Current Status of and Future Perspectives on Biologics in Rheumatic Diseases

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In recent years, treatment of rheumatoid arthritis (RA) with biological agents, also called biological disease-modifying antirheumatic drugs (bDMARDs), has become standard. bDMARDs are generally used for patients with an inadequate response to methotrexate and/or other conventional DMARDs. Thus far, tumor necrosis factor (TNF) inhibitors, an interleukin 6 inhibitor and a T cell-selective regulatory bDMARD have been approved for RA in Japan. The strategy of RA management has also changed. Clinical remission is recommended as a primary goal of treatment because this may prevent subsequent articular destruction and impairment of joint functions. TNF inhibitors are also prescribed to patients with other inflammatory rheumatic diseases, such as ankylosing spondylitis, psoriatic arthritis and Behcet’s disease, whose conditions have not adequately responded to conventional therapy. Furthermore, B cell depletion therapy with an anti-CD20 monoclonal antibody is an important option in the treatment of refractory anti-neutrophil cytoplasmic antibody–associated vasculitis, especially in granulomatosis with polyangiitis. In addition, biological agents have also been used for off-label indications. However, these agents are costly and may cause serious infections. This article reviews the current use of biological agents in adult rheumatic diseases.

Key words: biologics, rheumatoid arthritis, treatment, spondyloarthritis, systemic vasculitis

Biological agents are proteins manufactured similarly to human molecules. They are produced by biotechnology methods and other cutting-edge technologies, and designed to directly bind to targets such as cytokines, chemokines and cell-surface molecules. More than a decade has passed since the first biological agent was approved for rheumatoid arthritis (RA) in Japan, and these agents are currently used in daily practice in patients with RA as well as those with other inflammatory rheumatic diseases such as spondyloarthritis (SpA), anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis and Behcet’s disease. However, large post-marketing surveys on biologics in Japanese RA patients have contributed to our clear understanding of side effects, especially serious infections. This review summarizes the existing and future state of biological agents in adult rheumatic disorders.

Rheumatoid arthritis

RA is a systemic autoimmune disease characterized by chronic synovitis and articular destruction of peripheral joints. The development of RA treatments involving methotrexate and biologics, also known as "biological disease-modifying anti-rheumatic drugs (bDMARDs)," has greatly improved clinical and functional outcomes in patients with RA. A tumor necrosis factor (TNF) inhibitor was the first bDMARD, and currently several kinds of bDMARDs have been approved for RA in Japan. bDMARDs have demonstrated clinical and radiographic efficacy both as monotherapies and in combination with methotrexate, and in both early and established disease. Use of bDMARDs has become standard in the treatment of RA, however they are more expensive than conventional DMARDs and thus many patients cannot afford...
The development of these agents has also allowed for a change of strategy in RA management. Since articular damage starts early in the disease course and progresses rapidly in some patients, DMARDs should be commenced as early as possible once RA is diagnosed. And notably, it has been recommended that the primary goal in RA treatment be clinical remission, or at least low disease activity, as determined by composite measures of disease activity such as the 28-joint disease activity score (DAS28), clinical disease activity score (CDAI) and simplified disease activity score (SDAI). To achieve this goal, the therapy should be adjusted at least every 3 to 6 months (Figure-1). This strategy is now well-known as “treat to target (T2T)”.

Methotrexate, administered weekly at low doses, is a mainstay drug in treating RA. In general, when methotrexate or methotrexate combination therapy fails, any one of the bDMARDs is added to methotrexate. Most patients achieve remission or low disease activity with the first bDMARD, but switching to a second bDMARD is recommended following initial failure or relapse.

