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REVIEW

Treatment of post-menopausal osteoporosis: beyond bisphosphonates

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Abstract Osteoporosis is a highly prevalent condition, characterized by compromised bone strength and fragility fractures and with an important associated socio-economic burden. Bisphosphonates are well established as the first line treatment for osteoporosis. However, while randomized control trials have in general demonstrated reasonable anti-fracture efficacy at the spine, they have shown moderate reduction in fracture incidence for non-vertebral sites. Furthermore, oral bisphosphonates are commonly associated with adverse gastrointestinal effects and both oral and parenteral bisphosphonates have been linked with osteonecrosis of the jaw and atypical femoral fracture, two rare but debilitating side effects. In addition, bisphosphonates are not recommended in patients with GFR <35 ml/min/1.73 m^2. Hence, there is a clear requirement for newer agents, which are able to reduce fracture risk further, whilst overcoming the limitations of bisphosphonates. Over the past 20 years, knowledge and a deeper understanding of the various signalling pathways involved in bone remodelling has increased, enabling identification of additional targets for therapy. This review focuses on these newer therapies and includes anti-resorptive agents such as raloxifene and other selective oestrogen receptor modulators, the monoclonal antibody denosumab (which inhibits the RANKL pathway), odanacatib, a cathepsin K inhibitor and the anabolic agents, PTH analogue; PTH (1–34) and anti-sclerostin antibodies (activator of the Wnt pathway). Strontium ranelate will not be reviewed as recent reports highlight concerns surrounding its cardiovascular safety and together with an apparent increased risk of thrombosis, its future use remains uncertain. Some of these agents such as raloxifene, denosumab and teriparatide are already in clinical use whilst others are at varying stages of development. This review will provide an overview of the mechanisms of action of these therapeutic agents on the skeleton and assess their efficacy in osteoporosis and fracture prevention.

Keywords Denosumab · Teriparatide · Cathepsin K inhibitors · Anti-sclerostin antibody

Abbreviations

BRC	Bone remodelling compartment
RANKL	Receptor activator of nuclear factor kappa-B ligand
OPG	Osteoprotegerin
BMU	Basic multicellular unit
VEGF	Vascular endothelial growth factor
M-CSF	Macrophage colony stimulating factor
LRP 5/6	Low-density lipoprotein receptor-related protein 5 or 6
GSK	3beta-glycogen synthase kinase
Tcf/Lef	T cell factor/lymphoid enhancer factors
RUNX2	Runt-related transcription factor 2
PMW	Postmenopausal women
PTHR1	Parathyroid hormone receptor
PKA	Protein kinase A
PKC	Protein kinase C
SOST	Sclerostin gene

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ER-alpha	Oestrogen receptor-alpha
FasL	Fas-ligand
MAPK	Mitogen-activated protein kinase
AFF	Atypical femoral fracture
ONJ	Osteonecrosis of the jaw
SRE	Skeletal-related events
GIOP	Glucocorticoid-induced osteoporosis

Introduction

Osteoporosis is a skeletal disorder in which bone strength is compromised, predisposing the affected individual to fragility fractures. Over 2 million people suffer from osteoporosis in the United Kingdom (UK) and there are an estimated 300,000 fragility fractures per year, with hip fractures costing the National Health Service (NHS) as much as 1.9 billion in hospital and social care. Fractures are a grave source of morbidity and mortality for the patient and occur as a result of microarchitectural deterioration as well as low bone mass [1].

The process of bone remodelling

Impaired bone remodelling is one important mechanism which leads to osteoporosis. In order to understand the pathophysiology of the disorder, we will first describe the process of normal bone remodelling. Skeletal remodelling is a physiological process which occurs throughout adult life and relies on the coupled and balanced processes of bone formation and resorption within every basic multicellular unit (BMU). The function of the BMU is important in the repair of micro-damage caused by mechanical strain and fatigue which occur throughout the skeleton. It is thought apoptotic osteocytes at areas of micro-damage signal the location and extent of the damage which leads to the targeting of bone remodelling to the site of damage. Remodelling occurs over a time span of 90–130 days and relies on the coupled activity of osteoclasts and osteoblasts. This ensures that bone resorption and formation take place at the same rate and facilitate repair of the skeleton and its microcracks without adversely affecting bone mass (Fig. 1).

Remodelling is initiated by osteoclastic resorption, which occurs over several weeks. Osteoclasts attach to bone via a specialized membrane known as the ruffled border and secrete substances that solubilize bone mineral and degrade the matrix, most notably, chloride ions, protons and cathepsin K, a lysosomal cysteine proteinase. Cathepsin K is crucial to the resorptive function of osteoclasts and in humans who have a mutation in the gene that codes for the enzyme, a dense bone phenotype, known as pycnodysostosis, is seen [2]. Indeed, this is the rationale for the development of cathepsin K inhibitors for the treatment of osteoporosis.

The dissolution of bone liberates factors including transforming growth factor β (TGF-β), insulin-like growth factors (IGFs), and bone morphogenetic proteins (BMPs) from the calcified matrix and attracts lining cells and osteoblastic precursors to the resorptive pit and stimulates their differentiation. Furthermore, there is evidence to suggest that osteoclasts themselves are capable of synthesizing compounds that are pro-osteogenic, e.g. BMP-6, sphingosine-1-phosphate and cardiotrophin-1 [3, 4]. Newly formed bone is deposited by osteoblasts into existing lacunae over a period of 3 months. The osteoid is subsequently mineralized and lining cells cover the area. Osteoblasts that do not undergo programmed cell death are trapped within the matrix and are referred to as osteocytes. Osteoclasts undergo apoptosis once resorption is complete [5, 6].

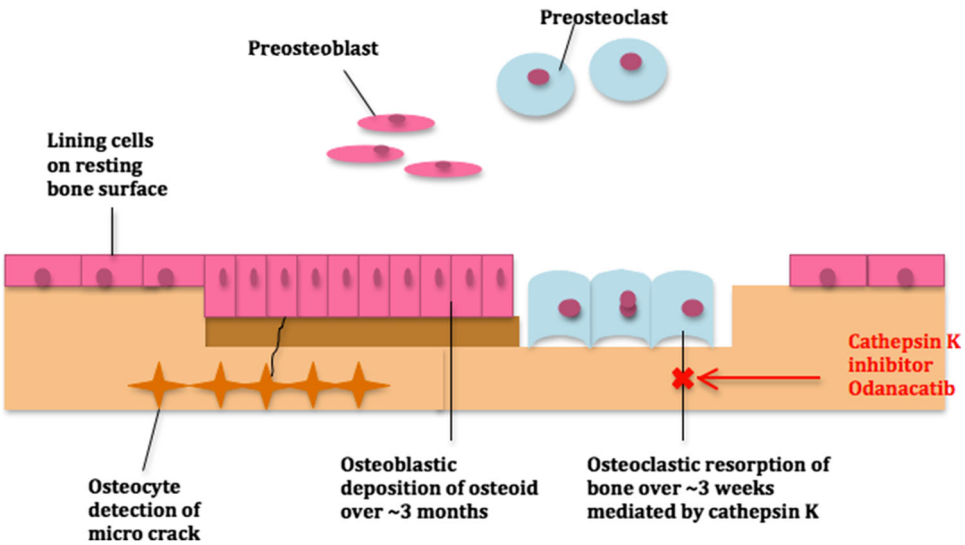

Fig. 1 The bone remodelling cycle. Bone is resorbed by osteoclasts and deposited by osteoblasts in a coupled process that serves to maintain the integrity of bone. Osteoblasts trapped within the matrix become known as osteocytes and function as mechanical sensors capable of detecting microdamage. Odanacatib inhibits cathepsin K, an enzyme imperative to the resorptive activity of osteoclasts, in order to halt loss of bone mass

