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Review

Effects of targeted therapies on the bone in arthritides

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ABSTRACT

Inflammatory arthritides, such as rheumatoid arthritis (RA) and spondyloarthritides (SpA) have been associated with both localized bone resorption and/or formation, and generalized osteoporosis. Systemic inflammation may be the major driver for bone loss in arthritis. In RA and peripheral SpA the RANK-RANKL-OPG network is involved in bone resorption, while in axial SpA the Wnt-β-catenin axis and its inhibitors (DKK-1, sclerostin) are the most relevant. Targeted therapies including biologics and small molecule tyrosine kinase inhibitors may interfere with inflammatory bone metabolism. Most of these compounds are able to slow down radiographic progression and osteoporosis in arthritides. In very early cases of non-radiological SpA, there may be a window of opportunity allowing to prevent syndesmophyte formation. The inability of targeted therapies to increase the production of DKK-1 and sclerostin may explain the lack of efficacy of TNF inhibitors to halt syndesmophyte formation in SpA. Further clinical trials are needed to better understand the bone effects of targeted therapies.

Contents

1. Introduction

Inflammatory arthritides, such as rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA) have been associated with generalized bone loss

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(osteoporosis), as well as localized inflammatory bone resorption and/or pathologic bone formation [1–7]. It has become evident that all targeted therapies approved for the treatment of arthritides may exert beneficial effects on the bone. In clinical trials, tumor necrosis factor α (TNF-α) blockers, as well as other biologics and JAK inhibitors have been shown to slow down bone destruction and inhibit radiological progression in RA [5,8,9]. In contrast, there have been lots of controversies with regards to the efficacy of biologics, primarily TNF inhibitors in halting bone formation and the development of syndesmophytes in axial SpA [10–12] In addition to their effects on localized bone turnover, most targeted therapies also exert systemic bone effects and thus influence the development and progression of generalized osteoporosis in conjunction with RA and SpA [1,2,5,13–16]. (See Figs. 1 and 2.)

In this review, we will give a brief introduction to osteoimmunology and discuss the molecular mechanisms of bone resorption and formation in arthritides. Then, data from clinical studies will be presented on the effects of targeted therapies on bone turnover and its biomarkers, localized bone loss and bone formation, as well as on secondary osteoporosis. We will also focus on associations with clinical and radiographic responses to targeted therapies.

2. Regulation of bone destruction and formation by inflammation

2.1. Effects of cytokines on catabolic osteoclast-dependent bone remodeling

The RANK-RANKL (receptor activator of nuclear factor-kappa B ligand) system is the major driver of bone destruction in inflammatory arthritis. In brief, TNF-α, a cytokine playing a central role in synovial inflammation is indirectly responsible for inducing bone loss via the induction of osteoclast differentiation from monocyte lineage precursor cells exposed to RANKL. TNF-α also stimulates RANKL expression by osteoblasts, T- and B-cells [1,6,17,18]. TNF-α, on one hand, indirectly stimulates osteoclastogenesis via RANKL [19,20], but also directly induces osteoclast function [19,21]. Direct stimulation of osteoclasts by TNF-α seems to require the presence of RANKL as well [19]. Other pro-inflammatory cytokines, such as IL-1, IL-6 and IL-17 also exert similar actions [1,6,17,18,20–22]. In accordance with these concepts, osteoprotegerin (OPG) is a decoy receptor of RANKL has shown to influence

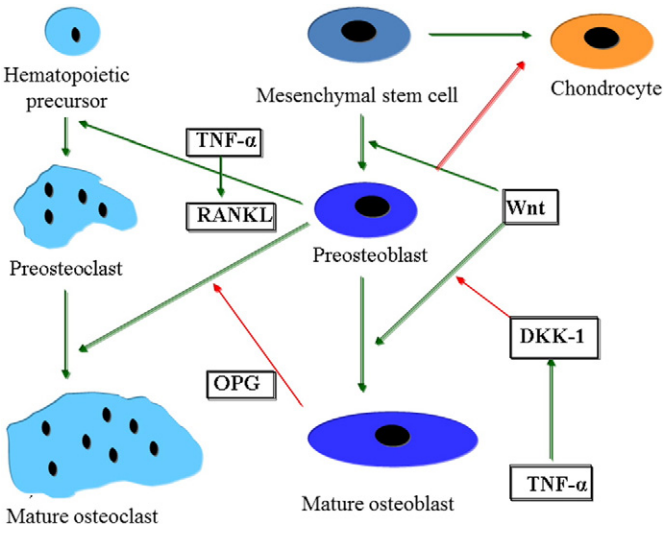

Fig. 1. Interactions of the RANKL-OPG and the Wnt-β-catenin systems with each other and with TNF-α. RANKL stimulates, while OPG inhibits osteoclastogenesis and bone resorption. Wnt induces bone formation. In RA and peripheral SpA, RANKL-mediated bone resorption overrides bone formation and leads to erosions. On the other hand, in axial SpA, there is excessive Wnt signaling with defective regulation by DKK-1 and sclerostin. TNF-α induces RANKL, as well as DKK-1 thus acting towards bone resorption and inhibition of bone formation. Green arrows indicate stimulation, red arrows mean inhibition.

