Non-estrogen based treatments for osteoporosis

1. Bisphosphonates

Bisphosphonates are analogues of inorganic pyrophosphate and have been used for the treatment of osteoporosis for many years. They inhibit bone resorption by inducing apoptosis of osteoclasts, thus preventing age related bone loss and deterioration of bone microarchitecture. Bisphosphonates that contain nitrogen (such as alendronate, risedronate, ibandronate, and zoledronic acid) have the most potent antiresorptive properties and are the most commonly used drugs in the treatment of osteoporosis. The bisphosphonate etidronate does not contain nitrogen, and although it is approved for treatment of postmenopausal osteoporosis, the evidence base is weaker and it is rarely prescribed nowadays. They are the most widely prescribed drugs, mainly due to their low cost and the generally favourable safety profile.

All bisphosphonates are poorly absorbed from the gut (usually <1% absorption) and must be given on empty stomach. Food or calcium-containing drinks (except water) inhibit absorption. Bisphosphonates bind avidly to bone mineral with no substantial affinity for other tissues. About 40–60% of the dose distributes to bone, the remainder is excreted unchanged in the urine, and there is no substantial metabolism. Once taken up by the bone, the elimination of alendronate from bone tissue is slow, ranging from 200 days in rats, 3 years in dogs and 12 years in humans. The long half-life of these drugs has enabled their intermittent administration. Oral bisphosphonates are administered every week (alendronate, risedronate) or every month (risedronate, ibandronate). Intravenous bisphosphonates are administered every three months (ibandronate) or once a year (zoledronic acid). Bisphosphonates increase bone mineral density and reduce the risk of vertebral fractures by 50% and the risk of hip fractures by 30-40%. Since no head-to-head trial concerning anti-fracture efficacy is available, there is inconclusive evidence to support that one drug is superior to another.

The most usual side effect is upper gastrointestinal irritation with oral agents and acute phase reactions (fever, arthralgia, myalgia) with the intravenous preparations. Osteonecrosis of the jaw is a rare event which occurs mainly in patients with cancer treated with high doses of IV bisphosphonates. Atypical femoral fracture (in the diaphysis of femur or subtrochanteric fracture) is another rare event occurring after prolonged treatment and is attributed to extreme suppression of bone turnover. Atrial fibrillation and oesophageal cancer have also been associated with the use of bisphosphonates; a causative relationship, however, cannot be substantiated.

<u>Prescribing tips</u>

Patient characteristics favouring bisphosphonates: older compliant women at risk of vertebral or hip fracture (first line therapy, oral preparations), non-compliant women (IV preparations), women with a personal history of hip fracture (first line therapy, IV preparation)

Patient characteristics not favouring bisphosphonates: younger women who are expected to receive antiresorptive therapy over a prolonged period of time, women with gastrointestinal problems (oral), women who cannot tolerate bisphophonates, non-high risk women with prolonged intake (>5 years)

<u>Drug holidays</u>

Discontinuation of bisphosphonates should be considered in all patients who have been treated for more than five years with alendronate or more than three years with risedronate or zoledronic acid. However No recommendations can be made for ibandronate.

Treatment re-initiation (usually 1–3 years after bisphosphonate withdrawal) depends on risk factors, new fractures and bone mineral density. Bisphosphonates, as well as other anti-osteoporotic treatments, including denosumab, teriparatide, SERMs and menopausal hormone therapy could be considered after a “drug holiday”.