The bone remodelling compartment

Bone remodelling is carried out in a specialized vascular structure known as the bone remodelling compartment (BRC). The BRC is a closed cavity, separate from the bone marrow, which is lined by a canopy of cells capable of secreting Receptor Activator of Nuclear factor Kappa-B ligand (RANKL) and Osteoprotegerin (OPG) [7]. It is penetrated by capillaries that serve as a conduit for transporting osteoblast and osteoclast precursor cells into the basic multicellular unit (BMU), a term that has become synonymous with Harold Frost after he showed osteoblasts, osteoclasts and osteocytes to be present within the remodelling cavity 40 years ago [8]. Furthermore, capillary endothelial cells secrete angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), angiopoietin and endothelin that have a dual role in regulating bone cell activity [9]. It is not unexpected then that osteoclasts and osteoblasts have been shown to possess VEGF receptors and are capable of VEGF production. VEGF is thought to contribute to the early phases of modelling and remodelling, possibly via its role as a chemoattractant in directing cell migration to sites of active remodelling [10–12].

Since the work of Frost in 1975, our understanding of the signalling pathways involved in bone remodelling has progressed greatly. It is now known that the confined space of the BRC is crucial for maintaining the delicate balance between resorption and formation and that this process is tightly regulated by local and systemic factors. Unregulated access to the remodelling space would result in interference from growth factors that are present in high concentrations within the marrow microenvironment and would offset local regulation. Enhanced bone loss results when the coupling of bone resorption and new bone formation is disrupted. This eventually results in reduction of bone mass, deterioration of bone architecture, loss of trabecular numbers and connectivity, increased cortical porosity, leading to osteoporosis and increased susceptibility to fracture [6].

Signalling pathways in bone cells

Osteoclast differentiation and the RANKL-RANK-OPG pathway

Bone remodelling relies on the complex interplay between numerous cell types. We have already discussed how factors derived from the bone matrix and/or osteoclasts during resorption serve to modulate osteoblastic activity. Similarly, osteoclastic differentiation relies on osteoblasts and its secretion of RANKL and macrophage-colony stimulating factor (M-CSF) [13].

Signalling of M-CSF via its receptor c-fms upregulates RANK expression in mononuclear precursor cells during the initial stages of osteoclastic differentiation. Its ligand, RANKL, is synthesized by osteoblasts and marrow stromal cells in response to hormonal stimulation and together with M-CSF is sufficient for promoting the development of mature osteoclasts. Activation of RANK leads to stimulation of the transcription factors NF-κB, AP-1 and NFATc1 [14], which in turn regulate transcriptional expression of genes essential for normal osteoclastic function, namely cathepsin K, MMP-9, TRAcP, DC-STAMP and β_3 integrin. The lifespan of osteoclasts is that of several weeks and survival is dependent on the ongoing signalling of M-CSF and RANKL. Osteoprotegerin (OPG) is a decoy receptor for RANKL secreted by osteoblasts and marrow cells and can interfere with RANK-RANKL interaction [13, 15]. A recently launched antibody directed against RANKL has proved to be an effective anti-catabolic treatment in the management of osteoporosis.

Osteoblast differentiation and Wnt signalling

Wnt is a glycoprotein that is crucial for normal bone formation. Canonical signalling (Wnt/β-catenin) regulates differentiation, function and survival of all osteoblastic-type cells (osteoprogenitors, pre-osteoblasts, osteoblasts, osteocytes and bone lining cells) and plays a role in committing multipotent mesenchymal stem cells to the osteoblastic lineage [16]. Although Wnt may also participate in non-canonical signalling (Wnt/Ca^{2+}; Wnt/planar polarity), it is the canonical pathway that is of particular importance in osteoblasts and will thus be the focus [17].

During canonical signalling, Wnt3a binds to a receptor complex comprised of the Frizzled receptor and low-density lipoprotein receptor-related protein 5 or 6 (LRP 5/6). This leads to downstream intracellular events that converge on the prevention of GSK-3β-directed breakdown of the protein β-catenin. Aided by T-cell factor/lymphoid enhancer factors (Tcf/Lef), β-catenin initiates transcriptional upregulation of osteoblastic marker genes, such as RUNX2 and Osterix. RUNX2 is the first osteoblastic marker expressed during cell differentiation and has been shown to regulate gene expression for VEGF, osteocalcin, RANKL, sclerostin and Dentin-Matrix Protein-1 [18, 19].

Endogenous inhibitors secreted by osteocytes and late osteoblasts antagonize Wnt signalling. Inhibitors fall into two major groups: those that bind directly to Wnt and impair its ability to activate its receptor complex (e.g. secreted frizzled protein (sFRP) and Wnt inhibitory factor-1 (WIF-1), and those that interfere with the LRP constituent (e.g. sclerostin and Dickkopf (DKK1) [20, 21]. Neutralizing antibodies directed against sclerostin have so far proven to be an effective anabolic approach in phase II

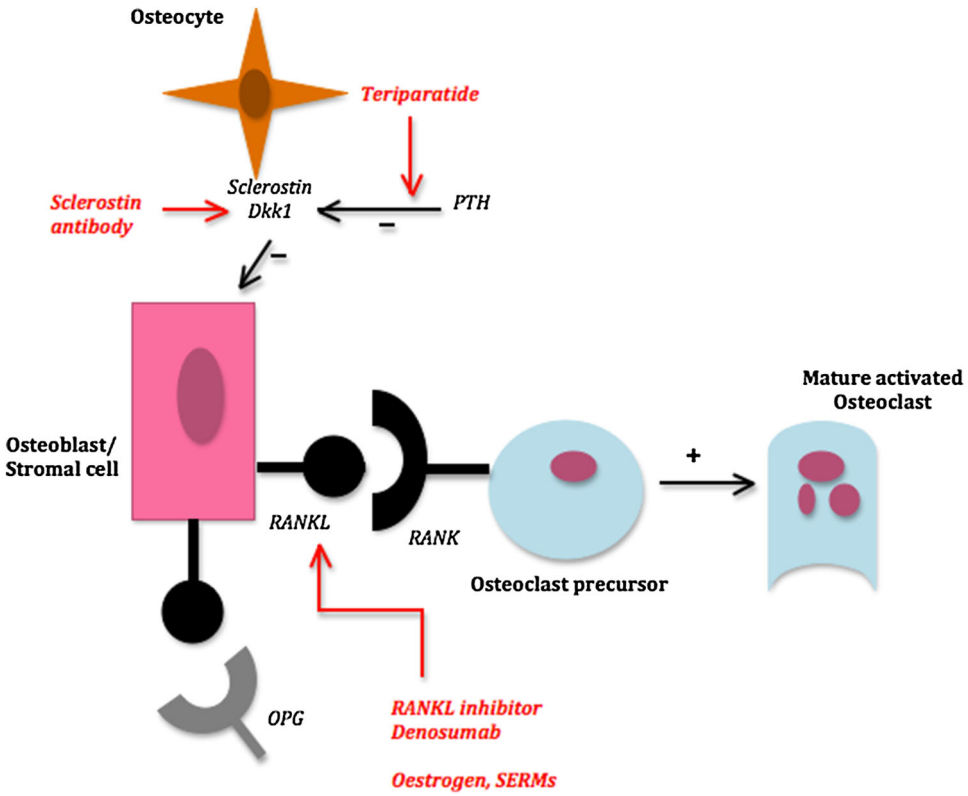

Fig. 2 Cross talk between bone cells, and sites of therapeutic intervention for osteoporosis. Osteocyte/Osteoblast cross talk: Wnt signalling in osteoblasts is antagonized by inhibitory factors sclerostin and DKK1. In addition, the Wnt pathway stimulates the production of osteoprotegerin (OPG), a soluble decoy receptor for the RANKL, preventing osteoclast (OC) differentiation and function. PTH attenuates osteocyte production of such inhibitors, thus favouring bone formation. Teriparatide, a recombinant form of PTH, and antibodies directed against sclerostin, have been shown to exhibit anabolic effects on bone. Osteoblasts stimulate and inhibit osteoclast differentiation via RANKL and OPG expression, respectively. Both denosumab and oestrogen target the RANK-RANKL pathway to disrupt osteoclast maturation

trials for treating osteoporosis (Fig. 2). The differentiation and maturation of osteoblasts are also regulated by a number of autocrine, paracrine and endocrine factors.

