Treatment of osteoporosis: whom, how and for how long?

ABSTRACT

Identification of patients at risk for fragility fractures is the first important step in the management of osteoporosis. Bisphosphonates have been the mainstay of treatment for decades, whereas denosumab and selective oestrogen receptor modulators are other available licensed antiresorptive drugs. Currently teriparatide is the only approved anabolic agent in Europe, while abaloparatide and romosozumab are awaiting approval and might be available in the near future.

For bisphosphonates, current guidance suggests an initial treatment course of 3–5 years and more prolonged treatment should be pursued in patients with higher fracture risk. For patients with lower risk, a period off treatment might be considered after this initial course to minimize the risks associated with more prolonged treatment, but this only applies to bisphosphonates and not denosumab or teriparatide.

This review discusses strategies for case finding of patients at risk, currently available treatment options, recent developments in pharmacological management and duration of treatment.

New agents for the treatment of osteoporosis have been developed recently, and there has also been debate about the optimal duration of treatment to minimize the risks associated with prolonged use of antiresorptive agents. This article discusses the current management of osteoporosis.

Definition and demographics

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to increased bone fragility and susceptibility to fractures. The burden of osteoporosis increases with advancing age and it is estimated that, worldwide, one in three women and one in five men above the age of 50 years will experience an osteoporotic fracture (International Osteoporosis Foundation, 2017). The personal and financial consequences of osteoporosis are huge and, in the UK, the annual estimated financial cost of fractures is around £4.4 billion (Svedbom et al, 2013). Hip fractures carry the highest burden, as they cause severe disability and high mortality, especially during the first year post-fracture.

Whom?

The identification of patients at risk of fragility fractures is of paramount importance for the management of osteoporosis.

Epidemiological studies show that there are several clinical factors that influence fracture risk (*Table 1*). These factors have been incorporated in calculation tools such as the Fracture Risk Assessment Tool (FRAX) and QFracture. The tools provide an estimate of an individual's 10-year probability of fracture and are a suitable first screening tool. The National Institute for Health and Care Excellence (2017) suggests that screening with FRAX or QFracture should be offered to specific age groups depending on the presence of risk factors (*Table 2*).

Table 1. Risk factors for fractures

Previous fragility fracture
Current use or frequent recent use of oral or systemic glucocorticoids
History of falls
Family history of hip fracture
Causes of secondary osteoporosis
Low body mass index (less than 18.5 kg/m^2)
Smoking
Alcohol intake >14 units per week for women and >21 units per week for men

The National Osteoporosis Guideline Group has set thresholds for treatment based on the fracture risk probability as measured by FRAX (Compston et al, 2017). These allow for a decision about treatment to be made without requirement for objective measurement of bone density in many cases. Where the fracture risk probability is in the region of the intervention threshold, rather than significantly above or below the threshold, the National Institute for Health and Care Excellence (2017) suggests measuring bone density.

There are several non-invasive methods to estimate bone mineral density and microarchitecture, and to calculate bone strength parameters (International Society for Clinical Densitometry, 2015). Dual energy X-ray absorptiometry is a technique in which calculation of soft tissue and bone absorption of two X-ray beams of different energy levels allows estimation of bone mineral density. It is widely used and results correlate well with fracture risk. However, it

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Table 2. Indications for fracture risk assessment with Fracture Risk Assessment Tool (FRAX) or QFracture

Age groups	When to screen
Women ≥65 years Men ≥75 years	Consider screening for everyone
Women 50–64 years Men 50–74 years	In the presence of at least one risk factor (*Table 1*)
Women <50 years Men <50 years	Only in the presence of major clinical risk factors such as current or frequent use of glucocorticoids, untreated premature menopause or previous fragility fracture

From National Institute for Health and Care Excellence (2017)

Table 3. Classification according to bone mineral density, as measured by dual energy X-ray absorptiometry, according to the World Health Organization and the International Society for Clinical Densitometry

Menopausal women and men >50 years		Pre-menopausal women and men <50 years	
T-score		**Z-score**	
> - 1	Normal	> -2	Within the expected range for age
-1 to -2.4	Osteopenia	≤ -2	Below the expected range for age
≤ -2.5	Osteoporosis		

For pre-menopausal women, men <50 years old and especially in children, osteoporosis should not be diagnosed only on the basis of a low bone mineral density (International Society for Clinical Densitometry, 2015)

is affected by several artefacts including prior fractures and degenerative spinal disease. Quantitative computed tomography provides a better measure of true volumetric bone density but assessment of spinal and hip bone density involves high dose radiation. High resolution quantitative computed tomography provides more detailed assessment of bone microarchitecture, structure and strength but is expensive and not widely available.

