NEW TREATMENTS FOR OSTEOPOROSIS

Several new therapies for the treatment of osteoporosis are currently undergoing phase II and phase III trials in hopes of transforming management of the disease. While published guidelines for the management of osteoporosis are available, limited data exists regarding appropriate first-line therapy. This issue of CLIPs briefly summarizes an article that introduces potential new therapies for treating osteoporosis, including several selective estrogen receptor modulators (SERMs) and denosumab. Additionally, zoledronic acid (Reclast) and raloxifene (Evista) will be reviewed. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Introduction

- Osteoporosis is becoming a more prevalent disease that affects the bone causing low bone mass and deterioration of bone structure. Osteoporosis is diagnosed by a decrease in bone mineral density (BMD).
- Osteoporosis is most common in women causing fractures in any bone especially hip, spine, wrist, and ribs.
- The current guidelines were last updated in 2006 and include prevention measures, risk assessment, diagnosis, and treatment.
- The pharmacologic agents available today include antiresorptive therapy (bisphosphonates, SERMs, calcitonin, estrogen) and anabolic therapy (parathyroid hormone).
- Considering the potential severity of osteoporosis, the development of new formulations of drugs currently used in treatment to improve the efficacy is important.

Zoledronic Acid (Reclast)

- IV bisphosphonate approved for treatment of osteoporosis in postmenopausal women.
- The long duration of action of zoledronic acid may offer an advantage over other agents. Zoledronic acid is dosed as 5 mg administered once yearly as an intravenous infusion over 15 minutes.
- Prior to initiation of therapy, patients should receive a dental examination, as osteonecrosis of the jaw is a potential risk of IV bisphosphonate use. This complication, however, is rare in postmenopausal women with osteoporosis. The majority of cases have been reported in oncology patients receiving high-dose intravenous bisphosphonates.
- Most adverse effects are mild and include fever, myalgias, and headache. One trial showed an increased risk of new onset atrial fibrillation in patients receiving zoledronic acid; however, this arrhythmia occurred more than 30 days postinfusion. A later study did not show any significant difference in the incidence of this arrhythmia in patients receiving zoledronic acid versus placebo.
- Cost may limit its use. Average wholesale price is $1301.93 per dose.
- Zoledronic acid is contraindicated in patients with creatinine clearances < 35 mL/min or uncorrected hypocalcemia.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs display agonistic and antagonistic effects on estrogen receptors in the body including the breast, bone and uterus. Specific estrogen receptors include ERα and ERβ.
- Advantages of SERMs include reduced risk for breast cancer and enhanced lipid panels. Disadvantages include the increased risk for VTE, vasomotor symptoms, and vaginal dryness.
- Raloxifene (Evista) [60-120 mg daily]
  - Beneficial effects are due to its antiresorptive effect on bone and include reducing the risk of breast cancer and vertebral fractures after 4 years and increasing the lumbar spine and femoral neck BMD after 7 years.
● Raloxifene has not been proven useful for nonvertebral fractures and it significantly increases risks for VTE.
● There are several SERMs currently undergoing phase II and phase III trials that offer advantages over the currently available medications on the market.
● Arzoxifene
  o Currently undergoing phase III trials to determine effects on postmenopausal osteoporosis. Further studies are being performed to evaluate the effects on bone fractures and incidence of breast cancer.
  o Bioavailability and antagonistic mechanism of action at uterine receptors is superior to raloxifene and is considered one of the most potent SERMs.
  o A head-to-head trial comparing raloxifene and arzoxifene in postmenopausal women is underway.
● Bazedoxifene
  o Also currently being investigated with multiple phase III trials being conducted.
  o Unlike most SERMs, bazedoxifene may have fewer uterine and vasomotor effects.
  o Use in combination with conjugated estrogens for menopausal symptoms, prevention of endometrial hyperplasia, and osteoporosis is being investigated, as well as effects on lumbar spine BMD after 24 months.
  o Bazedoxifene may potentially influence new guidelines to the management of osteoporosis once trials are completed due to its unique benefits compared to other therapies.
● Lasofoxifene
  o Phase III trials are currently being performed.
  o Advantages include increased bioavailability and potency compared to raloxifene.
  o The current safety profile is positive; however, limited data exists to fully recognize vasomotor symptoms or the risk of VTE.
  o Lasofoxifene has shown to increase BMD and decrease bone turnover.
  o Future head-to-head trials will investigate the efficacy in reducing new spinal fractures in women diagnosed with osteoporosis versus raloxifene.
● Ospemifene
  o Ospemifene is a metabolite of toremifene and is currently undergoing phase III trials for vaginal atrophy due to its positive effects on vasomotor symptoms.
  o A phase II trial confirmed ospemifene is similar to raloxifene in beneficial effects on bone.
  o More clinical trials need to be performed to incorporate it in the treatment of osteoporosis.
● Other SERMs under investigation include idoxifene, droloxifene, acolbifene and HMR 3339.

**Denosumab**

● A monoclonal antibody currently undergoing several phase III trials to explore its potential benefit, as well as safety and efficacy, in treating osteoporosis.
● Denosumab mimics osteoprotegerin (OPG), an inhibitor or RANKL. RANKL, when it activates its receptor, RANK, leads to enhanced bone resorption. Thus, theoretically, blocking of RANKL may limit its ability to bind RANK and thereby decrease osteoclastogenesis.
● Phase II trials comparing denosumab, alendronate, and placebo showed favorable results in the primary outcome, with the greatest increase in BMD seen in the denosumab group.
● Safety concerns exist about the use of denosumab, as RANK is expressed on other cells, including dendritic cells and T and B cells. Further studies are needed to clarify the possible adverse events associated with its use.
● Studies have demonstrated that 30 mg every 3 months or 60 mg every 6 months are optimal doses.
● Although current findings support continued investigation of denosumab, more data will be required before it replaces existing osteoporosis therapy.

**Summary**

● In summary, several new therapies for the treatment of osteoporosis are currently undergoing phase II and phase III trials.
● Several investigational SERMs, denosumab, as well as zoledronic acid and raloxifene have shown promise in transforming the management of osteoporosis.
● Head-to-head trials comparing these new therapies to the established treatments in the management of osteoporosis will hopefully shed light as to their proper place in the management of osteoporosis.