Patients with osteoporosis may require pharmacological treatment to increase bone mineral density and correct low levels of calcium and vitamin D — thereby lowering their risk of fracture

Osteoporosis management

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The National Institute for Health and Care Excellence has produced two technology appraisals of osteoporosis treatment, one looks at primary prevention and the other considers secondary prevention. However, this guidance is considered by many healthcare professionals to be challenging to implement, particularly with regard to prescribing alternative treatments when alendronate is not tolerated or is contraindicated.

Selecting second- and third-line treatments requires the use of complicated tables that involve bone mineral density (BMD) measurements and independent clinical risk factors (IRFs), such as history of parental hip fracture, alcohol consumption of more than four units a day and rheumatoid arthritis. In addition, there are other indicators of low BMD (low body mass index, ankylosing spondylitis, Crohn’s disease, prolonged immobility and untreated early menopause) that must be present before treatment can be offered.1,2

The NICE guidance makes recommendations for the treatment of post-menopausal women only and does not cover the treatment of corticosteroid-induced osteoporosis or the use of intravenous bisphosphonates. New clinical guidelines are in the process of being developed to address some of these limitations.

Guidance from the National Osteoporosis Guideline Group takes a risk-based approach to treatment and is preferred by many professional and patient groups. These guidelines recommend the calculation of fracture risk using the World Health Organization FRAX algorithm (see accompanying article, p87), with or without BMD measurements, to identify high-risk patients who could benefit from treatment.

Recommendations are made for men and women aged 50 years and older, and include the treatment of corticosteroid-induced osteoporosis. Guidance on primary and secondary prevention of osteoporotic fractures is summarised in Box 1 (p94).

SUMMARY

The aim of osteoporosis management is to reduce the risk of fracture by increasing bone mineral density and correcting deficiencies in calcium and vitamin D. Current guidelines recommend oral bisphosphonates first line for primary and secondary prevention of fractures.

However, undesirable side effects and strict administration requirements associated with these medicines can lead to poor adherence. Second- and third-line options include intravenous bisphosphonates, denosumab, raloxifene and strontium ranelate (with safety restrictions). Teriparatide is recommended only for patients who are at very high risk of fractures.

Neither set of guidance addresses falls risk, which is an important risk factor for fractures.

Bisphosphonates

Bisphosphonates are the most commonly prescribed medicines for the prevention and treatment of osteoporosis. They bind to the surface of bones undergoing active remodelling and block the activity of osteoclasts. Large phase III clinical trials have demonstrated that bisphosphonate therapy significantly reduces vertebral and hip fracture risk.

Oral

The use of oral bisphosphonates is frequently associated with gastrointestinal side effects and there have been reports of serious upper gastrointestinal damage...
Box 1: Primary and secondary prevention of osteoporosis

Primary prevention
The National Institute for Health and Care Excellence recommends that alendronate should be used first line for the primary prevention of osteoporosis for post-menopausal women who have a T-score, measured by dual-energy X-ray absorptiometry (DXA) scanning (see accompanying article, p87), of 2.5 standard deviations or more below the young adult reference mean and meet the following criteria:

- Aged under 64 years with an independent clinical risk factor (IRF) and at least one additional indicator of low bone mineral density (BMD)
- Aged 65–69 years with an IRF
- Aged 70 years or older with an IRF or an indicator of low BMD
- Aged 75 years or older with two or more IRFs or indicators of low BMD (DXA scanning is not required)

Risedronate, etidronate and strontium ranelate are recommended second and third line if patients meet certain criteria involving T-scores and numbers of IRFs and indicators of low BMD. Raloxifene and teriparatide are not recommended for the primary prevention of osteoporosis.

In contrast, the National Osteoporosis Guideline Group guidelines are less prescriptive. Generic bisphosphonates (alendronate and risedronate) are recommended first line for men and women aged 50 years or older who have been deemed suitable for treatment according to the FRAX algorithm. For individuals who are intolerant to generic bisphosphonates or in whom these medicines are contraindicated, alternative bisphosphonates, denosumab, raloxifene and strontium ranelate can be considered as treatment options. Teriparatide is recommended only for patients who are at very high risk of fractures, particularly vertebral fractures. Despite the increase in bone mass demonstrated by use of hormone replacement therapy, the side effects associated with its use make it no longer suitable for the prevention and treatment of osteoporosis.

