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Title: Current and emerging osteoporosis pharmacotherapy for women: state-of-the-art therapies for preventing bone loss.

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ABSTRACT

Introduction: Pharmacological options to address the imbalance between bone resorption and accrual in osteoporosis include anti-resorptive and osteoanabolic agents. Unique biologic pathways such as Wnt/β-catenin pathway have been targeted in the quest for new emerging therapeutic strategies.

Areas Covered: This review aims to provide an overview of existing pharmacotherapy for osteoporosis in women and explore state-of–the-art and emerging therapies to prevent bone loss, with an emphasis on the mechanism of action, indications and side effects.

Expert Opinion: Bisphosphonates appear to be a reliable and cost-effective option, whereas denosumab has introduced a simpler dosing regimen and may achieve a linear increase in BMD with no plateau being observed, along with continuous anti-fracture efficacy. Selective estrogen receptor modulators (SERMs) are synthetic non-steroidal agents which have varying estrogen agonist and antagonist activities in different tissues and antifracture efficacy. Abaloparatide, a parathyroid-hormone-related peptide (PTHrP)-analogue, approved by the FDA in April 2017, constitutes the first new anabolic osteoporosis drug in the US for nearly 15 years and has also proven its anti-fracture efficacy. Romosozumab, a sclerostin inhibitor, which induces bone formation and suppresses bone resorption, has also been developed and shown anti-fracture efficacy; however, concerns have arisen with regard to increased cardiovascular risk.

Keywords: osteoporosis, anti-resorptive medications, osteoanabolic agents, abaloparatide, sclerostin, romosozumab

1. Introduction

Osteoporosis is a metabolic bone disease characterized by an imbalance between bone resorption and accrual, resulting in microarchitectural disruption, reduced bone mineral density (BMD) and skeletal fragility[1]. Fragility fractures are common in the osteoporotic population and occur from forces not ordinarily resulting in fracture. The most common sites are the vertebral column, hip and wrist; however, fragility fractures of the humerus, pelvis and ribs are not uncommon[1].

Over the past decades, several medications with different mechanisms of action have been employed for the treatment and prevention of osteoporosis. Current pharmacological options include anti-resorptive and osteoanabolic agents as well as drugs with dual action. Anabolic agents are intended to inverse the imbalance of bone remodeling and stimulate bone formation, therefore increasing BMD; represented predominantly by teriparatide and abaloparatide.

On the other hand, anti-resorptive medications try to address the imbalance between bone resorption and accrual. They aim to inhibit bone resorption by decreasing bone turnover or disrupting osteoclast proliferation and maturation and include five principal classes of agents; bisphosphonates, selective estrogen receptor modulators (SERMs), estrogens, denosumab (monoclonal antibody) and calcitonin[2].

Most of the current pharmacological strategies are principally based on bone anti-resorptive agents. In clinical practice, bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) are utilized as first-line treatments since they constitute cheap and reliable agents, which are effective in reducing vertebral, non-vertebral and hip (except for ibandronate) fracture risk [3]. Denosumab is an anti-RANKL monoclonal antibody suppressing bone resorption with high and

continuous anti-fracture efficacy[3,4]. Selective estrogen receptor modulators (SERMs) are synthetic non-steroidal agents which have varying estrogen agonist and antagonist activities in different tissues and antifracture efficacy [3]. On the other hand, anabolic agents stimulate bone formation and reserved for high fracture risk individuals, providing vertebral and non-vertebral anti-fracture efficacy [5]; they are represented predominantly by teriparatide, a human recombinant parathyroid hormone (PTH), and abaloparatide, a synthetic PTH-related peptide (PTHrP) analogue.

New emerging therapeutic strategies target unique biologic pathways such as the Wnt/β-catenin pathway[6]. These strategies have the potential to substantially decrease bone resorption and be more effective in fracture reduction in osteoporotic patients.

This review maps out existing pharmacotherapy for osteoporosis in women with an emphasis on the mechanism of action and the state-of-the-art therapies to prevent bone loss. Our review also explores emerging pharmacological strategies and touches upon the future direction in the field.

2.1 Anti-resorptive medications

2.1.1 Bisphosphonates

Bisphosphonates are structurally linked to inorganic pyrophosphate, a naturally occurring compound consisting of two phosphate groups[7].Like pyrophosphate, bisphosphonates have demonstrated a very high affinity for hydroxyapatite crystals and are predominantly embedded in sites of augmented skeletal turnover[7].

First generation bisphosphonates (etidronate, clodronate, tiludronate) are characterized by non-nitrogen containing agents and have a distinct mechanism by which osteoclast apoptosis is fostered. Owing to their structural similarity to pyrophosphate, they become embedded in

adenosine triphosphate (ATP) molecules following osteoclast-mediated uptake[8]. Consequently, a high concentration of the above-mentioned ATP analogues exhibits a cytotoxic effect on osteoclasts, eventually promoting osteoclast apoptosis.