Absolute measurement of bone density by dual energy X-ray absorptiometry scanning varies with different machines and so results are expressed in relation to standard reference ranges. The T-score expresses the number of standard deviations of the result from the mean bone density of a population of healthy 20–30-year-old women (International Society for Clinical Densitometry, 2015). The Z-score expresses the number of standard deviations of the result from the mean bone density of a matched population. The World Health Organization defines osteopenia as a T-score between -1.0 and -2.5 and osteoporosis as a T-score of -2.5 or below (*Table 3*). The definition is most appropriately applied to postmenopausal women and to men >50 years of age. Z-scores are used for pre-menopausal women and men <50 years of age with a Z-score of -2.0 or below reflecting a bone density below the expected range for age (International Society for Clinical Densitometry, 2015).

Bone mineral density is inversely correlated with fracture risk and the lower the T-score the higher the risk. The bone mineral density scan result can be incorporated into the FRAX tool to provide a more accurate estimate of fracture risk and allow an informed decision to be made about treatment based on this risk, according to National Osteoporosis Guideline Group recommended thresholds.

Secondary prevention: fracture liaison services

A previous history of a fragility fracture is associated with a higher risk of subsequent fractures. A high percentage of patients admitted with hip fractures have a history of a previous fracture. Port et al (2003) showed that fewer than 20% of women and 10% of men in such cohorts were on treatment for osteoporosis at the time of admission, despite their history of a fragility fracture. Therefore, assessment of patients who have sustained a fragility fracture was suggested as a unique window of opportunity for identification of patients who would benefit from intervention.

This stimulated the development of fracture liaison services. Fracture liaison services are designed to systemically identify all men and women aged ≥50 years who present with a fragility fracture and to provide necessary assessments and treatment or recommendations for treatment depending on the fracture liaison service model. Women presenting with a fragility fracture may be considered for treatment without further assessment, particularly if aged over 75 years. Men should be assessed using fracture risk assessment tools as described above. Financial analyses have demonstrated that fracture liaison services in the UK are cost-effective for secondary prevention of osteoporosis fractures (McLellan et al, 2011). The National Osteoporosis Society (2015) has set specific standards for fracture liaison services.

How?

Anti-osteoporotic medications act mainly by suppressing bone turnover (antiresorptives), while there is limited availability of anabolic agents. Bisphosphonates have been the mainstay of treatment of osteoporosis for several years. They reduce bone resorption soon after treatment initiation and result in an increase in bone mineral density and reduction in fracture risk. Available agents include alendronate, risedronate, zoledronic acid and ibandronate.

Alendronate efficacy was assessed in the Fracture Intervention Trial (FIT), a randomized controlled trial in women with either a history of vertebral fracture or a femoral neck T-score of less than -2.5 (Black et al, 2000). Alendronate use was associated with a 53%, 48% and 30% reduction in hip, vertebral and all clinical fractures respectively compared to placebo.

Administration of risedronate in postmenopausal women with a history of vertebral fractures for 3 years resulted in a 41–49% and 33–39% reduction in the risk of new vertebral and non-vertebral fractures respectively

compared to placebo (Harris et al, 1999; Reginster et al, 2000). The reduction was already significant by 6 months of treatment (Reginster et al, 2000).

In the HORIZON-PFT study, administration of zoledronic acid 5 mg once a year in postmenopausal women for 3 years resulted in a 70%, 41% and 25% reduction in the risk of morphometric vertebral, hip and non-vertebral fractures respectively compared to placebo (Black et al, 2007). In a secondary prevention randomized controlled study, the HORIZON-RFT, zoledronic acid at a dose of 5 mg yearly was administered in women and men after sustaining a hip fracture. This resulted in a 35% reduction in the risk of any new clinical fracture and a 28% reduction in all-cause mortality (Lyles et al, 2007).

Ibandronate use for 3 years in postmenopausal women with a history of vertebral fractures was associated with a 50–62% reduction in the risk of new vertebral fractures compared to placebo. However, there was no significant effect on the risk of non-vertebral fractures (Chesnut et al, 2004).

