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Review Article

Emerging anti-osteoclast therapy for rheumatoid arthritis☆

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder characterized by progressive destruction of affected synovial joints. Recently, it was demonstrated that osteoclasts play critical roles in bone destruction in RA. Receptor activator of NF-κB ligand (RANKL), which belongs to the tumor necrosis factor superfamily, is indispensable for osteoclast differentiation and bone destruction in RA. Denosumab, a monoclonal antibody against human RANKL, not only increased bone mineral density, but also efficiently suppressed the progression of bone erosion in RA patients in a randomized controlled study. However, denosumab did not reduce the cartilage destruction or disease activity in RA, and further investigation is required to establish the appropriate positioning of denosumab in the treatment strategy of RA.

1. Introduction

Progressive and massive joint destruction in rheumatoid arthritis (RA) is caused by persistent synovitis, which deteriorates the activity of daily living and the quality of life of RA patients [1]. Therefore, suppressing joint destruction is one of the most important issues in the treatment of RA. Disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, reduce inflammatory synovitis in RA, and suppress joint destruction [2]. In addition, recent clinical studies have demonstrated that biological DMARDs such as cytokine inhibitors both suppress disease activity and ameliorate joint destruction in RA [3]. In accordance with an improvement in disease status, a trend of decreased incidence of orthopaedic surgeries in RA patients has been reported in recent years by many studies from different countries including Japan [4,5]. Current RA treatment has thus been considerably improved, but it is far from perfect because these drugs are not effective in all patients, and their usage is sometimes associated with serious adverse effects such as infection [6,7]. In addition, the high medical costs of these drugs burden both patients and society.

The present review proposes that osteoclasts are involved in the bone destruction in RA, and that a novel treatment strategy targeting osteoclasts is an effective and safe treatment option.

1.1. Involvement of osteoclasts in bone destruction in RA

Radiographic studies have shown that bone erosion in RA begins at the early stage of disease, and gradually (and sometimes rapidly) exacerbates. Proliferating synovium produces an elevated amount of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, and matrix-degrading enzymes matrix metalloproteinases and cathepsins, which are involved in bone and cartilage destruction [8]. Bone erosion usually begins at the interface of the cartilage and the proliferating synovium (bare area), and numerous bone-resorbing osteoclasts are present at the erosive synovium/bone interface. Histochemical and ultrastructural studies by Bromley and Woolley reported the presence of acid phosphatase-positive multinucleated cells along the surface of mineralized subchondral bone and mineralized cartilage [9]. These multinucleated cells exhibited the morphological features of osteoclasts, indicating osteoclasts are implicated in bone erosion in RA. More recently, Gravallese et al. demonstrated that multinucleated cells observed in the erosive surface expressed osteoclast-specific genes, such as tartrate-resistant acid phosphatase and calcitonin receptors using *in situ* hybridization [10]. To further understand the mechanism of osteoclast development in RA joints, Fujikawa et al. and Takayanagi et al. developed *in vitro* osteoclast formation systems using synovial cells obtained from RA patients [11,12]. Multinucleated cells that differentiated from synovial macrophages exhibited bone-resorbing activity when cultured on bone slices. These results suggest that RA synovial tissues

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provide a favorable microenvironment for monocyte-macrophage lineage cells to differentiate into osteoclasts.

The importance of osteoclasts in RA bone destruction was further evidenced by studies of various arthritis model animals. In mice generated by mating c-*fos*-deficient osteopetrosis mice, in which osteoclastogenesis is impaired, with human TNF-α-transgenic mice that spontaneously develop RA-like arthritis, bone destruction does not occur despite synovial inflammation and cartilage destruction [13]. In addition, we reported a case of RA associated with osteopetrosis [14], an inherited disorder characterized by increased bone mass caused by reduced bone resorption. The most frequent form of osteopetrosis has autosomal dominant (ADO) inheritance (incidence 5:100,000), which is also called Albers-Schönberg disease or ADO type II. ADO type II results from mutations in the *CLCN7* gene encoding type 7 chloride channels, and osteoclast activity is markedly reduced. We reported a very rare case of RA associated with ADO type II. Although the patient exhibited severe inflammation and rapid progression of cartilage destruction, bone destruction was only developed slowly because of reduced osteoclast activity [14]. These results indicate the essential role of osteoclasts in bone destruction in RA.