The second and third generation of bisphosphonates utilized for the treatment and prevention of osteoporosis (alendronate, pamidronate, ibandronate, risedronate and zoledronic acid) share a structural similarity since they have nitrogen-containing R^2 side chains[7]. Their anti-resorptive effect results from the inhibition of farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonic acid pathway. The mevalonate pathway is critical in regulating the production of isoprenoid lipids and sterols employed for the isoprenylation (post-translational modification) of GTP-binding proteins which play central roles in osteoclast function[7,9,10]. As a result, their anti-resorptive potency lies in their ability to promote osteoclast apoptosis.

Bisphosphonate potency is largely dependent on their activity to inhibit farnesyl pyrophosphate synthase; the rank order of potency is zoledronate>risedronate>> ibandronate > alendronate[11]. Bisphosphonates also differ in their bond strength to the mineral matrix, with zoledronic acid demonstrating the highest affinity to hydroxyapatite crystals[7], followed by alendronate, ibandronate and risedronate[12].Biochemical markers of bone turnover that reflect the activity of bone cells and hence can be utilised to measure bisphosphonate efficacy in the clinical setting, include bone resorption markers; mainly the degradation products of type I collagen, serum C-telopeptide of type I collagen (sCTX-1) and urine (uNTX) or serum N-terminal telopeptide (serum NTX), as well as bone formation markers, such as isoenzyme of alkaline phosphatase and serum type 1 procollagen (C-terminal or N-terminal) peptides C1NP or P1NP, respectively.

Owing to their unique mechanism of action and long halve-lives, bisphosphonates are accumulated and released from the skeleton for a long time after treatment is ceased. Notwithstanding technical

challenges in estimating bisphosphonate levels in serum and urine, studies have reported a slow elimination phase with an estimated biologic half-life greater than ten years following intravenous administration of high doses of alendronate[13]. The fact that they can protect an individual for an additional 3-5 years[10] has been the basis of advocating a ‘’drug holiday’’ after 5-10 years of continuous administration[14]. However, recommendations are to be individualized to each patient’s clinical picture. As reflected by international guidelines, such as those released by the American Society for Bone and Mineral Research (ASBMR), and the European Menopause and Andropause Society[15] risk should be stratified in women following five years of alendronate or three years of intravenous bisphosphonate therapy[16]. High-risk postmenopausal women should continue BP therapy since the benefit deriving from fracture risk reduction greatly outweighs the risk of serious adverse events. For women considered of low risk, a “drug holiday” can be considered, with periodic risk assessment[16].

All currently approved bisphosphonates are indicated for osteoporosis treatment and fracture prevention; namely reducing the incidence of spinal fractures. Alendronate, risedronate and zoledronic acid have also demonstrated efficacy in preventing hip and non-vertebral fractures, contrary to ibandronate [17]. Their indications and approved dosing can be found in Table 1.

A recently published systematic review and network meta-analysis encompassing thirty-six primary studies concluded that zoledronic acid demonstrated comparative efficacy in preventing vertebral and non-vertebral fractures, whereas both alendronate and zoledronic acid were the most effective in preventing hip fractures [18]. Results were concordant with a previously published comparative network meta-analysis reporting that zoledronic acid showed the highest overall probability of protecting from any fracture [19].

The commonest side effects include gastrointestinal irritation and acute phase reaction with intravenous administration, although they are frequently mild in severity[12]. Uncommon side effects involve musculoskeletal pain, while it has been suggested, that albeit rare, osteonecrosis of the jaw (ONJ) and atypical femoral bone fractures (AFFs) represent serious complications associated with long-term use of nitrogen bisphosphonates. However, the incidence of AFFs among patients receiving bisphosphonates is low, and a causal relationship has yet to be established. Owing to their rarity, none of the long-term trials was statistically powered to evaluate differences in the incidence of ONJ or AFFs.

2.1.2 Denosumab

Osteoclasts originate from cells of the monocyte/macrophage lineage upon stimulation of two major modulators of osteoclast formation, the monocyte/macrophage colony-stimulating factor (M-CSF) and the receptor activator of NF-κB ligand (RANKL), a type I transmembrane protein[20]. Other regulatory molecules involve cytokines and hormones such as PTH, prostaglandin E2, calcitriol, thyroxine, and interleukin-1 (IL-1) [21–23]. M-CSF binds to its receptor on the osteoclast, c-fms (colony-stimulating factor 1 receptor), a transmembrane tyrosine kinase-receptor, ameliorating survival and proliferation of osteoclast precursors [20,24]. However, the receptor activator of nuclear factor-κB ligand (RANKL) is considered to represent the primary osteoclast differentiation factor. RANKL, a type II transmembrane protein [25], belongs to the TNF (Tumour Necrosis Factor) ligand family and binds to RANK to stimulate the differentiation and multiplication of osteoclasts [25,26]. In more detail, RANKL activates c-Fos, a transcription factor, that in turn precipitates a chain reaction eventually leading to osteoclast differentiation and apoptosis inhibition [25]. Osteoprotegerin (OPG) is a soluble decoy receptor expressed in

osteoblasts and other tissues, such as spleen and bone marrow [25]. The role of the OPG in the bone resorption regulation lies in its ability to inhibit RANK/RANKL interaction, therefore inhibiting osteoclast differentiation and protecting from excessive bone resorption. Therefore, OPG and RANKL are competitors in the molecular milieu, with high OPG concentrations exerting an inhibitory effect on the RANK – RANKL signalling pathway.

