Rheumatoid arthritis (RA) is a representative inflammatory disease characterized with systemic, chronic and destructive synovitis and subsequent bone destruction that causes severe disability and mortality. Since joint destruction occurs from the early disease, its diagnosis and treatment have to be done timely. The combinational use of methotrexate and biologics targeting TNF and IL-6 has revolutionized the treatment of RA, producing significant improvements in clinical and structural outcomes. On the other hand, an anti-RANKL antibody denosumab possesses a potential to inhibit joint destruction and peri-articular osteoporosis as well as systemic and glucocorticoid-mediated osteoporosis. Thus, differential efficacy of different therapies in bone destruction and osteoporosis would warrant further study to clarify the mechanisms of bone and joints diseases.

Key words | inflammation, rheumatoid arthritis, osteoporosis, denosumab, RANKL, treatment

Rheumatoid arthritis (RA) is a representative systemic inflammatory disease that causes significant morbidity and mortality. RA is characterized with systemic, chronic and destructive synovitis and subsequent bone and joint damages. However, the combined use of biologics targeting TNF and methotrexate (MTX) has revolutionized RA treatment, producing significant improvements in clinical outcomes, as well as producing the emerging outcome of clinical, structural, and functional remission and maintenance of such remissions1-9. However, functional disabili-
be accomplished in treatment of RA. In this review a potential of anti-receptor activator of NF-κB ligand (RANKL) fully human monoclonal antibody denosumab for the treatment of bone erosion as well as systemic and peri-articular osteoporosis complicated with RA from results of recent clinical examinations.

Efficacy of denosumab for systemic osteoporosis in patients with RA

Bone metabolism in health and disease is based on a self-regulating cellular event. The two major processes of bone remodeling, bone formation and bone resorption, are closely regulated by multiple soluble factors and hormones[5]. The initial event in bone remodeling is an increase in osteoclastic bone resorption, which is tightly regulated by osteoblasts, namely, RANKL expressed on osteoblasts provides essential signals to osteoclast progenitors for their maturation. However, uncoupling of bone remodeling towards excessive maturation and activation of osteoclasts results in an imbalance of bone metabolism towards bone resorption, that is, osteoporosis. Furthermore, TNF, IL-1, IL-6, IL-17 and PGE₂ produced in inflammatory loci induce expression of RANKL on osteoblasts, which leads to maturation and activation of osteoclasts. Actually, in patients with RA even though they do not use glucocorticoid, incidence of vertebral fracture and hip fracture is known to 2.4 fold and 1.3 fold, respectively, compared to age- and sex-matched population. Accordingly, the novel biologic targeting RANKL has been emerging for the treatment of osteoporosis, by inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.

The marked efficacy of denosumab on systemic osteoporosis has been proven in the phase III clinical examination FREEDOM, in which 7868 women with primary osteoporosis between the ages of 60 and 90 years were enrolled[6]. As compared with placebo, 60 mg of denosumab every 6 months for 36 months reduced the risk of new radiographic vertebral fracture, hip fracture and nonvertebral fracture with a relative decrease of 68%, 40% and 20% compared to placebo, respectively. Accordingly, denosumab was approved for the treatment of osteoporosis and bone metastasis of cancers in United States of America and European Union.

The secondary osteoporosis and degenerative bone fracture are major complications of glucocorticoid therapy, which is widely used to treat a variety of inflammatory diseases such as RA[7,11]. Glucocorticoid decreases the number of osteoblasts and osteocytes by decreasing replication and increasing apoptosis, which leads to reduction of synthesis of bone matrix protein and skeletal growth factors. Glucocorticoid also enhances bone resorption, preventing apoptosis of mature osteoclasts, by inducing production of RANKL on osteoblasts. These phenomena observed in osteoblasts/osteocytes and osteoclasts result in impaired bone remodeling and severe loss in bone quality as well as bone quantity, represented by the incomplete repair of bone remodeling lacunae.

