Drug therapy for osteoporosis in older adults

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Lancet 2022; 399: 1080–92

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The goal of osteoporosis management is to prevent fractures. Several pharmacological agents are available to lower fracture risk, either by reducing bone resorption or by stimulating bone formation. Bisphosphonates are the most widely used anti-resorptives, reducing bone turnover markers to low premenopausal concentrations and reducing fracture rates (vertebral by 50–70%, non-vertebral by 20–30%, and hip by ~40%). Bisphosphonates bind avidly to bone mineral and have an offset of effect measured in months to years. Long term, continuous use of oral bisphosphonates is usually interspersed with drug holidays of 1–2 years, to minimise the risk of atypical femoral fractures. Denosumab is a monoclonal antibody against RANKL that potently inhibits osteoclast development and activity. Denosumab is administered by subcutaneous injection every 6 months. Anti-fracture effects of denosumab are similar to those of the bisphosphonates, but there is a pronounced loss of anti-resorptive effect from 7 months after the last injection, which can result in clusters of rebound vertebral fractures. Two classes of anabolic drugs are now available to stimulate bone formation. Teriparatide and abaloparatide both target the parathyroid hormone-1 receptor, and are given by daily subcutaneous injection for up to 2 years. Romosozumab is an anti-sclerostin monoclonal antibody that stimulates bone formation and inhibits resorption. Romosozumab is given as monthly subcutaneous injections for 1 year. Head-to-head studies suggest that anabolic agents have greater anti-fracture efficacy and produce larger increases in bone density than anti-resorptive drugs. The effects of anabolic agents are transient, so transition to anti-resorptive drugs is required. The optimal strategy for cycling anabolics, anti-resorptives, and off-treatment periods remains to be determined.

Introduction

Osteoporosis is conventionally defined as a systemic skeletal disease involving bone tissue, leading to bone fragility and susceptibility to fracture.[1] Although this description of the osteoporotic process is apt, regarding osteoporosis as a disease is often unhelpful, since it implies specific diagnostic criteria, and that diagnosis will be closely linked to a decision to treat. Specific diagnostic criteria have been proposed (in terms of bone mineral density [BMD] or fracture history), but the use of such criteria can be counterproductive, since it sometimes results in withholding of treatment from individuals with high absolute fracture risk who do not meet the criteria. BMD and fracture history are but two of many risk factors for fracture, with age, ethnicity, and bodyweight being just as important. Therefore, it is better to regard bone loss as a process present in almost all individuals older than 50–60 years, to discard the concept of diagnosing osteoporosis, and to base treatment decisions on estimations of fracture risk. This approach is justified by the demonstration that anti-resorptive therapies prevent fractures across a wide range of bone densities.[2]

Search strategy and selection criteria

We searched Embase, MEDLINE, Scopus, and the Cochrane Library for English-language articles published between Jan 1, 2018, and Oct 12, 2021, using the search terms "osteoporosis", "fractures", "therapy", "treatment", "management", "abaloparatide", "teriparatide", "zoledron", "alendron", "risedron", "ibandron", or "denosumab". We focused on studies in humans, in particular randomised controlled trials, systematic reviews, and large observational studies.

In addition to ageing-related bone loss, many illnesses are associated with increased risk of fractures, via mechanisms such as hypogonadism, chronic inflammation causing high levels of osteoclast stimulating cytokines, weight loss with reduced amounts of anabolic hormones, and increased frequency of falls. Glucocorticoids cause bone loss predominantly via reduced bone formation, resulting from apoptosis of osteoblasts and osteocytes. This pathogenic diversity suggests that anti-resorptive or anabolic (ie, formation stimulating) therapies should be deployed, depending on the cause of bone loss, but this hypothesis has not yet been comprehensively tested in clinical trials. Reduced bone resorption and increased bone formation each produce a positive bone balance and are broadly effective across a range of osteoporosis types.

Non-drug therapies for osteoporosis

Although not the focus of this Therapeutics paper, non-medication approaches to fracture prevention are important, as reviewed elsewhere.[3] Lifestyle advice to correct specific risk factors (eg, cessation of smoking, moderation of alcohol intake, maintaining body-mass index above 20, and minimisation of glucocorticoid dose where appropriate) is important. Falls are a frequent cause of fractures, so patients with a history of falls should be assessed for underlying causes and provided with advice accordingly.[4] Modifications to the home environment, optimisation of vision, exercise programmes (impact plus high-intensity resistance, together with balance training),[5] minimisation of sedative use, and prevention of postural hypotension might each be important. Protein supplements might be of value in patients who are malnourished,[6] and vitamin D deficiency should be prevented with regular safe sunlight exposure, or with supplements (400–1000 IU/day). Higher doses of vitamin D have not been shown to be beneficial, and can accelerate bone loss[7] and increase the risk of falls and fractures.[8–10] Significant non-skeletal benefits from vitamin D use have not been confirmed in trials.[11–13] Calcium intakes of greater than 500 mg/day are generally recommended, although lower intakes are common throughout much of the world without evidence of increased fracture rates.[14] Calcium intake is unrelated to bone loss in women older than 65 years.[15] Additionally, calcium supplements in community-dwelling adults do not prevent fractures[16,17] and are associated with gastrointestinal side-effects, renal calculi, and, possibly, cardiovascular adverse effects.[18] Therefore, the diet is the preferred source of calcium.

Anti-resorptive therapies

Bisphosphonates

Bisphosphonates have been the most widely used treatments for osteoporosis for more than two decades. Available agents are shown in the table and their mode of action is shown in figure 1.

	Dose	Registered indications	Administration considerations	Adverse effects	Treatment duration and follow-up
Anti-resorptive agents					
Bisphosphonates					
Alendronate	70 mg/week orally (10 mg/day); or 35 mg/week orally (5 mg/day)	70 mg/week: treatment of postmenopausal, male, and glucocorticoid osteoporosis; 35 mg/week: prevention of postmenopausal osteoporosis	Take fasting with a glass of water while sitting or standing; remain upright and fasting for 30 min; safety when eGFR <30–35 mL/min not established; contraindicated in active upper gastrointestinal disease	Upper gastrointestinal symptoms in 20–30% of patients; risk of AFF increases with duration of therapy; <2·5 cases per 10 000 patient-years for treatment duration <5 years; incidence of ONJ <0·01%	Suggested treatment duration of ~5 years followed by a drug holiday of 1–2 years
Risedronate	5 mg/day; 35 mg/week; 75 mg twice per month; 150 mg/month; all orally	Treatment or prevention of postmenopausal osteoporosis; treatment of male and glucocorticoid osteoporosis	Take fasting with a glass of water while sitting or standing; remain upright and fasting for 30 min; safety when eGFR <30–35 mL/min not established; contraindicated in active upper gastrointestinal disease	Upper gastrointestinal symptoms in 20–30% of patients; too few reports of AFF and ONJ to estimate incidence	Suggested treatment duration of ~5 years followed by a drug holiday of 0·5–1 years
Ibandronate	150 mg/month orally; or 3 mg/month intravenously	150 mg/month orally: treatment or prevention of postmenopausal osteoporosis; 3 mg/month intravenously: treatment of postmenopausal osteoporosis	150 mg/month orally: take fasting with a glass of water while sitting or standing, but remain upright and fasting for 60 min, requires eGFR >30 mL/min, and is contraindicated in active upper gastrointestinal disease; 3 mg/month intravenously: inject in 15–30 s. Requires eGFR >30 mL/min. Ensure vitamin D-replete before infusion	150 mg/month orally: upper gastrointestinal symptoms in 20–30% of patients, and too few reports of AFF and ONJ to estimate incidence; 3 mg/month intravenously: self-limited acute phase response (flu-like illness) in 30–40% of patients after first dose, too few reports of AFF and ONJ to estimate incidence	Suggested treatment duration of ~5 years followed by a drug holiday of 1–2 years
Zoledronate or zoledronic acid	5 mg/year intravenously; or 5 mg every 2 years intravenously	5 mg/year: treatment of postmenopausal, male, and glucocorticoid osteoporosis, and fracture prevention after hip fracture; 5 mg every 2 years: prevention of postmenopausal osteoporosis	Intravenous infusion in 100 mL in at least 15 min, requires eGFR >30–35 mL/min, ensure vitamin D-replete before infusion	Self-limited acute phase response ("flu-like illness") in 30–40% of patients after first dose; too few reports of AFF and ONJ to estimate incidence	With annual dosing, treat for 3–6 years followed by drug holiday of 3–5 years; alternative is to dose every 1·5 years initially, increasing the interval to 2–3 years over time
Selective oestrogen receptor modulator					
Raloxifene	60 mg/day orally	Prevention and treatment of postmenopausal osteoporosis	NA	Venous thromboembolism risk increased up to 3x, but reduced risk of breast cancer	Bone benefit probably does not outlast treatment duration
Mixed steroid receptor agonist					
Tibolone	2·5 mg/day orally	Prevention of postmenopausal osteoporosis in patients for whom other treatments are contraindicated (UK)	NA	Doubles stroke risk, conflicting evidence of its effects on breast cancer	Bone benefit probably does not outlast treatment duration
Monoclonal antibody against RANKL					
Denosumab	60 mg every 6 months subcutaneously	Treatment of postmenopausal, male, and glucocorticoid osteoporosis, and patients at high fracture risk	Ensure vitamin D-replete before initiation; have a plan for discontinuation before initiation	Risk of hypocalcaemia, especially in renal dysfunction; risk of rebound vertebral fractures; do not delay dose by >1 month; too few reports of AFF to estimate incidence; probably similar to bisphosphonates	Treatment up to 10 years appears safe and effective; drug holidays are not appropriate; follow with another anti-resorptive agent or romosozumab

