

REVIEW

Revolutionary Change in Rheumatoid Arthritis Management with Biological Therapy

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Biological agents targeting a specific molecule have extraordinarily fine specificity and powerful functional capabilities. By the introduction of biological therapy, management of rheumatoid arthritis has undergone a revolution and a paradigm shift. In this review, I will summarize the role in the pathogenesis of rheumatoid arthritis of the molecules targeted by biological agents. Providing evidence obtained in clinical trials and investigator-initiated clinical studies in Japan, the effectiveness and safety of biological therapy in rheumatoid arthritis are discussed. Finally, studies aiming at a personalized strategy with biological agents are listed and the future perspectives toward tailor-made medicine in the field of rheumatology are discussed. (Keio J Med 60 (3) : 75–81, September 2011)

Keywords: tumor necrosis factor, IL-6, remission, safety

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that results in joint destruction and disability. Biological agents that target a specific molecule provide an effective means for therapeutic management of RA due to their specificity and powerful functional capabilities, and this approach has resulted in a paradigm shift in the treatment strategy for this disease. A dramatic improvement in the signs and symptoms of a patient with RA was first reported with the chimeric anti-tumor necrosis factor (TNF)- α monoclonal antibody infliximab in 1993.¹ This observation was confirmed in a double-blind, randomized, controlled study comparing this biological agent with a placebo in 1994.² The first approved biologic for RA was the TNF receptor IgG1 fusion protein etanercept in the United States in 1998. At present, nine biological agents have been approved for RA worldwide. This revolutionary change in RA management with biological therapeutics in Western countries and Japan³ is reviewed.

Target Molecules in RA

Three major cell types (blood vessels, lymphocytes, and synovial cells) gather prominently in the synovial tissues of patients with RA (**Fig. 1**). Through interactions among these cells, pro-inflammatory mediators are released or cells activate each other by direct cell-to-cell contact, facilitating a lowering of the pain threshold, activation of T and B cells, further proliferation of synovial cells, increased expression of adhesion molecules on endothelial cells, formation of blood vessels, degradation of cartilage and cartilage matrix, and activation of osteoclasts among other processes. Of the multiple events in the inflamed synovium of RA patients, one of the upstream events, an indispensable factor, was demonstrated to be the enhanced release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin-1, and interleukin-6. Also, it has been postulated that T and B cells play important roles in autoimmune-mediated processes for perpetuating inflammation.

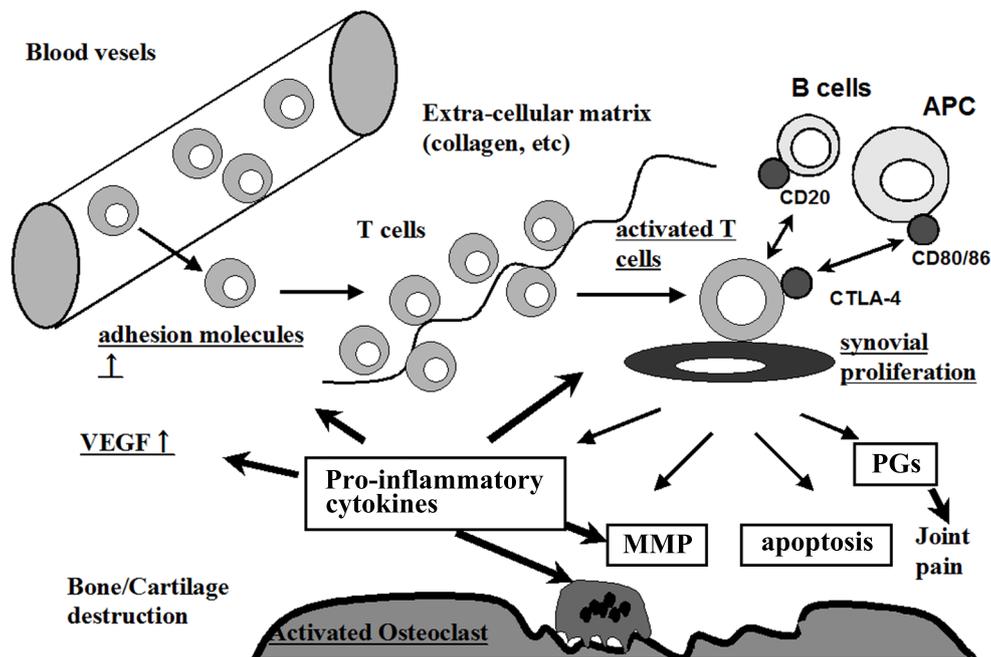


Fig. 1 Molecular targets in patients with rheumatoid arthritis (RA).