Further reading

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2. Denosumab

Denosumab is human monoclonal antibody against RANKL, an osteoclast stimulating cytokine. By inhibiting RANKL, denosumab exerts a powerful antiresorptive action, lowering, bone turnover and inhibiting bone loss. Denosumab is approved for the treatment of osteoporosis in women at high risk of fracture and it is administered as a subcutaneous injection every 6 months. It increases bone mineral density (BMD) in all sites including the forearm and in the pivotal FREEDOM trial decreases vertebral fractures by 68% and hip fractures by 40%. In the extension of the FREEDOM trial denosumab treatment for up to 8 years was associated with persistent reductions of bone turnover markers, continued BMD gains, low fracture incidence, and a consistent safety profile. In contrast to bisphosphonates, bone turnover markers return soon to normal upon discontinuation. Since bone loss resumes within 6 months after discontinuation of denosumab, other antiosteoporotic agents must be considered in those women at highest risk who stop therapy. The safety profile is generally favourable. Skin reactions (rash, eczema, dermatitis) or rarely cellulitis were documented adverse events in clinical trials. Being a potent antiresorptive agent, caution must be exerted with the long-term use of denosumab, as sporadic cases of osteonecrosis of the jaw and atypical femur fractures have been reported after prolonged exposure.

<u>Prescribing tips</u>

Patient characteristics favouring denosumab: older women at high risk for vertebral or hip fracture, women not wishing daily, weekly or monthly regimens, non-compliant or institutionalized women, women intolerant to bisphosphonates, women with renal insufficiency.
Patient characteristics not favouring denosumab: women taking immunosuppressant therapy, women with medical conditions causing immune suppression, women with long-standing uncontrolled diabetes, women with skin diseases
The evidence regarding denosumab discontinuation is limited but caution is advised, as there may be a “rebound effect” with regard to fractures.

Further reading

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3. Parathyroid hormone (PTH)

Prolonged elevation of circulating PTH causes osteoporosis, as is the case of primary hyperparathyroidism. However, intermittent administration of PTH can preferentially stimulate osteoblasts, leading to bone formation. The intact molecule (amino acids 1-84), as well as recombinant PTH (amino acids 1-34, teriparatide)are approved for the treatment of postmenopausal osteoporosis as daily subcutaneous injections. Teriparatide use is associated with marked increases in bone mineral density, mainly in the spine and with a 65% decrease in the risk of vertebral fractures and a 53% decrease in the risk of non-vertebral fractures. Teriparatide promotes bone architecture and geometry in a mechanism not applicable to antiresorptive agents, increasing thus bone strength. In a post-hoc analysis in the pivotal trial, patients who received more than 18 months teriparatide had an 80% reduction of vertebral and non-vertebral fractures. The use of the intact PTH molecule is associated with 40% decrease in the risk of vertebral fractures, with no documented efficacy in non-vertebral fractures.

Abaloparatide is recombinant human parathyroid hormone-related peptide 1–34. It may be more potent than teriparatide, and may have more rapid onset of fracture reduction than teriparatide. Approved by the FDA in 2017 the recommended dose is 80 μg administered subcutaneously once daily into the periumbilical region of the abdomen. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.
PTH treatment may cause hypercalcemia, which is more frequent with the intact molecule. Calcium measurements are advised after the first month of treatment and every 3 months thereafter. Infrequent side effects include nausea, vomiting and dizziness. Long-term toxicologic experiments in rats have shown a link of PTH use with the development of osteosarcoma. Although no such finding was observed in humans, either from clinical trials or from post-market pharmacovigilance, the use of PTH for the treatment of osteoporosis is limited to 2 years. Parallel use of antiresorptive agents attenuates the effect of PTH, although this may not apply to antiresorptives with extended time interval of administration, like denosumab and zoledronic acid. After PTH, treatment should continue with an antiresorptive agent to prevent the ensuing bone loss.

<u>Prescribing tips</u>
Patient characteristics favouring PTH: women with prevalent fractures or spine

deformity, women with extremely low T-scores (<-3.5), women who fracture or markedly decrease BMD while on antiresorptive therapy
Patient characteristics not favouring PTH: treatment-naive women without fractures, women with hypercalcemia.