Denosumab is an IgG2 monoclonal antibody that suppresses bone resorption by mimicking the action of OPG in bone microenvironment and has been approved for fracture treatment and prevention of osteoporosis. In particular, denosumab is used for preventing spinal, hip and non-vertebral fractures. Denosumab binds to RANKL preventing its binding to RANK, hence reducing osteoclast proliferation, survival and bone resorption. Its chemical structure consists of four chains; two heavy chains consisting of 448 amino acids with four intramolecular disulfides and two light chains consisting of 215 amino acids [27]. Alike other monoclonal antibodies, denosumab has demonstrated non-linearity in its pharmacokinetics dependent on the dose. It is characterized by a unique biochemical profile of prolonged absorption and β phase, whereas the terminal phase is more rapid [27].

A pooled analysis of 22,944 serum denosumab concentrations in 1,564 subjects defined the subcutaneous bioavailability of denosumab to be 64% and the RANKL degradation rate 0.00148 h^{-1} [28]. The first-order absorption rate constant (k_a) utilized to characterize absorption was determined to be k_a=0.00883 h^{-1} [28]. Dosing adjustment based on the patient's baseline characteristics is not deemed necessary as the non-linear pharmacokinetic profile is probably attributed to RANKL binding [28]. Pharmacokinetic and pharmacodynamic properties of different antiresorptive agents are presented in Table 2.

Denosumab is administered subcutaneously at a dose of 60mg once every six months. Available higher-level research evidence supports the superiority of denosumab against other anti-osteoporotic drugs. In a dose-response-based meta-analysis encompassing 142 RCTs, denosumab demonstrated greater BMD gains compared with other drug classes; namely alendronate, risedronate, zoledronic acid, ibandronate, raloxifene and calcitonin [29]. In concordance, a recently published meta-analysis involving 2,968 non-naïve patients reported superiority of denosumab in augmenting BMD at all skeletal sites measured compared with other anti-osteoporotic drugs [30]. Owing to its dosing frequency and regimen simplicity, denosumab has also achieved higher persistence rates compared with bisphosphonates [31–33].

A unique characteristic of denosumab is that no apparent plateau in BMD gains has been demonstrated in the numerous trials so far. The FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months) was the largest phase III registration trial for studying denosumab. It included of 7,808 postmenopausal women with lumbar spine BMD T-scores < 2.5 that were randomly assigned to 60 mg denosumab / 6 monthly or placebo for three years [34]. The reported results unveiled a relative risk reduction (RRR) in the incidence of new vertebral fractures of 68%, $p < 0.0001$, while denosumab also reduced hip and non-vertebral fractures (RRR 40%, $p < 0.04$ and RRR 20%, $p < 0.01$)[34]. Recently published results revealed that ten years of denosumab administration resulted in a linear increase in lumbar spine BMD accounting for a cumulative 21.7% increase [35].

Unlike bisphosphonates, denosumab is not characterised by a long biologic half-life nor is it incorporated into the bone; hence its antiresorptive effect ceases after suspension of treatment. Several reports have described cases of multiple vertebral fractures upon discontinuation of denosumab, raising concerns about a rebound in bone turnover and BMD losses [36–39].

Following a systematic review of reported case series and a renewed analysis of the FREEDOM and FREEDOM Extension Trial, recommendations were issued by a working group formed by the European Calcified Tissue Society (ECTS); re-stratification of risk should be performed after five years of administration and denosumab cessation should not be considered without alternative osteoporosis treatment[40].

Owing to the drug's pharmacological mechanism of action, concerns had been raised regarding the potentiality to provoke immunosuppression and immune system dysfunction. According to post-market safety surveillance reports, serious adverse reactions involved AFFs, ONJ, severe symptomatic hypocalcemia (SSH) and anaphylaxis (Table 3) [41]. Four cases were adjudicated as consistent with AFF while another 32 were consistent with the ONJ, with the exposure to denosumab estimated at 1,252,566 patient-years. Anaphylaxis occurred in five patients with no fatal outcomes reported. In eight study subjects, SSH was evident, with chronic kidney disease identified as a risk factor in this group [41]. Of note, none of the existing RCTs has reported a higher incidence of AFF or ONJ with the administration of denosumab and a causal relationship has not been established yet.