(Table continues on next page)

	Dose	Registered indications	Administration considerations	Adverse effects	Treatment duration and follow-up
(Continued from previous page)					
Anabolic agents					
Parathyroid hormone analogue					
Teriparatide	20 μg/day subcutaneously for 18–24 months	Treatment of postmenopausal, male, and glucocorticoid osteoporosis, and patients at high fracture risk	NA	Mild hypercalcemia in 6–11%, might require dose adjustment; FDA recommends considering >2 years of cumulative use during a patient's lifetime only if fracture risk remains high	Usually treat for up to 2 years and follow with anti-resorptive agent
PTHrP analogue					
Abaloparatide	80 μg/day subcutaneously for 18–24 months	Treatment of postmenopausal osteoporosis in patients at high fracture risk	Inject into the periumbilical region; administer initial doses where the patient can lie down if orthostatic hypotension occurs	Nausea, dizziness, and headache in up to 10% of patients; palpitations in 5%; mild hypercalcaemia in 3%; FDA recommends that cumulative use during a patient's lifetime is not >2 years	Treat for up to 2 years and follow with anti-resorptive agent
Monoclonal antibody against sclerostin					
Romosozumab*	210 mg/month subcutaneously for 12 months	Treatment of postmenopausal osteoporosis in patients at high fracture risk or those who have failed or are intolerant to other available osteoporosis therapy	Dose provided as two 105 mg syringes; should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year	Possible increased risk of serious cardiovascular events compared with alendronate treatment; cases of AFF and ONJ reported in pivotal registration trial; real-world incidence unknown	Treat for 12 months and follow with anti-resorptive agent

eGFR=estimated glomerular filtration rate. AFF=atypical femur fracture. ONJ=osteonecrosis of the jaw. FDA=US Food and Drug Administration. PTHrP=parathyroid hormone-related peptide. *Has both anabolic and antiresorptive effects.

Table: **Principal medications for management of osteoporosis by class**

Efficacy

Bisphosphonates produce progressive increases in BMD, which plateau after 3–4 years from treatment onset (figure 2A).[19–21] The magnitude of these increases varies between agents and tends to be greater at sites rich in trabecular bone, such as the spine, where baseline turnover is higher. Despite the variability in BMD responses among the potent amino-bisphosphonates, amino-bisphosphonates have similar efficacies with regard to preventing vertebral fracture (reducing risk of such fractures by 50–70%). Alendronate, risedronate, and zoledronate have been shown to reduce hip fractures by about 40% and all non-vertebral fractures by 20–30% (figure 3).[22] The effects of osteoporosis medications on BMD in men are similar to those in women, although fracture studies are absent for most treatments, other than zoledronate.[23]

Rates of offset of anti-resorptive effects vary between agents, reflecting their different affinities for bone mineral. Bone turnover rises over a few months after ceasing ibandronate and after about 6 months from cessation of risedronate, whereas alendronate effects persist for 1–2 years, and effects of zoledronate last for more than 5 years. Sustained fracture prevention was seen in a zoledronate trial lasting 6 years,[24] and some studies suggest that anti-fracture efficacy persists for 3–5 years after alendronate and zoledronate discontinuation.[19,25]

Safety

Oral bisphosphonates produce upper gastrointestinal symptoms in 20–30% of patients, so patients are advised to remain upright for at least 30 min after dosing to minimise the risk of gastro-oesophageal reflux. These drugs are contraindicated in individuals with active upper gastrointestinal disease. The use of intravenous zoledronate or ibandronate avoids these problems, but an acute phase response (flu-like illness) occurs in about a third of patients receiving their first intravenous bisphosphonate treatment. This response can include fever, musculoskeletal pain, and malaise, which are usually mild and pass within 2–3 days. Symptoms are greatly improved with the use of paracetamol or ibuprofen. Sometimes symptoms are more widespread, and are rated as severe in 2–3% of treated patients. The acute phase response might include eye inflammation, typically uveitis, occurring in 1% of bisphosphonate-naive patients[26] and rapidly responsive to topical corticosteroids. The acute phase response is less severe in individuals who have previously received oral bisphosphonates, and it decreases in severity with increasing age. Symptoms are substantially less frequent and less severe following second infusions and are seldom observed thereafter.

Potent anti-resorptive agents can cause hypocalcaemia in patients with severe vitamin D deficiency (ie, 25-hydroxyvitamin D <25 nmol/L), so appropriate repletion before treatment is important. Bisphosphonates are restricted to individuals with an estimated glomerular filtration rate (eGFR) of more than 30–35 mL/min, although oral agents are sometimes administered to patients with eGFRs of 30 mL/min or below without apparent problems.[27,28] Osteonecrosis of the jaw and atypical femoral fractures are adverse events associated with both bisphosphonates and denosumab, and are discussed later.

Denosumab

Denosumab is a monoclonal antibody directed at the protein RANKL (TNFSF11), an osteocyte-derived regulator of osteoclast development. Denosumab is administered by subcutaneous injection and reduces bone resorption markers to undetectable levels within days. Bone formation markers decline by more than 60% over the following few months. Bone biopsies provide evidence for profound inhibition of both bone formation and resorption, with a median bone formation rate of zero after 2–3 years of use.[29] In marked contrast to bisphosphonates, treatment effects have a rapid offset following discontinuation of denosumab. Bone resorption markers rise rapidly in the 7–9 months after the last injection, peaking at greater than 150% of pre-treatment concentrations after 1 year. BMD returns to baseline in the 18 months after the last injection.[30]

Efficacy

BMD responses to denosumab follow a pattern similar to the bisphosphonates, although the increases are larger and continue through to 10 years (figure 2A). Anti-fracture effects in the 3-year, phase 3 trial were very similar to those of zoledronate—vertebral fractures reduced by 68%, hip fractures reduced by 40%, and non-vertebral fractures reduced by 20%.[31] A 10 year open follow-up of a diminishing number of participants from the denosumab group of this trial suggested that anti-fracture efficacy was maintained.[21]

Safety

Denosumab is well tolerated with no clincially significant post-dose effects. As with the bispho-sphonates, there were no reports of either atypical femoral fractures or osteonecrosis of the jaw in the phase 3 study, although both have occurred during the study extension and in a post-marketing database.[21,32] As with other potent anti-resorptive treatments, it is important to correct severe vitamin D deficiency before treatment, to avoid hypocalcaemia. In contrast to the bisphosphonates, denosumab can be used in patients with an eGFR of less than 30 mL/min, but with an increased risk of hypocalcaemia.[32]

The principal safety concern with denosumab is the occurrence of clusters of vertebral fractures in the 12 months after the drug is discontinued. In the extension to the phase 3 study, 15% of women discontinuing denosumab had a subsequent vertebral fracture, and in two-thirds of these patients, fractures were multiple.[33] The risk of these fractures is greatest in patients with pre-existing vertebral deformities