1.2. Regulation of osteoclast development by the RANKL–RANK pathway

Receptor activator of nuclear factor kappa B ligand (RANKL) is a transmembrane protein belonging to the TNF superfamily [15,16]. RANKL binds to its specific receptor RANK, a member of the TNF receptor superfamily, expressed in monocyte-macrophage lineage osteoclast precursor cells, mature osteoclasts, and dendritic cells. Osteoprotegerin (OPG) is a soluble decoy RANKL receptor that suppresses RANKL function by competitively inhibiting RANKL-RANK binding [15,16]. Although RANKL was originally identified as a dendritic cell survival factor produced by activated T cells, subsequent *in vitro* and *in vivo* studies have shown that RANKL is indispensable for the differentiation and activation of osteoclasts. Targeted disruption of the *Rankl* or *Rank* gene induced osteopetrosis in mice because of the lack of osteoclasts, while knock-out of the *Opg* gene induced severe osteoporosis via a marked increase in osteoclasts, indicating the essential role of the RANKL-RANK pathway in the differentiation of osteoclasts from precursor cells [15]. Numerous studies have shown that the RANKL-RANK system is implicated in physiological bone resorption, and also plays an important role in pathological bone destruction [16].

The important role of the RANKL/RANK/OPG system in the development of bone destruction in RA has been recently established [17] (Fig. 1). Several groups simultaneously reported that RANKL is highly expressed in the synovial tissues of RA patients [17–19]. The cells expressing RANKL are considered to be activated T lymphocytes and/or synovial fibroblastic cells. Kong et al. reported that when murine bone marrow precursors were cocultured with activated $CD4^+$ T cells fixed with paraformaldehyde, osteoclasts were differentiated *in vitro* [20]. We found that in a coculture system containing synovial fibroblasts and peripheral monocytes, 1α,25-dihydroxyvitamin D_3 treatment induced RANKL expression in synovial fibroblasts and induced osteoclast differentiation from monocytes [19]. Kong et al. also reported that blocking RANKL by OPG treatment prevented joint destruction but not inflammation in adjuvant arthritis rats. In addition, Pettit et al. reported that RANKL knockout mice were protected from bone erosion in a serum transfer model of arthritis [21]. Several clinical studies have shown that the RANKL:OPG ratio in serum or synovial fluid may predict the progression of joint destruction in RA patients. A recent cohort study demonstrated that the RANKL:OPG ratio independently predicted annual radiological damage over 11 years [22]. These results strongly suggest that RANKL-induced osteoclast formation critically regulates bone destruction in RA, and that anti-RANKL therapy may be useful for the prevention of bone destruction.

2. Clinical benefits of denosumab for osteoporosis and RA

Denosumab is a fully human monoclonal anti-RANKL antibody that specifically inhibits the interaction between RANKL and RANK, and strongly suppresses osteoclast differentiation and bone resorption. In the pivotal Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study, denosumab significantly reduced osteoporotic fractures in postmenopausal women with osteoporosis. Denosumab significantly increased BMD and reduced the risks of vertebral, hip, and non-vertebral fractures [23]. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw. In a phase III clinical trial conducted to evaluate the effect of denosumab on Japanese osteoporosis patients, denosumab significantly reduced the risk of new or worsening vertebral fracture by 65.7% at 24 months. No apparent difference in adverse events was found between denosumab and placebo groups [24].

Recently, it was demonstrated that denosumab was also effective in ameliorating bone destruction in RA. Cohen et al. investigated joint destruction in RA patients who received placebo, denosumab 60 mg, or denosumab 180 mg by subcutaneous injection Q6M for 12 months. The progression in erosion score analyzed by MRI at 6 months was lower in the 60 mg denosumab group and significantly lower in the 180 mg denosumab group compared with the placebo group. The modified Sharp erosion scores in both denosumab groups were significantly lower than those in the placebo group at 12 months, while the progression of joint-space narrowing or RA disease activity was unchanged [25].

A phase II clinical trial was conducted to analyze the effect of denosumab in Japanese RA patients with a disease duration of 6 months to less than 5 years [26]. Patients were randomly assigned to receive one of four treatments: placebo, denosumab 60 mg Q6M, Q3M or every Q2M. While denosumab significantly inhibited the progression of bone erosion at 12 months at all doses compared with placebo, it had no protective effect on joint-space narrowing, which was consistent with the results reported by Cohen et al. (Fig. 2). There was no apparent difference in the safety profiles of denosumab and placebo, including infection. All denosumab groups significantly increased lumbar spine and total hip BMD compared with the placebo group at 6 and 12 months. These results provide strong evidence to suggest denosumab prevents the progression of bone erosion in the early stage of RA, but has little or no effect on cartilage deterioration or disease activity. A subsequent phase III clinical trial showed that denosumab 60 mg Q6M and Q3M significantly suppressed bone erosion at 12 months in Japanese RA patients [27]. Based on these results, denosumab was approved for "inhibition of the progression of bone erosion associated with RA" in Japan.

Denosumab has additional benefits in RA patients by preventing osteoporosis and osteoporotic fractures. RA patients are at increased risk of osteoporotic fractures. Although the proportion of RA patients who achieve remission has greatly increased, recent studies reported the number of fractures in RA patients was not reduced [28,29]. This discrepancy is at least partly accounted for by the multifactorial nature of osteoporosis in RA patients, with contributory factors other than inflammation, such as immobility,

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