Cross talk

Cross talk between the OPG/RANKL/RANK system and Wnt pathways may play an important part in the pathophysiology of postmenopausal osteoporosis. There is evidence to suggest that β-catenin positively regulates OPG expression and that serum β-catenin levels are significantly reduced in postmenopausal women (PMW) with osteoporosis in relation to PMW without osteoporosis [22, 23]. Recently it was also shown that sclerostin, a key antagonist of Wnt signalling, could stimulate RANKL expression [24]. Based on findings such as these, we now know that Wnt signalling in osteoblasts can decrease osteoclast activation and differentiation whilst simultaneously enhancing bone formation [25].

Systemic regulation of remodelling

There are four main hormones involved in the regulation of bone remodelling, parathyroid hormone (PTH), $1,25(OH)_2D_3$, calcitonin and oestrogen. Secretion of the first three hormones is propelled by a need to keep calcium concentration between 2.2 and 2.6 mM, and deficiency of the latter is of particular significance in postmenopausal osteoporosis. Hormonal regulation is modified by environmental cues such as paracrine cytokines and mechanical strain.

Parathyroid hormone

Role in calcium and phosphate metabolism

PTH is an 84-amino acid peptide produced by the parathyroid glands and has a key role in calcium and phosphate metabolism. It is secreted in response to low blood calcium and restores calcium levels in three main ways: first, it has a direct action on the kidney where it reduces renal excretion of calcium whilst promoting phosphorous excretion; second, PTH stimulates osteoclastic-mediated resorption to liberate calcium and phosphorous from bone and into the circulation; and last, PTH indirectly increases intestinal absorption of calcium and phosphorous through its activation of 1α-cholecalciferol hydroxylase—an important enzyme involved in the synthesis of active vitamin D [26].

Stimulation of the vitamin D receptor (VDR) and retinoid X receptors in osteoblasts by $1,25(OH)_2D_3$ increases M-CSF and RANKL production and indirectly stimulates osteoclastic bone resorption. In contrast, calcitonin can

directly inhibit bone resorption by binding to receptors on the osteoclast [15, 27].

Role in skeletal homeostasis

Intermittent vs. continuous PTH exposure The anabolic effect of PTH on bone is somewhat more complex than its endocrine role in the maintenance of calcium homeostasis. Continuous PTH production in primary hyperparathyroidism is associated with enhanced osteoclastogenesis and bone loss, whereas intermittent exposure to low doses of PTH has anabolic effects and leads to improved bone microarchitecture and increased bone volume. PTH is a potent inducer of osteoblastic activity when administered intermittently. This pattern of pulsatile treatment is employed by teriparatide injections (PTH 1–34 given daily) and stimulates bone formation earlier and to a greater extent than bone resorption, thus generating a temporal "anabolic window" [28, 29].

Anabolic and catabolic action of PTH The biological effects of PTH are mediated by PTH1R, a high-affinity G-protein coupled receptor that is expressed on the surface of osteoblastic (and renal tubular) cells. Following PTHR1 stimulation two signalling pathways are activated: the protein kinase A (PKA) and the protein kinase C pathway (PKC). The main route of PTH signalling in bone is the cAMP-PKA pathway [30].

PTH reduces osteoblast apoptosis, accelerates the recruitment of newly formed osteoblasts from bone lining cells and increases the number of active osteoblasts. PTHR1 activation in osteoblasts directly promotes canonical Wnt signalling through its rapid phosphorylation of LRP6, which results in subsequent Axin recruitment and β-catenin stabilization [31, 32]. PTH also transcriptionally suppresses SOST gene expression in osteocytes to facilitate canonical signalling and perpetuate the pro-osteoblastogenic signal (Fig. 2) [33].

Although PTH and Wnt represent the two major anabolic pathways in the skeleton and promote bone formation, only Wnt inhibits resorption of bone. PTH induces osteoblastic production of RANKL to indirectly stimulate osteoclast activity [5].

The RANKL:OPG ratio ultimately determines the extent of osteoclastic differentiation and activation and is regulated differentially depending on the mode of PTH administration. In rats, continuous PTH infusion resulted in a sustained increase and decrease in RANKL and OPG mRNA, respectively, thus favouring a resorptive state, whereas intermittent PTH injections resulted in a transient elevation and decline in OPG and RANKL mRNA, respectively, with levels rapidly returning to baseline levels within 3 h of the injection [34].

Oestrogen

Effect on bone cells

Oestrogen is crucial for maintaining a normal ratio of osteoblasts and osteoclasts, and hormone deficiency following menopause is a significant risk factor for the development of osteoporosis in women. Oestrogen activates oestrogen receptor-alpha (ER-α) via 3 mechanisms, classic genomic signalling, oestrogen response element (ERE)-independent and non-genotropic signalling, in order to regulate bone remodelling [35].

Genomic action of oestrogen directly controls osteoclast lifespan and induces apoptosis of osteoclasts and pre-osteoclasts via Fas and Fas ligand (FasL) signalling. Gene transcription of FasL is regulated through the binding of ligand-bound ER-α dimers to EREs present on DNA. Because oestrogen is able to stimulate FasL upregulation in osteoclasts and osteoblasts, it exhibits both autocrine and paracrine behaviour, respectively. Tamoxifen and raloxifene, two selective oestrogen receptor modulators (SERMs), act via an osteoblast-dependent mechanism to attenuate osteoclastic-mediated resorption of trabecular bone [36, 37].

Ligand-activated ER-α can also function independently of ERE, by binding to alternative transcription factors and forestalling interaction with their response elements. The inhibition of interleukin-6 (IL-6) transcription, a cytokine that would otherwise contribute to bone loss in oestrogen deficiency states, occurs as a result of ER-α binding to P50 and P65 subunits of the NF-κB complex [35].

During growth, bone is deposited at the periosteal surface to increase cross sectional area and removed from the endocortical compartment to increase the size of the medullary cavity. Non-genomic signalling of oestrogen in osteoblast progenitors acts to retard endocortical resorption and preserve cortical bone mass [35, 38].