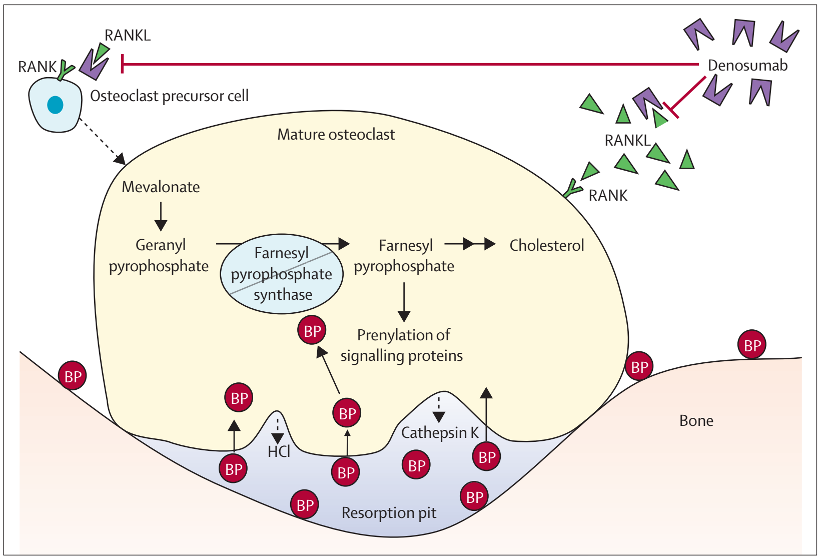

Figure 1: **Mechanisms of action of amino-bisphosphonates and denosumab on osteoclasts**
The health of the adult skeleton is maintained by bone remodelling. This remodelling takes place at tens of thousands of sites across the bone surface , and begins with excavation of resorption pits by osteoclasts followed by their refilling by osteoblasts. Remodelling cycles last about 3–4 months and are triggered by local loading, cytokines, and hormonal factors. The fall in oestrogen concentration after the menopause causes increased osteoclast activity resulting in bone loss, which continues until the end of life. The primary role of increased bone resorption in driving postmenopausal bone loss provides a sound theoretical basis for the use of anti-resorptive agents in managing this condition. Stimulation of RANK by its ligand RANKL causes differentiation of osteoclast precursor cells into mature osteoclasts. Denosumab is a monoclonal antibody that binds RANKL, preventing it from activating RANK. Mature osteoclasts attach to the bone surface where they form resorption pits and release hydrochloric acid and proteases, such as cathepsin K, which degrade bone matrix. The resorption process is dependent upon stimulation of RANK by RANKL. Osteoclast function and integrity is also dependent on the mevalonate pathway, which synthesises cholesterol and facilitates the prenylation of crucial cellular signalling proteins. Bisphosphonates bind tightly to bone mineral, where they remain for years. Bisphosphonates are taken up by osteoclasts during bone resorption. Within the osteoclast, amino-bisphosphonates (eg, alendronate, risedronate, zoledronate) block the mevalonate pathway by inhibiting the enzyme farnesyl pyrophosphate synthase. Blocking the pathway impairs osteoclast resorptive ability and cellular integrity, also triggering apoptosis. Non-nitrogen-containing bisphosphonates (eg, etidronate) have other cellular targets, but these drugs are now rarely used. The specificity of the bisphosphonates for the skeleton arises from their avid uptake onto bone surfaces, the rapid excretion of the balance of the dose unaltered in the urine (minimising exposure of other cells to the bisphosphonate), and the fact that cells other than osteoclasts do not resorb bone. Bisphosphonates are poorly absorbed: only a small proportion of an oral dose enters the circulation, so dosing in a fasting state and taking medication with water alone is crucial to its bioavailability. Bisphosphonates are very stable and are not metabolised in humans. BP=bisphosphonate. HCl=hydrochloric acid.

and increases the longer a patient is on denosumab before stopping.[34,35] There are case reports of up to nine fractures in a single patient, indicating that this problem could result in substantial long-term morbidity. A nationwide cohort study in Taiwan found that the hazard ratios (HRs) for hospital admissions with major osteoporotic fracture were 1·6 (95% CI 1·2–2·1) for patients discontinuing denosumab after 1 year of use compared with those who continued to take denosumab, and 2·6 (1·5–4·6) for patients discontinuing after 2 years; this increased risk was not observed in individuals stopping bisphosphonates.[36]

Transition to another anti-resorptive therapy, particu-larly zoledronate, shows partial prevention of post-denosumab bone loss, although study results are inconsistent.[37–39] Transition to romosozumab, an anti-sclerostin antibody, also appears to prevent this problem,[40] but transition to teriparatide, a parathyroid

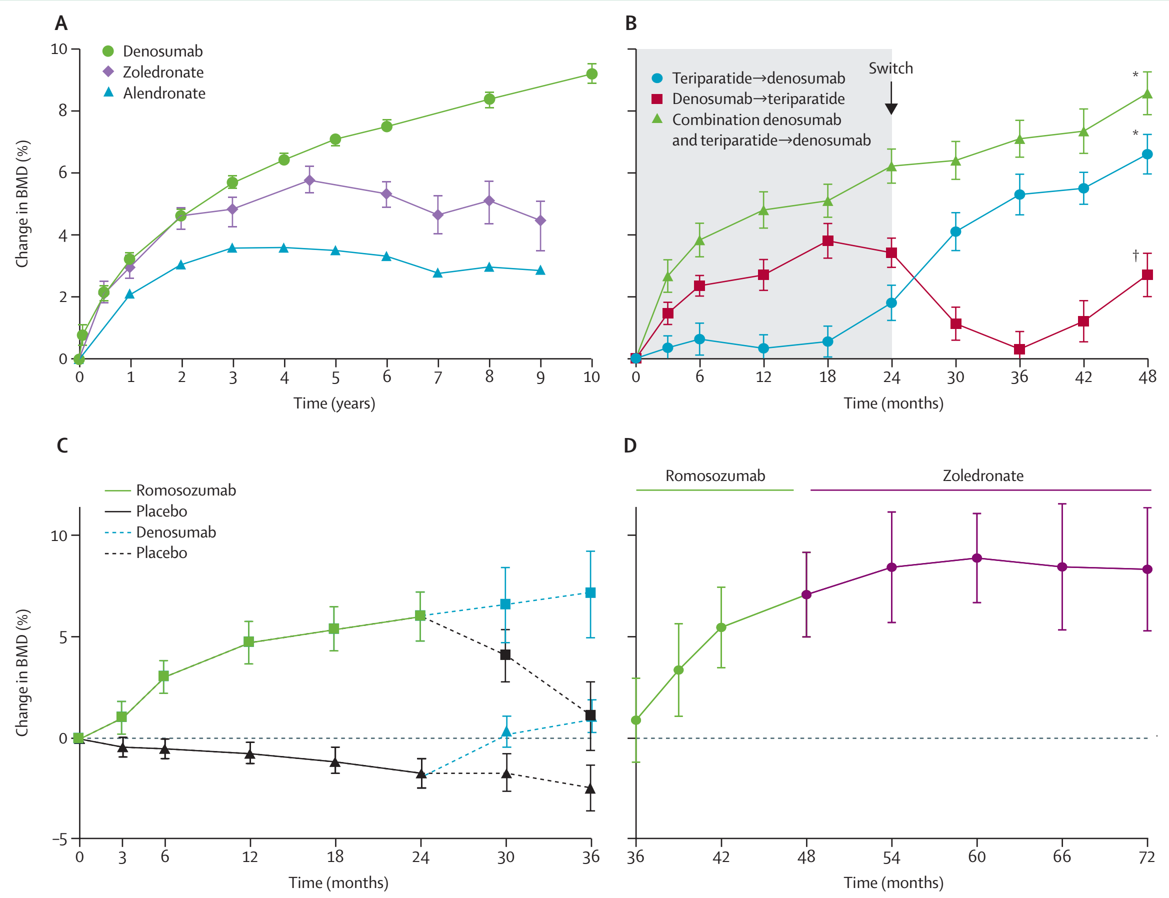

Figure 2: **Effects of osteoporosis treatments on total hip bone mineral density**
(A) Change in total hip BMD in patients assigned to alendronate (5 or 10 mg/day orally) in the FLEX trial,[19] zoledronate (5 mg intravenously annually) in the HORIZON trial,[20] and denosumab (60 mg subcutaneously every 6 months) in the FREEDOM trial.[21] Data are derived from separate studies, so comparisons between changes in BMD have not been made. (B) Change in total hip BMD in responses to the treatment sequences shown, from the DATA-Switch study.[41] Error bars show standard error of the mean. Women with osteoporosis were randomly assigned to teriparatide (20 mg/day), denosumab (60 mg 6-monthly), or both drugs (combination). At 24 months, women originally assigned to teriparatide switched to denosumab, women originally assigned to denosumab switched to teriparatide, and women originally assigned to the combination received denosumab for an additional 24 months. Between-groups differences are significant at all timepoints ($p<0·001$). Reproduced from Leder and colleagues.[41] (C) Change in total hip BMD in patients from the phase 2 romosozumab study.[72] Patients were randomly assigned to romosozumab or placebo for the first 2 years, then re-randomised to denosumab or placebo in year 3. Reproduced from McClung and colleagues.[72] (D) Change in total hip BMD in the romosozumab phase 2 study, showing effects in participants who received romosozumab (210 mg every month) during months 36–48 and then received a single dose of zoledronate (5 mg).[73] Reproduced from McClung and colleagues.[73] For panels A, C, and D, datapoints are mean values and error bars show 95% CIs. For panel B, datapoints are mean values and error bars show SEM. BMD=bone mineral density. *$p<0·05$ versus both other groups. †$p<0·0005$ versus both other groups.

hormone analogue, is associated with marked bone loss in the radius and hip, so teriparatide is contraindicated (figure 2B).[41] Whether these transitions prevent rebound fractures has not yet been adequately assessed, but observational studies suggest that transition to zoledronate does.[34,42] Therefore, it is important to emphasise to patients before they start denosumab that close adherence to the 6-monthly dosing regimen is needed, and a transition plan should be in place before the drug is initiated. Since intolerance of bisphosphonates is one reason for using denosumab, transition to bisphosphonates might not always be a practical solution, and these issues should be considered during primary therapy selection.