There are several distinctive features of the synovial tissues of patients with RA, including new blood vessel formation, infiltration of lymphocytes, and synovial cell proliferation. Pro-inflammatory cytokines and the molecules involved in the activation of T and B cells are ideal candidates for molecular targets in RA. VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; APC, antigen presenting cells; PGs, prostaglandin.

Structure of Biological Agents

With candidate molecular targets in the pathogenesis of RA identified, much effort has been expended to develop appropriate biological agents. There are two major types of biological agents: monoclonal antibodies and receptors/ligands fused to the Fc portion of immunoglobulin G (IgG-Fc fusion protein). As shown in **Figure 2**, the first monoclonal antibody approved for patients with RA was chimeric, in which the antigen-binding portion of IgG came from a mouse monoclonal antibody and the rest of the molecule from a human antibody, resulting in about 25% of the protein consisting of mouse amino acid sequences. These biologics include chimeric monoclonal antibodies against TNF α (infliximab) and CD20 (rituximab). Infliximab was approved in Japan in 2003, but rituximab has yet to be approved in Japan. Through dramatic progress in cellular and molecular biology techniques, humanized and further fully human monoclonal antibodies are being engineered. The humanized monoclonal antibody against the IL-6 receptor is tocilizumab, which was developed in Japan and approved for RA treatment in 2008. A polyethylene glycol-modified humanized Fab' fragment against TNF α (certolizumab pegol) was recently developed and approved in several

countries, though not yet in Japan. Fully monoclonal antibodies against TNF α include adalimumab, which has been approved since 2005 in several Western countries and since 2008 in Japan, and golimumab, which has just been approved in several countries, though not in Japan. IgG-Fc fusion proteins include the TNFR2-Fc fusion protein etanercept and the CTLA4-Fc fusion protein abatacept. Etanercept was approved in Japan in 2005 and abatacept was just approved in Japan in 2010. Finally, a naturally occurring regulatory protein designated as an IL-1 receptor antagonist with some amino acid modifications is anakinra, which has not been approved in Japan. All of these agents are delivered by either intravenous or subcutaneous injection.

Mechanism of Action of Anti-TNF Biologics

As shown in **Figure 3**, three anti-TNF biologics now available for RA in Japan appear to have different modes of action against TNF. Two monoclonal antibodies, infliximab and adalimumab, can neutralize serum TNF α and inhibit the production of TNF α through lysis or apoptosis of macrophages with membrane-bound TNF α . In contrast, etanercept can neutralize not only TNF α , but also another family member, lymphotoxin α . However,