Effect on the immune system

Components involved in the regulation of the immune system can influence the production of osteoclastic factors. These factors have a number of effects and can influence bone resorption. For instance, IL-6, IL-1 and TNF-α have been shown to enhance RANKL and OPG expression [39]. Part of oestrogen's action on bone is therefore due to its inhibitory effects on RANKL-inducing cytokines. Oestrogen attenuates production of the paracrine signals IL-1β and TNF-α from immune cells such as monocytes [40] and synthesis of IL-6 from marrow and osteoblastic cells [41]. IL-1 and TNF-α have also been shown to promote stromal cell M-CSF expression in ovariectomised mice [42]. Hence, a reduction in circulating oestrogen is linked to

cytokine elevation and favours osteoclastic development. However, correlating circulating cytokine levels to osteoporosis in postmenopausal women has proved difficult for it is likely that cytokine production occurs within the *local* microenvironment of the BRC. Measuring systemic concentrations would reflect production by a whole host of different tissues [43].

Furthermore, immune cells such as B and T lymphocytes can directly produce RANKL and contribute to the bone loss associated with sex steroid deficiency. In one experiment it was found that T-cell deficient mice that had undergone ovariectomy were protected from bone loss, and a study comparing postmenopausal women to premenopausal controls found the former to have significantly increased RANKL production by T-cells [44–46].

ER-α signalling

Accumulating evidence suggests that ER-α signals independently of oestrogen, in order to transduce mechanical strain into pro survival cues in bone forming cells.

In osteoblast progenitor cells, ER-α has been shown to potentiate canonical Wnt signalling and accrual of cortical bone in response to mechanical stimulation in vitro [38]. Through this mechanism, ER-α signalling sensitizes osteoblastic cells to mechanical loading and encourages the transition of osteoblast progenitors (expressing Osterix-1 gene) to mature osteoblasts, whilst suppressing adipocytic differentiation [47]. Additionally, strain and not oestrogen instigates membrane localization of ER-α, where ER-α interacts with caveolin-1 resulting in mitogen-activated protein kinase (MAPK) activation and subsequent inhibition of osteoblast/osteocyte apoptosis [48, 49].

Interestingly, although the response of bone cells to strain and oestrogen both require ER-α, evidence gathered from rat osteosarcoma cells suggests that it is only the latter that regulates receptor cellular concentration. Therefore, down regulation of ER-α in the absence of oestrogen would impair the bone's anabolic response to strain [48].

Pathophysiology of postmenopausal osteoporosis

For the reasons stated, declining oestrogen levels after menopause enhance the age-related changes in bone remodelling and predispose PMW to primary osteoporosis. Hormonal deficiency prolongs the survival of osteoclastic cells and favours adipocytic differentiation over osteoblastic, thereby shifting skeletal equilibrium in the direction of increased bone resorption. The average age of menopause is 51 years old and affects trabecular bone more than cortical bone, which is unsurprising given that trabecular bone has a far greater surface area [50].

Treatment of postmenopausal osteoporosis

Issues with bisphosphonates

Bisphosphonates are the first line treatment for osteoporosis and are approved for use in postmenopausal, glucocorticoid-induced and male osteoporosis. However, bisphosphonate treatment is not without its issues.

Firstly, bisphosphonates reduce non-vertebral and hip fractures by only 20–40 % whilst reducing vertebral fractures by approximately 60–70 % [51, 52]. Secondly, when administered orally (daily/weekly/monthly) the drugs predispose to esophageal irritation and gastrointestinal side effects and leads to discontinuation of the drug in up to 20 % of subjects. Intravenous (quarterly/yearly) bisphosphonate infusion is associated with an acute phase reaction which leads to transient flu-like symptoms in about 20–30 % of cases, although these symptoms tend to be more pronounced after the first dose. Third, given that drug clearance occurs via the kidney, and that high affinity of bisphosphonates for bone mineral results in prolonged skeletal retention and accumulative drug exposure, intravenous bisphosphonates are not advised in those with renal dysfunction (eGFR <35 ml/min/1.73 m^2) [53]. And lastly, while uncommon long term treatment is linked to an increased incidence of atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ) [54, 55].

In summary, the sole use of bisphosphonates as treatment for osteoporosis is imperfect and there is an important requirement for the development of newer drugs that reduce fractures with equivalent or greater efficacy to bisphosphonates, whilst at the same time free from their constraints. Treatment methods fall into two main categories, namely anti-resorptive and anabolic.

Anti resorptive versus anabolic therapy

Anti-resorptive drugs inhibit not only bone resorption but also bone formation indirectly since the two processes are tightly coupled. The inevitable decline in remodelling rate associated with these agents benefits bone strength by increasing mineral deposition/unit volume of bone tissue and, therefore, BMD, and by maintaining bone architecture, thus leading to a reduction in fracture risk. Oestrogen, SERMs, denosumab and bisphosphonates are all anti-resorptives.

In contrast, anabolic agents enhance bone formation and as coupled to resorption increase the rate of remodelling, but in favour of formation, which increases the amount of bone laid down within each remodelling compartment. The result is an ongoing gain in bony tissue with subsequent enhancement of bone strength, and it is this that differentiates the effects of anabolic therapy (e.g. intermittent PTH)

from other high remodelling disease states otherwise detrimental to bone health (e.g. oestrogen deficiency). Teriparatide is an anabolic agent approved for use in postmenopausal osteoporosis, male osteoporosis and glucocorticoid-induced osteoporosis [56]. Although true fracture reduction is the most important outcome, surrogate markers such as changes in turnover markers and BMD, which are more easily demonstrated, are sometimes used when evaluating new treatment options.

Anti-resorptive treatment

Oestrogen

Prior to bisphosphonates, oestrogen was commonly used to treat osteoporosis. Although findings published by the Women's Health Initiative revealed that oestrogen (conjugated equine oestrogens, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day) was efficacious at improving BMD and preventing osteoporotic fractures, its use declined dramatically after the same study demonstrated an increase in the risk of breast cancer and cardiovascular events associated with use [57, 58].

Selective oestrogen receptor modulators (SERMs)

Indications and use Non-steroidal SERMs have beneficial skeletal effects and are capable of inducing tissue-specific ER activity [59]. Therefore, they do not exhibit the same adverse effects on the breast, endometrium and heart as oestradiol; in fact raloxifene (60 mg orally/day), which is the only FDA approved SERM for treatment of postmenopausal osteoporosis, reduces the risk of breast cancer by 65 %, and its use is associated with a 30–50 % reduction in risk of vertebral fracture, although this may not be comparable to the 50 % fracture risk reduction achieved with bisphosphonates due to differences in population selection and severity of osteoporosis [60, 61].

Pivotal trials The MORE trial, a multicenter, blinded, randomized, placebo-controlled study, enrolled 7705 PMW with osteoporosis who had spine or hip *T* scores of <-2.5, with or without existing fractures. Participants were randomized to receive raloxifene orally (60 mg/day or 120 mg/day) or placebo, but all received supplemental cholecalciferol and calcium. The reduction in risk of new vertebral fractures and percentage increase in BMD were evaluated at the end of a 36-month follow-up period. It was found that raloxifene induced a modest increase in BMD at both the spine and hip and significantly decreased the risk of new vertebral fractures (Fig. 3). Unfortunately, raloxifene failed to reduce the incidence of hip and other non-vertebral fractures, demonstrating it to be the least potent of the anti-resorptive agents (Table 1). Moreover, its effect on bone turnover and BMD was modest when compared to that of bisphosphonates and denosumab, which suggests that a greater degree of bone suppression must be achieved to decrease risk of non-vertebral fractures [62, 63]. Indeed, one study found Zoledronic acid to reduce urinary N-telopeptide of type 1 collagen (NTX) to a significantly greater extent than raloxifene ($p < 0.001$) at all time points (2, 4 and 6 months). Similar findings were obtained with serum bone-specific ALP in PMW with low bone mass [64].

