Zoledronic acid

It is a nitrogen-containing, third-generation bisphosphonate that has recently been approved for the treatment of postmenopausal osteoporosis as an annual intravenous infusion. Zoledronic acid is an antiresorptive agent which has a high affinity for mineralized bone and especially for sites of high bone turnover (1).

Administered as a 5 mg intravenous infusion annually has been shown to decrease bone turnover markers such as serum C-telopeptide by 49-52%, decrease the vertebral fracture rate by approximately 70%, and significantly increase bone mineral density at total hip, femoral neck, and lumbar spine by 6.02%, 5.06%, and 6.71%, respectively. Furthermore, some women may prefer the convenience of once-yearly intravenous zoledronic acid to daily or weekly oral bisphosphonates.

In clinical trials that compared once-yearly zoledronic acid infusion with weekly oral alendronate, participants preferred zoledronic acid and found its adverse effect profile to be more favorable(2-4).

Most common side effects are post-dose fever, flu-like symptoms, myalgia, arthralgia and headache which usually occur in the first 3 days after infusion. Rare adverse effects include renal dysfunction, hypocalcemia, atrial fibrillation, and osteonecrosis of the jaw (1).

Denosumab

Receptor activator of nuclear factor-kB (RANK), its ligand (RANKL) and its decoy receptor osteoprotegerin (OPG) together play a key role in osteoclastogenesis. Alterations in the RANKL/OPG ratio are central in the pathogenesis of bone loss, from osteoporosis in all its forms to malignancy-induced bone loss. This fact has led to the search for drugs capable of targeted RANKL inhibition in the management of skeletal disorders associated with bone loss. Promising preclinical data using OPG have paved the way for the development of the new agent denosumab, a high-affinity, high-specificity, fully human monoclonal antibody to RANKL, shown to be able to induce a dose-dependent, rapid, profound and sustained inhibition of bone resorption lasting for months after a single subcutaneous injection in healthy postmenopausal women, men and patients with multiple myeloma or metastatic breast cancer. Data from a phase II study in postmenopausal women with low bone mineral density (BMD) demonstrate that the sustained inhibition of bone resorption induced by three or six monthly subcutaneously administered denosumab was associated with significant increases in BMD for up to two years of treatment. Antifracture efficacy and long-term skeletal and extraskeletal safety of denosumab are being addressed in ongoing phase III trials. The potential of denosumab to prevent bone loss has also been demonstrated in malignancy-induced bone loss (5).

Denosumab treatment for 12 months resulted in an increase in bone mineral density at the lumbar spine of 3.0 to 6.7 percent (as compared with an increase of 4.6 percent with alendronate), at the total hip of 1.9 to 3.6 percent (as compared with an increase of 2.1 percent with alendronate), and at the distal third of the radius of 0.4 to 1.3 percent (as compared with decreases of 0.5 percent with alendronate). Near-maximal reductions in mean levels of serum C-telopeptide from baseline were evident three days after the administration of denosumab. The duration of the suppression of bone turnover appeared to be dose-dependent (6).

In postmenopausal women with low bone mass, denosumab increased bone mineral density and decreased bone resorption. In another study, denosumab increased BMD at all measured skeletal sites and decreased
concentrations of bone turnover markers compared with placebo at 24 mo. At the lumbar spine, BMD increases with denosumab ranged from 4.13% to 8.89%. BMD changes with denosumab 30 mg every 3 mo and > or =60 mg every 6 month were similar to, or in some cases greater than, with alendronate.

The incidence of adverse events was similar in the placebo, denosumab, and alendronate treatment groups. Exposure-adjusted adverse events over 2yr of treatment were similar to those reported during the first year of treatment (7).

These preliminary data suggest that denosumab might be an effective treatment for osteoporosis. Despite these beneficial effects, denosumab was associated with increased rates of sore throat, rash and infections requiring hospitalization. Furthermore, the studies are limited by lack of information on antifracture efficacy, although such information will presumably be forthcoming in the near future (8).

These findings suggest that denosumab might represent a novel anti-osteoporosis agent. Nonetheless, further investigations of efficacy and long-term safety are needed before denosumab can be adopted into routine clinical practice.

Conclusion

Hence, yearly and twice yearly pharmacotherapy options for treatment of postmenopausal osteoporosis are promising for future mainly because of their efficacy and compliance. However, cost remain one important concern in opting this option. At present no major menopausal organization including International Menopause Society, North American Menopause Society or any international endocrinol or osteoporosis organization recommends / advocate its use as first line agents.

References