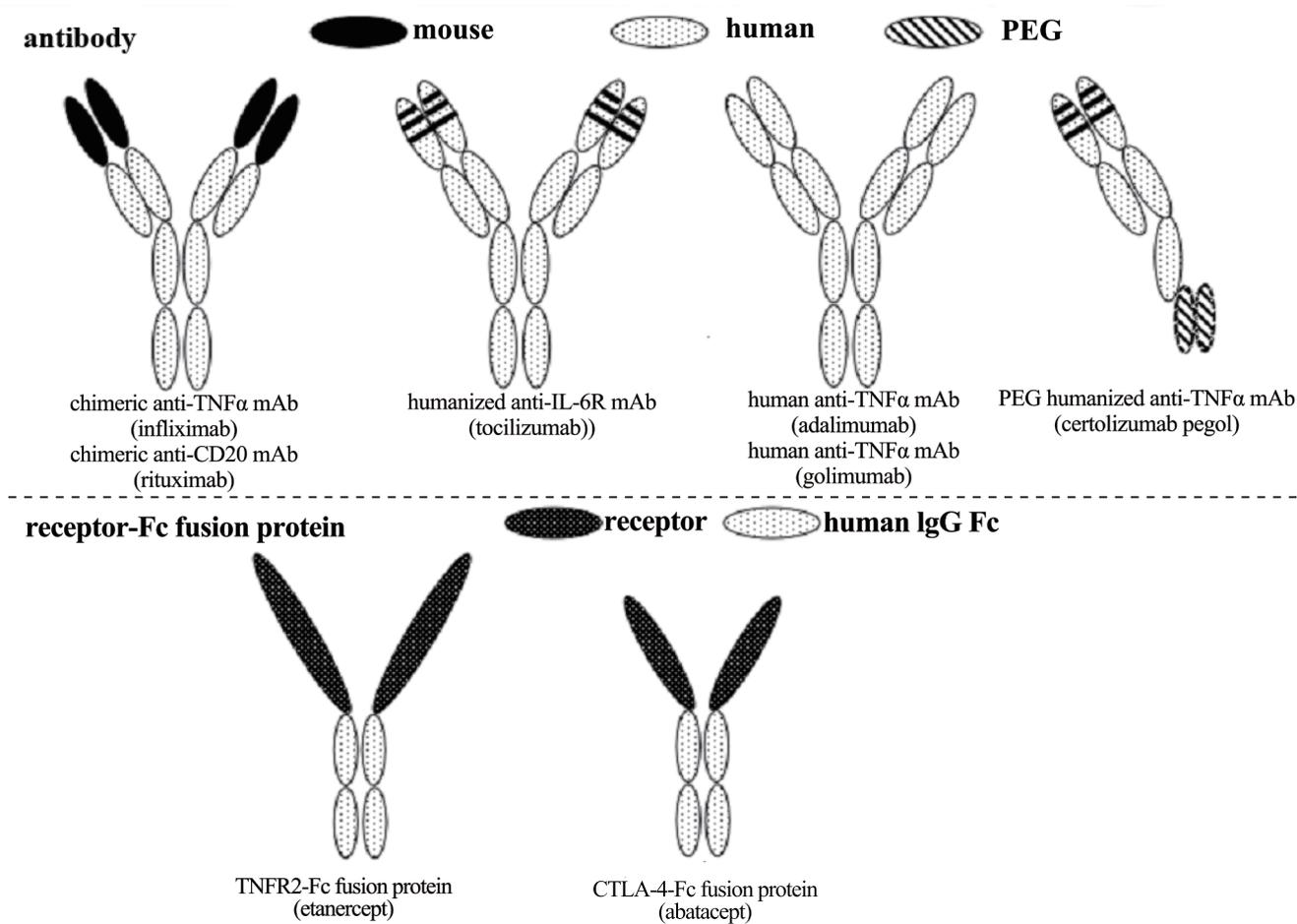


Fig. 2 Structure of biological agents.

The upper panel shows biological agents generated based on antibody molecules. The lower panel shows those based on the Fc portion of the immunoglobulin-fusion protein, including receptor-Fc fusion protein. PEG, polyethylene glycol; mAb, monoclonal antibody.

it has been reported that etanercept cannot lyse TNF α -expressing macrophages in a complement-dependent fashion because of the lack of a complement-binding portion in the etanercept molecule.⁴

Efficacy of Biological Agents in Japanese Patients Q5

Several multi-center, randomized, double-blind clinical trials of biologics have been conducted in Japan and have exhibited excellent American College of Rheumatology (ACR) 20 responses in patients, as shown in **Figure 3**.^{5–7} In addition, clinical remission achieved in the clinical trials and studies reached about 20–40% of Japanese RA patients (**Fig. 4**), implying that clinical remission is a realistic goal of treatment (**Table 1**). The details for each biological agent are discussed below.

a) *Infliximab*

A series of investigator-initiated clinical studies, including RECONFIRM,⁸ RECONFIRM-2,⁹ and RECONFIRM-2 J,¹⁰ have demonstrated that a 3-mg/kg dose of infliximab at 0, 2, and 6 weeks, followed by every 8 weeks thereafter, exhibited excellent clinical responses as well as inhibition of radiographic progression in RA patients. However, there was a slight dip in the clinical response around 30–38 weeks,⁹ implying a secondary loss of efficacy with infliximab, which may have been due to insufficient serum trough levels of infliximab at the subsequent infusion. Previous studies have suggested anti-biologics antibodies and/or an infusion reaction to biologics may be the mechanism for insufficient serum levels or secondary loss of response to biologics. We examined the anti-biologics antibody and (SNPs) of Fc gamma re-