2.1.3 Selective estrogen receptor modulators (SERMS)

Estrogen receptors are found both in osteoclasts and osteoblasts, contributing to bone remodelling regulation. It has been established that estrogen deficiency increases bone resorption [42]. The exact mechanism seems to be mediated by T-cells, which in an estrogen deplete-state, increase the secretion of tumor necrosis factor (TNF)–alpha, interleukin-6 (IL-6) and IL-1 [22,23,43]. These cytokines, in turn, enhance the production of RANKL and M-CSF [44] amplifying

osteoclastogenesis and osteoclast differentiation. Recent studies demonstrated that the intestinal microbiota modulates inflammatory responses caused by sex steroid deficiency, leading to trabecular bone loss. Estrogen depletion increased the permeability of the gut expanding Th17 cells, and upregulating the osteoclastogenic cytokines TNFα (TNF), RANKL, and IL-17 in the small intestine and bone marrow in murine models [a].

[a] Li JY, Chassaing B, Tyagi AM, et al. Sex steroid deficiency-associated bone loss is microbiota dependent and prevented by probiotics. J Clin Invest. 2016 Jun 1;126(6):2049-63.

Overcoming estrogen depletion emerged as another promising pharmacological target for the treatment and prevention of osteoporosis in post-menopausal women. Over the past decade, SERMs have been intensively studied [45]. They are synthetic, structurally different non-steroidal agents that have tissue-specific estrogen receptor agonist or antagonist activity in varying magnitudes. Their biological activity is mainly attentive to ER-alpha (ER-α) and ER-beta (ER-β) subtypes for the ER family. ER-α is expressed in a greater tissue variety and is considered to be the principle ER expressed in bone tissue, whereas ER-β is mainly expressed in the ovaries, prostate and lungs [46]. SERMs exhibit different affinity properties, resulting in unique agonist/antagonist effects[47–49]. Notably, most SERMS exert estrogen-agonistic effects on bone and lipid metabolism and estrogen-antagonistic effects on uterine endometrium and breast tissue. In particular, by binding to estrogen receptors in bone tissues, SERMs interfere with bone homeostasis by down-modulating the activity of osteoclasts in a transforming growth factor-β3-dependent manner leading to reduced bone resorption [50].

SERMs have been studied as a subject of great scientific interest, due to their theoretical ability to retain the beneficial effects of oestrogens while eliminating unwanted side-effects related to oestrogen-receptor binding in non-targeted tissues. There are two main classes of agents used in clinical practice: a) the triphenylethylene derivatives, tamoxifen and toremifene, which are employed for the treatment of breast cancer and b) raloxifene (benzothiophene derivative), bazedoxifene and lasofoxifene (naphthalene derivative), which are indicated for the prevention and treatment of osteoporosis [51].

Raloxifene, a second-generation SERM, has been established as a third-line treatment for the secondary prevention of osteoporotic fragility fractures in postmenopausal women [52], excluding hip and non-vertebral fractures. Further development of SERM compounds, led to another generation of SERMs with comparable chemical and molecular structure to raloxifene but optimised side-effect profile named as bazedoxifene (TSE-424) and lasofoxifene (CP-336156) [45].

In the 1990s, the idea of combining bazedoxifene with conjugated estrogen was introduced aiming to achieve greater estrogenic and anti-estrogenic effects than either of the components alone. The latter combination resulted in the introduction of a new classification named as tissue selective estrogen complex (TSEC) [53,54]. Phase III RCTs exploring the combination of bazedoxifene with conjugated estrogens in healthy post-menopausal women with osteoporosis have confirmed the aforementioned superiorities, showing improvement in vasomotor symptoms and little or no stimulation of breast or endometrium oestrogen receptors (ER) [55,56].

The incidence of new vertebral fractures in post-menopausal women with diagnosed osteoporosis (n=7,492), was significantly lower with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), than placebo (4.1%), and comparable to raloxifene 60 mg (2.3%), as demonstrated by a 3-year

phase III RCT [57]. Interestingly, secondary endpoints of the above study showed that bazedoxifene (with or without conjugated estrogen) also had a positive effect on lumbar spine BMD in healthy post-menopausal women, compared with placebo groups, which was maintained after five to seven years of treatment [58]. Bazedoxifene has been approved by the European Medicines Agency (EMA) for the treatment of osteoporosis in 2009, while the U.S. Food and Drug Administration (FDA) granted approval of bazedoxifene with conjugated estrogen as a combinational drug in 2013, for the prevention of postmenopausal osteoporosis and vasomotor symptomatology.

Lasofoxifene has been described as another 3rd generation SERM, with comparable clinical effects to bazedoxifene. Lasofoxifene demonstrates high-affinity selective binding to both ERα and ERβ receptors [59]. Unlike bazedoxifene, it is characterized by a remarkable oral bioavailability, which is attributed to increased resistance in intestinal wall glucuronidation [60,61]. Lasofoxifene has demonstrated linear pharmacokinetics over a wide dose range (from 0.01 to 100 mg/d), and interestingly a Cmax of ~ 6 hours. Elimination has also been studied, and terminal elimination half-life ($t_{1/2}$) has been estimated to be reached at day 6 [62].

