.*

Introduction

Osteoporosis occurs with increased prevalence in individuals with inflammatory bowel disease (IBD), and as such, these patients are at risk for osteoporosis-related fractures. Although bisphosphonates remain the most commonly used class of drugs for managing osteoporosis, the effectiveness of oral bisphosphonates in patients with IBD may be diminished due to distressing gastrointestinal side effects, which hinder compliance, and also due to poor absorption by diseased intestine.

While intravenous bisphosphonate therapy remains an option for these patients, denosumab has emerged in recent years as an alternative bone-modifying agent. Denosumab received FDA approval for treatment of postmenopausal osteoporosis in 2010 and clinical trials have demonstrated that this medication is both efficacious and well tolerated. Hypocalcemia is a known adverse effect of this medication, although in clinical trials, denosumab has been well tolerated, and numerous trials, most notably the FREEDOM trial (and its two-year extension trial), have failed to demonstrate a significant risk of hypocalcemia while receiving denosumab [1]. However, there have been no formal studies assessing for the risk of hypocalcemia while receiving denosumab in patients who have gastrointestinal disorders such as IBD. This report details a patient with a history of corticosteroid-treated Crohn's disease, who developed severe, symptomatic hypocalcemia shortly after beginning denosumab therapy.

Case Presentation

A 64-year-old Caucasian woman presented to the emergency department with a two-week history stiffening of her hands and face, myalgias, weakness, and edema of the hands and feet. Additionally, on the day of presentation, she developed garbled speech. The patient had a past medical history significant for Crohn's disease, for which she was status-post ileocolectomy with only six feet of remaining intestine; osteoporosis; gouty arthritis; breast carcinoma with left mastectomy in 2006; renal carcinoma with ablation in 2009; and lymphoma. 72 hours prior to initial onset of symptoms, the patient was started on denosumab to treat her osteoporosis. Of note, the patient was taking prednisone 10 mg per day for the past year to manage her Crohn's disease.

Physical exam in the emergency department was remarkable for positive Chvostek and Trousseau signs, and patient was alert but unable to speak, due to mandibular tetany. Blood testing revealed hypocalcemia with serum calcium of 3.9 mg/dL. Other notable laboratory findings included a PTH of 5,679 pg/mL (normal 15-65 pg/mL), a 25-hydroxy vitamin D of 9 ng/mL (normal 30-80 ng/mL), a creatinine of 1.4 mg/dL, and an alkaline phosphatase of 205 IU/L. She was admitted to the medical intensive care unit and placed on telemetry due to concerns that the patient might develop hypocalcemia-induced prolonged QT interval. Throughout the patient's three-day hospital stay, she received a total of 28 grams of IV calcium gluconate. Additionally, she was started on calcitriol 0.25 mg/day and oral calcium (350 mg) and vitamin D (200 IU) 3 tablets, three times per day. At the time of discharge, the patient's signs and symptoms of hypocalcemia had resolved, although her calcium level remained relatively low at 6.6 mg/dL. Of note, baseline calcium and vitamin D levels were not obtained prior to starting the patient on denosumab.

Discussion

Inflammation-Induced Osteoporosis

Osteoporosis is thought to be present in up to 70% of patients with IBD, depending on the population, due to a number of factors including inflammation, malabsorption (due to disease activity and/or extensive intestinal resection), generalized poor nutritional status, and glucocorticoid use[2,3]. Inflammation in IBD leads to bone density loss, as over-activation of T cells and the resulting cytokine release stimulates the receptor activator of nuclear factor KB ligand (RANKL). RANKL, in turn, binds to RANK receptors on osteoclasts, promoting osteoclastic activity, and thus bone resorption. In understanding this physiology, it could be reasoned that denosumab may be the ideal bone-modifying agent for these patients. Denosumab, a human monoclonal antibody, acts by binding to and inhibiting RANKL. This inhibitory action effectively counteracts the cytokine release by proinflammatory cells as it prevents osteoclast formation, decreases bone resorption and increases bone mass.

