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EDITORIAL

Biologics for Osteoporosis: Where Do We Stand?

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Osteoporosis is a common disease with wide prevalence, especially in seniors. Fractures induced by osteoporosis not only decrease the patient's quality of life, but also cause heavy financial burden to the society during medical treatment making this major metabolic bone disease a growing health-economic problem worldwide [1]. Estimated annual costs for osteoporotic fractures are between $10 billion and $17 billion in the United States [2] with a provisional estimation by year 2025 to rise up to $25.3 [3]. While in the European Union annual estimation costs is $30.9 billion [4]. 70% of these costs in elderly people being at the age of seventy five or older seniors [5].

The main clinical consequences to osteoporosis are bone fractures, which often lead to patient disability or even death [6]. Bone is a dynamic tissue that is continuously renewed throughout life by the process of bone remodeling. There is disturbance in this equilibrium with increased resorption by osteoclasts and less bone formation by osteoblasts, leading bone to become weaker and more prone to fractures [7].

The remodeling process is the result of interactions between these cells (osteoclasts and osteoblasts) and multiple molecular agents, including hormones, growth factors and cytokines [8]. It is a disease characterized by abnormalities in the amount and architectural arrangement of tissues which lead to impaired skeletal strength. Primary osteoporosis occurs in both sexes at all ages but often follows menopause in women and occurs later in men. In contrast secondary osteoporosis is a result of medication, other conditions, or diseases [9].

Altered bone remodeling-excessive resorption and/or impaired formation-is a key risk factor for osteoporotic fracture [10]. The remodeling cycle is tightly regulated such that bone formation is coupled with bone resorption and mass is maintained. The exceptions to this occur in menopause and older age when resorption exceeds formation [11]. Increased resorption is associated with a decrease in bone mineral density (BMD) and an increased risk of fracture [12]. Osteoporosis is characterized by a decrease in bone mass and deterioration in micro-architecture leading to an enhanced fragility of the skeleton [13].

There is a direct relationship between the lack of estrogen after menopause and the development of osteoporosis [14]. Bone turnover increases during menopause, with osteoclast-mediated bone resorption exceeding bone formation. Recent discoveries in bone biology have demonstrated that, receptor activated nuclear factor kappa ligand (RANKL), a cytokine member of the tumor necrosis factor super-family, is an essential mediator of osteoclast formation, function and survival. An anti-osteoporotic drug is Denosumab. It is a fully human monoclonal antibody (mAb) with a high affinity and specificity for human RANKL. By binding to its target, denosumab prevents the interaction of RANKL with its receptor RANK on osteoclasts and their precursors and inhibits osteoclast-mediated bone resorption [15].

The majority of pharmacological osteoporosis therapies, including bisphosphonates, calcitonin, hormone replacement therapy, and selective estrogen receptor modulators, prevent bone loss by reducing bone resorp-

tion. Restoration of bone mass in patients suffering from osteoporosis is an area of medical interest [16]. Biologic therapies for rheumatic diseases provide an alternative to the existing treatment methods of disease-modifying anti-rheumatic drugs and other immunosuppressive medications. However, their current drawbacks such as the inconvenience of intravenous administration, high costs and adverse events, prevent their wide use as first-line medications [17].

Although it has long been recognized that inflammation, a consequence of immune-driven processes, significantly impacts bone turnover, the degree of centralization of skeletal and immune functions has only begun to be dissected recently. Although numerous inflammatory cytokines are now recognized to promote osteoclast formation and skeletal degradation, with just a few exceptions, RANKL is now considered to be the final downstream effect or cytokine that drives osteoclastogenesis and regulates osteoclastic bone resorption [18].

Biologic therapies including tumor necrosis factor alpha (TNF-α) blockers have been shown to reduce disease activity measures and joint damage progression. However, their effects on systemic osteoporosis remain to be elucidated in rheumatoid arthritis patients [19]. It is advantageous to have a range of effective biologic drugs available for patients suffering from severe osteoporosis. With the various available biologic therapies, the therapy can be tailored to the individual patient. As the complexity of preparing biologics has diminished, costs may be driven down, allowing them to be used at early stages of disease and hence enable prevention of irreversible damage [17].

