RANKL is a therapeutic target of bone destruction in rheumatoid arthritis [version 1; peer review: 2 approved]

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

Abstract
Although remarkable advances have been made in the treatment of rheumatoid arthritis (RA), novel therapeutic options with different mechanisms of action and fewer side effects have been expected. Recent studies have demonstrated that bone-resorbing osteoclasts are critically involved in the bone destruction associated with RA. Denosumab, a human antibody against receptor activator of nuclear factor-kappa B ligand (RANKL), efficiently suppressed the progression of bone erosion in patients with RA by suppressing osteoclast differentiation and activation in several clinical studies, although it had no effect on inflammation or cartilage destruction. Denosumab, in combination with anti-rheumatic drugs, is considered a pivotal therapeutic option for the prevention of bone destruction in RA.

Keywords
Denosumab, osteoclast, RANKL, rheumatoid arthritis
Corresponding author: Sakae Tanaka (TANAKAS-ORT@h.u-tokyo.ac.jp)

Author roles: Tanaka S: Writing – Review & Editing


Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2019 Tanaka S. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Tanaka S. RANKL is a therapeutic target of bone destruction in rheumatoid arthritis [version 1; peer review: 2 approved] F1000Research 2019, 8(F1000 Faculty Rev):533 (https://doi.org/10.12688/f1000research.17296.1)

First published: 23 Apr 2019, 8(F1000 Faculty Rev):533 (https://doi.org/10.12688/f1000research.17296.1)
Introduction

Rheumatoid arthritis (RA) is an inflammatory disorder of unknown etiology, characterized by chronic inflammation of the synovial joints through autoimmune mechanisms\(^1,2\). Remarkable progress in the treatment of RA has been achieved during the last 20 years. Methotrexate (MTX) has been considered an anchor drug and is used as the first-line therapeutic modality for RA. MTX monotherapy was reported to achieve repair of severely damaged joints (radiographic healing) by suppressing joint inflammation\(^3\). The emergence of biological agents like tumor necrosis factor (TNF) inhibitors has had a remarkable impact on therapeutic strategies for RA and greatly improved disease control in patients with RA. In addition, two targeted synthetic disease-modifying anti-rheumatic drugs—tofacitinib and baricitinib—that target Janus kinases have recently been introduced and showed equal efficacy to biologics in the treatment of RA. Despite the excellent effects of these novel therapeutic agents, there are still several limitations in their treatment of RA. First, and most importantly, almost all currently available anti-rheumatic drugs basically suppress the immunological function of patients and thus are inevitably associated with a wide range of immunosuppression-related side effects such as infections. Furthermore, the effects of these drugs are not perfect, and a fair number of patients do not respond well to treatment. Therefore, novel therapeutic options with different mechanisms of action and fewer side effects have long been expected.

Involvement of osteoclasts in bone destruction associated with rheumatoid arthritis

Osteoclasts are multinucleated giant cells primarily responsible for bone resorption. They originate from hematopoietic stem cells and differentiate from monocyte/macrophage-lineage precursor cells. Previous studies showed that osteoclasts are critically involved in not only physiological bone metabolism but also pathologic bone destruction such as that observed in RA, osteoporosis, and cancer bone metastasis\(^8\). In particular, the primary role of osteoclasts in the bone destruction associated with RA has attracted a great deal of attention. Multinucleated giant cells with characteristics of osteoclasts are frequently observed at the interface between the inflammatory synovium and the eroded bone of patients with RA\(^1\) (Figure 1), and Gravallese \textit{et al.}\(^6\) reported that these multinucleated cells expressed osteoclast-specific genes like tartrate-resistant acid phosphatase and calcitonin receptor. We previously reported that differentiation to multinucleated osteoclasts was induced when synovial fibroblasts from patients with RA were co-cultured with peripheral blood mononuclear cells in the presence of 1\(\alpha\),25-dihydroxyvitamin D\(_3\) [1\(\alpha\),25(OH)\(_2\)D\(_3\)] and macrophage colony-stimulating factor (M-CSF)\(^7\).

The critical role of osteoclasts in bone destruction associated with RA was confirmed by findings in a rare human case. An inherited disorder characterized by increased bone mineral density (BMD), osteopetrosis arises from a defect in osteoclast differentiation or activation\(^8\). We described a patient whose type II autosomal dominant osteopetrosis was diagnosed in his youth and demonstrated markedly reduced osteoclast activity\(^9\). The patient coincidentally developed RA but showed a slow progression of bone erosion despite severe inflammation and rapid progression of cartilage destruction\(^9\). These results suggest that the normal activity of osteoclasts is required for the bone destruction in RA.

