Current and future drug treatments for the management of osteoporosis

In The Journal’s latest article on science, Wasim Baqir and Carmel Copeland look at some of the current treatments and upcoming novel treatments for managing osteoporosis and fracture risk.

Osteoporosis is a metabolic bone disease characterised by a reduction in the mass and quality of an individual’s bones. As a consequence, sufferers are at increased risk of fracture, particularly of the hip, wrist and spine. Hip fractures are usually regarded as the most serious consequence of osteoporosis because it is estimated that up to 20 per cent of patients die in the first year following a hip fracture. The significant morbidity and mortality makes osteoporosis a substantial public health problem as well as creating a huge financial burden on the NHS (estimated at £1.73bn annually — and more than two million hospital bed days in England each year).2

National guidelines published by the National Osteoporosis Guideline Group3 and two technology appraisals produced by the National Institute for Health and Clinical Excellence4,5 propose treatment strategies based on the risk of future fracture, in turn based on reduced bone mass and the presence of risk factors (eg, previous fractures). It is hoped that these guidelines will help raise awareness of osteoporosis and help prescribers initiate treatments to reduce risk of future fractures.

Current pharmacological treatments
Calcium and vitamin D
Calcium and vitamin D play an important role in bone development and remodelling. There is scant evidence to support use of calcium and vitamin D alone for treatment and prevention of osteoporosis. However, there is evidence of some benefit in housebound elderly patients.1 It is generally accepted that doses of 1.2g (30mmol) calcium and 20µg (800 units) of vitamin D (as colecalciferol or ergocalciferol) should be used in conjunction with a bisphosphonate or strontium ranelate (unless sufficient dietary intake can be assured).

There are many preparations on the market that contain combinations of calcium and vitamin D although, unfortunately, many patients find them unpalatable. It may be necessary to offer alternative brands or formulations if they are to be encouraged to persevere with treatment.

Bisphosphonates
Bisphosphonates are generally regarded as the first-line treatment for both primary and secondary prevention of osteoporosis. They have an inhibitory action on osteoclast activity (cells involved in bone resorption). They are effective agents that significantly reduce the risk of fracture, but are limited by their adverse effects.6,7 Recently, atrial fibrillation has been linked with the intravenous bisphosphonate zoledronic acid and there has been some suggestion that this may be a group effect. Osteonecrosis of the jaw has also been linked with bisphosphonates. This may be precipitated in patients who have undergone a dental procedure. There is insufficient evidence to warrant any specific advice but prescribers should warn patients to report any adverse events following dental procedures.

Recently, the Medicines and Healthcare products Regulatory Agency has warned prescribers to be aware of insufficiency fractures (atypical stress fractures) with bisphosphonates, especially alendronate. Bisphosphonates have complex administration directions for patients to follow. Because they have low oral bioavailability (approximately 5 per cent) and their absorption is further reduced by the presence of food in the stomach, patients should be advised to take them after an overnight fast and at least 30 minutes before food. There is also a risk that they can damage the lining of the oesophagus, causing oesophageal ulceration. This is minimised by advising patients to swallow the tablets with a full glass of water and remain upright for 30 minutes post dose. Adherence with bisphosphonates is poor, negating their potential for good.8

Strontium ranelate
Strontium ranelate works by reducing bone resorption and increasing bone formation. It is licensed for use by postmenopausal women for reducing the risk of vertebral and hip fractures. Strontium ranelate is an effective agent in both primary and secondary prevention of fracture. However, nausea and diarrhoea are common side effects.9,10 Also, there are reports of a slightly higher risk of venous thromboembolism compared with placebo. At a cost of £300 per annum per patient, strontium remains a second-line option after bisphosphonates.

Hormonal treatments
Hormone replacement therapy should only be used for prevention of osteoporosis in women where other treatments have failed. The long-term risks associated with the long duration of treatment necessary to prevent osteoporosis limit its attraction as a treatment option. These include thromboembolic risks, breast cancer risk and risk of precipitation of heart disease.

