Special Issue: Novel targeted therapies

Mini Review

JAK inhibitor: tofacitinib, a new disease modifying anti-rheumatic drug

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Treatment of rheumatoid arthritis (RA) with biologic agents targeting inflammatory cytokines and cell surface molecules such as tumor necrosis factor and Interleukin-6 is generally more efficacious than traditional disease-modifying antirheumatic drugs when combined with MTX. However, not only do ~30% of patients poorly respond to treatment but also parenteral mode of administration and expense are issues to be solved. Recently, a kinase inhibitor targeting Janus kinases (JAKs), has shown high efficacy in active RA in clinical trials. Among several JAK inhibitors in clinical trials for RA, tofacitinib is a step ahead for use in clinical practice. Kinase inhibitors are orally available, which is a major advantage over biologic agents, in addition to being less expensive. This review describes recent advance in JAK inhibitors for RA and its possible mechanism of action.

Rec./Acc.8/24/2011, pp349-353

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Key words rheumatoid arthritis, Janus kinase, kinase inhibitor, tofacitinib

Introduction

Rheumatoid arthritis (RA) is an auto-inflammatory disease where inflammatory cytokines play important roles in pathogenesis. For a long period of time, treatment has been conducted mainly by disease modifying anti-rheumatic drugs (DMARDs) that was able to modify the disease course, but could not fully prevent progressive joint destruction. Biological agents targeting inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6 have shown dramatic effects, and have revolutionized the treatment goal of RA[1]. However, ~30% of patients show poor response and some patients discontinue their treatment due to adverse events or loss of efficacy. It is important to note that not only the parenteral administration, but also the expense of biologic agents, is overwhelming for patients

which also causes discontinuation of treatment. Under these circumstances, kinase inhibitors that are orally available, have a short half-life, and can be synthesized with low cost compared to biological agents have gathered attention.

Development of protein kinase inhibitors

The human genome comprises 518 protein kinases with 90 kinases belonging to the protein tyrosine kinase (PTK) subfamily. The kinase domain, which includes the ATP-binding site is highly conserved among typical protein kinases. Therefore, an inhibitor of one kinase is often found to inhibit other structurally related or unrelated kinases. For instance, imatinib (Gleevec) targets the kinase BCR-Abl and has revolutionized the treatment of chronic myeloid leukemia. However, it also inhibits other PTKs such as c-kit receptor tyrosine kinase and platelet derived growth factor-receptor. This outgrowth effect has turned out to be a benefit for treating gastrointestinal stromal tumors and hypereosinophilic syndrome. It is now considered that partial inhibition of multiple kinases presumably contributes to efficacy and less toxicity[2]. In terms of anti-inflammatory effect of kinase inhibitors, compounds specific for Janus kinase (JAK) and spleen tyrosine kinase (Syk) are, so far, the most efficacious in RA[3, 4]. Both kinases are activated immediately after the activation of the specific receptors on the cell surface.

JAKs and STATs and its role in RA

Janus kinase (JAK) is a tyrosine kinase that is critical for cytokine receptor binding-triggered signal transduction through STAT to the nuclei of cells. The JAK family consists of four members: JAK1, JAK2, JAK3 and Tyk2. Upon cytokine binding to its receptor on the cellular membrane, JAKs are activated and phosphorylate cytokine receptors creating docking sites for signaling molecules, especially for members of the STAT family (Fig.1). The STAT proteins form homo- or heterodimers and translocate to the nucleus where they induce transcription of target genes. Seven STAT genes have been identified and more than 40 different cytokines and growth factors have been shown to activate specific combinations of JAK and STAT proteins[5]. Expression of JAK-STAT in rheumatoid synovium was first described by Muller-Ladner et al[6] showing JAK1 and IL-4 STAT expressed at the messenger RNA level at the site of inflammatory infiltrates. Subsequently, Frucht DM et al. have shown STAT4 expression in macrophages in synovial tissue and Li et al. have shown functional involvement of JAK-STAT pathway describing activation of JAK1, JAK2, JAK3 and STAT1 inducing expression of metalloproteinases by chondrocytes[7, 8]. Additionally,