Dosing regimens were compared in a phase II RCT were BMD increase was measured as a biomarker with both doses of lasofoxifene, compared with baseline (increases of 1.8% and 2.2% for 0.25 mg and 1.0 mg/day, respectively, $p \leq 0.05$), and with placebo (3.6% and 3.9% for 0.25 mg and 1.0 mg/day, respectively, $p \leq 0.05$) [61]. Lasofoxifene has been evaluated in multiple phase III clinical trials including the PEARL [63] (Postmenopausal Evaluation and Risk Reduction With Lasofoxifene), OPAL [64] (Osteoporosis Prevention and Lipid-Lowering study), CORAL [61] (Comparison of Raloxifene and Lasofoxifene trial), where it repetitively demonstrated an improvement in bone mass and a reduction in the risk of vertebral and non-vertebral fractures. As

concluded after the completion of all the aforementioned trials, lasofoxifene, demonstrated a dose-related optimized side effect profile compared to placebo. The RRR in the absolute incidence of invasive breast cancer was 85% for 0.5 mg/day ($p<0.05$), 21% for 0.25 mg/day ($p>0.1$) and for the incidence of major coronary heart disease 1.8% for 0.5 mg/day $p<0.05$ and 2.4% for 0.25mg/day $p>0.1$[65].In line with the risk of deep vein thrombosis (DVT) pertaining to estrogen replacement regimens, lasofoxifene was associated with an approximately 2-fold increased risk of DVT, as evidenced by the findings of the PEARL study follow-up. In fact, pulmonary embolism occurred less frequently than deep vein thrombosis (0.2% vs 0.8%, respectively) but was also significantly increased in patients treated with the active drug compared with placebo [hazard ratio (HR): 4.49, 95% confidence interval (CI), 0.97–20.79 for lasofoxifene 0.5 mg/d and HR: 5.98, 95% CI, 1.33–26.72 for lasofoxifene 0.25 mg/d] [66].

To date, the FDA has yet to approve the use of lasofoxifene following the last rejection in January 2009. Nevertheless, EMA approved its use for the treatment of osteoporosis-related fractures in post-menopausal women, the same year. This followed by a cessation of the validity of the marketing authorization in 2012 as lasofoxifene had not been marketed in Europe since its initial marketing authorization.

2.2 Anabolic agents

Anabolic agents stimulate bone formation and are represented predominantly by teriparatide, a human recombinant parathyroid hormone (PTH) containing the first 34 amino acids of the endogenous hormone, and abaloparatide, a synthetic PTH-related peptide (PTHrP) analogue. The

biological activities of PTH and PTHrP analogues on bone are mediated through activation of the parathyroid hormone 1 receptor (PTH1R) [73], a G-protein coupled receptor with two different high-affinity conformations R0 and RG, expressed in a plethora of tissues including osteoblasts and osteoclasts [74].Notably, osteoanabolic potency has been demonstrated only with intermittent administration of PTH and PTHrP analogues, whereas continuous stimulation of PTH1R has been shown to augment bone turnover and consequently result in bone resorption [75]. In the clinical setting, teriparatide has reportedly led in spine and hip BMD gains, vertebral and non-vertebral risk reduction in postmenopausal women, as well as in men and individuals suffering from glucocorticoid-induced osteoporosis [76]. The recent VERO study demonstrated also that teriparatide was significantly more effective in reducing the new vertebral fractures compared to alendronate after 24 months therapy in postmenopausal women with severe osteoporosis meaning at least two moderate or one severe vertebral fracture and a BMD T score of less than or equal to -1·50 [b].

[b] 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 Jan 20;391(10117):230-240.

Abaloparatide is a selective activator of the PTH1R, exhibiting a higher selectivity to the RG confirmation than teriparatide [77]. The aforementioned difference is translated into a more transient response to ligand binding [74], hence minimizing stimulation of bone resorption. Initial attempts at evaluating the therapeutic potential of abaloparatide in animal studies unveiled encouraging results. Abaloparatide exhibited its osteoanabolic potency by increasing bone formation and BMD gains both in ovariectomized rats and ovariectomized cynomolgus monkeys [78,79]. Subsequently, as the agent moved swiftly from animal to human trials, concordant results

were reported. A phase II multicentre, double-blind, RCT investigated the efficacy and safety of various dosing regimens of abaloparatide, against teriparatide and placebo [80]. Upon comparison of abaloparatide with placebo, significant BMD gains were reported in total hip and lumbar spine with the 40- and 80-μg once daily regimens and in femoral neck BMD with the 80-μg regimen. Notably, abaloparatide was superior to teriparatide in augmenting total hip BMD [80].