Regulation of osteoclast development by RANKL–RANK pathways

Receptor activator of nuclear factor-kappa B ligand (RANKL) belongs to the TNF superfamily. RANKL was originally identified as an activated T cell–producing factor that modulates...
reported that the expression of RANKL
α
. Denosumab was induced in response to interleukin-6 (IL-6) signaling and
later, Hashizume
reported that, when started in the early stage of RA, osteoclast-
destruction was confirmed in a series of animal experiments. OPG treatment ameliorated arthritis bone destruction in
adjuvant arthritis rats
and markedly reduced bone erosion in RANKL-deficient mice with serum transfer-induced arthritis
. In addition, systemic bone loss, as well as local bone erosion, was
ameliorated by OPG injection combined with an anti-TNF-α antibody in TNF-α transgenic mice
.

Denosumab is a fully human IgG2a monoclonal antibody that specifically binds to human RANKL and inhibits its interaction
with RANK, thereby suppressing bone resorption. In the pivotal Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study, denosumab treatment for 3 years significantly and continuously increased BMD and reduced the risks of vertebral, non-vertebral, and hip fractures
. Denosumab was effective in treating not only osteoporosis but other pathologic conditions such as bone cancer diseases and giant cell tumor of bone
.

The effects of denosumab in patients with RA have been examined in several clinical trials. Cohen et al.
reported that the progression in the erosion score at 6 months on magnetic resonance imaging was lower in the denosumab group compared with the placebo group. In contrast, denosumab had no protective effect on the progression of joint-space narrowing or RA disease activity, probably because it cannot ameliorate the synovial inflammation in RA. The effect of denosumab in Japanese patients with RA was more recently reported
. Patients with RA were randomly assigned to subcutaneous injection of placebo or denosumab 60 mg every 6 months (Q6M), Q3M, or Q2M. Compared with placebo, denosumab at all doses significantly inhibited the progression of bone erosion at 12 months as determined by the modified Sharp erosion score but had no obvious effect on joint-space narrowing (Figure 2). Notably, no apparent difference in the safety profiles of denosumab and placebo was reported. These results give strong evidence that, in the early stage of RA, denosumab can prevent the progression of bone erosion but has little or no effect on cartilage deterioration or disease activity. Moreover, Hasegawa et al.
reported that, compared with biological agent treatment alone, the concurrent use of denosumab with biological agents was more efficacious in inhibiting structural damage in RA patients without increasing adverse events. Interestingly, Ebina et al.
reported that, compared with continuing oral bisphosphonates or switching to teriparatide, switching oral bisphosphonates to denosumab significantly reduced radiographic joint destruction at 12 months. Based on these results, denosumab obtained approval for “inhibition of the progression of bone erosion associated with RA” in Japan
.

Conclusions

We have proposed a novel therapeutic approach to prevent bone destruction in RA by targeting RANKL
. Denosumab effectively prevents bone destruction but has no effect on joint inflammation or cartilage destruction in RA. Therefore,
Figure 2. Denosumab significantly suppresses the bone erosion score but has no effect on the joint-space narrowing score determined by modified Sharp scores. (a) Modified Sharp erosion score. (b) Modified Sharp joint-space narrowing score. CI, confidence interval; Q2M, every 2 months; Q3M, every 3 months; Q6M, every 6 months. Modified from a figure in an article by Takeuchi et al.30.
denosumab should be used together with other therapeutic agents, like MTX and biologics, for the treatment of RA. However, several clinical questions remain to be addressed. These questions include whether denosumab should be started immediately after diagnosis of RA and whether it can be stopped. The latter question is important because multiple vertebral fractures were reported to be observed after discontinuation of denosumab in patients with osteoporosis. Further clinical and basic studies are required to address these questions and to establish the appropriate role of denosumab in treatment strategies for RA.

Grant information
The author(s) declared that no grants were involved in supporting this work.

Figure 3. Schematic representation of the mechanism for osteoclast development and denosumab action in rheumatoid arthritis. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-17 directly or indirectly induce receptor activator of nuclear factor-kappa B ligand (RANKL) expression in synovial fibroblasts or osteoblasts or both. RANKL stimulates osteoclast differentiation from monocyte/macrophage-lineage precursor cells, leading to bone erosion in rheumatoid arthritis. Denosumab specifically binds to RANKL and suppresses osteoclast differentiation.

References


Open Peer Review

Current Peer Review Status: ✅ ✅

Editorial Note on the Review Process
F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1 Naoyuki Takahashi
   Institute for Oral Science, Matsumoto Dental University, Nagano, 399-0781, Japan
   **Competing Interests:** No competing interests were disclosed.

2 Seoung Hoon Lee
   Department of Oral Microbiology and Immunology, College of Dentistry, Wonkwang University, Jeonbuk, 54538, South Korea
   **Competing Interests:** No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com