Role of Malabsorption

However, as mentioned above, this inflammatory-induced cytokine cascade is only one mechanism of several that are thought to contribute to the development of osteoporosis in these

patients. Another major contributing factor is from bone loss secondary to nutrient malabsorption. Patients with Crohn's disease, in whom the small intestine is involved—specifically patients with inflammation, chronic fibrosis or who are status post removal of the terminal ileum—may have decreased absorption of vitamin D, and thus decreased calcium levels, due to impaired bile salt reabsorption [2]. Poor vitamin D and calcium absorption leads to the development of secondary hyperparathyroidism, which in turn increases bone loss as a result of increased resorption. A multitude of studies exploring the prevalence of vitamin D deficiency in patients with Crohn's disease have yielded variable results, with a range of 27-68%[4]. For example, a 2011 prospective study sought to assess for Vitamin D deficiency in 81 patients with Crohn's disease, and found that 63% of studied patients had subnormal levels[5]. Interestingly, of these 63% of patients with low levels of vitamin D, 43% were actively taking a vitamin-D containing supplement. Of note, most patients who were taking a supplement were taking a multivitamin containing a relatively low dose of vitamin D (200-400 IU) [5]. This finding suggests that providers may need a more aggressive approach for vitamin D (and calcium) supplementation in patients who are at risk for deficiency due to comorbid conditions (malabsorptive diseases, chronic kidney disease). Osteoporosis secondary to vitamin D deficiency cannot be corrected with denosumab or other bone-modifying agents.

Glucocorticoid-Induced Osteoporosis

Glucocorticoids further contribute to osteoporosis in a number of ways. They stimulate osteoclasts by increasing RANKL levels, while increasing osteoblast apoptosis and decreasing osteoblast function and life span. Glucocorticoids also stimulate osteocyte apoptosis. Furthermore, they inhibit calcium absorption from the gastrointestinal tract and induce renal calcium loss[6,7]. The role of denosumab in treating patients with IBD who are receiving glucocorticoid therapy is less clear. While this medication can correct glucocorticoid-induced osteoclast stimulation, osteoclast activity appears to play a smaller role in the pathogenesis of glucocorticoid-induced osteoporosis than it does in the pathogenesis of other types. There are additional concerns that concurrent use of glucocorticoids and denosumab may increase a patient's infection risk[6,7].

Hypocalcemic Effect of Denosumab

While denosumab seems promising for treating osteoporosis in patients with IBD, osteoclast inhibition raises concerns for hypocalcemia, as the body has lost its means for harvesting additional calcium when blood levels drop. Fortunately, this complication is rare; current estimates of hypocalcemia incidence while taking denosumab are 1.7%[8,9]. Despite this apparently low occurrence, the FDA label does caution about the potential for patients to develop hypocalcemia due to post-marketing reports of severe, symptomatic hypocalcemia with denosumab use. Not surprisingly, patients with chronic kidney disease and malabsorption syndromes are most at risk for developing this complication[1]. Importantly, denosumab has not been formally studied in patients with gastrointestinal disorders. The FREEDOM study, which is perhaps the most well-known clinical trial for assessing denosumab efficacy and safety, failed to uncover an increased risk of hypocalcemia in its study patients, but also excluded patients with any conditions that could affect bone metabolism (malabsorptive disorders, kidney disease) from participating in the study[10]. As such, the results of this study should not be generalized to this

population of patients. Patients with these conditions are clearly more likely to develop severe hypocalcemia while undergoing denosumab treatment because many have hypocalcemia at baseline.

In 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) released a report warning of the possible risk of severe symptomatic hypocalcemia. Although the greater concern for hypocalcemia occurs with the 120 mg dose (Xgeva) which is used for prevention of skeletal related events in patients with bone metastases, symptomatic hypocalcemia has also been reported in patients receiving the 60 mg dose (prolia). Based on these reported hypocalcemic events, the MHRA cautioned healthcare professionals to avoid use of denosumab 60 mg (for osteoporosis indications) in patients with any degree of hypocalcemia. The MHRA also reiterated the importance of adequately supplementing calcium and vitamin D in patients receiving this medication, and vigilantly following blood levels of these nutrients in patients[11].