With regard to clinically translatable outcomes, the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) Trial, a phase III, double-blind RCT, evaluated the effect of abaloparatide, teriparatide and placebo on the incidence of new vertebral fractures and BMD changes[81]. Both active agents demonstrated superiority against placebo in reducing fractures and augmenting BMD at all skeletal sites studied. When compared with teriparatide, the 80-μg regimen demonstrated no difference concerning efficacy endpoints, albeit the incidence of hypercalcemia was lower [81].

Finally, abaloparatide received approval for the treatment of postmenopausal osteoporosis by the FDA in April 2017 constituting the first new anabolic osteoporosis drug in the US for nearly 15 years [82]. EMA however, refused at the moment approval of the abaloparatide for the treatment of postmenopausal osteoporosis having mainly concerns about the effectiveness of the drug in the prevention of non-vertebral fractures and possible effects on heart function as the increase in the heart rate and palpitations.

Interestingly, several RCTs have attempted to adjudicate the effect of combining PTH analogs with other active agents. When compared with alendronate and PTH monotherapy, the combination of both failed to show any additive BMD increase [83]. In contrast, the Denosumab and Teriparatide Administration (DATA) study proved combined denosumab and teriparatide therapy to be superior to either agent alone[84]. With regard to abaloparatide, an extension of the ACTIVE trial was designed to assess the effect of the concurrent administration of alendronate in

patients previously treated wither with abaloparatide or placebo. Results confirmed that gains in BMD and RRR increased even further for the abaloparatide/alendronate group compared with the placebo/alendronate group[85].

3. Sequential therapy

In general, the optimal therapeutic strategy after discontinuation of an anti-osteoporotic therapy, has not been established. However, several data have emerged and are presented as follows.

3.1. Anti-resorptive after osteo-anabolic therapy

The sequential therapy with anti-resorptive agents has been evaluated to test the BMD gain following the cessation of anabolic therapy. Alendronate led to a further increase in BMD, especially in the trabecular bone after completion of PTH (1-84) therapy [c]. Raloxifene also showed a beneficial effect in maintaining lumbar spine and increasing hip BMD after one year of teriparatide therapy [d]. The ACTIVExtend study was the first to test as the primary end-point, the incidence of vertebral and nonvertebral fractures and changes BMD of the sequential administration of an anti-resorptive agent (alendronate) after completion of the prespecified therapy of an anabolic compound. Abaloparatide followed by alendronate regimen effectively reduced the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures and increased BMD compared with placebo followed by alendronate [e].

[c] D.M. Black, J.P. Bilezikian, K.E. Ensrud, et al., One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis, N Engl J Med 353(6) (2005) 555-65.

[d] R. Eastell, T. Nickelsen, F. Marin, 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 24(4) (2009) 726-36.

[e] H.G. Bone, F. Cosman, P.D. Miller, et al., ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis, J Clin Endocrinol Metab 103(8) (2018) 2949-2957.

3.2. Osteo-anabolic after anti-resorptive therapy

Teriparatide treatment for 24 months significantly increased the BMD in patients with and without previous antiresorptive therapy use [f,g]. Prior antiresorptive agent treatment, however, especially those of longer skeletal half-lives, modestly blunted the expected BMD response to teriparatide [f] but this has not been confirmed in all studies [g]. Romosozumab has also been evaluated in women previously treated with bisphosphonates for at least three years, in a head-to-head comparison with teriparatide. Romosozumab induced significantly greater hip BMD changes compared with teriparatide at one-year follow-up [h].

[f] B.M. Obermayer-Pietsch, F. Marin, E.V. McCloskey, et al., Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment, J Bone Miner Res 23(10) (2008) 1591-600.

[g] S. Boonen, F. Marin, B. Obermayer-Pietsch, et al., Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis, J Clin Endocrinol Metab 93(3) (2008) 852-60.

[h] B.L. Langdahl, C. Libanati, D.B. Crittenden, 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 390(10102) (2017) 1585-1594.

2.3 Emerging therapies

2.3.1 Anabolic agents with antiresorptive properties

Sclerostin – an osteocyte secreted glycoprotein coded for by the SOST gene [17q12-q21] - is a key regulator of osteoblast differentiation and function [6]. It binds to LRP-5/6 co-receptors preventing interactions between Wnt and its receptor, ultimately, leading to phosphorylation and degradation of ß-catenin [101]. As a result, Wnt target genes are not activated, downregulating the canonical Wnt singling pathway responsible for osteoblast differentiation, proliferation and function[86]. Notably, sclerostin has also been shown to promote osteoclast formation through a RANKL-dependent pathway [102]. From a clinical perspective, a study of patients with sclerostin genetic deficiency (van Buchem disease) found that patients had increased bone mass, strength and reduced fracture rates, corroborating the importance of sclerostin in bone metabolism [103]. The synthesis of molecular and clinical evidence rendered sclerostin blocking with a monoclonal antibody an attractive therapeutic target for osteoporosis.