Tibolone is a synthetic steroid with oestrogenic, progestogenic and androgenic activity. As well as being used for the treatment of oestrogen deficiency symptoms in post-

References

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menopausal women, it is licensed for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are unable to tolerate other treatments, or for whom other treatments are contraindicated. Since this is a hormone replacement treatment, it carries the long-term risks outlined above.

The selective oestrogen receptor modulator (SERM) drug raloxifene, at a dose of 60mg daily, has been shown to reduce vertebral fractures in women with osteoporosis, or previous vertebral fracture.[12] There is no current evidence to demonstrate a reduction in non-vertebral fractures. The drug is associated with an increased risk for venous thromboembolic events and should not be given to patients with a history of venous thromboembolism. Newer SERMS are showing promising results in clinical trials. For example, arzoxifene, in early clinical trials, significantly increased bone mineral density (BMD): lumbar spine (+2.9 per cent) and total hip (+2.2 per cent).[13] Lasofoxifene has been associated with low risk of vertebral fractures.[14] Bazedoxifene and drosobufen are currently in phase III clinical trials.

Teriparatide is produced using recombinant DNA technology. It is identical to a fragment of endogenous human parathyroid hormone. Its action on bone formation is two-fold — direct action by stimulating osteoblasts (cells involved in bone formation), and indirect action by increasing absorption and reabsorption of calcium in the gut and kidneys, respectively. It is approved for treatment of osteoporosis in postmenopausal women and men at high risk of fracture. It is given by subcutaneous injection daily at a dose of 20µg.[15] It has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women, but there is no evidence for hip fracture reduction rates.

Calcitonin is a hormone produced by the thyroid gland. It inhibits bone resorption by the osteoclasts, and stimulates bone formation by the osteoblasts. Calcitonin is also found in fish, and a synthetic salmon calcitonin has been developed to treat a variety of bone disorders. The actions of calcitonin reduce blood calcium levels, hence its use in hypercalcaemia of malignancy. It is also used to reduce bone turnover and bone pain in Paget’s disease, and it is used intranasally with additional calcium and vitamin D to reduce the risk of vertebral fractures in osteoporosis (there is no evidence for reduction of other types of fracture).

Novel therapies

As discussed above, the current treatment strategies for osteoporosis have been reasonably successful, but are not without their limitations. As a result, the pharmaceutical industry is actively researching novel agents to treat osteoporosis.

Osteoclasts can degrade bone tissue through complex processes of mineral dissolution and enzymatic degradation. Receptor activator of NF-κB, ligand (RANKL), is a cytokine that modulates bone resorption through the osteoclastic receptor NF-I, (RANK). It has been hypothesised that skeletal cells are sources and targets of RANKL. Osteoprotegerin, a ligand that binds to RANKL, may have a role in treating or preventing osteoporosis.[16] with studies showing a positive effect in postmenopausal women.[11]

There is, however, a possibility that antibodies can develop against osteoprotegerin, thus limiting its use as a therapeutic agent. To overcome this problem, denosumab, a human monoclonal antibody that can bind to RANKL, was developed. To date, denosumab has had promising results in clinical trials, showing a significant improvement in BMD,[17] as well as being more effective than the current market leader, alendronate.[18] In one phase III clinical trial, women with osteopenia taking no other osteoporosis treatment were randomised to receive placebo or denosumab 60mg.[18] The primary endpoint was the change in BMD at the lumbar spine after 24 months. After 24 months, BMD (lumbar spine) increased by 6.5 per cent for the denosumab group, compared with 0.6 per cent for the placebo group. A three-year denosumab trial reduced rates of hip, vertebral and non-vertebral fractures.[19]

Future therapies that involve the inhibition of cathepsin K (an enzyme expressed in osteoclasts and involved in the degradation of the bone matrix), sclerostin inhibitors and integrin antagonists are all being investigated.[20] These compounds are currently being researched for their application in osteoporosis.

Conclusion

Osteoporosis is set to become a major health concern with an ageing population. Current treatments, although effective, are not without problems and new classes of agents, such as denosumab, will be a welcome addition to the armamentarium of osteoporosis drugs.

References