Rare anti-resorptive adverse events

Medication-related osteonecrosis of the jaw

Osteonecrosis of the jaw is defined as the presence of exposed bone in the mouth that remains unhealed after 6–8 weeks of appropriate management, in the absence of local radiotherapy.[43] This condition was first observed in patients with disseminated malignancy receiving monthly infusions of bisphosphonates for prevention of skeletal-related events. It occurs with similar frequency in patients with cancer receiving monthly denosumab, suggesting that its cause is related to very low bone turnover rather than to direct bone toxicity from bisphosphonates. The development of osteonecrosis of the jaw is usually triggered by an invasive dental procedure, such as an extraction, and histology shows necrotic bone covered with microbial biofilms. These lesions have been reported in patients with osteoporosis treated with most currently used therapies, with incidences of 0·2–10 per 10 000 patient-years.[21,44] Some large databases suggest incidence is unrelated to osteoporosis drug treatment,[44] but others show increased risk with use of osteoporosis drugs in the last year, high adherence to the regimen, and long-term use of osteoporosis drugs.[45] Clinical trials have not shown an increase in risk of osteonecrosis of the jaw, but the frequency is so low that most trials are not powered to evaluate this increase in risk.

Atypical femoral fractures

This is a predominantly transverse fracture of the subtrochanteric femur, with minimal comminution, and occurring after little or no trauma.[46] Atypical femoral fractures are major fractures that require surgical management. They develop initially as stress fractures of the lateral cortex, which might be painful, then extend medially. These fractures were not reported from the bisphosphonate or denosumab clinical trials, but have occurred in studies of odanacatib and romosozumab, and in the denosumab (but not zoledronate) trial extension. Most reported cases have been associated with alendronate use—whether the risk is similar with other oral bisphosphonates is unknown. Cases are extremely rare, with an incidence in the first year of alendronate use of 0·2 per 10 000 patient-years, but rising to 2·5 per 10 000 patient-years in years 3–5, and to 13 per 10 000 patient-years with more than 8 years of treatment.[47] The risk of an atypical femoral fracture drops by more than half in the first year after stopping an oral bisphosphonate, and by more than 80% at 3 years,[47] suggesting that drug holidays every 5 years are appropriate with long-term oral bisphosphonate treatment. There is little evidence of atypical femoral fracture occurrence in patients who have used only intravenous bisphosphonates,[20,24] although the extent of their use is substantially less than that of oral agents.

Oestrogen receptor agonists

Administration of oestrogen to postmenopausal women increases BMD and reduces fractures. In the Women's Health Initiative, which used conjugated equine oestrogen, hip and spine fractures were each reduced by 34% and total fractures by 24%.[48] The many extra-skeletal effects of oestrogen (eg, breast, endometrial, and colorectal cancers; coronary heart disease; stroke; and thromboembolism) make it difficult to determine the balance of risks and benefits, resulting in a decrease in oestrogen usage in osteoporosis. However, in women with an elevated fracture risk in the decade following the menopause, the balance of benefit versus risk with oestrogen appears to be positive.[49,50]

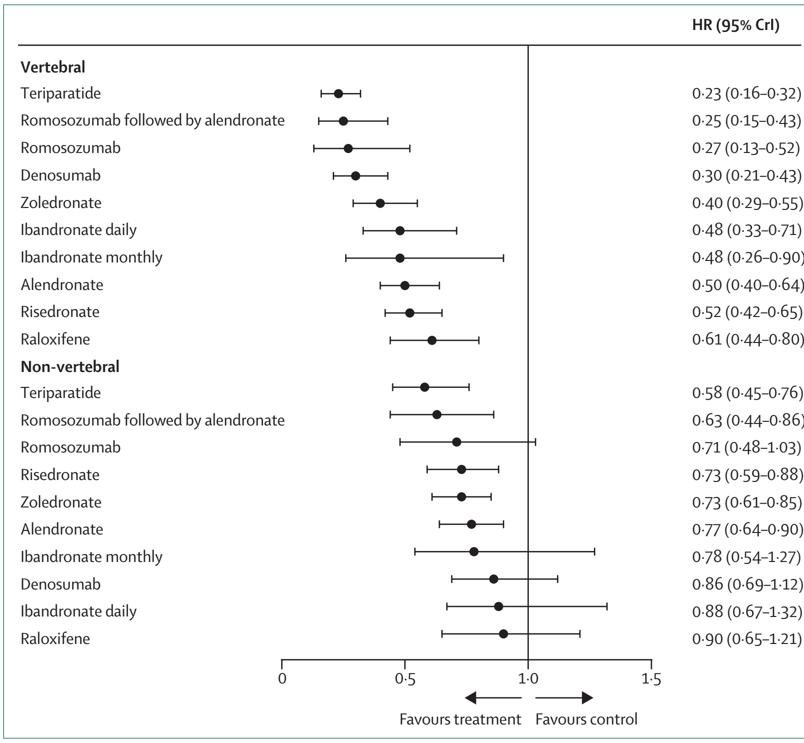

Figure 3: **Forest plot of risk of vertebral and non-vertebral fractures according to osteoporosis treatment**
Data are from a network meta-analysis commissioned by the UK National Institute of Health Research.[22] HR and 95% CrIs for the effects of each treatment relative to placebo are presented. HR=hazard ratio. CrI=credible interval.

Selective oestrogen receptor modulators (eg, raloxifene) bind to the oestrogen receptor, producing mixed agonist–antagonist effects, which vary by tissue. Clinically available agents have weak anti-resorptive effects in bone, reduce the risk of vertebral but not non-vertebral fractures, and reduce breast cancer risk.[51,52] Risk of thromboembolic disease in treatment groups is increased up to three-fold compared with the control groups. Tibolone is a synthetic steroid with weak oestrogenic, progestogenic, and androgenic effects. Tibolone prevents vertebral and non-vertebral fractures;[53] however, there is conflicting evidence of tibolone's effects on breast cancer, and it does increase stroke risk. Tibolone is used in Europe for osteoporosis treatment and management of menopausal symptoms, but not in North America.

Anabolic medications

Although anti-resorptive drugs preserve existing bone, anabolic medications offer the possibility of replacing lost bone, leading to greater effects on BMD and fracture risk. The available agents are either agonists of parathyroid hormone type 1 receptors (teriparatide and abaloparatide), or antibodies to sclerostin (romosozumab; figure 4). Parathyroid hormone receptor activation increases activity of both osteoblasts and osteoclasts. When receptor activation is continuous, as in primary hyperparathyroidism, bone resorption usually predominates, resulting in bone loss.