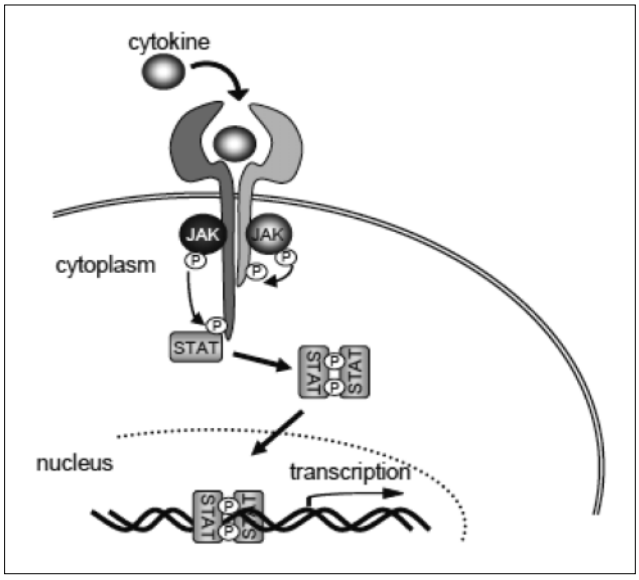

Fig.1 The JAK-STAT signaling pathway

STAT1 expression and activation in synovial tissue in relation to RA disease activity and STAT3 promoting survival of RA synovial fibroblasts have been reported[9-11]. More recently, JAK3, STAT1, STAT4 and STAT6 expression in dendritic cells associated with RA disease activity was reported. All these findings suggest the involvement of JAK-STAT pathway in the pathology of RA providing substantial reasons to inhibit this pathway.

JAK inhibitors for treatment of RA

A number of kinase inhibitors targeting JAK have been developed and utilized in animal models of transplantation and autoimmune disease to prove their efficacy. However, most of them were with low potency[12]. At the present day, there are multiple JAK inhibitors in clinical trials at different phases. Overall, there are 3 compounds under clinical examination for RA, tofacitinib, VX-509 and INCB28050. Among these three JAK inhibitors, detailed results of tofacitinib have been published. Tofacitinib was initially published with significant prolonged survival in a murine model of heart transplantation and in cynomolgus monkeys receiving kidney transplants[13]. Efficacy on arthritis was first suggested with murine collagen-induced and rat adujuvant-induced arthritis. In addition to significant attenuation of joint swelling, inflammatory cell influx and joint damage, tofacitinib showed therapeutic efficacy at the early time-point after initiation of therapy with decreased serum IL-6 concentration which exceeded the effect of anti-TNF treatment[14]. Even though the superior effect of tofacitinib can be due to the aspect of the animal model, it suggests that tofacitinib can be useful as an anti-

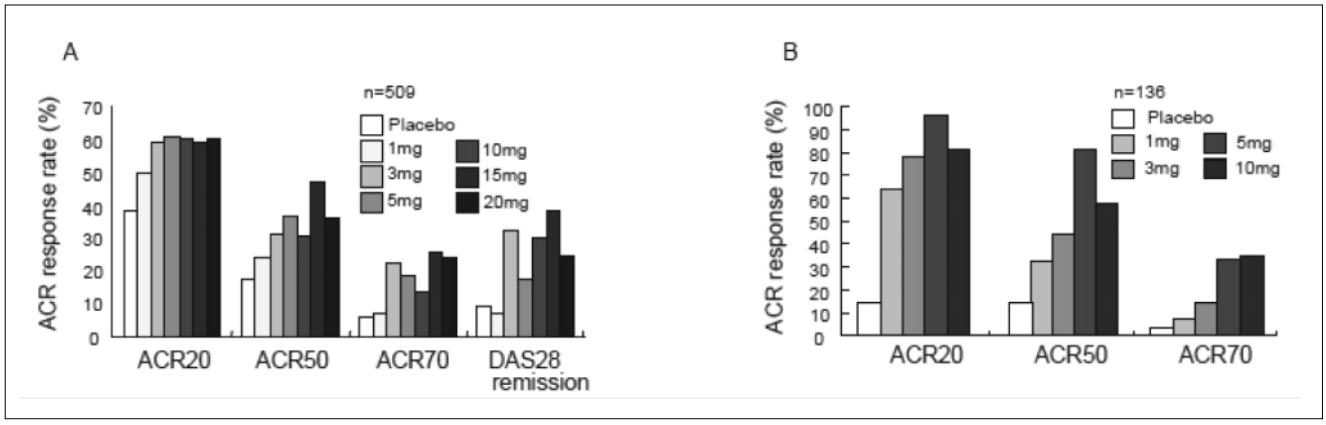

Fig.2 ACR response rate of tofacitinib on active RA in combination with MTX
(A): Tofacitinib in combination with MTX in patients with active RA with an inadequate response to MTX
(B): Tofacitinib in Japanese patients with active RA with an inadequate response to MTX

inflammatory drug with different mechanism of actions from anti-TNF agents.