The potential of denosumab for glucocorticoid-induced osteoporosis was also reported in the phase II clinical examination, in which 227 patients with RA concurrently receiving treatment with bisphosphonates or glucocorticoids[12]. 60 or 180 mg of denosumab every 6 months increased mean lumbar spine and hip bone mineral density (BMD) and reduced bone resorption marker such as serum type I C-telopeptide (sCTX-I) compared with placebo through 12 months, regardless of baseline BMD or marker levels or concomitant bisphosphonate or glucocorticoid use. Furthermore, increases in BMD were similar for denosumab-treated patients in the glucocorticoid and non-glucocorticoid subgroups, indicating that the potential of denosumab for the treatment of glucocorticoid-induced osteoporosis. Thus, denosumab increases BMD and reduces bone turnover regardless of glucocorticoid use and may provide a new therapeutic option for reducing systemic bone loss in patients with RA.

Efficacy of denosumab for the joint destruction of RA

Peri-articular osteoporosis and joint destruction are a major complication of RA. Osteoclasts play a pivotal role in resorption of sub-chondral bone in RA[6,7]. Actually, multinuclear osteoclasts exist at the interface of synovial membrane and bone, resolve bone tissue and make bone erosion there. However, osteoclasts are not around osteoclasts, although RANKL expressed on osteoblasts provides essential signals to osteoclast maturation. It is noteworthy that synovial fibroblasts and T cells accumulated around osteoclasts express RANKL in RA synovium. Strong stimuli for the induction of RANKL on fibroblasts and T cells are brought about by pro-inflammatory cytokines such as TNF, IL-1, IL-6, and IL-17 produced in a large amount in RA synovium, which induce RANKL through the activation of a transcription factor NF-κB. T cells and fibroblasts possessing RANKL, thereby, efficiently induce maturation of osteoclasts instead of osteoblasts, even in the absence of osteoclasts. Thus, RANKL is a key mediator of increased formation, function and survival of osteoclasts and treatment targeting RANKL has been expected for bone erosion as well as systemic and focal osteoporosis in RA.

The efficacy of denosumab on structural damage was reported
in the phase II study, in which 227 patients with RA receiving MTX (Fig.1)\(^{13}\). The increase in the magnetic resonance images (MRI) erosion score of the hands/wrist from baseline at 6 months in patients treated with placebo and 60 mg or denosumab is shown in the left panel. The changes in the radiographic modified Sharp erosion score of the hands/wrists and feet from baseline to 12 months in placebo group and 60 mg or 180 mg every 6 months denosumab group are shown in the right panel. Cited from reference 13.

Fig.1 The efficacy of denosumab on structural damage in 227 patients with RA receiving MTX in the phase II study

The increase in the MRI erosion score of the hands/wrist from baseline at 6 months in patients treated with placebo and 60 mg or denosumab is shown in the left panel. The changes in the radiographic modified Sharp erosion score of the hands/wrists and feet from baseline to 12 months in placebo group and 60 mg or 180 mg every 6 months denosumab group are shown in the right panel. Cited from reference 13.

Osteoporosis and joint destruction judging from treatments

The difference of treatment results of osteoporosis and bone destruction by different treatment strategy suggests differential pathological mechanisms of osteoporosis and bone erosion (Fig.2). For instance, TNF inhibitors completely control joint destruction, but are invalid for systemic osteoporosis, whereas an anti-RANKL antibody control both bone erosion and osteoporosis, but are invalid for disease activity of RA\(^{12-14}\). Also, bisphosphonates are highly effective on systemic osteoporosis, but do not affect bone destruction as well as disease activity of RA\(^{15}\). From the difference of denosumab and TNF inhibitors, denosumab not only controls osteoclasts in bone remodeling cycle in osteoblast-dependent and TNF-independent manner, but also reduce osteoclast maturation in RA synovium in osteoblast-independent and TNF-dependent manner. From the difference of denosumab and bisphosphonate, denosumab can be diffusely distributed in subcortical to endocortical bone under the distribution of blood flow without a microstructural influence, whereas bisphosphonate deposits hydroxyapatite in bone matrix\(^{16}\). In RA, since subcortical and subchondral bone is first attacked by invasive inflammatory synovium, denosumab may have an advantage by its diffuse distribution in subcortical to endocortical bone, although precise mode of action remains unclear.

Taken together, an anti-RANKL antibody denosumab inhib-
its bone erosion, periarticular osteoporosis and systemic osteoporosis without influencing disease activity in patients with RA. Based on these results, the next phase of a double-blind controlled trial of denosumab in patients with RA would be warranted. Also, considering the differential effects of different treatments on bone and joint damage, a new approach would be expected to understand mechanism of diseases and novel treatment strategy.

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