Further reading
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4. Selective Estrogen Receptor Modulators (SERMS)
SERMS are compounds that act through the estrogen receptor, but depending on the tissue target they exert either estrogen-agonist activity (e.g. bone) or estrogen-antagonist activity (e.g. breast). In bone tissue they inhibit bone resorption and reduce bone turnover. The first SERM approved for clinical use was tamoxifen, indicated as adjuvant therapy for the treatment of hormone sensitive breast cancer, as well as for primary prevention of breast cancer in high-risk women. Tamoxifen has been shown to prevent postmenopausal bone loss in women with breast cancer. There is inconclusive evidence that fracture incidence may be lower in women taking tamoxifen compared to women taking aromatase inhibitors. There are no data, however, on the efficacy of tamoxifen in women at risk of postmenopausal osteoporosis. Tamoxifen increases the risk of venous thromboembolism and of endometrial hyperplasia. Its use is not recommended for the sole purpose of osteoporosis treatment.

Raloxifene is the first SERM approved for the treatment of postmenopausal osteoporosis. Raloxifene, taken orally on a daily basis, increases bone mineral density and reduces the incidence of vertebral fracture by 50% in women with no previous fracture and by 30% in women with prevalent fractures, as documented in its pivotal trial (MORE). There is no documented efficacy of raloxifene in non-vertebral or hip fractures. In the pivotal trial women in the raloxifene arm had a 72% lower incidence of invasive breast cancer compared to women in the placebo arm. In a head-to-head study raloxifene had comparable efficacy to tamoxifen in reducing the risk of invasive breast cancer. Raloxifene does not increase the risk of endometrial hyperplasia, its use, however, is associated with a higher risk of venous thromboembolism and hot flushes.
Bazedoxifene is a newer SERM approved for the treatment of postmenopausal women at risk of fracture. It increases bone mineral density and decreases the risk of vertebral fracture by 40%. In primary analyses bazedoxifene was not shown to be effective in preventing non-vertebral or hip fractures. In subgroups of women at high risk of fracture, however, bazedoxifene reduced the incidence of non-vertebral fractures by 50%. Bazedoxifene has a favourable endometrial safety profile with long term use.

<u>Prescribing tips</u>
Patient profile favouring SERMS: women at high risk of vertebral fracture, younger women concerned about long-term safety issues of bisphosphonates, women with gastrointestinal problems, women at high risk of breast cancer
Patient profile not favouring SERMS: women with menopausal symptoms, women at high risk of hip fracture, women at risk of venous thromboembolism.
In 2017 the American College of Physicians recommended against using raloxifene for the treatment of osteoporosis in women.

Further reading
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5. Strontium Ranelate

Strontium ranelate was granted marketing authorisation in 2004 for the treatment of severe osteoporosis in postmenopausal women and adult men who are at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible. Its manufacturer ceased distribution in August 2017 and therefore it can no longer be prescribed.

Further reading

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31 May 2017. [Accessed 15 January 2018]

6. Calcitonin

Calcitonin is an antiresorptive agent available since 1973 by intramuscular injection or intravenous infusion and since 1987 with intranasal administration. Its prolonged use has been associated with a small but significant increase of all cancers. As the efficacy of this drug is inferior to the more recently available medicines, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended in 2012 that calcitonin-containing medicines should only be authorised for short-term use in Paget's disease, acute bone loss due to sudden immobilisation and hypercalcaemia caused by cancer. The Committee also concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in the treatment of osteoporosis and that they should no longer be used for this condition.

Further reading

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7. Future treatments

Newer biological agents are being investigated which target signalling pathways affecting bone formation and resorption. These include anti-sclerostin antibodies(romosozumab, blosozumab), anti DKK1 antibodies and cathepsin K inhibitors. In postmenopausal women with osteoporosis who were at high risk for fracture, a randomised trial romosozumab treatment for 12 months followed
by alendronate resulted in a significantly lower risk of fracture than alendronate alone. At the time of writing romosozumab has not been approved by the FDA because of a higher rate of serious adverse cardiovascualr events. With regard to cathepsin K inhibitors, potential concerns related to off-target effects of the inhibitors against other cathepsins and cathepsin K inhibition at non-bone sites, including skin and perhaps cardiovascular and cerebrovascular sites, is delaying development.

Further reading

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