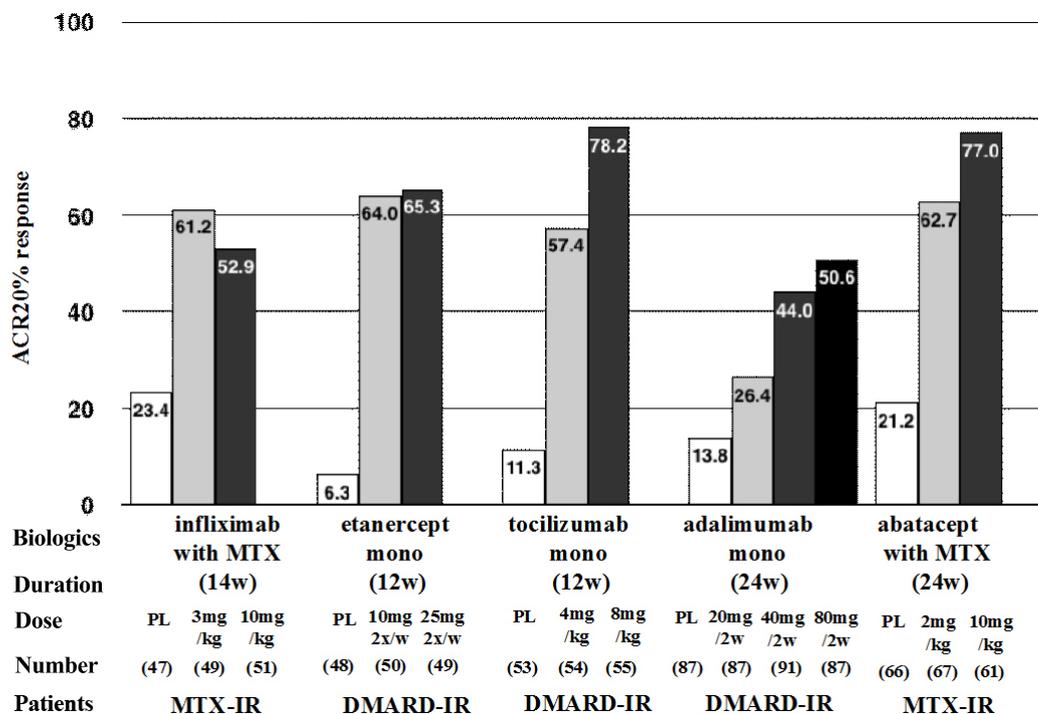


Fig. 3 Efficacy of biological agents in Japanese RA patients.

ACR 20 response data from Japanese clinical trials for each biological agent are shown. The different shaded bars are defined by the dose data. MTX, methotrexate; MTX-IR, MTX-inadequate responder; DMARD-IR, disease-modifying anti-rheumatoid drug/inadequate responder; PL, placebo.

ceptors, demonstrating that FcγR3B high-affinity SNP NA1/NA1 is significantly associated with infusion reactions, leading to drop out, in addition to anti-biologics antibody.¹¹ Finally, in the RISING study, 10 mg/kg of infliximab showed a significantly greater clinical response than lower doses at 54 weeks with a DAS28 remission of 45% with increased serum trough levels,¹² as shown in **Figure 4**. Recently, it has been demonstrated that baseline plasma levels of TNFα predict clinical responses to a standard dose of infliximab (3 mg/kg),¹³ enabling us to identify in advance RA patients who will require an in-

creased dose of infliximab.

b) Etanercept

To determine whether the addition of, or switch to, etanercept is better in MTX-resistant patients, an investigator-initiated clinical study (JESMR) was started. The results have demonstrated that the strategy of adding-on showed a significantly higher remission rate, compared to switching, not only at 24 weeks (27% vs. 9%, respectively),¹⁴ but also at 52 weeks (35% vs. 18%, respectively).¹⁵ In

Table 1 Provisional treatment goals for RA in Japan (2010)

1. Immediate clinical remission inductiona)and its maintenance.
2. Halting progression of structural damageb)(structural remission).
3. In early disease, functional remissionc)should be the aim to achieve complete remission ultimately.d)
4. After achieving clinical remission for 12-24 months, biologics-free and drug-free remission should be considered.
a) Clinical remission: DAS28(ESR)<2.6 or DAS28(CRP)<2.3
b) Halting progression of structural damage: no new erosion and JSN on X-ray
c) Functional remission: HAQ-DI ≤0.5, or J-HAQ ≤0.5
d) Complete remission: satisfy all of 1 to 3