Since then, three monoclonal antibodies have been developed: romosozumab (AMG-785), blosozumab (LY251546) and BPS804 [98]. Animal studies with romosozumab in ovariectomized rats and primates showed increases in bone mass and strength owing to the increased bone

formation and reduced resorption [104,105]. Early human trials of romosozumab showed that the agent reaches peak serum concentration within a week, demonstrating a high binding affinity for sclerostin while displaying non-linear kinetics with biphasic elimination (t1/2=11-18 and 6-7 days) [106–108].

A Phase II RCT investigated the efficacy and safety of various dosing regimens of romosozumab against placebo, alendronate and teriparatide in post-menopausal women with low BMD [109]. When compared with placebo and active comparators, the 140mg and 210mg once monthly dosing regimens of romosozumab were significantly better in increasing lumbar spine, total hip and femoral neck BMD after 12 months of treatment. Indeed, bone formation biomarkers increased, albeit transiently (for ~2 months), with bone resorption assays demonstrating a sustained reduction of bone turnover for the duration of the trial. These results are suggestive of an uncoupling of bone remodelling such that osteoclast inhibition does not lead to reduced bone formation [86]. Similar results were also obtained in a placebo-controlled trial of blosozumab, further confirming the efficacy of sclerostin inhibition[110]. In a subgroup analysis of the phase II RCT, investigators assessed bone strength at the LS and TH by quantitative computed tomography (QCT) in patients receiving placebo, open-label teriparatide (20 μg daily) or romosozumab (210 mg monthly). Reportedly, romosozumab achieved significantly greater gains in volumetric BMD and strength compared to teriparatide [111].

Romosozumab is the first agent of its class to have progressed to phase III trials with the proposed regimen of 210mg subcutaneously injected once monthly. The STRUCTURE trial investigating romosozumab vs. teriparatide in high-risk for fracture postmenopausal women transitioning from a bisphosphonate showed superiority of romosozumab in hip, lumbar and femoral neck BMD gains (2.6% vs -0.6%, 3.2% vs -0.2%, 9.8% vs. 5.4%, p for all comparisons <0.0001) [112]. Similar

significant hip, lumbar and femoral neck BMD gains in favour of romosozumab vs. placebo were noted in the BRIDGE study of men with osteoporosis[113].

In terms of the clinically relevant end-points of reduction in new vertebral fractures, romosozumab was superior to placebo in the ARCH and FRAME studies; results sustained after the addition of alendronate and denosumab respectively [114,115]. However, only ARCH showed a significant reduction in new vertebral, non-vertebral and hip fractures with romosozumab treatment. The discrepancy was cautiously attributed by the FRAME investigators to the recruitment of patients from a particular geographic region (Latin America) with a lower-than-expected non-vertebral fracture rate; effectively underpowering the trial for this end-point. Notably, a post-hoc analysis excluding patients from Latin America showed a significant reduction in new non-vertebral fractures favouring romosozumab[115].

Romosozumab was well-tolerated amongst recipients with discontinuation rates of 9.2%-11.2%, not significantly different from comparator group discontinuation rates whether active or placebo[112,114,115]. Regarding its safety, romosozumab inhibits sclerostin, whose secretion is confined mainly to the musculoskeletal system. However, the canonical Wnt signalling pathway is active in the cardiovascular and haematological systems [116–118]. Nonetheless, malignancy rates were similar in patients receiving romosozumab compared with control groups [114,115]. On the other hand, the signal with adjudicated serious adverse cardiovascular events is mixed; the FRAME study found no difference when romosozumab was compared to placebo (1.1% vs 1.2% respectively) [115], though the ARCH and BRIDGE studies showed numerically higher serious adverse cardiovascular events with romosozumab when compared to alendronate (2.5% vs 1.9%) and placebo (4.9% and 2.5%) respectively [113,114]. The latter underscored the FDA's request for data from all three romosozumab trials prior to its final licensing decision.

Although the exact pathogenetic mechanism has yet to be clarified, the loss of the sclerostin inhibitory role on vascular calcification and the potential cardioprotective role of alendronate have been proposed [113,114]. Recently, Romosozumab, however, received approval in Japan for the treatment of osteoporosis in patients at high risk of fracture [i]

[i] Pharmaceuticals and Medical Devices Agency Prescription Drug Database http://www.info.pmda.go.jp/go/pack/39994C7G1022_1_02/

Nonetheless, the aforementioned results show that sclerostin inhibition is a potential therapeutic target for osteoporosis. To date, no phase III trials with blosozumab are being conducted while BPS804 is now undergoing phase IIa trials for osteogenesis imperfecta after withdrawing from the ever-competitive osteoporosis market.