Denosumab (Prolia) was recently approved by the United States Food and Drug Administration for treatment of postmenopausal osteoporosis in the year 2010. Patients treated with denosumab experienced significant gains in bone mineral density, rapid reductions in markers of bone turnover, and a reduced risk for new vertebral fractures [20-22]. Given its mechanism of action, it is an anti-resorptive therapy that is administered as a 60-mg subcutaneous injection every 6 months. It is the first biologic anti-resorptive therapy that has shown to be a promising drug, having safety in patients with renal impairment [23]. Denosumab is a fully human monoclonal antibody (mAb) [24] which is available for treatment of osteoporosis [25].

Wnt signaling is involved in the coupling process decreasing bone resorption with new bone formation [26]. The changes in bone turnover markers associated with denosumab treatment of postmenopausal osteoporosis include a significant increase in sclerostin similar to those seen after long-term treatment with bisphosphonates and a significant decrease in DKK1. This latter observation might explain the continuous increase over 5 years in BMD observed during treatment of postmenopausal osteoporosis with denosumab [27]. As osteoporosis is a chronic disease requiring prolonged treatment, characterization of the long-term efficacy and safety of denosumab is essential for clinical practice [24]. Denosumab, has been approved in Japan, Europe and the US for the treatment of postmenopausal osteoporosis as well as bone metastasis [27]. With limited healthcare resources, economic evaluations are increasingly being used by decision-makers to optimize healthcare resource allocation and evaluate the cost-effectiveness of denosumab [21].

A combination of teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with approved therapies. Combination treatment might, therefore, be useful to treat patients at high risk of fracture [28]. The most common adverse reactions to denosumab include back pain, pain in extremities, musculoskeletal pain, and cystitis. Serious, but rare, adverse reactions include the development of serious infections, dermatologic changes, and hypocalcemia [22]. Adverse events did not increase with long-term administration of denosumab [29]. Furthermore, the mechanism of adverse events of denosumab, such as hypocalcemia and osteonecrosis of the jaws, has not been completely explained [27].

Other biologic agents increase bone formation. A neutralizing Dkk-1 antibody is expected to increase bone mass by increased bone formation by osteoblasts and thus preventing osteoporotic fractures. PF-04840082 is a humanized prototype anti-Dkk-1 monoclonal antibody for the treatment of osteoporosis. It binds human, mouse, rat, and cynomolgus monkey Dkk-1 *in vitro* with high affinities [16]. A sclerostin neutralizing monoclonal antibody (Scl-AbII) for bone formation has been identified and tested in an aged ovariectomized rat model of postmenopausal osteoporosis. Scl-AbII treatment had robust anabolic effects, with marked increases in bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. This not only resulted in complete reversal, at several skeletal sites, but also further increased bone mass and strength. Antibody-mediated inhibition of sclerostin represents a promising new therapeutic approach for the anabolic treatment of bone-related disorders, such as postmenopausal osteoporosis [30] and fracture trials are underway [31]. All dose levels of romosozumab were associated with significant increases in bone mineral density at the lumbar spine compared with alendronate and teriparatide. Romosozumab was also associated with large increases in BMD at the total hip and femoral neck, as well as transitory increases in bone-formation markers and sustained decreases in a bone-resorption marker. Except for mild, generally nonrecurring injection-site reactions with romosozumab, adverse events were similar to other therapeutics. Romosozumab binds to sclerostin, an osteocyte-derived inhibitor of osteoblast activity and increases bone formation [32].

It has been suggested that infliximab treatment may limit the risk of osteoporosis in rheumatoid arthritis (RA) patients [33]. Low body mass index, early disease onset, high corticosteroid doses and, anti-TNF-α therapy are associated with increased risk of osteoporosis. Lower T scores in patients on infliximab occur as patients receiving this therapy have more severe inflammation, which is associated with elevated osteoclastogenic factors, rather than as a side-effect of the anti-TNF-α therapy [34]. On evaluating the influence of rituximab on markers of bone metabolism, there was no significant change of the bone formation markers such as: alkaline phosphatase and c-terminal propeptide of collagen I. It appears that rituximab lowered osteoclast activity often found increased in active RA contributing to osteoporosis in this disease [35].

Conflict of Interest

None.

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