MHLW study group 『Study on systematization of remission induction in RA.』

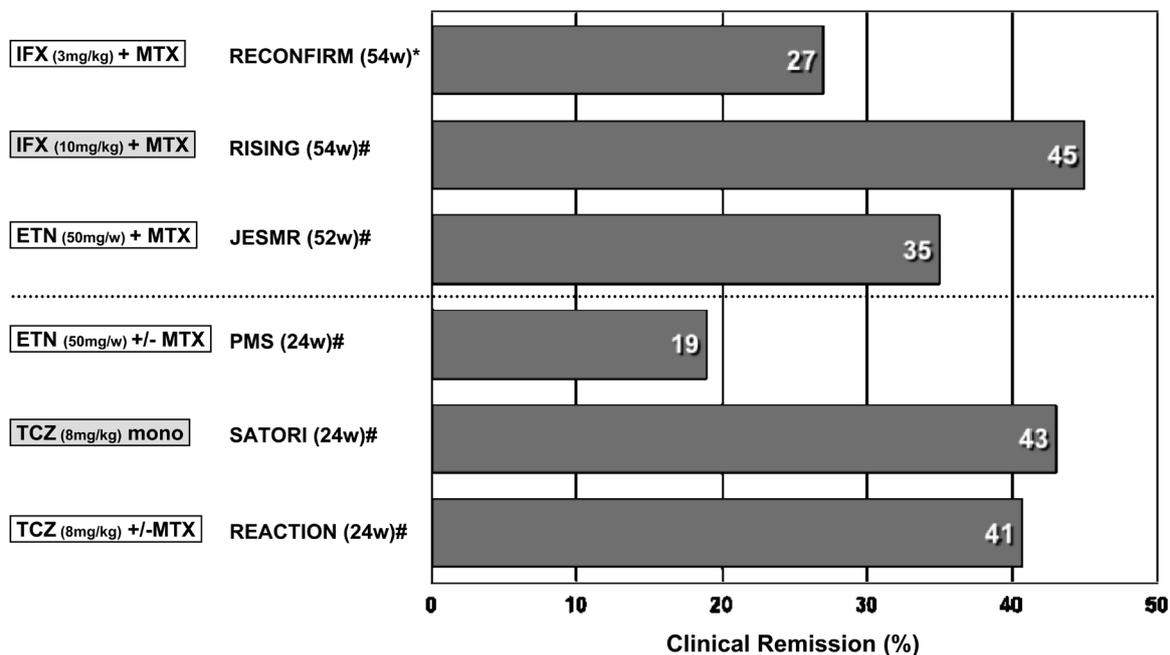


Fig. 4 Clinical remission in Japanese RA patients treated with each biological agent.

The figure shows the percentage of RA patients achieving clinical remission. IFX: infliximab; ETN: etanercept; TCZ: tocilizumab. Duration of the study is shown in parentheses. *Clinical remission was judged by DAS28-CRP. #Clinical remission was judged by DAS28-ESR.

addition, erosion scores after a 52-week treatment were significantly lower in patients with etanercept + MTX compared to those who switched from MTX to etanercept alone. These results indicate that etanercept should be added on to MTX in MTX-resistant RA patients when etanercept is started.

c) Adalimumab

It is interesting to note the higher incidence of anti-adalimumab antibody development (40.2%, 44.0%, and 26.4% at 24 weeks for doses of 20 mg, 40 mg, and 80 mg every 2 weeks, respectively, in Japan, compared to 15–20% for a 40 mg dose in Western countries) in an adalimumab monotherapy trial.⁷ This may have been the cause of the lower response rates to doses of 20 mg every 2 weeks, and implies that different genetic backgrounds affect the production of anti-biologic antibodies.

d) Tocilizumab

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was first approved in 2008 for RA treatment in Japan, followed by approval in Europe and the USA. The excellent efficacy and safety of tocilizumab monotherapy has been demonstrated in Japanese patients.^{6,16} The effectiveness of tocilizumab in daily

clinical practice was also confirmed in the Reaction study, which found a high remission rate at 24 weeks¹⁷ and 52 weeks¹⁸ (Fig. 4).