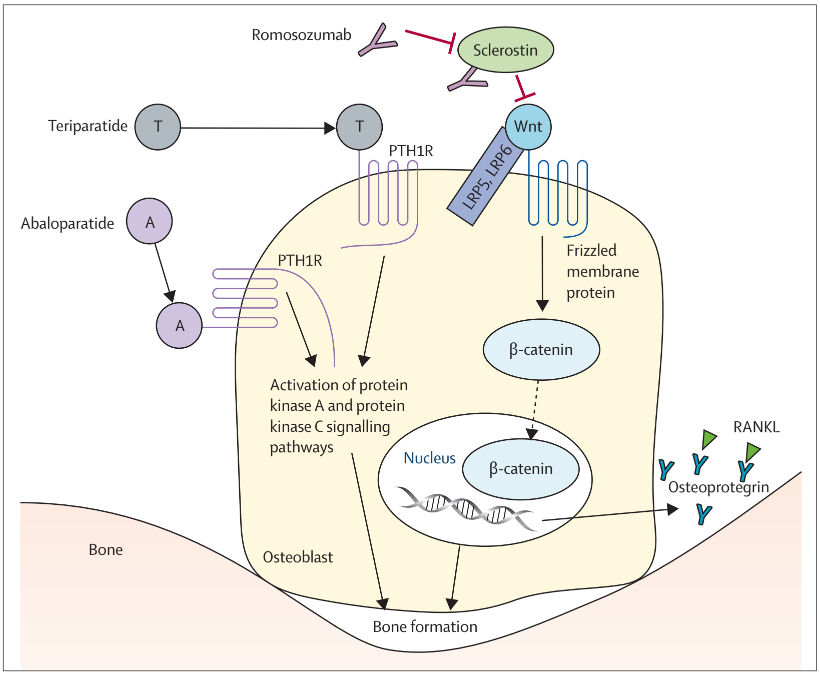

Figure 4: **Mechanisms of action of teriparatide, abaloparatide, and romosozumab on osteoblasts**
Bone formation is regulated by the PTH receptor and the canonical Wnt pathway in osteoblasts. Transient stimulation of PTH1R by PTH or PTHrP results in activation of the cAMP-dependent protein kinase A pathway and the phospholipase C–protein kinase C pathway, leading to transcription of proteins required for bone formation. Wnt stimulation of the LRP5 and LRP6 and frizzled membrane co-receptor complex permits translocation of cytoplasmic β-catenin into the nucleus, resulting in protein transcription and anabolic effects. The Wnt pathway also upregulates transcription of osteoprotegrin, which binds RANKL and has an anti-resorptive effect. The Wnt pathway is inhibited by sclerostin, which is in turn inhibited by PTH. Teriparatide and abaloparatide act by stimulating PTH1R. Romosozumab is a monoclonal antibody against sclerostin. PTH=parathyroid hormone. PTH1R=parathyroid hormone 1 receptor. PTHrP=parathyroid hormone-related protein.

In contrast, administration of parathyroid hormone receptor agonists as daily or less frequent pulses leads to net bone gain, particularly in axial trabecular bone.

Teriparatide

Efficacy

Teriparatide is human parathyroid hormone (1–34). Its BMD effects are greatest in the spine, where linear increases of about 7% occur at 2 years. There is little effect on proximal femoral BMD in the first 12 months of use and it sometimes declines slightly,[54] although at 24 months increases of 2–3% are observed (figure 2B). In the distal radius, there is no positive effect on bone density, and some studies actually show bone loss.[41,55,56] In the phase 3, placebo-controlled trial in women with osteoporosis, vertebral fracture numbers were reduced by two-thirds and non-vertebral fractures were reduced by a third over a median treatment period of 21 months.[55] A subsequent 2-year, active-controlled trial in a similar population compared teriparatide with risedronate, and produced very similar results: the relative risk of vertebral fracture was 0·44 (95% CI 0·29–0·68) and the HR for non-vertebral fracture was 0·70 (0·46–1·05).[57] Neither study found a significant reduction in hip fractures, but a significant reduction has been reported in a meta-analysis of 23 studies with various comparators, which together had only 34 incident hip fractures.[58] In men, BMD effects were similar to those in women over a 1-year study, but anti-fracture efficacy has not been established.[59] In glucocorticoid-induced osteoporosis, teriparatide produces larger BMD increases than alendronate, and substantially reduces vertebral, but not non-vertebral, fracture risk.[60]

There is not much experience with teriparatide in doses other than 20 μg/day. A 40 μg dose was assessed in the phase 3 trial, and although its fracture efficacy was similar to the 20 μg dose, side-effects were more marked. A 40 μg/day dose for 9 months combined with denosumab resulted in larger increases in BMD than 20 μg plus denosumab, but meaningful fracture data are unavailable.[61] Weekly injections of 56·5 μg were assessed in a Japanese study; vertebral fractures were reduced by 80%, but there was no effect on non-vertebral fractures (relative risk 0·98 [95% CI 0·47–2·07]).[62] This weekly regimen prevented vertebral fractures more effectively than alendronate did (rate ratio 0·78 [95% CI 0·61–0·99]), but non-vertebral fractures were unaffected.[63]

Treatment duration with teriparatide is restricted to 24 months in most countries because of concerns regarding osteosarcoma. Therefore, a transition plan should be in place when teriparatide is initiated, since the BMD gains are lost in the 1–2 years after drug cessation.[64] A switch to an anti-resorptive (either a bisphosphonate or denosumab) is the usual practice (figure 2B).

Safety

Nausea and headaches are common with doses greater than 20 μg/day.[55,62] Mild, transient, post-dose hypercalcaemia developed in a small proportion of patients receiving 20 μg/day. Dose adjustment is sometimes required to correct this side-effect. Limb pain has been anecdotally reported as a problem in clinical practice, but was not more common in the treated groups than in the control groups in trials. The principal safety concern with teriparatide is osteosarcoma, which was found to be significantly increased in rats given very high doses of teriparatide over several years. Follow-ups over 15 years have not shown that osteosarcoma is a problem in humans,[65] and the US Food and Drug Administration now permits teriparatide use for more than 2 years in patients at continuing high risk.

Abaloparatide

Abaloparatide is an analogue of human parathyroid hormone-related peptide (1–34) and has a mechanism of action similar to teriparatide. It is available in the USA and Japan, but not in Europe.

Efficacy

An 18-month phase 3 trial randomly assigned 2463 women with postmenopausal osteoporosis to either placebo, abaloparatide 80 μg/day, or open-label teriparatide 20 μg/day.[66] 1901 participants completed the study.

Teriparatide increased bone turnover markers (both formation and resorption) more than abaloparatide, but increases in BMD were greater with abaloparatide than with teriparatide. Both interventions reduced vertebral fractures by 80% or more, compared with placebo. Non-vertebral fracture effects were more modest (abaloparatide HR 0·57 [95% CI 0·32–1·00); teriparatide HR 0·72 [0·42–1·22]).

At 19 months, 92% of women from the abaloparatide and placebo groups completing the core study were switched to treatment with alendronate, and continued for another 2 years.[67] Over the entire 43-month trial period, there was an 84% relative risk reduction for vertebral fractures (p<0·001) and a 39% reduction for non-vertebral fractures (p=0·04) when comparing the abaloparatide–alendronate group with the placebo–alendronate group. BMD showed further small increases following the transition from abaloparatide to alendronate.

Safety

There were more study discontinuations secondary to adverse events in the abaloparatide group (9·9%) than the teriparatide (6·8%) or placebo groups (6·1%). Nausea, dizziness, headache, and palpitations were the principal problems. These adverse events and abaloparatide's marginal effects on non-vertebral fracture contributed to the non-registration of abaloparatide in Europe.[68] Rat studies with abaloparatide have also found an increased risk of osteosarcoma, so the duration of use for abaloparatide is restricted to 2 years.

Anti-sclerostin antibodies

Sclerostin is an osteocyte protein released at the bone surface, where it inhibits Wnt signalling in osteoblasts. Sclerostin blockade both stimulates bone formation and inhibits bone resorption. The inhibition of bone resorption is achieved via effects on osteoprotegerin levels. Romosozumab, a humanised monoclonal anti-sclerostin antibody, is available for osteoporosis treatment.

Efficacy

Romosozumab 210 mg/month doubles bone formation markers and reduces resorption markers by 30% in the first month of use.[69] From month 3, these markers return close to baseline, but substantial increases in BMD are ongoing, exceeding those seen with either alendronate or teriparatide at both the spine and hip. Similar BMD effects are seen in men treated for 1 year.[70] Smaller BMD gains occur in year 2 of treatment, but are substantially reversed when the drug is discontinued, unless it is replaced with an anti-resorptive, such as denosumab[71,72] or zoledronate (figure 2C, 2D).[73] A second course of romosozumab after 1 year on denosumab maintains but does not increase hip BMD, suggesting that repeated cycles of this drug will not increase efficacy.[71] Bone histomorphometry provides evidence for a substantial anabolic effect together with a substantial reduction in osteoclast numbers, particularly in trabecular bone.[74]

There have been two phase 3 trials of romosozumab in postmenopausal osteoporosis. In FRAME, 7180 participants were randomly assigned to placebo or romosozumab for 1 year, then both groups received denosumab alone for a further year.[75] At 1 year, romosozumab reduced the risk of new vertebral fractures by 73% (p<0·001) and non-vertebral fractures by 25% (p=0·1), with similar results at 24 months. A study extension provided a further 1 year of denosumab to both groups. Analysis over the 3-year period showed initial randomisation to romosozumab was associated with a 66% reduction in vertebral fractures (p<0·001) and a 21% reduction in non-vertebral fractures (p=0·04).[76]

The ARCH study randomly assigned 4093 women to monthly romosozumab or weekly alendronate (70 mg) for 12 months, followed by open-label alendronate alone in both groups. In the primary analysis, at a median time of 2·7 years, new vertebral fractures were reduced by 48% (p<0·001), non-vertebral fractures by 19% (p=0·04), and hip fractures by 38% (p=0·02) in the romosozumab–alendronate group compared with individuals receiving alendronate throughout.[77] The reduction in clinical and non-vertebral fractures remained at 48 months.