Head to head trials A meta analysis of seven head to head randomized controlled trials comparing efficacy of raloxifene with ALN concluded that, despite ALN being more effective at increasing BMD, the efficacy of the drugs in preventing fractures; vertebral ($p = 0.45$) and non vertebral ($p = 0.87$) did not differ significantly at the end of the 2-year follow-up period [65].

Side effects and precautions Raloxifene increases the risk of stroke in PMW at risk of coronary heart disease and increases venous thromboembolic events and hot flushes [66]. Other SERMs have been studied and abandoned for various reasons. Rather more recently, the agent lasofoxifene was investigated in a randomized control trial and was found to significantly reduce risk of vertebral and non-vertebral fractures, along with stroke, coronary heart disease and ER-positive breast cancer. But despite these encouraging findings, there was a 37 % rise in mortality when one of the two dosages was evaluated (0.25 mg/day); hence the future for lasofoxifene is unsure [67].

Denosumab

Indications and use Denosumab is a human monoclonal antibody that opposes RANKL and inhibits osteoclast function and survival, to combat the excessive bone loss of osteoporosis. In May 2010 the European Commission afforded marketing authorization (Prolia, Amgen) for the treatment of postmenopausal women with osteoporosis who have elevated fracture risk, and this was quickly followed by approval from the FDA [68].

Pivotal trials Although numerous clinical trials have been conducted with denosumab, the 3-year randomized placebo-controlled study, named the FREEDOM trial is the largest study to date. The FREEDOM trial enrolled 7,808 women between 60 and 90 years of age who had *T* scores ranging from -2.5 to -4.0 (assessed at the spine or total hip) and randomized them to receive either denosumab (60 mg biannually as a subcutaneous injection) or placebo. All participants received a daily minimum of 400 IU vitamin D and 1,000 mg calcium supplementation. When

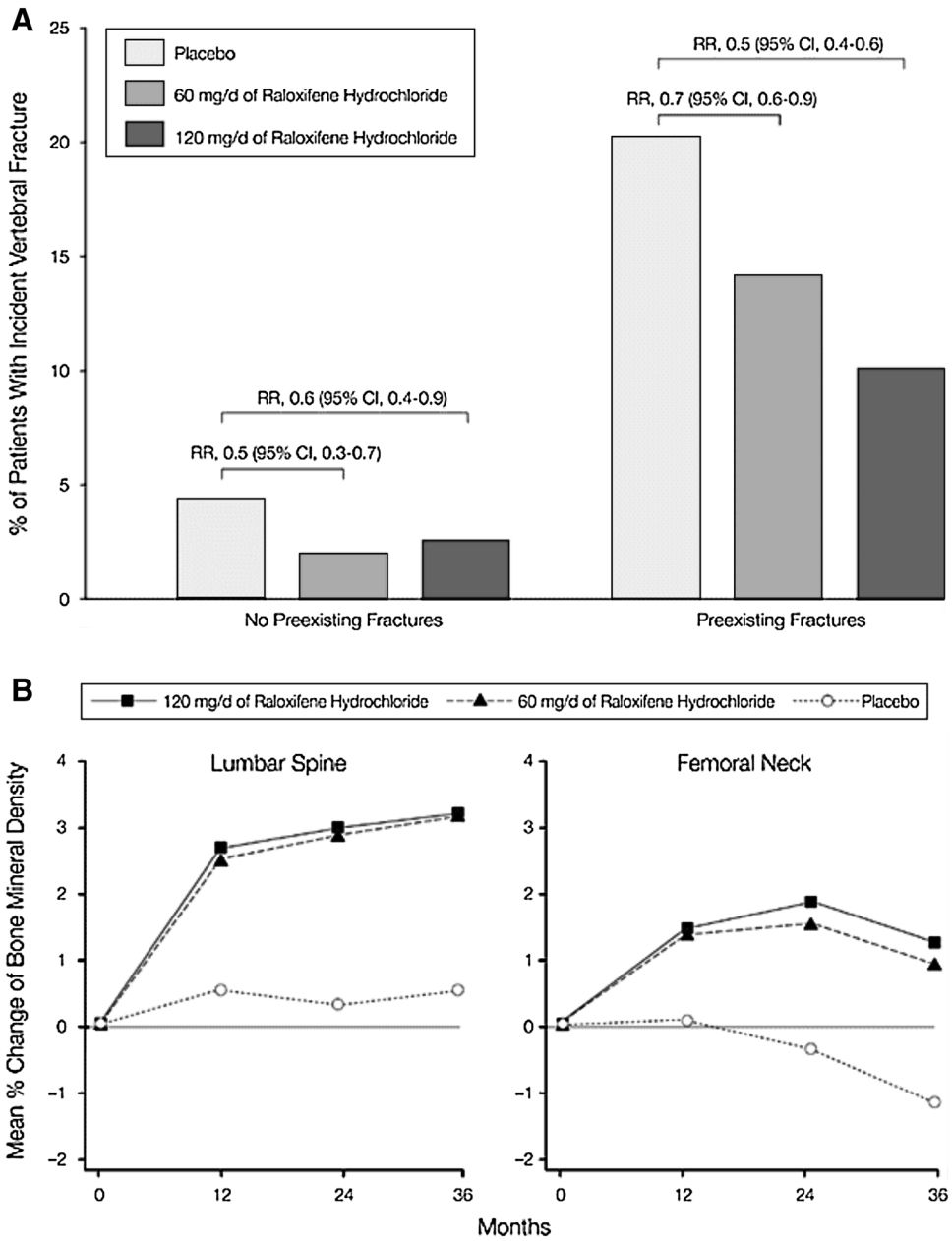

Fig. 3 New vertebral fracture reduction amongst osteoporotic PMW ($n = 6{,}828$), and percentage change in lumbar spine and femoral neck BMD after 36 months of Raloxifene. **a** The risk of new vertebral fractures was reduced by 55 % (60 mg/day) and 40 % (120 mg/day) in women with no prevalent baseline fractures and by 31 % (60 mg/day) and 49 % (120 mg/day) in women with prevalent baseline fractures compared to placebo, ($p < 0.001$ for all comparisons). **b** Compared to placebo, 60 mg raloxifene increased BMD by 2.6 and 2.1 % and 120 mg raloxifene increased BMD by 2.7 and 2.4 % at the spine and femoral neck, respectively ($p < 0.001$ for all comparisons). *RR* relative risk, *CI* confidence interval. Reproduced with permission from Ettinger et al. [62]

fracture reduction at 36 months was assessed, denosumab was found to significantly reduce the incidence of new vertebral fractures compared to placebo (with a cumulative incidence of 7.2 % placebo vs 2.3 % denosumab, a relative decrease of 68 %, $p < 0.0001$) and also non-vertebral (1.2 vs 0.7 %, 40 %, $p = 0.04$) and hip fractures (8.0 vs 6.5 %, 20 % $p = 0.01$) (Table 1) [69]. Fracture risk reduction occurred by the same order of magnitude as bisphosphonates and was irrespective of baseline fracture risk [53, 70]. Denosumab also increased BMD and decreased bone turnover (Fig. 4).

Of note, studies conducted with denosumab in women with breast cancer receiving aromatase inhibitor treatment and in men with prostatic cancer on androgen deprivation therapy, also demonstrated an increase in BMD and reduction in vertebral fractures [71, 72].

