
Special Issue: Novel targeted therapies

Brief Review

Recent progress in small molecular products for the treatment of joint and bone diseases: an overview

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The development of biological products has changed the treatment strategies of various inflammatory diseases. Among them the monoclonal antibody technology which was first presented by Köhler and Milstein in 1975 has been emerging from the late 20th century. For instance, the revolution of the treatment has been carried out by the monoclonal antibodies in rheumatoid arthritis (RA), a representative systemic and chronic inflammatory disease. TNF and IL-6 play a pivotal role during the pathological processes of RA and bring destructive inflammatory synovitis and multiple organ manifestations. Although disease-modifying anti-rheumatoid drugs (DMARD) such as methotrexate (MTX) have been used for the treatment of RA, their efficacy for the joint destruction has not been well accepted. However, monoclonal antibodies targeting TNF and IL-6 and fusion protein of soluble receptor for TNF and immunoglobulin (Ig) have promoted revolution of the treatment. Namely, the combinational

application of TNF-inhibitors and MTX has brought about a paradigm shift in management of RA and the treatment target of RA has evolved to clinical remission, structural remission and functional remission from just the release from polyarthralgia¹⁻³⁾.

Although biological agents have brought enormous power and flexibility, we have also realized the following concerns in their contexts. First, clinical remission can be obtained only in 1/3 of patients with RA even though they are intensively treated with biologics. Next, biologics have to be used by intravenous or subcutaneous administration and usually possess economic problems because of their expense. Also, anti-product antibody is often experienced unless the products are used with immunosuppressants such as MTX and long term safety of the therapy has been fully unresolved. Accordingly, orally available low molecular weight products targeting key molecules during the disease processes currently attract particular attention. Among

them, small molecular products targeting kinase proteins have been emerging because multiple signaling kinases are involved in the pathological processes, and can be designed to recognize particular conformation of target molecules, like the relations of a key and the key hole, during the signaling cascade. For example, imatinib which Druker and others reported in 1996 is the derivative which was designed to antagonize an ATP binding site of the tyrosine kinase of BCR-ABL protein peculiar to chronic myelogenous leukemia and induces apoptosis of leukemic cells⁴.

The similar trials as leukemia using low molecular weight products targeting kinase proteins have been undertaken in the treatment of RA. The multiple cytokines and cell surface molecules play a pivotal role in the pathogenesis of RA and binding of these molecules to their ligands on the cell surface induce various signals including phosphorylation of kinase proteins. The tyrosine kinase is the first intracellular signals to be phosphorylated and 14 tyrosine kinases are known to be involved in RA⁵. Among them, members of Janus kinase (Jak) family are essential for the signaling pathways of various cytokines and are implicated in the pathogenesis of RA. An orally available Jak3 inhibitor tofacitinib is currently in clinical trials for RA with satisfactory effects and acceptable safety^{6,7}. A phase 2 double-blinded study was carried out to investigate the efficacy and safety of tofacitinib in Japanese patients with active RA and inadequate response to MTX. Tofacitinib in combination with MTX was efficacious and had a manageable safety profile and tofacitinib 5 and 10 mg twice a day appear suitable for further evaluation to optimize their potential for the treatment of RA⁸. The success in the Jak3 inhibitor has prompted the development of additional kinase inhibitors targeting Jak1/2, spleen tyrosine kinase (Syk) and p38 mitogen-activated protein kinase (MAPK), which are currently on the clinical examination. Furthermore, low molecular inhibitors for cyclin-dependent kinase (CDK), rho kinase, phosphoinositide 3-kinase (PI3K), inhibitor of kappa B ($I\kappa B$)-kinase and many are developed at the pre-clinical stage.

The similar progress in the treatment strategies has been experienced in the field of osteoporosis. Systemic osteoporosis and secondary osteoporosis due to glucocorticoid are major complications of inflammatory diseases such as RA. Bisphosphonate targeting osteoclasts has been the most evident therapy of osteoporosis for the latest decade. However, recent multiple reports have indicated concerns regarding osteonecrosis and certain bone fracture in patients treated with bisphosphonate. On the other hand, osteoblasts not only play a central role in bone formation by synthesizing bone matrix proteins, but regulate osteoclast maturation by cognate interaction, resulting in bone

resorption. Receptor activator of NF- κ B ligand (RANKL) expressed on osteoblasts provides essential signals to osteoclast progenitors for their maturation. Accordingly, the novel biologic targeting RANKL has been emerging and an anti-RANKL antibody denosumab has been approved for the treatment of osteoporosis and bone metastasis of cancers in United States of America and European Union⁹ and clinical examination using denosumab for bone destruction in RA are currently undertaken in Japan. More recently, odanacatib, a specific small molecular inhibitor of the osteoclast protease cathepsin K, has been emerging, because it inhibits osteoclast activity rather than osteoclast viability, thus allowing physiological communication between osteoclasts and osteoblasts with maintained osteoblastic bone formation¹⁰. Taken together, since it is possible to design low molecular weight products recognizing particular conformation of target molecules, the success in imatinib, tofacitinib and odanacatib will facilitate the new development of multiple products for many inflammatory diseases.

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