Adverse events from the use of bisphosphonates include gastrointestinal toxicity with the use of oral agents and an acute phase reaction with the use of intravenous agents, most commonly after the first infusion (Papapoulos, 2011). Intravenous bisphosphonates, in particular, may negatively impact renal function and therefore adequate hydration before administration is important and they should not be used in patients with creatinine clearance <35 ml/min. Initial concerns about an association between bisphosphonates and atrial fibrillation were not confirmed by subsequent studies (Papapoulos, 2011). Osteonecrosis of the jaw and atypical femoral fractures, although rare, are also of concern, especially where higher drug doses are given to manage bony metastases.

Denosumab is a monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL). It strongly suppresses bone resorption, resulting in increases in bone mineral density and reduction in the risk of fractures. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial, administration of denosumab in postmenopausal women with osteoporosis for 3 years resulted in a 68%, 40% and 20% reduction in the risk of vertebral, hip and non-vertebral fractures respectively compared with placebo (Cummings et al, 2009). This was accompanied by increases in bone mineral density and suppression of bone turnover markers. Continuation data from the use of denosumab up to 10 years have demonstrated progressive persistent increases in bone mineral density and sustained reduction of fractures with an acceptable safety profile (Bone et al, 2017). Eczema and severe cellulitis have been reported as adverse events in the clinical trials. Hypocalcaemia has occurred following denosumab injection, most commonly where the creatinine clearance is <30 ml/min. Risks of osteonecrosis of the jaw and atypical femoral fractures are similar to those seen for bisphosphonate use.

“Adverse events from the use of bisphosphonates include gastrointestinal toxicity with the use of oral agents and an acute phase reaction with the use of intravenous agents.”

Raloxifene is a selective oestrogen receptor modulator that reduces bone turnover and is associated with small increases in bone mineral density. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene at a dose of 60 mg daily was administered in postmenopausal women with osteoporosis for 3 years and resulted in a 30% reduction in the risk of new vertebral fractures without having any effect on the risk of non-vertebral fractures (Ettinger et al, 1999). Raloxifene can exacerbate symptoms of postmenopausal hot flushes and has been associated with a higher risk of venous thromboembolism. There is, however, some reduction in risk of breast cancer.

Hormone replacement therapy has proven efficacy in reducing the risk of vertebral, non-vertebral and hip fractures in unselected postmenopausal women, but because of the high risk–benefit ratio in older women, it is advised that its use is restricted to young postmenopausal women who are at high risk of fractures only when they also suffer from menopausal symptoms (Compston et al, 2017).

Teriparatide is currently the only approved anabolic agent for the treatment of osteoporosis in Europe. Teriparatide consists of the first 1-34 aminoterminal aminoacids of the parathyroid hormone molecule and binds to the parathyroid hormone receptor 1 in the surface of osteoblasts and osteocytes (Dede et al, 2017). Intermittent administration of parathyroid hormone and its analogues exerts anabolic effects on bones, in contrast to the continuous exposure to parathyroid hormone as observed in primary hyperparathyroidism, which is associated with bone loss. In a phase 3, randomized controlled study, daily administration of teriparatide in postmenopausal women resulted in 65% and 53% reduction in the risk of vertebral and non-vertebral fractures respectively compared with placebo (Neer et al, 2001). Adverse events included occasional nausea, headache and mild hypercalcaemia as well as injection site reactions. Its high cost has restricted its use although this may change if biosimilar agents are developed following the expiry of teriparatide’s patent.

There has been significant controversy about the effects of calcium and vitamin D supplements on fracture risk. Several meta-analyses have demonstrated beneficial effects (Avenell et al, 2014; Weaver et al, 2016) although these are largely restricted to institutionalized individuals. It should be noted that all the interventional studies discussed above included administration of calcium and vitamin D supplements both in the intervention and the placebo groups, and so it is advised that patients on antiresorptive agents should also receive adequate amounts of calcium and vitamin D.

> Teriparatide is only recommended for secondary prevention in postmenopausal women, 65 years or older, who meet specific thresholds of T-score and clinical risk factors.

National Institute for Health and Care Excellence guidance

According to the National Institute for Health and Care Excellence (2018), oral bisphosphonates are cost effective as treatment options for osteoporosis in adults who are eligible for fracture risk assessment and where the 10-year probability of osteoporotic fragility fracture is at least 1%, as calculated either by FRAX or QFracture. Intravenous bisphosphonates are cost effective in the same scenario as above when oral bisphosphonates are contraindicated or not tolerated and alternatively, if the 10-year probability of osteoporotic fragility fracture is at least 10%.