Secondary prevention
Alendronate is recommended first line by NICE for the secondary prevention of fragility fractures in post-menopausal women who have a confirmed diagnosis of osteoporosis (T-score –2.5). BMD testing is not required for women over the age of 75 years for treatment to be initiated. Second- and third-line treatments (risedronate, etidronate, strontium ranelate and raloxifene) are recommended on the basis of meeting additional criteria. Teriparatide is recommended as an alternative for individuals in whom other treatments are contraindicated, ineffective or poorly tolerated. Specific criteria have been outlined for the subset of patients who can be offered teriparatide. Again, NOGG guidelines recommend using the FRAX algorithm to identify patients who should be offered treatment for secondary prevention. Oral bisphosphonates are recommended first line and alternative treatment options should only be considered if bisphosphonates are unsuitable.

Zoledronic acid should be avoided in patients with an eGFR of less than 35ml/min. Patients should be adequately hydrated before the infusion and have their renal function monitored. Hypocalcaemia can occur with bisphosphonate treatment and is more common with intravenous therapy. Existing hypocalcaemia should be corrected before starting treatment. Furthermore, the risk of osteonecrosis of the jaw (see Box 2, p96) is higher for patients receiving intravenous bisphosphonate therapy. Since zoledronic acid became available as a generic it is now a more cost-effective option.

Drug holidays There have been increasing concerns about the safety of the long-term use of bisphosphonates (Box 2, p96) and questions have been raised as to what the optimum length of treatment should be. It is recommended that a treatment review should be performed after at least five years’ treatment with oral bisphosphonates and after three years of zoledronic acid treatment.

Long-term use of bisphosphonates can provide a residual anti-resorptive effect after treatment is stopped. There is a lack of safety data on the use of oral bisphosphonates for patients with renal impairment; therefore, alendronate and risedronate are not recommended for patients with an estimated glomerular filtration rate (eGFR) of less than 35ml/min and 30ml/min, respectively. Gastrointestinal side effects and strict administration requirements are common reasons for non-adherence to bisphosphonate therapy. Thorough counselling should be provided to patients who are being started on these medicines and regular monitoring to assess adherence is advised.

Intravenous
Poor adherence to oral bisphosphonate therapy has led to an increase in the use of intravenous bisphosphonates. Zoledronic acid is the most potent bisphosphonate available and is administered as an intravenous infusion once a year. Data obtained from the HORIZON study found that, over three years, zoledronic acid reduced vertebral fractures by 70%, hip fractures by 41% and non-vertebral fractures by 25%.

Take bisphosphonates on an empty stomach at least 30 minutes before breakfast (or other oral medicines)
Swallow tablets whole with plenty of water while sitting or standing
Sit upright or stand for at least 30 minutes after taking a dose

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Long-acting G-CSF for quick ANC recovery

Secondary end-point of a Phase III breast cancer study. Mean time to ANC recovery in Cycle 1 was 5.9 days (SD ±3.4 days) in 94 patients treated with 6mg lipegfilgrastim approximately 24 hours after receiving myelosuppressive chemotherapy. ANC recovery was defined as the first day with ANC ≥2.0 x 10^9/L after any day with ANC <2.0 x 10^9/L. Time to ANC recovery was calculated as day of ANC recovery minus day of CTX (Day 1). If no ANC values ≥2.0 x 10^9/L were measured for a patient, the time to ANC recovery was set to 0.

G-CSF, granulocyte-colony stimulating factor; ANC, absolute neutrophil count.

Please refer to the Summary of Product Characteristics (SmPC) for full prescribing information

Lonquex® (lipegfilgrastim) 6mg solution for injection

Presentation: Lipegfilgrastim 6mg solution for injection in 0.6ml pre-filled syringe.

Indications: Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Dosage and administration: Lonquex treatment should be initiated and supervised by physicians experienced in oncology or haematology. One 6mg dose of lipegfilgrastim for each chemotherapy cycle should be subcutaneously administered, approximately 24 hours after cytotoxic chemotherapy, in the abdomen, upper arm or thigh. Elderly: No relevant age-related difference with regards to safety or efficacy. Impaired renal/hepatic function: The pharmacokinetic profile is not expected to be affected. However, no recommendation on dosing can be made. Children/Paediatrics: No data available. Containments: Hypersensitivity to the active substance or to any of the excipients.