e) Effect on structural damage

In the SAMURAI trial,¹⁹ not only the total Sharp score (TSS), but also the erosion and joint narrowing scores were significantly lower in tocilizumab monotherapy compared to disease-modifying anti-rheumatoid drug (DMARD) therapy, showing the first evidence that biologics are superior to DMARDs in Japanese patients for inhibiting structural damage. Subsequent clinical trials and studies of infliximab¹² revealed a striking inhibition of structural damage when compared to those reported from studies in Western countries,²⁰ and these trials generated interest for examining the effect of tocilizumab + MTX combination therapy on joint damage over tocilizumab therapy alone in Japanese RA patients.

Safety of Biological Agents in Japanese Patients

For close monitoring of adverse events associated with biologics, and to confirm their effectiveness, post-marketing surveillance (PMS) of all RA patients who have received biologics has been conducted in Japan. The primary objectives of PMS are to determine the exact

frequency of drug-related adverse events, particularly related to opportunistic infections such as tuberculosis, and the factors affecting drug safety and efficacy. To date, PMS for infliximab and etanercept has been completed and reported,^{21,22} showing that adverse drug reactions (ADRs) for infliximab and etanercept were observed in 28.0% and 30.6% of patients, respectively, and severe ADRs were observed in 6.2% and 4.6% of patients, respectively. When compared to those patients treated with the oral DMARD tacrolimus (results of a company-initiated PMS for 24 weeks: $n = 3175$, ADR = 36.0%, severe ADR = 6.4%),²³ incidences of ADRs and severe ADRs in infliximab and etanercept were comparable, indicating that biologics are tolerated by Japanese RA patients. Of the severe ADRs, pneumonia, tuberculosis, and Pneumocystis jiroveci pneumonia (PJP) were found to be important.³ In particular, PJP is an important opportunistic infection in acquired immunodeficiency syndrome, but the exact incidence of PJP in RA patients treated with TNF inhibitors is not well known. Japanese PMS for infliximab first demonstrated that the incidence of PJP in 5000 patients treated with infliximab was 0.4%,²¹ which is more than ten times higher than the self-reported incidences in Western countries. It is interesting to note that the clinical features and radiographic patterns for PJP in RA patients receiving infliximab appear to differ from those of patients with human immunodeficiency virus infections.²⁴ During PMS for etanercept, PJP developed in 0.2% of the patients, and 6 of these 25 patients died, raising concern for PJP in TNF blockade and highlighting the need for prophylaxis against patients at risk with sulfamethoxazole-trimethoprim (ST) compounds. In this regard, serum beta-d glucan was anticipated to be useful for the diagnosis and monitoring of PJP development,²⁵ and this was confirmed in RA patients.³

Future Perspectives for Biological Agents in RA Treatment

When utilizing a number of powerful tools such as biological agents to manage RA, a personalized strategy of RA treatment is required. For example, it has been shown that infliximab can be stopped in early RA after achieving low disease activity or remission.^{26,27} To test whether this is the case for established RA, investigators initiated a clinical study.²⁸ Among 102 patients who could be evaluated, around half of the patients had successfully discontinued infliximab after 1 year. Among those, 67% of the patients showed no radiographic progression.²⁸ For a treatment strategy with tight control while utilizing biologics, with the goal of clinical remission or low disease activity, a discontinuation of the biologics may be possible for some patients. This strategy is now being examined in Japanese patients for several biologics, including infliximab, etanercept, tocilizumab, and abatacept.

In order to identify predictive factors for a given bio-

logical agent, genetic polymorphism^{29,30} and comprehensive mRNA expression analysis^{31,32} have been employed. Following this line, many investigators are extensively searching for predictive factors of ADRs, including infection³³ and infusion reactions of biologics.¹¹

Conclusion

Experiences with biologics in Japan show a greater efficacy than those in Western countries, but several important side effects such as opportunistic infections with some increased incidence underline the risks of biologics.³ We should pay much more attention to the variables in RA patients, and we need to maximize the efficacy and minimize the risk of biologics in individual RA patients. In addition to clinical information for the personalization of biologic treatments, research to identify predictors of the responses to, and the risks of, biologics is required.

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