Denosumab is recommended for primary prevention of fracture in postmenopausal women who are at increased risk of fractures, when oral bisphosphonates are contraindicated or not tolerated and who meet a threshold of a combination of age, low T-score and clinical risk factors. For secondary prevention, denosumab is recommended in postmenopausal women at increased risk of fracture when oral bisphosphonates are contraindicated or not tolerated.

Raloxifene is not indicated for primary prevention but is recommended for secondary prevention in women who are not able to receive oral bisphosphonates and meet a threshold of a combination of age, low T-score and clinical risk factors.

Finally, teriparatide is only recommended for secondary prevention in postmenopausal women, 65 years or older, who meet specific thresholds of T-score and clinical risk factors, when oral bisphosphonates are contraindicated or not tolerated or when response to treatment with alendronate or risedronate has been unsatisfactory.

Recent and future developments in pharmacological interventions

Abaloparatide, a parathyroid hormone-related peptide analogue, is a new anabolic agent that was recently approved by the Food and Drug Administration for the treatment of postmenopausal osteoporosis. In the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) trial, administration of abaloparatide for 18 months was compared to placebo and to teriparatide (Miller et al, 2016). Abaloparatide resulted in 86% and 43% reduction in risk of vertebral and non-vertebral fractures respectively compared with placebo. In this study, the effects of abaloparatide and teriparatide were similar in terms of vertebral fracture risk reduction but teriparatide did not reduce the risk of non-vertebral fractures and was associated with higher rates of hypercalcaemia. The application for approval of abaloparatide has recently been rejected by the European Medicines Agency and the developing company plans to appeal.

Romosozumab is a monoclonal antibody targeting sclerostin (an inhibitor of the Wnt signaling pathway which is important for normal bone formation) and was recently under consideration for approval from the Food and Drug Administration. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), administration of romosozumab for 12 months resulted in a 73% reduction in the risk of new vertebral fractures compared with placebo, without evidence of reduction in the risk of non-vertebral fractures (Cosman et al, 2016). In an active comparator study investigating romosozumab *vs* alendronate for 12 months, followed by alendronate for another 12 months, administration of romosozumab resulted in a reduction of new vertebral, clinical and non-vertebral fractures compared to alendronate although the romosozumab group had a higher rate of cardiovascular serious adverse events (Saag et al, 2017). Even though this was not observed in any of the other romosozumab studies, the Food and Drug Administration has requested more data on this issue. Romosozumab is currently awaiting approval by the European Medicines Agency.

Odanacatib is an inhibitor of cathepsin K, an enzyme involved in bone resorption. In the Long-Term Odanacatib Fracture Trial (LOFT) and its extension, administration of odanacatib resulted in a reduction in vertebral, hip and non-vertebral fractures compared with placebo (McClung et al, 2016). However, odanacatib was associated with a higher risk of stroke and the developing company therefore opted to discontinue development of the drug.

Strontium ranelate was recommended by National Institute for Health and Care Excellence for secondary prevention of osteoporosis in postmenopausal women who were unable to receive alendronate or risedronate, depending on their clinical risk factors and T-score. However, it has recently been withdrawn by the marketing company and is no longer available because of concerns about the risk of thromboembolism and cardiovascular events.

Several other agents are currently in earlier stages of development, but none are likely to be approved in the near future (Dede et al, 2017).

For how long?

Adverse events resulting from the use of antiresorptive agents, including osteonecrosis of the jaw and atypical femoral fractures, have received great attention in recent years. These side effects are very uncommon in patients treated for osteoporosis and occur predominantly in cancer patients treated with higher doses of the drugs. In the context of treatment for osteoporosis, incidence rates of osteonecrosis of the jaw are estimated at 0.001–0.01% (Khan et al, 2015), and of atypical femoral fractures range from 3.2 to 50 cases per 100 000 person-years (Shane et al, 2014).

There is evidence that the risk of serious side effects increases with more prolonged use of these agents. Thus, there have been discussions about the optimal duration of treatment, in order to minimize the risk of adverse events without overly compromising benefits from treatment. This is particularly relevant with bisphosphonates which bind strongly to the skeleton with a long terminal tissue half-life and may be identified in blood long after discontinuation (Papapoulos, 2011). These agents exert a prolonged protective effect even after treatment discontinuation (Papapoulos, 2011; Eriksen et al, 2014), implying that a period off treatment ('drug holiday') would be reasonable. Data relating to effects of continuing *vs* withdrawing medication stem from extension studies of the major interventional studies in postmenopausal osteoporosis. Continuation of treatment with zoledronic acid for more than 3 years and with alendronate for more than 5 years resulted only in lower risk of morphometric vertebral fractures and for clinical vertebral fractures respectively with no benefit seen for risk of hip fractures (Eriksen et al, 2014).