Learning Points

- Osteoporosis is prevalent in patients with IBD, particularly Crohn's disease, and its cause is multifactorial.
- Denosumab, a RANKL inactivator, may prove helpful in minimizing osteoporosis induced by the large inflammatory component of IBD and its resulting stimulation of the RANKL-RANK interaction for osteoclast activation. However, concerns for hypocalcemia and a lack of clinical trials studying denosumab' s effects in patients with malabsorptive disorders should limit its use in this patient population at this time.
- Should denosumab be used for patients with malabsorptive disorders, it is imperative that these patients have normal calcium and vitamin D levels prior to beginning treatment, and calcium and vitamin D levels should be monitored frequently throughout duration of treatment. Baseline levels must be obtained.
- More research is needed to identify target calcium and vitamin D levels (and thus appropriate supplementation dosages) for osteoporotic patients with malabsorptive disorders who may benefit from denosumab therapy.

References

1. Diab, Dima L., and Nelson B. Watts. "Denosumab in Osteoporosis." *Expert Opinion on Drug Safety* 13.2 (2014): 247-53.
2. Targownik, Laura E., Charles N. Bernstein, and William D. Leslie. "Inflammatory Bowel Disease and the Risk of Osteoporosis and Fracture." *Maturitas* 76.4 (2013): 315-19.
3. Hogezand, R. A Van, and N. A. T. Hamdy. "Skeletal Morbidity in Inflammatory Bowel Disease." *Scandinavian Journal of Gastroenterology* 41.S243 (2006): 59-64
4. Javorsky, Bradley R., Nelly Maybee, Shetal H. Padia, and Alan C. Dalkin. "Vitamin D Deficiency in Gastrointestinal Disease." *Practical Gastroenterology* 36th ser. (2006): 52-72

5. Suibhne, Treasa Nic, Gerry Cox, Martin Healy, Colm O'morain, and Maria O'sullivan. "Vitamin D Deficiency in Crohn's Disease: Prevalence, Risk Factors and Supplement Use in an Outpatient Setting." *Journal of Crohn's and Colitis* 6.2 (2012): 182-88.
6. Adler, Robert A. "Glucocorticoid-Induced Osteoporosis: Management Update." *Current Osteoporosis Reports* 8.1 (2010): 10-14.
7. Dore, R. K. "How to Prevent Glucocorticoid-induced Osteoporosis." *Cleveland Clinic Journal of Medicine* 77.8 (2010): 529-36.
8. Katz, Seymour, and Stuart Weinerman. "Osteoporosis and Gastrointestinal Disease." *Gastroenterology and Hepatology* 6.8 (2010): 506-17.
9. Bridgeman, Mary Barna, and Rolee Pathak. "Denosumab for the Reduction of Bone Loss in Postmenopausal Osteoporosis: A Review." *Clinical Therapeutics* 33.11 (2011): 1547-559.
10. Moen, Marit D., and Susan K. Keam. "Denosumab: A Review of Its Use in the Treatment of Postmenopausal Osteoporosis." *Drugs Aging* 28.1 (2011): 63-82.
11. "Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment—monitoring recommended." *Drug Safety Update* 6.3 (2012).

Unusual presentation of Coxsackie B Rhabdomyolysis: Case Report and Literature Review

October 6, 2014 Diagnostic Dilemma, Issues, October-December 2014 Issue:Volume 6 Issue 4
Keywords coxsackie B Rhabdomyolysis

Sajal Patel MD[1], Rajasekhar Mulyala MD2, Natraj Katta MD, FACP[2]

[1]Division of Internal Medicine and Child Health, University of Missouri, School of Medicine, Columbia, MO

[2]Division of Hospital Medicine, Department of Medicine, University of Missouri, School of Medicine, Columbia, MO

Address Correspondence: Sajal Patel

Citation: S Patel, R Mulyala, N Katta. Unusual presentation of Coxsackie B Rhabdomyolysis: Case Report and Literature Review. Journal of Academic Hospital Medicine 2014, Volume 6, Issue 4.

Introduction: Coxsackie virus infections occur throughout the year, but have an increased in the summer and fall (1). It is often self-limited and resolves with only symptomatic treatment, but the virus has been linked to rhabdomyolysis in case reports. Though the exact mechanism of viral rhabdomyolysis is still unknown, the end result is destruction of myocytes and the release of toxins into the circulation (2, 3). The results of rhabdomyolysis can be limited to myalgia or can be severe enough to require dialysis (2,4). It is therefore important to recognize viral causes