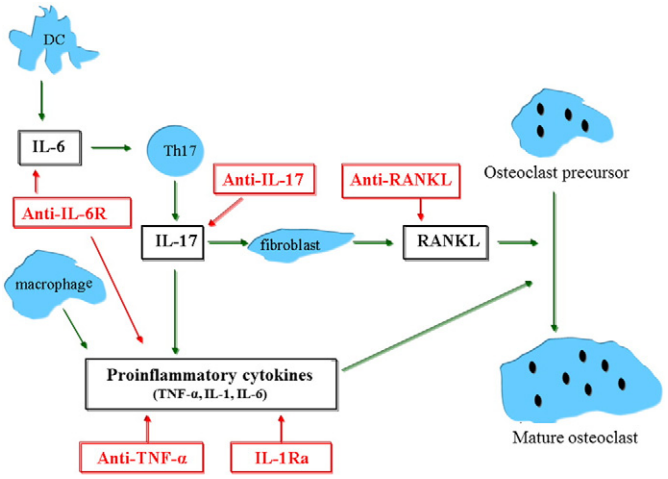

Fig. 2. Effects of targeted therapies on bone metabolism.

arthritic bone erosions [23]. Hence a low OPG/RANKL ratio has been associated with future progression of radiographic damage in RA [24,25]. Thus, anti-cytokine biologics may have significant effects on bone resorption in arthritides and other inflammatory conditions [20,26].

2.2. Effects of cytokines on anabolic osteoblast-dependent bone remodeling

With respect to bone formation, wingless-related integration site (Wnt) proteins emerge as central regulators, including Wnt1 and Wnt3a expressed by preosteoblasts, upon osteoblast activation, a multi-molecular complex composed of low-density lipoprotein receptor related protein 5 and 6 (LRP5/6), frizzled-related proteins (FRP), phosphoprotein Dishevelled (Dsh), axin, glycogen synthase kinase 3 (GSK3) and, most importantly, β-catenin is formed. LRP5 and LRP6 are members of the lipoprotein receptor family. Wnt3a activates LRP5/6 and FRPs. Upon activation, axin, Dsh and GSK3, all regulated by LRP5/6 stay together within the cell surface molecular complex. Thus, β-catenin becomes free, and after its stabilization, it is transported to the nucleus, where it mediates the transcription of Wnt-induced genes responsible for bone formation. This process can be inhibited by soluble FRPs (sFRP), acting as decoy receptors, Dickkopf-1 (Dkk-1) and sclerostin (sclerostin). DKK-1 and sclerostin block the formation of the aforementioned molecular complex by binding to and thereby inactivating LRP5/6. In turn, the molecular complex will fall into pieces. Axin and GSK3 bind to β-catenin, which leads to the destabilization of this complex. Thus, β-catenin will be degraded and its messenger function will be lost. One important effect of some (like TNF-α) but not all pro-inflammatory cytokines is the stimulation of DKK-1 and thus the inhibition of the Wnt-β-catenin pathway leading to bone resorption [6,18,20,27–29]. There is a direct interaction between DKK-1 and sclerostin. Blockade of DKK-1 in animal models suppress sclerostin production [30]. TNF-α induces DKK-1 and DKK-1 stimulates sclerostin production by osteocytes. Both DKK-1 and sclerostin are *anti*-anabolic and they block the differentiation and function of osteoblasts [20]. Tight interaction between DKK-1 and OPG was proposed in experimental arthritis models suggesting that the antiresorptive property of DKK-1 inhibition is also caused by increased OPG expression [27]. The effects of IL-6 on DKK-1 production is rather controversial. In a recent study, IL-6 has been inversely correlated with DKK-1 expression in RA and SpA. Moreover, in synovial fibroblasts, while TNF-α induced, IL-6 clearly inhibited DKK-1 expression [31]. On the other hand, IL-6 blockade has shown to decrease DKK-1 production [32,33], which however may be explained by indirect effect through inhibition of inflammation and associated down-regulation of cytokines other than IL-6.

In conclusion, TNFα is involved both in the production of RANKL and DKK-1 and thus plays a central role in inflammatory bone