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Novel therapies for osteoporosis

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ABSTRACT

Since the identification of osteoporosis as a major health issue in aging populations and the subsequent development of the first treatment modalities for its management, considerable progress has been made in our understanding of the mechanisms controlling bone turnover and disease pathophysiology, thus enabling the pinpointing of new targets for intervention. This progress, along with advances in biotechnology, has rendered possible the development of ever more sophisticated treatments employing novel mechanisms of action. Denosumab, a monoclonal antibody against RANKL, approved for the treatment of postmenopausal and male osteoporosis, significantly and continuously increases bone mineral density (BMD) and maintains a low risk of vertebral, non-vertebral, and hip fractures for up to 8 years. Currently available combinations of estrogens with selective estrogen receptor modulators moderately increase BMD without causing the extra-skeletal adverse effects of each compound alone. The cathepsin K inhibitor odanacatib has recently been shown to decrease vertebral, non-vertebral, and hip fracture rates and is nearing approval. Romosozumab, an anti-sclerosin antibody, and abaloparatide, a PTH-related peptide analog, are at present in advanced stages of clinical evaluation, so far demonstrating efficaciousness together with a favorable safety profile. Several other agents are currently in earlier clinical and preclinical phases of development, including dickkopf-1 antagonists, activin A antagonists, β-arrestin analogs, calcilytics, and Src tyrosine kinase inhibitors.

1. Introduction

Current treatments for osteoporosis target either the osteoclast, by inhibiting bone resorption (antiresorptive agents), or the osteoblast, by stimulating bone formation (osteoanabolic agents). However, the decrease in bone resorption induced by antiresorptives is soon accompanied by a decrease in bone formation, due to the coupling effect, thereby limiting their efficacy. Likewise, increased bone formation by osteoanabolics is followed by an increase in bone resorption. Therefore, efforts are being made to develop molecules that achieve uncoupling of bone formation from resorption. Furthermore, identification of new pathways and molecules involved in bone biology is setting novel and more sophisticated targets and thereby

Abbreviations: AE, adverse event; AFF, atypical femoral fractures; ASBMR, American Society for Bone and Mineral Research; BZA, bazedoxifene; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; BTM, bone turnover marker; CatK, cathepsin K; CaSR, calcium-sensing receptor; CE, conjugated estrogens; CKD, chronic kidney disease; CTx, carboxy-terminal telopeptide of type 1 collagen; Dkk-1, dickopff-1; FN, femoral neck; LRP, lipoprotein-receptor related protein; LS, lumbar spine; NTx, amino-terminal telopeptide of type 1 collagen; ONJ, osteonecrosis of the jaw; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; PTH1R, parathyroid hormone receptor type 1; RANKL, receptor activator of nuclear factor κ-B ligand; SERM, selective estrogen receptor modulator; ODN, odanacatib; OPG, osteoprotegerin; OVX, ovariectomized; TH, total hip; Wnt, canonical wingless.

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raising hope for the development of innovative treatment strategies that are effective and safe for the management of osteoporosis in the years to come.

In this review, we summarize treatment options for osteoporosis in order of development, starting with recently available agents possessing novel mechanisms of action, followed by agents in advanced phases of development, and, finally, agents in earlier phases of clinical or preclinical development as well as newly identified treatment targets.

2. Recently approved medications

2.1. *Denosumab*

Denosumab is a human monoclonal IgG2 antibody that binds and inhibits the receptor activator of nuclear factor κ-B ligand (RANKL) with high specificity and affinity [1]. RANKL is essential for the activation of its receptor, RANK, on the surface of osteoclasts and their precursors and enhances their differentiation, survival, and function [2] (Figs. 1 and 2). Osteoprotegerin (OPG) is the natural antagonist of RANKL (Fig. 1) and RANKL/OPG imbalance is associated with osteoporosis and other metabolic bone diseases [3].

Denosumab's specificity for RANKL is far superior to the previously tested recombinant OPG or RANK molecules, resulting in prolonged antiresorptive effects [4,5] (Fig. 2). A single subcutaneous (s.c.) dose leads to dose-dependent suppression of bone remodeling for up to 6 months [4]. Bone resorption markers decline rapidly (within the first 12 hours) and profoundly (>80% from baseline), reaching a nadir at about 1 month and being maximally suppressed for the subsequent 3 months, while bone formation markers decrease by 55%–75% at 2–3 months following injection [6,7]. The decrease of bone remodeling reduces serum calcium and phosphate levels, causing an increase of parathyroid hormone (PTH) levels, especially during the first 1–2 months [4,8]. The approved dose for osteoporosis treatment is 60 mg s.c. every 6 months, which inhibits RANKL equally to equivalent weight-based dose adjustments, with no need for modifications based on age, gender, and race or in renal function [1,9].