Head to head trials Evidence suggests that denosumab is as efficacious as Zoledronate (ZOL), although this does not take into account the observed 28 % reduction in mortality seen following treatment with zoledronate after a hip fracture [73]. Zoledronate is the bisphosphonate with the greatest potency and is more potent than oral Alendronic acid (ALN), the first line treatment in osteoporosis. This is supported by findings from the DECIDE study, a phase III, double blind trial in which 1,189 PMW (with a *T* score of

Table 1 A summary of the treatment effect of raloxifene, denosumab, teriparatide and strontium ranelate on fracture risk

Drug name	Average relative risk (95 % confidence interval)			Indication	Method of administration	Standard dosage regimen (frequency and dose)
	Vertebral fracture	Nonvertebral fractures	Hip fracture			
Raloxifene [62]	0.7 (0.5–0.8)	0.9 (0.8–1.1)		Prevention and treatment of PMO	Oral	60 mg once daily
Denosumab [69]	0.32 (0.26–0.41)	0.8 (0.67–0.95)	0.6 (0.37–0.97)	Primary and secondary prevention of osteoporotic fractures in postmenopausal women at increased risk of fractures	SC injection	60 mg every 6 months
Teriparatide [82]	0.35 (0.22–0.55)	0.47 (0.25–0.88)		Treatment of PMO, and men at increased risk of fractures Treatment of corticosteroid-induced osteoporosis	SC injection	20 μg daily Max duration of treatment 24 months (course not to be repeated)
Strontium ranelate [114]	0.68 (0.5–0.92)	0.69 (0.52–0.92)	0.68 (0.42–1.1)	Treatment of PMO, and men at increased risk of fractures	Oral	2 g/day mixed with water

Treatment with bisphosphonates (alendronate, risedronate and zoledronate) also leads to significant reduction in fracture risk [115]

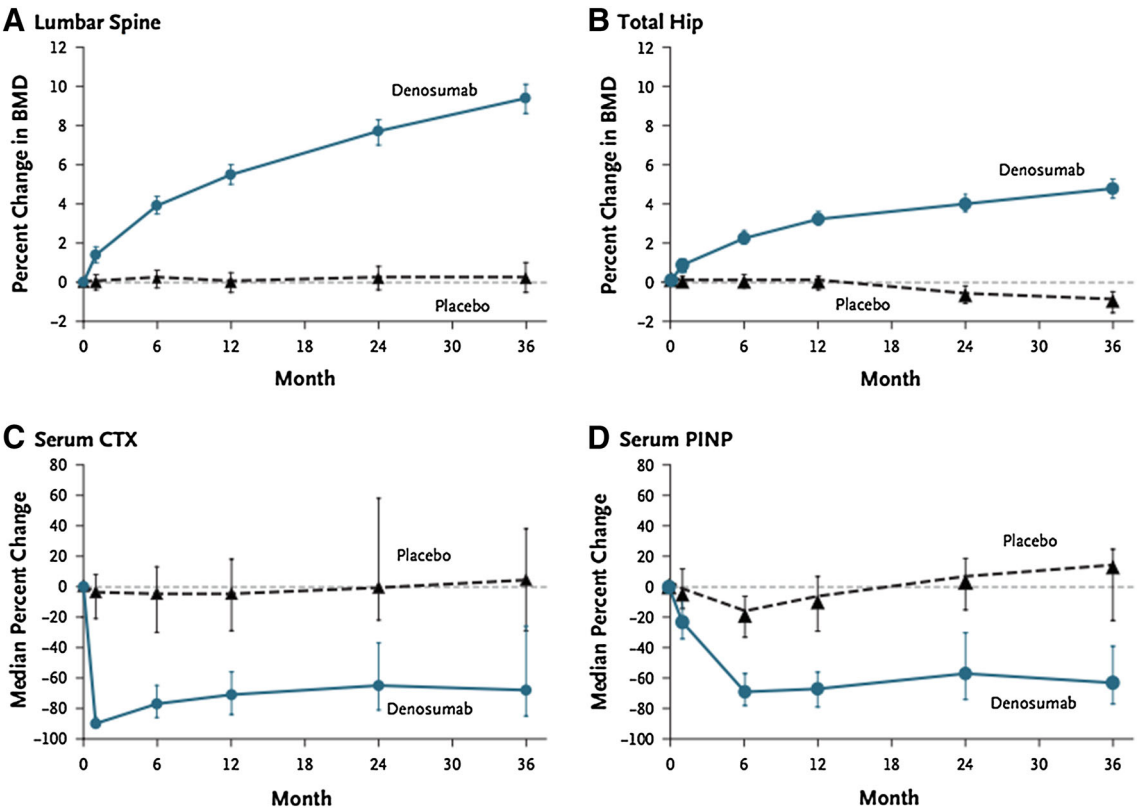

Fig. 4 Percentage change in BMD ($n = 441$) and biochemical bone turnover markers ($n = 160$), compared to placebo. **a**, **b** After 36 months, participants assigned to denosumab experienced a relative increase of 9.2 % at the lumbar spine, and 6.0 % at the total hip, with respect to placebo. **c**, **d** Denosumab decreased serum C-telopeptide by 86 and 72 %, and P1NP by 18 and 76 %, at 1 and 36 months, respectively, compared to placebo. $p < 0.001$ for all comparisons between groups and at all time points. Reproduced with permission from Cummings et al. [69]

≤ -2.0 at the total hip or lumbar spine) were randomized to receive either denosumab (60 mg/6 months) or oral ALN (70 mg/week) over a 1-year period. Percentage change in BMD and bone turnover markers from baseline was assessed. There was a significantly larger increase in BMD at all skeletal sites at 12 months with denosumab compared to ALN, particularly at the total hip (3.5 vs 2.6 %, $p < 0.0001$). Treatment difference at the femoral neck was 0.6 %; trochanter, 1.0 %; lumbar spine, 1.1 % and 1/3 distal radius, 0.6 % ($p \leq 0.0002$ at all sites). The same trial showed a significant reduction in bone turnover markers with denosumab compared to ALN, although bone quality, an important determinant of fracture risk, was not assessed [74].

The STAND trial explored the effect of denosumab on BMD in PMW transitioning from ALN treatment, thus simulating a potential clinical scenario. Total hip BMD increased by a further 1.90 % at 12 months when switched to denosumab compared to 1.05 % in those who remained on ALN, a statistically significant difference ($p < 0.0001$); lumbar spine BMD increased by 3.03 and 1.85 % ($p < 0.0001$), respectively. There was also a greater decrease in serum CTX in transitioning patients [75].

Denosumab was compared to Zoledronic acid in a study assessing skeletal related events (SRE) in patients with bony metastases from advanced cancer. A combined analysis of three pivotal phase III trials showed denosumab to be superior to ZOL in delaying the duration of the first SRE (median delay of 8 months). Incidence of ONJ was similar between groups ($p = 0.13$) [76].

Side effects and precautions Denosumab can induce hypocalcaemia in susceptible individuals who have severe renal impairment or are receiving dialysis [77]. In addition, the FREEDOM trial found the incidence of eczema and cellulitis including erysipelas, to be significantly greater in denosumab-treated women compared to placebo (3 vs. 1.7 % and 0.3 vs. <0.1 %, respectively), although the risk of serious side effects such as cancer, infection and cardiovascular events remained consistent between groups [69]. The small increase in recurrent neoplasms observed with denosumab was deemed statistically insignificant; however, because of shared signalling between the immune and skeletal systems further scrutiny of the potential risks of therapy is warranted [78].