Safety

Romosozumab is well tolerated; in FRAME, there was one atypical femoral fracture and two cases of osteonecrosis of the jaw in the romosozumab group. In ARCH, there were six atypical femoral fractures and two cases of osteonecrosis of the jaw, all occurring after month 12. During year 1 in ARCH, serious cardiovascular adverse events (such as cardiac ischaemia, heart failure, and cerebrovascular events) were more common with romosozumab than with alendronate (2·5% *vs* 1·9%), an imbalance not seen in the much larger FRAME study. The reason for this difference between the studies is debated, with some inferring a cardioprotective effect of alendronate in ARCH, although a cardioprotective effect has not been clearly established in the many other trials of that drug. Animal studies of romosozumab have not found adverse cardiovascular effects,[78] but sclerostin might inhibit vascular calcification.[79] In some jurisdictions, romosozumab carries a warning regarding cardiac safety.

Drug combinations

Combination therapy can involve giving two drugs in sequence or giving two medicines simultaneously. Sequential treatment has been assessed in the romosozumab ARCH trial, which showed superior fracture prevention with romosozumab followed by alendronate, compared with alendronate monotherapy. Sequential therapy is the rule when using anabolic agents, since they are not approved for long-term administration and their effects are transient, so should be followed by an anti-resorptive. Cyclic use of anabolics with denosumab has not been shown to increase BMD gains.[71,80]

Although trials have focused on giving anabolic agents first, the more common clinical situation is a patient already treated with an anti-resorptive who then gets a fracture, creating the desire to transition to a more potent intervention, such as an anabolic. In an open-label trial, women already on alendronate for more than 18 months were randomly assigned either to receive teriparatide in addition to the bisphosphonate, or to switch from alendronate to teriparatide. More positive changes in BMD resulted from teriparatide addition rather than substitution.[56] Another study by the same group showed that a second course of teriparatide produced a further boost in spine, but not hip, BMD.[81] Transitioning from alendronate to romosozumab has more positive effects on spine BMD and avoids the marked loss of hip cortical bone seen with transition to teriparatide.[54]

Some of the largest increases in BMD in any osteoporosis trials have resulted from combining teriparatide with an anti-resorptive—either zoledronate or denosumab (figure 2B). The zoledronate–teriparatide combination produced rapid increases in BMD and prevented the transient decrease in femoral neck seen with teriparatide monotherapy.[82] Clinical fractures (reported as adverse events) were less frequent with combination therapy than with zoledronate alone ($p=0·04$). Denosumab plus teriparatide increases spine and hip BMD gains compared with either agent alone (figure 2B).[41] These gains can be maintained for more than 2 years with a single infusion of zoledronate.[39] A meta-analysis of studies that compared parathyroid hormone analogues with combinations of an analogue plus an anti-resorptive found a fracture risk reduction of about a third with combination therapy compared with monotherapy.[83] Combination therapy is, of course, more costly and might cause more side-effects.

Who to treat

Fracture risk in older people varies substantially, as do the costs of osteoporosis medications, which can range from a few dollars annually for generic bisphosphonates up to tens of thousands of dollars for injectable anabolic therapies. This variety in cost suggests that treatment recommendations should be guided by cost-effectiveness rather than single risk factors such as a specific bone density or fracture history. Costs also vary between countries and will continue to change as new generics and biosimilars (eg, teriparatide and denosumab) become available. Intervention thresholds of a 10-year hip fracture risk of 3% or a major osteoporotic fracture risk of 15–20% are widely used, but these thresholds were based on annual treatment costs of US$600.[84] With generic drugs costing less than 10% of this amount, thresholds as low as a 1% 10-year hip fracture risk might now be economically justifiable, if clinically appropriate. Expensive drugs can only be justified at much higher fracture risks.

Unfortunately, fracture risk prediction remains an imprecise science, and screening strategies based on fracture risk prediction have produced disappointing results.[85] In three studies, screening resulted in intervention in only 6–18% of participants with no resulting change in total fracture numbers, although osteoporotic fractures were slightly reduced (HR 0·95, 95% CI 0·89–1·00). The criteria for treatment were probably too restrictive in these studies; when targeting treatment to patients with either a femoral neck T-score of less than –2·5 (WHO definition of osteoporosis) or with a 10-year osteoporotic fracture risk of greater than 20%, less than 30% of patients who subsequently sustain a fracture during more than 5 years of follow-up are detected.[86] Broader treatment criteria suggested by the US National Osteoporosis Foundation (any of the following: T-score <–2·5, hip fracture risk >3%, osteoporotic fracture risk >20%, history of hip or spine fracture) have a 71% sensitivity for subsequent fracture in women aged 70–79 years, and still achieve a number needed to treat of 19.[86] Six large clinical trials of anti-resorptive therapies have shown substantial decreases in fracture numbers in women not identified as being at high fracture risk.[2,24] This finding suggests that broader use of generic bisphosphonates in women selected by age or fracture risk could result in a cost-effective reduction in total fracture numbers.

Selection of treatment

In most patients, the first-line treatment is a bisphosphonate, due to their efficacy, safety, and affordability. An oral agent is often preferred since there is no need to provide infusion facilities, but many patients prefer zoledronate due to its infrequency of dosing and absence of gastrointestinal side-effects. A flu-like illness after the first dose is the downside of parenteral bisphosphonates, and adequate renal function is a prerequisite for their use. Denosumab can be used as first-line therapy, but is more expensive and requires strict adherence to the 6-month dosing interval to prevent a rebound increase in bone resorption. For this reason, denosumab cannot be stopped without transition to another agent. Denosumab can be used in patients with marked renal impairment, but hypocalcaemia is more common in this context. Comparisons among trials of different drugs show that agents producing greater increases in BMD result in better fracture prevention.[87] This finding is not necessarily relevant in the subset of drugs shown to prevent non-vertebral fractures; agents with the greatest effects on BMD are not necessarily superior to the other agents in this group (figure 3).

The VERO and ARCH studies suggest that anabolic agents have superior anti-fracture efficacy to oral bisphosphonates, so might be preferred in patients with a high fracture risk. However, direct comparisons of anabolics with the most potent anti-resorptives (zoledronate and denosumab) are not available. Although anabolics are much more expensive than anti-resorptives, anabolics can still be cost-effective in patients at high risk,[88] and biosimilars are reducing prices in some countries. Teriparatide has minimal effects on proximal femoral BMD in the first year of treatment, so its use as a monotherapy might not be ideal in patients at high risk of femoral neck or other cortical fractures. Co-administration of zoledronate or denosumab overcomes this problem. Romosozumab robustly increases spine and hip BMD, and these gains are sustained for at least 2 years by a single infusion of zoledronate,[73] suggesting that this sequence might become an attractive alternative to the ARCH regimen in high-risk patients.

Long-term management

Osteoporosis is not a self-limiting condition unless there is a specific reversible cause, such as the use of glucocorticoids. Therefore, lifelong management is required, which might include periods off treatment. The occurrence of atypical femoral fractures with continuous use of alendronate has given rise to drug holidays with this drug, which is a period off the drug that appears to rapidly reduce atypical femoral fracture risk.[47,89] Typically these holidays are taken after about 5 years of treatment and have a duration of 1–2 years. BMD is well maintained for 2 years after stopping alendronate,[90] but holidays of more than 2 years have been associated with increased fracture risk in some,[91] but not all,[92] studies. During drug holidays of 3–5 years, fracture risk is increased in patients with a hip T-score of less than –2·5,[93,94] or a recent fracture.[94] After 5 years' use, alendronate's effects can be maintained with half the standard dose (ie, 70 mg every 2 weeks),[19] but the effect of this dose reduction on atypical femoral fracture risk is unknown. Although evidence on this risk with other oral bisphosphonates is sparse, holidays are also recommended. Risedronate has a more rapid offset of anti-resorptive effect, so shorter holidays (6–12 months) might be more appropriate.