Based on these studies, the National Osteoporosis Guideline Group suggests an initial treatment course with bisphosphonates of 3–5 years (3 for zoledronic acid and 5 for alendronate, ibandronate and risedronate). After this period patients should have treatment reviewed and fracture risk re-assessed. More prolonged treatment of osteoporosis should be considered in specific situations (*Table 4*) (Compston et al, 2017). For those patients for whom discontinuation of treatment is advised, the National Osteoporosis Guideline Group suggests re-evaluating fracture risk after 18 months to 3 years, or when the patient sustains a new fracture. At that stage, resumption of treatment should be considered if bone mineral density has decreased during the off-treatment period and/or if biochemical markers of bone turnover suggest that bone turnover is no longer suppressed.

It should be noted that this guidance applies only to bisphosphonates and should not be applied to treatment with other antiresorptive agents such as denosumab. There are data relating to use of denosumab for up to 10 years that are reassuring in terms of risk:benefit ratio. However, there is a paucity of longer term data and, for some patients who achieve high bone mineral density and reduced fracture risk with denosumab, stopping treatment might be appropriate even before 10 years. Discontinuation of denosumab, however, is associated with a rapid increase in bone turnover markers and decrease of bone mineral density with reports of multiple vertebral fractures (Tsourdi et al, 2017). It has therefore been suggested that when discontinuation of denosumab is considered, patients are switched to an alternative antiresorptive, such as a bisphosphonate, to dampen the rebound increase in bone resorption. Unfortunately, case reports to date have shown that a single zoledronic acid infusion is not effective in managing the rebound fracture risk (Reid et al, 2017). It is possible that switching to an oral bisphosphonate or administering the zoledronate acid infusion when bone turnover markers start to rise might be more effective strategies but the optimal plan after discontinuing denosumab remains to be determined.

Table 4. National Osteoporosis Guideline Group criteria for continuation of treatment with bisphosphonates beyond 3–5 years

Age ≥75 years
Previous history of hip or vertebral fracture
Occurrence of one or more low trauma fractures during treatment (after excluding poor adherence to treatment and/or causes of secondary osteoporosis)
Current treatment with oral glucocorticoids ≥7.5 mg prednisolone/day or equivalent
Hip bone mineral density T-score at 3–5 years ≤–2.5
Fracture Risk Assessment Tool (FRAX) (with bone mineral density) derived fracture risk at 3–5 years above the National Osteoporosis Guideline Group intervention thresholds

From Compston et al (2017)

The duration of treatment with anabolic agents is predetermined and cumulative use of parathyroid hormone analogues for more than 24 months in an individual's lifetime is not recommended. It is recommended that patients who complete a treatment course with teriparatide or abaloparatide are switched to an antiresorptive agent to maintain the benefits of the anabolic drug.

Conclusions

Identification of patients at risk of fragility fractures is the first important step in the management of osteoporosis. This may be achieved in large part by use of fracture risk assessment tools, with use of bone density scanning being required to direct treatment decisions for a minority of individuals. Bisphosphonates remain the mainstay of treatment although denosumab, raloxifene and teriparatide represent appropriate alternative treatment options for some individuals. Courses of treatment followed by drug holidays are recommended in order to reduce risks of long-term treatment with antiresorptive agents. New agents are under development and may become available in the near future. **BJHM**

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Bone HG, Wagman RB, Brandi ML et al. 10 years of denosumab

KEY POINTS

- Case finding of patients at risk for fractures is extremely important and screening is recommended for those who have known clinical risk factors.
- Online calculation tools such as the Fracture Risk Assessment Tool (FRAX) and QFracture are designed to provide an estimate of a patient's 10-year fracture risk probability.
- Fracture liaison services aim to identify all men and women aged ≥50 years who present with a fragility fracture.
- Currently available treatment options include bisphosphonates, denosumab, teriparatide and selective oestrogen receptor modulators.
- For bisphosphonates, an initial treatment course of 3–5 years is advised and then patients need to be re-assessed, while more prolonged treatment should be considered for those at higher risk.

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