One case of ONJ was reported during the aftermath of the FREEDOM trial, and several cases have been noted since [79]. The mechanism is likely to be due to its potent anti-resorptive effect as ONJ has also been described as a rare complication of bisphosphonate therapy, occurring with an incidence of 1:100,000 to 1:10,000 in osteoporotic individuals [55]. To reduce the risk of ONJ, patients taking denosumab with additional risk factors (e.g. chemotherapy, glucocorticoids, dental diseases, radiation) should be aware of the importance of good dental hygiene. Of note, atypical femoral fracture is associated with denosumab use for similar reasons to ONJ.

Denosumab vs. bisphosphonates in clinical practice

Denosumab does not accumulate in the skeleton in the same way as bisphosphonates do since it targets RANKL. It is thus a potent suppressor of bone turnover and has a rapid onset of action. A dose-dependent inhibition of serum CTX can be observed as early as 3 days after administration. Furthermore, drug discontinuation swiftly restores CTX levels to values *above* baseline and in one study even exceeded those of the placebo group but normalized shortly after. It is not yet known if this rebound effect leads to an increased risk of fractures [80]. The reversible nature of denosumab action necessitates that a reminder system be put in place for patients approaching their next injection and that there be a follow up regime with an alternative anti-osteoporotic agent in the event of discontinuation.

Additional differences exist between denosumab and bisphosphonate therapy. Denosumab has a longer dosing interval compared to oral bisphosphonates and is administered biannually and subcutaneously. This coupled with the fact that it is relatively free from gastrointestinal side effects translates into improved drug adherence long term. Denosumab has a shorter skeletal retention time compared to bisphosphonates and is not limited to those patients with good renal function, since drug excretion does not occur via the kidneys [81].

Anabolic treatment

Teriparatide

Indications and use Teriparatide is a recombinant form of human PTH (1–34 N-terminal fragment) and is FDA approved for use in PMW with osteoporosis, hypogonadal or primary osteoporosis in men and in both men and women suffering from glucocorticoid-induced osteoporosis (GIOP). Because of cost and inconvenience of daily injections, use is reserved for those with severe disease in UK or Europe. Selected patients should be at high risk of fracture, for example those with multiple risk factors, those with a previous fragility fracture and those who have experienced drug failure/intolerance. In patients with a T score of <-3 who have other risk factors for fracture, teriparatide can be used as first line treatment [82].

Teriparatide is given subcutaneously as a once daily 20 μg injection into the abdomen or thigh. Drug use was initially approved for 18 months but has since been

extended to 2 years, as there is some concern about prolonged drug use and osteosarcoma risk.

Clinical trials with teriparatide Teriparatide induces the largest increase in BMD to date when compared to any other osteoporosis therapy and reduces the risk of vertebral and non-vertebral fracture (excluding hip fracture) in PMW with previous vertebral fracture. A phase III trial showed a 65 % reduction in the risk of new radiographic vertebral fractures (9.7 % increase in lumbar spine BMD vs. 1.1 % placebo) and a 53 % reduction in non-vertebral fractures in patients treated with 20 μg teriparatide for 12 months compared to placebo. The same study also demonstrated that dosing with 40 μg/day was not superior to 20 μg/day in its effects (Table 1) [83].

PTH-treated patients exhibit the largest increase in BMD (10–14 %) at the lumbar spine (comprised of trabecular bone), a less marked increase (<5 %) at the femoral neck (mixed trabecular/cortical bone), with the measured BMD even falling somewhat (by 1–2 %) at the distal radius (cortical bone); however, the significance of the last finding is unknown [56].

Studies assessing the effect of teriparatide on glucocorticoid-induced osteoporosis (GIO) are in keeping with the trend whereby the greatest increase in BMD occurs in the lumbar region, followed by a less marked increase in the region of the hip. Furthermore, they show that teriparatide is able to induce an early rise in markers of bone formation, along with a slower increase in resorptive markers, reinforcing the concept of the 'anabolic window', in which there is an initial uncoupling of bone turnover in favour of bone formation. For instance, in the first 3 months of PTH (1–34) treatment, formation markers increased by 150 % and resorption markers by only 100 % [84, 85].

Head to head trials A head to head trial comparing the effects of teriparatide (40 μg/day, greater than the approved dose) with that of ALN (10 mg/day) showed a significantly greater increase in BMD and markers of bone formation from baseline with teriparatide than with ALN after 14 months of treatment. Although this study also demonstrated the frequency of non-vertebral fractures to be significantly lower in those given teriparatide compared to the ALN-treated group (4 versus 14 %), some of these incidents may have been due to high-impact trauma [86].

Similar outcomes were obtained when teriparatide was compared to calcitonin and strontium ranelate, and in the latter study P1NP levels rose significantly with teriparatide at 1 month and continued to rise until 6 months [87, 88]. Another study found a positive significant correlation between bone turnover status at baseline and BMD changes, with P1NP being the most accurate predictor of lumbar BMD response at 18 months [89].

Pretreatment with anti-resorptive therapy Pretreatment with antiresorptive drugs can impair the anabolic action of PTH and its ability to stimulate osteoblastic activity, due to a global reduction in bone remodelling. The scenario of sequential therapy arises when a patient continues to fracture and/or lose BMD despite being on antiresorptive therapy or else exhibits drug intolerance and is therefore switched to an anabolic agent.

There is accumulating evidence to suggest that long-term therapy with a bisphosphonate prior to initiating teriparatide blunts the effectiveness of PTH [90–92]. In one study it was found that the increase in lumbar spine BMD after 18 months of teriparatide (20 μg/day) was only 4.1 % in PMW who had been previously treated with ALN for 18–36 months. In contrast, patients pretreated with raloxifene, also an antiresorptive agent, resulted in an incremental increase of 10.2 % (ALN vs. raloxifene, $p < 0.05$), suggesting that this observation does not hold true for SERMs [92]. However, it is possible that the differences in incremental increase in BMD may be related, in part, to variations in disease severity which may have affected the selection of first line treatment agents.

Combination therapy with antiresorptive agents Two randomized controlled trials have looked at the effects of combining teriparatide with other drugs for osteoporosis, with one study conducted in PMW treated with intact PTH (100 μg/day) [93] and the other in men treated with teriparatide (40 μg/day) [94]. Neither study found a synergy between teriparatide and ALN. Furthermore, there were no additive effects on BMD gains when intact PTH and ALN were combined, and ALN was even found to reduce BMD gains when compared to teriparatide alone. However, the effects of PTH alone failed to surpass combination therapy at the total hip ($p = 0.08$). These findings have important ramifications when planning optimal PTH treatment for severely osteoporotic patients, given they are likely to be receiving bisphosphonates before starting teriparatide. In contrast, combined treatment with teriparatide and denosumab led to a greater increase in spinal, femoral neck and hip BMD (9.1, 4.2, 4.9 %, respectively) compared to teriparatide (6.2 %, $p = 0.014$, 0.8 %, $p < 0.007$, 0.7 %, $p < 0.001$) or denosumab alone (5.5 %, $p = 0.0005$, 2.1 %, $p = 0.0238$, 2.5 %, $p = 0.001$) [95].

Interestingly, neither oestrogen nor SERMs (such as raloxifene) appear to blunt the effects of PTH, despite being anti resorptive in nature. When teriparatide was administered to PMW on oestrogen replacement, the response that occurred was consistent with that of previous trials (13 % increase spinal BMD, 2.7–4.4 % hip) [96, 97].