Kremer JM. et al. have published the results from the randomized, double-blind, placebo-controlled, phase II trial on active RA patients. Patients had active RA (n = 264) and showed inadequate response to, or discontinued therapy due to unacceptable toxicity from methotrexate (MTX) or TNF inhibitors (eternacept, infliximab, or adlimumab). Three different doses (5mg, 15mg, 30mg) of tofacitinib were orally administered twice daily for 6 weeks after discontinuation of all DMARDs and immunosuppressive and/or immunomodulatory therapy for at least 4 weeks prior to the first dose of the study drug. At baseline, female gender (84.1 to 87%), mean age (47.9 to 51.8 years) and the mean duration (8.7 to 10.2 years) of RA was similar between the groups. Improvements in disease activity in all treatment groups were observed as early as week 1. American College of Rheumatology 20% improvement criteria (ACR20) at week 6 exceeded 70% in all treatment groups (5mg; 70.5%, 15mg; 81.2%, 30mg; 76.8%) compared with 29.2% in the placebo group. According to the mechanism of action of the study drug, hematologic disorders were the prominent concern. In fact, a dose-dependent increase in anemia and leukopenia was obsereved with 4.3% and 8.7% respectively with the group treated with 30mg twice daily suggesting the drug affects the hematopoietic system through JAK2 inhibition. The most common adverse events were headache and nausea. Mean serum total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels all increased in a dose-dependent manner. However, the ratios of total cholesterol to HDL cholesterol, which is a measure of atherogenic risk, were unchanged. From this phase II study, the proper dose for treatment of RA was considered to be 5mg to 15mg twice daily.

Another phase II study with RA patients (n = 507) who had an inadequate response to MTX alone was randomized equally to 1, 3, 5, 10, 15mg twice daily or 20mg once a day with stable background MTX (7.5-25mg/week). Doses of 3mg twice daily and higher were efficacious compared to the placebo group. More importantly, approximately 30% of the patients treated with 3mg twice daily and higher achieved remission at week 12 (Fig.2A)[15]. A phase II study was conducted in Japan with active RA patients (n = 136) who had inadequate response to MTX alone. Patients were randomized equally to 1, 3, 5 or 10mg twice daily and placebo. All treatment groups resulted in an excellent outcome evaluated by ACR20, ACR50 and ACR70. What was striking was that within the 5mg twice daily group, 96.3% achieved ACR20 and more than 30% of the 5mg and 10mg twice daily group achieved remission at week 12 (Fig.2B)[16]. According to these clinical trials and other studies under investigation, tofacitinib dosed at 5mg and 10mg were considered to have a reasonable risk/benefit profile.

Mechanism of action

In a recent survey of kinase inhibitors against a large panel of kinases, tofacitinib was shown to be a selecetive JAK inhibitor with little activity toward most other kinases[17]. Interesting results from the clinical trials are that the therapeutic effect can be observed within the first couple of weeks with further improvement throughout the study which is reminiscent of biological agents[6]. The results from the animal arthritis model showing decreased IL-6 by administration of tofacitinib, and dose-depen-

dent increase of serum levels of lipids during clinical trials evokes the possible inhibitory effect of IL-6. However, further and detailed evaluation is necessary not only to reveal the mechanism of action but also to predict the future side effects in long term use. Involvement of JAK-STAT in bone metabolism has been suggested by a number of reports. Both osteoclasts and osteoblasts have been analyzed with conflicting results[18-21]. Thus, efficacy of tofacitinib on joint destruction and bone damage remains unclear. However, because clinical efficacy and induction ratio to clinical remission with the combination of tofacitinib and MTX are comparable to the combination of TNF-inhibitors and MTX, if tofacitinib can bring about similar efficacy on joint destruction to TNF-inhibitors, the treatment algorithm will be changed and tofacitinib will become the first choice in anti-rheumatic drugs.

Conclusions

Biologics have shown prominent effects in RA treatment. However, parenteral administration and cost might limit their availability to vast numbers of patients, especially in developing nations. The high cost of the biologic agents may also limit the access to those treatments in many patients whose care depends on health systems with less resources. Small-molecule inhibitors of enzymes in the inflammatory pathways constitute an attractive approach for the control of RA. Most surprising of all was that inhibitors do not necessarily have to be highly specific against a single molecule. Adequate specificity and non-specificity, which is two sides of the same coin, seems to contributes to high efficacy with tolerable side effects. It is highly likely that we will have an oral JAK inhibitor that will be available in clinical practice in the near future. The cost, and results from long term treatment will suggest where it should fit in the treatment paradigm.

Conflict of interest

Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe Pharma, Chugai Pharma, Eisai Pharma, Pfizer, Abbott Immunology Pharma, Daiichi-Sankyo, Janssen Pharma, AstraZeneca, Takeda Industrial Pharma, Astellas Pharma, Asahi-kasei Pharma and GlaxoSmithKline and has received research grant support from Mitsubishi-Tanabe Pharma, Bristol-Myers Squibb, Takeda Industrial Pharma, MSD, Astellas Pharma, Eisai Pharma, Chugai Pharma, Pfizer and Daiichi-Sankyo.

Acknowledgement

The authors thank Chad E. Pashcall for critical reviewing of this manuscript.

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