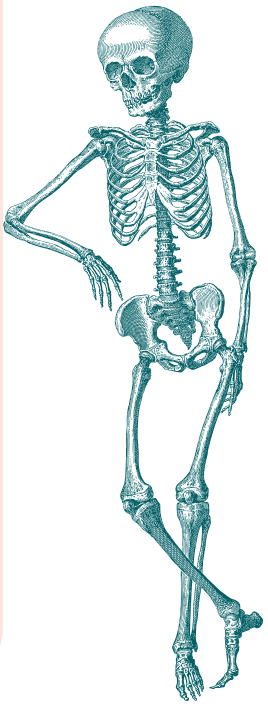
Denosumab — “Handle with care”

CASE

Your 75 year-old female pt with various chronic conditions such as hypertension, type 2 diabetes mellitus, was admitted to the hospital for recurrent falls and new low back pain. She was treated for a UTI and an L4 compression fracture. Discharge medication changes included the recommendation to switch oral alendronate to denosumab SC q 6 months.

Pt was transferred to temporary convalescent care, then back home with family. However, as the level of care was more than what the family could provide, the pt was moved to independent living then finally settled in long-term care. Amid the changes in environment were also changes in the provider and community pharmacy. The denosumab prescription was filled once during convalescence but eventually it was lost in the shuffle. It is now 10 months since the last injection.



1. Role of Denosumab

- Denosumab is often prescribed for osteoporosis treatment when bisphosphonates are contraindicated or if there is substantial intolerance, to reduce the risk of fractures in those who are intermediate to high risk. It is also used for primary prevention of osteoporotic fractures in women with breast cancer who are receiving aromatase inhibitors.
- It is a monoclonal antibody which binds to RANKL, preventing osteoclast formation, which results in anti-resorptive effects.

2. Prescribing Denosumab

- Usual directions for osteoporosis: denosumab 60mg subcutaneous every 6 months
- If CrCl < 30mL/min: no dosage adjustment necessary, but use in conjunction with guidance from patient's nephrology team, as osteoporosis is difficult to distinguish from chronic kidney disease related mineral bone disease
- Risks (severe hypocalcemia, which is markedly increased in patients with chronic kidney disease-mineral disorder) must be weighed against the accuracy of the diagnosis of the underlying bone disease

SPECIAL AUTHORITY CRITERIA: A OR B

A. For the treatment of women with postmenopausal osteoporosis or men with osteoporosis. Must qualify with:

- Clinical or radiographically documented fracture due to osteoporosis AND
- Contraindication to oral bisphosphonates: EITHER immune-mediated hypersensitivity reaction to oral bisphosphonates; OR abnormalities of the esophagus that delay esophageal emptying such as stricture or achalasia
- Approval indefinite

B. For primary prevention of osteoporotic fractures in women with breast cancer who are receiving aromatase inhibitor therapy (approved for 5 years)

3. Adverse effects

- Hypocalcemia: rare if normal renal function and adequate calcium and vitamin D intake
- Risk increases with renal impairment: < 1% (eGFR 30-60 mL/min), 4% (15-30 mL/min), 24-42% (<15mL/min)
- Other risk factors for hypocalcemia: hypoparathyroidism, thyroid or parathyroid surgery, malabsorption syndromes, previous hypocalcemia
- Other common adverse effects: flatulence, nausea, injection site reaction, limb pain, eczema, rash, cellulitis, and other infections (ENT, GI, cellulitis – absolute risk 0.6% in 1-3 years)
- Rare: osteonecrosis of the jaw (ONJ) (0.05-0.7% over 7-10 years), atypical femur fracture (0.06%)

4. Precautions

Denosumab has a rapid offset of effect, increasing the risk of multiple vertebral fractures following discontinuation/treatment interruption with no other osteoporosis treatment in its place. Vertebral fractures and a decrease in BMD were reported starting 7 months after last dose, i.e. 1 month late (average: 19 months).

5. Pro-tips for prescribing denosumab

A. Who may be best suited for denosumab? Factors to consider besides efficacy:

- Administration: is the pt okay with subcutaneous injections?
- Are there systems and supports in place for timely refills?
- Consider the different processes that need to be in place if the pt were living at home, or independent living facility, versus assisted living or long-term care
- Does your office have a good system in place if the pt were to miss an appointment in the context of coming in for denosumab refill/injection?

B. Be vigilant during transitions of care

- Pt admitted to the hospital may be temporarily transferred to another facility
- Medication reconciliation is essential. Be sure to review the Pharmanet beyond the past 6 months. This may not be possible on Pharmanet if the number of refills exceed the maximum reportable limit (e.g. pt is daily dispensed and on a lot of medications)
- Consider enlisting the help of your community pharmacist or clinical pharmacist. If your patient is consistently at the same community pharmacy, their records may go back a few years

C. Have an exit strategy/transition plan at the time of initiation

- Osteoporosis Canada suggests long-term uninterrupted therapy
- If discontinuing after ≤ 4 doses, transition to a bisphosphonate; if discontinuing after ≥ 5 doses, seek advice from a consultant with osteoporosis expertise

D. Monitoring

- Check baseline serum calcium and correct preexisting hypocalcemia if present (i.e. adequate calcium and vitamin D supplementation); those with advanced CKD (eGFR <30) should be evaluated for chronic kidney disease mineral and bone disorder with intact parathyroid hormone, serum calcium, and vitamin D
- Product monograph suggests clinical monitoring of calcium levels before each dose, and within 2 weeks of initial dose for those predisposed to hypocalcemia
- Preventative dentistry is recommended if risk factors for ONJ are present
- These factors include: previous treatment with bisphosphonates, older age, smoking, a diagnosis of cancer, concomitant therapies (eg, chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, invasive dental procedures (e.g. dental extractions, dental implants, oral surgery), and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, ill-fitting dentures, anemia, coagulopathy, infection).
- Clinical symptoms of hypocalcemia include: muscle spasms/cramps, mental/mood changes (such as irritability or confusion), numbness/tingling (especially around lips/mouth or in fingers/toes), fast/irregular heartbeat, severe dizziness/fainting, seizures

Back to our case

After a thorough process of medication reconciliation when the pt was transferred back to long-term care, the medical team repeated baseline blood work, including serum calcium, electrolytes, albumin, renal parameters, and thyroid function. All results were normal. In discussion with the patient, they decided to supplement with calcium and vitamin D given low dietary intake, and restarted denosumab 60mg SC every 6 months. They were able to obtain special authority for denosumab given high risk of fractures and a history of esophageal dysmotility.

References

- BC Provincial Academic Detailing (PAD) Service – Medications for osteoporosis: an update (Aug 2024)
- BC Special Authority program
- Lexidrug
- Prolia product monograph
- Rxfiles