Following the phase I [4] and II [7] studies which defined the dose and efficacy of denosumab in terms of bone mineral density (BMD) accrual and bone turnover marker (BTM) suppression, the pivotal phase III FREEDOM trial [10] showed significant relative risk reduction for hip (40%), vertebral (68%), and non-vertebral fractures (20%) compared to placebo after 3 years of treatment. BMD increased progressively, reaching overall 9.2% at the lumbar spine (LS) and 6% at the total hip (TH) compared to placebo, and the change in TH BMD accounted for over 70% of the reduction in vertebral and non-vertebral fractures with denosumab [11]. Denosumab was effective across a broad range of study subjects' renal function, with estimated GFR as low as 15 ml/min [12]; however, there is an elevated risk of hypocalcemia in patients either with severe renal deficiency or on dialysis [11,13–15].

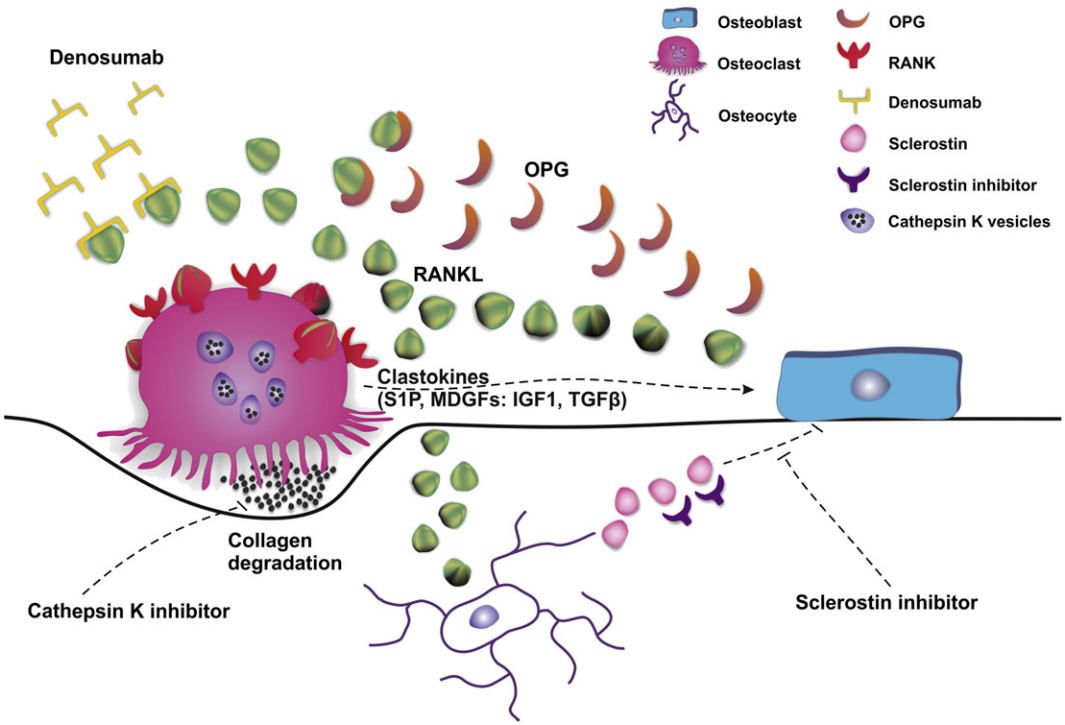

Fig. 1 – The mechanism of action of novel osteoporotic treatments at cellular level: Denosumab binds RANKL in a similar way as osteoprotegerin (OPG) thereby preventing its binding to RANK and the activation of the osteoclast; cathepsin-K inhibitors prevent collagen degradation by cathepsin-K; sclerostin inhibitors bind sclerostin and prevent its inhibitory effect on the osteoblasts.
Abbreviations: **IGF1, insulin growth factor 1; MDGFs, matrix derived growth factors; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor κB; RANKL, receptor activator of nuclear factor κB ligand; TGFβ, transforming growth factor β.**