Contraindications: Not to be used in patients with sickle cell anaemia since sickle cell crisis has been associated with the use of G-CSF in these types of patients. Hypokalaemia may occur. It may not be safe in pregnant women or whilst breastfeeding. No data available with regards to fertility.

References:
1. Lonquex (lipegfilgrastim) Summary of Product Characteristics

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hip or vertebral fracture, or who are taking long-term oral corticosteroids (equivalent to 7.5mg or more of prednisolone daily)

- Patients who sustain one or more low trauma fractures during treatment (in whom poor adherence to treatment and causes of secondary osteoporosis have been excluded); in such cases treatment choice should be re-evaluated

- Patients whose total hip or femoral neck BMD T-scores are more severe than −2.5

If treatment is discontinued, fracture risk should be reassessed after two years if no new fracture occurs, or after any new fracture, regardless of when this occurs.

**Denosumab**

Denosumab is licensed for the prevention and treatment of osteoporosis. It is a human monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand (RANKL), an important regulator of osteoclast development and activity (see accompanying article, p97).

**Box 2: Complications of therapy**

**Atypical femoral fracture**

There is an increased risk of atypical femoral fracture (AFF) occurring with bisphosphonate use, mainly in patients receiving long-term treatment. Patients who develop prodromal pain of the thigh, groin or hip during treatment with these medicines must be advised to report the symptoms immediately. Patients who develop AFFs should have their bisphosphonate treatment discontinued and alternative treatment options should be considered. There have been case reports of AFF occurring in patients taking denosumab, but it remains to be determined if this has been caused by denosumab treatment or other factors.

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw occurs rarely in patients receiving bisphosphonate or denosumab therapy for osteoporosis. Good oral hygiene should be maintained during treatment and routine dental check-ups should be advised. Bisphosphonate or denosumab therapy should not be regarded as a contraindication to necessary dental treatment.

Clinical trials have shown that treatment with denosumab increases BMD and decreases fragility fractures in patients with osteoporosis. However, there have been no head-to-head trials comparing the efficacy of denosumab in the reduction of fractures with that of other available treatments.

NICE recommends denosumab for the secondary prevention of osteoporotic fragility fractures in post-menopausal women who have an intolerance or contraindication to oral bisphosphonates, or who are unable to comply with the administration instructions. Additional criteria are required for denosumab to be used for primary prevention; it is not recommended in patients with a T-score more severe than −1.8.

Denosumab is administered by subcutaneous injection every six months and can be done so in primary care. Calcium and vitamin D deficiency must be corrected before treatment begins (see p97). Patients who are at high risk of hypocalcaemia (eg, those with renal impairment or who are on dialysis) should have their calcium levels monitored during treatment. However, there is no dose adjustment of denosumab needed for patients with renal impairment. Denosumab is more expensive than bisphosphonate treatment, but substantially cheaper than teriparatide.

**Raloxifene**

Raloxifene is a selective oestrogen receptor modulator. It mimics the effect of oestrogen on the skeletal system without causing the adverse effects that are commonly associated with oestrogen use, but is contraindicated in patients with a history of venous thromboembolism.

Selective oestrogen receptor modulators decrease the accelerated rate of bone remodelling that is associated with oestrogen deficiency in post-menopausal women, thereby increasing bone mass. Although raloxifene has been shown to reduce vertebral fractures, research has not demonstrated any efficacy in the prevention of hip or other non-vertebral fractures.

**Teriparatide**

Teriparatide is a human recombinant parathyroid hormone that can increase osteoblast activity — stimulating bone formation — when given in intermittent doses of 20µg daily. Serum calcium, parathyroid hormone and 25-hydroxy-vitamin D levels must be checked before treatment (hypercalcemia and hyperparathyroidism are among the contraindications to teriparatide therapy).