3. Conclusions

Existing anti-resorptive pharmacotherapy strategies for osteoporosis in women encompass bisphosphonates, denosumab and SERMS. The third generation of bisphosphonates employed to date for the treatment of osteoporosis (alendronate, ibandronate, zoledronate, risedronate) appears to be a reliable and cost-effective option. However, concerns have been raised with respect to their link to ONJ and AFFs. In addition, poor compliance has been reported owing to complex dosing regimen, while long-term efficacy (> 5 years) is yet to be established. Denosumab introduced a novel mechanism of action by inhibiting the interaction between RANK and its ligand, therefore reducing osteoclast maturation, survival and bone resorption. Dosing frequency and regimen simplicity have contributed to higher persistence and compliance rates, whereas recently published

data confirmed its unique characteristic of achieving a linear increase in BMD with no plateau being observed. Concerns regarding its association with ONJ and AFFs have not been confirmed as postmarket safety reports and higher-level evidence published failed to establish a causal relationship.

Teriparatide and abaloparatide constitute the only approved osteoanabolic therapies currently used in the treatment of osteoporosis. They have a vital role in the management of high fracture risk patients and can be combined or precede anti-resorptive therapy to maximize their effect. One should note though their limitations, of the parenteral delivery route and high cost [76].

Refined knowledge regarding the molecular mechanisms and pathophysiology underlying bone remodelling, resulted in the development of state-of-the-art pharmacotherapies with dual action. Indeed, the efficacy of sclerostin inhibition was proved since both romosozumab and blosozumab achieved a significant increase in BMD in phase II studies. Concordant results were reported in phase III trials, where romosozumab - the only agent of its class to progress to late-stage clinical development – augmented BMD in all skeletal sites measured. Recently Romosozumab received approval in Japan for the treatment of osteoporosis in patients at high risk of fracture.

4. Expert Opinion

Anti-resorptive drugs are used to suppress bone resorption and have spearheaded efforts to address the bone loss in osteoporosis, as well as the imbalance between bone formation and resorption. To date, four classes of agents are available: bisphosphonates, calcitonin, SERMS and denosumab. Two other drugs with unique mechanisms of action were either discontinued due to an unforeseen increase in stroke risk (odanacatib – cathepsin K inhibitor) or currently awaiting FDA’s final

licensing decision (romosozumab – sclerostin inhibitor that demonstrates both anabolic and anti-resorptive properties). Osteoanabolic agents have also proven to be a beneficial therapeutic option and can be combined with other active agents, particularly in patients classified as high fracture risk. As evidenced by current trials, osteoanabolic agents exhibit maximal effect when they precede anti-resorptive therapy. Moreover, while the combination of teriparatide and bisphosphonates does not appear to offer any additional benefit compared with monotherapy, results from the concurrent use of denosumab and teriparatide have been encouraging as additional BMD gains have been observed.

Despite the proven biochemical and clinical efficacy of established agents, the use of anti-osteoporosis drugs has been on the decline [119,120]. Indeed, widely disseminated issues of osteonecrosis of the jaw [121], atrial fibrillation and cardiovascular adverse events [122,123] may have contributed to this decline. However, the risk-benefit ratio of anti-osteoporotic therapy remains favourable [124] with some animal studies also showing potential in reducing arresting aortic valve and coronary artery calcification [125,126]. Recently, advances elucidating the cellular and molecular regulatory mechanisms of bone remodelling have spearheaded efforts to develop and establish novel therapies [127,128].

Traditional molecular techniques and animal models have been proven effective in identifying potential targets for new therapies; notwithstanding, a downturn in the number of new osteoporosis drugs has been observed. Abaloparatide, gaining approval by the FDA in April 2017, has been the first new anabolic anti-osteoporotic medication in the US for nearly 15 years. Considering the major breakthroughs achieved in the field of modern genetics, there may be more efficient ways in the quest for novel drug targets. Indeed, a recent retrospective analysis concluded that

medications with direct genetic support demonstrated a significantly higher success rate across the drug developing pipeline [129].

With the available spectrum of anti-resorptive drugs, the overall burden of osteoporosis could potentially be alleviated. However, low public awareness in addition to adverse-effect profile and lack of long-term fracture data have contributed to poor compliance and to a decline in the use of anti-osteoporotic drugs. There is need of public health awareness and healthcare provider education regarding screening, prevention and treatment of osteoporosis, as well as accurate adverse effect description. We also need new pharmacological approaches that will fill unmet needs, specifically having a favourable safety profile, lacking the adverse effects of at AFFs and ONJ, employing a well-defined and simple dosing regimen and demonstrating long-term efficacy in reducing fracture rate or augmenting BMD.

Article Highlights:

•Anti-resorptive drugs have spearheaded efforts to address bone loss in osteoporosis, while osteoanabolic agents play a key role in high risk patients and combination therapy.

- Abaloparatide, approved by the FDA in April 2017, has been the first new anabolic anti-osteoporotic medication in the US for nearly 15 years.
- Principles of existing antiosteoporotic medications in women, including mechanism of action, pharmacokinetics and safety profile are analysed.
- An overview of the key clinical trials conducted in the field of antiresorptive and osteoanabolic agents to date is presented.

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