Antiresorptive therapy after PTH Because BMD has a tendency to fall after the discontinuation of teriparatide, it has been suggested that anti-resorptives be used in the follow up period, to maintain the newly accrued bone and attenuate loss. In a follow-up study of the fracture prevention trial (FPT), participants who were treated with bisphosphonates for at least 24 months during the 30-month post-teriparatide treatment phase demonstrated additional increases in BMD [4.3 % increase in total hip BMD from FPT baseline in the former 20 μg group ($p = 0.005$ versus placebo) and a 6.8 % increase in the former 40 μg group ($p < 0.001$ versus placebo)]. In contrast, those who did not receive any anti-resorptive therapy during this time period experienced a reduction in BMD that was similar to placebo ($p < 0.05$) [98]. A comparable improvement in BMD occurred when teriparatide was followed by raloxifene [99, 100].

Side effects and precautions The side effects of teriparatide are usually mild but can include weakness, muscle pain, nausea, headache and dizziness. Orthostatic hypotension may also occur, usually within the first 4 h of teriparatide injection. However, this can be avoided by advising patients to remain seated during initial administration, since orthostasis is typically limited to the first few doses [82].

Osteosarcoma Two of the major trials [83, 86] with teriparatide were terminated early after it was found by a carcinogenicity study in rats that the drug could induce osteosarcoma [101]. However, to date there is no substantive clinical evidence to suggest that osteosarcoma is induced in states of high and/or prolonged PTH secretion, e.g. renal osteodystrophy. Moreover, no osteosarcomas were found during the pivotal teriparatide trial, questioning the relevance of the rat carcinogenicity findings [83]. Since the launch of teriparatide in 2002, Eli Lilly has identified one potential osteosarcoma case but the cause–effect relationship remains unproven [102]. Despite this, teriparatide is best avoided in patients with an elevated risk of osteosarcoma and history of cancer. This includes adolescents in whom the epiphyses have not yet closed, those with Paget's disease or prior skeletal radiation, and patients with unexplained increases in ALP [82]. A number of countries recommend the use of teriparatide only after the menopause, although there is no reliable evidence to support this.

Novel therapies

Cathepsin K inhibitors

Given that the protease cathepsin K is central to enzymatic bone degradation, inhibitors of cathepsin K represent a novel therapeutic approach in the treatment of osteoporosis. Currently, the only agent under clinical evaluation is odanacatib, since it alone displays adequate affinity and specificity for cathepsin K (rather than cathepsins S, L and B). This is significant given that trials with less specific cathepsin K inhibitors have been halted following the discovery of skin reactions such as rashes and scleroderma-like thickening [103, 104].

A phase II trial conducted with odanacatib (50 mg/week) in 399 PMW with low BMD (*T* scores of between −2 and −3.5) found that after 24 months of oral therapy, BMD was increased by 5.7 % at the lumbar spine, 4.1 % at the total hip and 4.7 % at the femoral neck compared to placebo. Further to this, a dose-dependent decrease of resorption markers was noted, along with a transient and moderate decline in formation markers without suppression of bone formation rate. Cutaneous lesions resembling scleroderma were not observed and adverse outcomes were similar to that of placebo [105]. A large phase III trial (NCT00529373) has now been completed.

A second cathepsin K inhibitor called ONO-5334 was evaluated at varying doses as part of the phase II OCEAN study. Lumbar spine BMD (LSBMD) at 12 months was compared to baseline BMD in 265 PMW with low BMD. LSBMD increased significantly with ONO-5334 [3.7 ± 0.5 % (50 mg twice daily), 3.1 ± 0.48 % (100 mg once daily) and 5.1 ± 0.49 % (300 mg once daily)] compared to placebo (0.6 ± 0.48 %). Total hip and femoral neck BMD exhibited significant increases of 3.0 ± 0.36 % and 2.6 ± 0.44 %, respectively, with 300 mg ONO-5334. Further clinical trials are required to evaluate drug efficacy and safety long term [106].

The OCEAN study also showed a reduction in resorptive markers with ONO-5334 comparable to placebo, but no accompanying suppression of bone formation rate, hence providing a clue to the mechanism of action of cathepsin K inhibitors [106]. Since these agents interfere with the process of resorption rather than impairing osteoclast viability, signalling between osteoclasts and osteoblasts is preserved and bone formation unaffected. This uncoupling action of the drugs contrasts that of denosumab and bisphosphonates, two antiresorptives that function by reducing osteoclast differentiation and promoting apoptosis, respectively [81].

Inhibitors of Wnt antagonists

Sclerostin The observation that SOST gene inactivation occurs in sclerosteosis and van Buchem, two rare diseases characterized by high bone mass, has provided the rationale for targeting sclerostin in osteoporosis. An antibody against sclerostin tested in a rat model of postmenopausal

osteoporosis, increased BMD at all sites and prevented oestrogen deficiency-associated bone loss [107].

A human monoclonal sclerostin antibody, called AMG 785, which inhibits the binding of sclerostin to LRP5/6, has been developed and evaluated as part of a randomized, double-blind placebo controlled phase I trial. The study recruited 72 postmenopausal women and men and demonstrated a 5.3 % increase in BMD at the lumbar spine and 2.8 % at the total hip after 85 days in participants given a solitary subcutaneous dose of 10 mg/kg compared to placebo. Furthermore, bone formation markers (P1NP, osteocalcin, bone-specific ALP) increased whilst resorption markers (serum CTX) decreased, indicating an uncoupling action and large anabolic window, possibly due to cross talk with RANKL/OPG with a subsequent increase in OPG [108]. A phase II study [NCT00896532] is currently underway, in which the efficacy of the sclerostin antibody will be compared with ALN and teriparatide. Zoledronic acid, a potent bisphosphonate, leads to increases in sclerostin when given for post-menopausal osteoporosis [109]. This explains, in part, the suppressive effects of zoledronate on bone formation. It is, therefore, interesting to speculate whether the use of a sclerostin antibody with zoledronate may attenuate the negative effect of zoledronate on bone formation and, therefore, enhance its efficacy in fracture prevention.

Enhanced Wnt signalling has been linked to malignancies such as hepatocellular and colorectal cancer [110]. Indeed, 75 % of osteosarcomas were found to have a deficiency of Wnt inhibitory factor 1 (WIF), leading to increased Wnt signalling [111]. As a result phase III trials gauging the long-term safety of the antibody are awaited.

Dkk-1 Dkk-1 is also an inhibitor of Wnt signalling. The assessment of Dkk1 inhibitors has thus far been restricted to preclinical trials and has yet to be considered in the context of osteoporosis, although it has been shown to be effective at preventing bone loss in rheumatoid arthritis [112] and multiple myeloma [113]. However, the wide tissue expression of DKK1 may limit the use of DKK1 antibodies.

Conclusion

Recent discoveries in the field of bone cell biology have led to the development of novel therapeutic compounds for osteoporosis and fracture prevention which is the goal of all treatment. These new drugs coupled with existing therapies are increasing the range of non-bisphosphonate treatment options that will become available for patients. Although established antiresorptive drugs such as denosumab suppress bone remodelling via a coupling effect, newer drugs in development such as odanacatib exhibit an uncoupling effect, enabling greater bone formation. Sclerostin antibodies offer an exciting new anabolic treatment which until now is limited to teriparatide only. Teriparatide induces the greatest increase in BMD at the spine compared to anti-resorptive agents. It is anticipated that sclerostin antibodies will have a similar if not greater t anabolic profile as unlike teriparatide it does not increase bone resorption. As these drugs transition from preclinical evaluation to use in the clinical setting, patients will be able to receive increasingly individualized therapy, targeted to their specific clinical requirements.

Conflict of interest The authors declare no conflict of interests.

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