Teriparatide has been shown to reduce vertebral and non-vertebral fractures in post-menopausal women. There is no evidence to suggest it can reduce hip fractures specifically. Teriparatide is expensive and only recommended for secondary prevention of fractures for patients with severe osteoporosis in whom other treatment options are unsuitable or have failed.

**Strontium ranelate**

The mechanism of action of strontium ranelate is not fully understood. It is believed to reduce bone resorption and maintain bone formation. Although there is sufficient evidence to support the effectiveness of strontium ranelate, particularly in vertebral fracture prevention, post-marketing surveillance has raised concerns about its
cardiovascular safety. This has been investigated by the European Medicines Agency and final recommendations, which were based on the analysis of pooled data from randomised studies involving 7,500 post-menopausal women, were released in February 2014. The use of strontium ranelate has now been restricted to the following groups:

- Individuals in whom other treatments are contraindicated, ineffective or cannot be tolerated
- Post-menopausal woman with severe osteoporosis

Further EMA recommendations regarding the use of strontium ranelate are:

- The drug must not be used for patients with an established, current or past medical history of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or uncontrolled hypertension
- Treatment should only be started by a clinician who has experience in the treatment of osteoporosis
- Cardiovascular risk should be monitored every six to 12 months
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or uncontrolled hypertension
- All patients who are currently prescribed strontium ranelate should be reviewed as necessary

Supplementation
Adequate calcium and vitamin D intake is important for maintaining skeletal health and this has been supported by several observational studies and randomised trial data. 

For individuals who are deficient, calcium and vitamin D supplementation alongside osteoporosis treatment is recommended.

Low levels of vitamin D impair the intestinal absorption of calcium. This causes a compensatory rise in parathyroid hormone leading to excessive bone resorption.

The inactive form of vitamin D is synthesised when skin is exposed to sunlight and so a lack of sunshine can lead to vitamin D deficiency; populations at risk include elderly and housebound patients, and those who avoid sun exposure for cultural or religious reasons. Vitamin D deficiency can also result from inadequate dietary intake, malabsorption of vitamin D and genetic abnormalities in vitamin D metabolism.

Calcium and vitamin D supplementation is a safe and inexpensive way to reduce fracture risk for people being treated with bisphosphonates or denosumab and who have established vitamin D deficiency or are at a particularly high risk. Vitamin D levels are usually assessed by measuring serum concentrations of 25-hydroxy-vitamin D, the most abundant form of the hormone in the blood. Vitamin D status is categorised according to 25-hydroxy-vitamin D levels (see Box 3).

National Osteoporosis Society guidelines recommend a loading regimen of approximately 300,000iu of vitamin D (colecalciferol) divided over six to 10 weeks, followed by maintenance therapy of 800–2,000iu daily for patients who require rapid correction of levels. Where the correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive medicine, maintenance therapy may be started without the use of loading doses.

Falls prevention
Falls risk is an independent risk factor for fractures. Medication reviews can be carried out to identify medicines that can cause postural hypotension, hyponatraemia or drowsiness and have the potential to increase a person’s risk of having a fall. This is particularly important for secondary prevention of osteoporotic fractures.

Looking ahead
Romosozumab is a human monoclonal antibody that targets and inhibits sclerostin, a protein secreted by bone cells, leading to bone formation. In phase II studies,
Osteoporosis

Lifelong Learning questions are available to complete in an online module on the Clinical Pharmacist section of PJ Online — accessible via www.clinicalpharmacist.com.

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Questions

This month’s Lifelong Learning questions are based on the CLINICAL FOCUS articles on osteoporosis, which were commissioned from independent authors. The information in the Box (below) is there to help you identify knowledge gaps and undertake continuing professional development. This online module will close on 17 July 2014.

Answers

When you have completed the online module, your answers will be submitted for marking and Clinical Pharmacist will send you a certificate and your results by email within two weeks of the module closing.

How to undertake continuing professional development

Test your knowledge by completing the questions at www.clinicalpharmacist.com

Reflect on your gaps in knowledge

What is osteoporosis and what are fragility fractures?

What are the risk factors for developing osteoporosis and who is most likely to be affected by it?

How is fracture risk assessed?

What are the pharmacological options for treating osteoporosis?

Act to enhance your practice

Read the CLINICAL FOCUS articles in this issue (pp87–98)

References