Zoledronate was administered annually in the phase 3 trials, although dosing every 18 months has similar anti-fracture efficacy over 6 years.[24] The phase 3 trial extension suggested there was little benefit in continuing annual dosing for more than 6 years, and that a 3-year holiday could then be taken.[20] In recognition of the long duration of action of zoledronate, it now seems more logical to dose at 18–24 months initially and extend the dose interval to 3 years subsequently, modified according to BMD responses.[95]

It is common to re-assess BMD after 2–6 years of treatment, to check that appropriate responses have occurred. This assessment is most important for oral medications, for which suboptimal compliance and variable drug absorption can affect efficacy. Change in total hip BMD at follow-up is associated with ongoing fracture risk.[96] Falling BMD during treatment raises the possibility of an underlying condition contributing to ongoing bone loss, and suggests the need for appropriate investigations. In patients receiving oral agents, non-compliance and inadequate absorption of medication are the most common reasons for suboptimal BMD effects, and these problems should be detectable after 2–3 months of treatment using bone turnover markers.[97] When anti-resorptive drugs do not suppress markers below the premenopausal mean value, improved dosing practices or a change to parenteral medication is required. Bone loss in the presence of adequate suppression of turnover suggests that the addition or substitution of an anabolic drug should be considered.

A fracture during treatment does not necessarily mean that the treatment did not work. Current

Panel: The future

The past 30 years have witnessed a sustained push to develop novel therapies for osteoporosis. We now have potent interventions to both reduce bone resorption and increase bone formation. The pace of development has slowed substantially, with no major novel compounds currently in advanced clinical trials. As a result, the research agenda now needs to move to optimal use of the available agents for individuals at risk of fracture, as follows.

- Comparative studies between types of fracture liaison services are needed to determine how these services can work more effectively to identify patients with recent fractures, to ensure these patients are offered appropriate pharmaceutical interventions and rehabilitation, and to optimise adherence to these interventions
- Large, fracture-endpoint, randomised controlled trials in patients at high fracture risk are needed to compare the efficacy of different treatment sequences (eg, an anabolic–anti-resorptive sequence or vice-versa), cycles of such sequences, and combined (ie, anti-resorptive plus anabolic) treatment.
- Trials have found that anti-resorptives prevent fractures in women at moderate fracture risk; this work needs to be repeated to support the safety and cost-effectiveness of this approach, in comparison with models of screening and more selective treatment
- Very large, long-term observational studies are necessary to clarify the safety of existing agents, particularly beyond 10 years of treatment, assessing the long-term risk of atypical femoral fracture with agents other than alendronate, the efficacy of drug holidays in preventing atypical femoral fracture, and the risk of osteosarcoma with parathyroid hormone-related protein analogues

The size of these studies will require multicentre design, and the studies are likely to require public-good funding, since the absence of novel agents has diminished industry activity in osteoporosis research.

treatments are only partly effective with respect to fracture prevention, and the risk factors for fracture are essentially the same on treatment as off,[98,99] with evidence that poor compliance is a further contributor.[100] Measuring bone turnover markers is one way of objectively assessing compliance.[97] Priorities for future research now need to elucidate how we can best use currently available therapies (see panel).

Contributors

The first draft was produced by both authors and then critically revised by both.

Declaration of interests

IRR has received honoraria from Novartis and Sandoz, and research funding from the Health Research Council of New Zealand. EOB has received an honorarium from Eli Lilly, and EOB's institution has received research funding from Amgen. EOB is a member of the Scientific Advisory Council of Osteoporosis Canada.

Acknowledgments

We are grateful to Greg Gamble for help in preparing figure 3.

References

1 Peck WA, Burckhardt P, Christiansen C, et al. Consensus development conference—diagnosis, prophylaxis, and treatment of osteoporosis—rapid publication. *Am J Med* 1993; **94:** 646–50.
2 Reid IR. A broader strategy for osteoporosis interventions. *Nat Rev Endocrinol* 2020; **16:** 333–39.
3 Reid IR. Bone-friendly lifestyle and the role of calcium or vitamin D supplementation. *Climacteric* 2021; **28:** 1–6.
4 Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. *JAMA* 2017; **318:** 1687–99.
5 Cauley JA, Giangregorio L. Physical activity and skeletal health in adults. *Lancet Diabetes Endocrinol* 2020; **8:** 150–62.
6 Rizzoli R, Biver E, Brennan-Speranza TC. Nutritional intake and bone health. *Lancet Diabetes Endocrinol* 2021; **9:** 606–21.
7 Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA* 2019; **322:** 736–45.
8 Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010; **303:** 1815–22.
9 Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: a randomized clinical trial. *J Steroid Biochem Mol Biol* 2017; **173:** 317–22.
10 Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline a randomized clinical trial. *JAMA Intern Med* 2016; **176:** 175–83.
11 Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019; **380:** 33–44.
12 Scragg R, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease: the vitamin D assessment (ViDA) study (a randomized controlled trial). *JAMA Cardiol* 2017; **2:** 608–16.
13 Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA* 2020; **324:** 1855–68.
14 Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int* 2012; **23:** 2239–56.
15 Bristow SM, Horne AM, Gamble GD, Mihov B, Stewart A, Reid IR. Dietary calcium intake and bone loss over 6 years in osteopenic postmenopausal women. *J Clin Endocrinol Metab* 2019; **104:** 3576–84.
16 Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA* 2017; **318:** 2466–82.
17 Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: systematic review. *BMJ* 2015; **351:** h4580.
18 Reid IR, Bolland MJ. Controversies in medicine: the role of calcium and vitamin D supplements in adults. *Med J Aust* 2019; **211:** 468–73.
19 Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; **296:** 2927–38.
20 Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2015; **30:** 934–44.
21 Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017; **5:** 513–23.
22 Davis S, Simpson E, Hamilton J, et al. Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation. *Health Technol Assess* 2020; **24:** 1–314.
23 Kaufman J-M. Management of osteoporosis in older men. *Aging Clin Exp Res* 2021; **33:** 1439–52.
24 Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. *N Engl J Med* 2018; **379:** 2407–16.
25 Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012; **27:** 243–54.
26 Patel DV, Horne A, House M, Reid IR, McGhee CNJ. The incidence of acute anterior uveitis after intravenous zoledronate. *Ophthalmology* 2013; **120:** 773–76.
27 Robinson DE, Ali MS, Pallares N, et al. Safety of oral bisphosphonates in moderate-to-severe chronic kidney disease: a bi-national cohort analysis. *J Bone Miner Res* 2021; **36:** 820–32.
28 Evenepoel P, Cunningham J, Ferrari S, et al. European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4–G5D. *Nephrol Dial Transplant* 2021; **36:** 42–59.
29 Reid IR, Miller PD, Brown JP, et al. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. *J Bone Miner Res* 2010; **25:** 2256–65.
30 Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab* 2011; **96:** 972–80.
31 Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009; **361:** 756–65.
32 Geller M, Wagman RB, Ho PR, et al. Early findings from Prolia post-marketing safety surveillance for atypical femoral fracture, osteonecrosis of the jaw, severe symptomatic hypocalcemia, and anaphylaxis. *Osteoporos Int* 2014; **25** (suppl 2): 56–57.
33 Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res* 2018; **33:** 190–98.
34 Burckhardt P, Faouzi M, Buclin T, Lamy O. Fractures after denosumab discontinuation: a retrospective study of 797 cases. *J Bone Miner Res* 2021; **36:** 171–28.
35 Sosa-Henríquez M, Torregrosa O, Déniz A, et al. Multiple vertebral fractures after suspension of denosumab. A series of 56 cases. *Int J Clin Pract* 2021; **75:** e14550.
36 Fu S-H, Wang C-Y, Hung C-C, et al. Increased fracture risk after discontinuation of anti-osteoporosis medications among hip fracture patients: a population-based cohort study. *J Intern Med* 2021; **290:** 1194–205.
37 Sølling AS, Harsløf T, Langdahl B. Treatment with zoledronate subsequent to denosumab in osteoporosis: a 2-year randomized study. *J Bone Miner Res* 2021; **36:** 1245–54.
38 Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab* 2020; **106:** 264–81.

39 Ramchand SK, David NL, Lee H, Eastell R, Tsai JN, Leder BZ. Efficacy of zoledronic acid in maintaining areal and volumetric bone density after combined denosumab and teriparatide administration: DATA-HD study extension. *J Bone Miner Res* 2021; **36:** 921–30.

40 McClung MR, Bolognese MA, Brown JP, et al. Skeletal responses to romosozumab after 12 months of denosumab. *JBMR Plus* 2021; **5:** e10512.

41 Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet* 2015; **386:** 1147–55.

42 Everts-Graber J, Reichenbach S, Gahl B, Ziswiler HR, Studer U, Lehmann T. Risk factors for vertebral fractures and bone loss after denosumab discontinuation: a real-world observational study. *Bone* 2021; **144:** 115830.

43 Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015; **30:** 3–23.

44 Lin TC, Yang CY, Kao Yang YH, Lin SJ. Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population. *Osteoporos Int* 2014; **25:** 1503–11.

45 Eiken PA, Prieto-Alhambra D, Eastell R, Abrahamsen B. Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users. *Osteoporos Int* 2017; **28:** 2921–28.

46 Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014; **29:** 1–23.

47 Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med* 2020; **383:** 743–53.

48 Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.

49 Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77.

50 Prentice RL, Aragaki AK, Chlebowski RT, et al. Randomized trial evaluation of the benefits and risks of menopausal hormone therapy among women 50–59 years of age. *Am J Epidemiol* 2021; **190:** 365–75.

51 Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; **282:** 637–45.

52 Yavropoulou MP, Makras P, Anastasilakis AD. Bazedoxifene for the treatment of osteoporosis. *Expert Opin Pharmacother* 2019; **20:** 1201–10.

53 Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008; **359:** 697–708.

54 Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* 2017; **390:** 1585–94.

55 Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344:** 1434–41.

56 Cosman F, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab* 2009; **94:** 3772–80.

57 Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018; **391:** 230–40.

58 Díez-Pérez A, Marin F, Eriksen EF, Kendler DL, Krege JH, Delgado-Rodríguez M. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: a systematic review and meta-analysis. *Bone* 2019; **120:** 1–8.

59 Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003; **18:** 9–17.

60 Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 2007; **357:** 2028–39.

61 Tsai JN, Lee H, David NL, Eastell R, Leder BZ. Combination denosumab and high dose teriparatide for postmenopausal osteoporosis (DATA-HD): a randomised, controlled phase 4 trial. *Lancet Diabetes Endocrinol* 2019; **7:** 767–75.

62 Nakamura T, Sugimoto T, Nakano T, et al. Randomized teriparatide [human parathyroid hormone (PTH) 1-34] once-weekly efficacy research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. *J Clin Endocrinol Metab* 2012; **97:** 3097–106.

63 Hagino H, Sugimoto T, Tanaka S, et al. A randomized, controlled trial of once-weekly teriparatide injection versus alendronate in patients at high risk of osteoporotic fracture: primary results of the Japanese Osteoporosis Intervention Trial-05. *Osteoporos Int* 2021; **32:** 2301–11.

64 Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). *J Bone Miner Res* 2009; **24:** 726–36.

65 Gilsenan A, Midkiff K, Harris D, Kellier-Steele N, McSorley D, Andrews EB. Teriparatide did not increase adult osteosarcoma incidence in a 15-year US postmarketing surveillance study. *J Bone Miner Res* 2021; **36:** 244–51.

66 Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide *vs* placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA* 2016; **316:** 722–33.

67 Bone HG, Cosman F, Miller PD, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2018; **103:** 2949–57.

68 Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet* 2019; **393:** 364–76.

69 McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014; **370:** 412–20.

70 Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab* 2018; **103:** 3183–93.

71 Kendler DL, Bone HG, Massari F, et al. Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. *Osteoporos Int* 2019; **30:** 2437–48.

72 McClung MR, Brown JP, Diez-Perez A, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. *J Bone Miner Res* 2018; **33:** 1397–406.

73 McClung MR, Bolognese MA, Brown JP, et al. A single dose of zoledronate preserves bone mineral density for up to 2 years after a second course of romosozumab. *Osteoporos Int* 2020; **31:** 2231–41.

74 Chavassieux P, Chapurlat R, Portero-Muzy N, et al. Bone-forming and antiresorptive effects of romosozumab in postmenopausal women with osteoporosis: bone histomorphometry and microcomputed tomography analysis after 2 and 12 months of treatment. *J Bone Miner Res* 2019; **34:** 1597–608.

75 Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; **375:** 1532–43.

76 Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. *J Bone Miner Res* 2019; **34:** 419–28.

77 Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; **377:** 1417–27.

78 Turk JR, Deaton AM, Yin J, et al. Nonclinical cardiovascular safety evaluation of romosozumab, an inhibitor of sclerostin for the treatment of osteoporosis in postmenopausal women at high risk of fracture. *Regul Toxicol Pharmacol* 2020; **115:** 104697.

79 Claes KJ, Viaene L, Heye S, Meijers B, d'Haese P, Evenepoel P. Sclerostin: another vascular calcification inhibitor? *J Clin Endocrinol Metab* 2013; **98:** 3221–28.
80 Cosman F, McMahon D, Dempster D, Nieves JW. Standard versus cyclic teriparatide and denosumab treatment for osteoporosis: a randomized trial. *J Bone Miner Res* 2020; **35:** 219–25.
81 Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. *J Bone Miner Res* 2009; **24:** 1110–15.
82 Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res* 2011; **26:** 503–11.
83 Lou S, Lv H, Yin P, Li Z, Tang P, Wang Y. Combination therapy with parathyroid hormone analogs and antiresorptive agents for osteoporosis: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int* 2019; **30:** 59–70.
84 Tosteson AN, Melton LJ 3rd, Dawson-Hughes B, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int* 2008; **19:** 437–47.
85 Merlijn T, Swart KMA, van der Horst HE, Netelenbos JC, Elders PJM. Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis. *Osteoporos Int* 2020; **31:** 251–57.
86 Crandall CJ, Schousboe JT, Morin SN, Lix LM, Leslie W. Performance of FRAX and FRAX-based treatment thresholds in women aged 40 years and older: the Manitoba BMD registry. *J Bone Miner Res* 2019; **34:** 1419–27.
87 Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol* 2020; **8:** 672–82.
88 Söreskog E, Lindberg I, Kanis JA, et al. Cost-effectiveness of romosozumab for the treatment of postmenopausal women with severe osteoporosis at high risk of fracture in Sweden. *Osteoporos Int* 2021; **32:** 585–94.
89 Reid IR. Bisphosphonate holidays. *Drug Ther Bull* 2021; **59:** 35–36.
90 Naylor KE, Bradburn M, Paggiosi MA, et al. Effects of discontinuing oral bisphosphonate treatments for postmenopausal osteoporosis on bone turnover markers and bone density. *Osteoporos Int* 2018; **29:** 1407–17.
91 Curtis JR, Saag KG, Arora T, et al. Duration of bisphosphonate drug holidays and associated fracture risk. *Med Care* 2020; **58:** 419–26.
92 Adams AL, Adams JL, Raebel MA, et al. Bisphosphonate drug holiday and fracture risk: a population-based cohort study. *J Bone Miner Res* 2018; **33:** 1252–59.
93 Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res* 2010; **25:** 976–82.
94 Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? *J Clin Endocrinol Metab* 2014; **99:** 4546–54.
95 Grey A, Horne A, Gamble G, Mihov B, Reid IR, Bolland M. Ten years of very infrequent zoledronate therapy in older women: an open-label extension of a randomized trial. *J Clin Endocrinol Metab* 2020; **105:** e1641–47.
96 Leslie WD, Martineau P, Bryanton M, Lix LM. Which is the preferred site for bone mineral density monitoring as an indicator of treatment-related anti-fracture effect in routine clinical practice? A registry-based cohort study. *Osteoporos Int* 2019; **30:** 1445–53.
97 Naylor KE, Jacques RM, Paggiosi M, et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int* 2016; **27:** 21–31.
98 Díez-Pérez A, Adachi JD, Adami S, et al. Risk factors for treatment failure with antiosteoporosis medication: the global longitudinal study of osteoporosis in women (GLOW). *J Bone Miner Res* 2014; **29:** 260–67.
99 Reid IR, Horne AM, Mihov B, et al. Predictors of fracture in older women with osteopenic hip bone mineral density treated with zoledronate. *J Bone Miner Res* 2021; **36:** 61–66.
100 Kline GA, Lix LM, Leslie WD. Patient outcomes in the years after a DXA-BMD treatment-monitoring test: improved medication adherence in some, but too little too late. *J Bone Miner Res* 2021; **36:** 1425–31.