The TNF includes TNF-α, lymphotoxin-α (TNF-β) and lymphotoxin-β. TNF-α and lymphotoxin-α bind to the common TNF receptor. TNF-α is a key cytokine in a subset of RA patients. TNF-α is mainly produced by activated macrophages, and induces activation and proliferation of effector T cells and B cells, upregulation of adhesion molecules on endothelial cells, and production of matrix metalloproteinase-3, collagenase (stromelysin) and prostaglandins by synovial cells (Figure-2). Furthermore, TNF-α also enhances osteoclast differentiation by stimulating osteoclast precursor mononuclear cells and upregulating expression of the receptor activator of nuclear factor κB ligand (RANKL) on synovial fibroblasts. These functions of TNF-α are partly dependent on IL-6, GM-CSF, and IL-1. For example, TNF-α upregulates GM-CSF production by synovial cells, which in turn induces monocyte/macrophage to produce inflammatory cytokines and express HLA-class II. TNF-α-induced osteoclastogenesis is mediated mainly by IL-6 and IL-1, and angiogenesis by IL-6. Inhibition of TNF-α rapidly ameliorates synovial inflammation and prevents bone and cartilage destruction. Concomitant use of methotrexate significantly enhances the effects of TNF-α inhibition even in cases of inadequate methotrexate response. IL-6 is another crucial cytokine that also...
induces activation of macrophages, T cells, B cells, endothelial cells, synovial cells and osteoclasts. TNF inhibitors are suggested to be more effective when IL-6 is suppressed along with TNF-α.

Of the five TNF inhibitors, four are monoclonal antibodies to TNF-α (infliximab, adalimumab, golimumab, and certolizumab pegol) while the other, etanercept, is a recombinant soluble TNF receptor (Table-1). In addition, a biosimilar product to infliximab was also approved. The clinical efficacy of these agents is comparable, and is usually rapid, within days or weeks. Infliximab is a chimeric monoclonal antibody that has a mouse amino acid sequence in its antigen-binding site, hence the concomitant use of methotrexate is essential to prevent production of anti-infliximab antibodies. Adalimumab is a humanized antibody, but anti-adalimumab antibodies are detected nevertheless, possibly more frequently in Japanese patients.

These anti-agent antibodies may reduce drug efficacy. Trough concentrations of TNF-α antibodies are raised by concomitant use of methotrexate or other conventional DMARDs, and influence the clinical response and anti-agent antibody production. Golimumab, a more recent anti-TNF-α antibody, is derived from human TNFα-immunized human immunoglobulin G (IgG) transgenic mice, and clinical trials have demonstrated a much lower frequency of anti-agent antibody positivity. Another anti-TNF-α antibody, certolizumab pegol, is also likely to have less immunogenicity due to its novel structure as a PEGylated, Fc-free (Fab') fragment. Among TNF inhibitors, only etanercept is a soluble TNF receptor agent that has low immunogenicity. It is a dimeric fusion protein consisting of two identical extracellular ligand–binding portions of the human 75 kilodalton (p75) TNF receptor linked to the Fc portion of human IgG1, and is capable of binding to both TNF-α and lymphotoxin-α. Etanercept is less cytotoxic to membrane-bound TNF-expressing cells than other anti-TNF-α antibody agents, which may result in a lower risk of tuberculosis.

Tocilizumab, a humanized anti-IL-6 receptor antibody, was developed in Japan. A meta-analysis of randomized trials revealed that tocilizumab was efficacious as monotherapy as well as in combination with methotrexate, both in patients who were
bDMARD naïve and those with failed trials of other TNF inhibitors. While TNF inhibitors are more effective when used with methotrexate, the combination of methotrexate with tocilizumab shows less additional clinical efficacy compared to tocilizumab monotherapy. Clinical trials of anti-IL-6 antibodies are ongoing. Abatacept is not a cytokine inhibitor, but a fusion protein of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and the Fc portion of IgG; it binds to CD80/CD86 on antigen-presenting cells and inhibits T cell activation through CD28. Addition of abatacept to methotrexate showed comparable clinical and radiographic effects to adalimumab in active and bDMARD-naïve RA patients with an inadequate response to methotrexate. Rituximab, a B cell–targeting drug, has been approved in other countries but not yet in Japan. Interestingly, the clinical effects of abatacept and rituximab are more significant in anti-citrullinated protein/peptide autoantibody (ACPA) – positive RA patients.

Tapering these bDMARDs can be considered in patients in persistent remission. It was reported that approximately half of patients who discontinued infliximab showed sustained low disease activity even one year later, whereas the relapse rate was higher after cessation of tocilizumab and abatacept. The safety of bDMARDs has been extensively investigated in Japan by post-marketing surveys in thousands of cases. Infections are the most noteworthy adverse events associated with bDMARDs, and clinicians should be particularly aware of the potential for serious infections such as pneumocystis pneumonia and tuberculosis. Screening for tuberculosis by chest X-ray, a tuberculin reaction, and interferon-γ releasing assays is necessary before commencing bDMARDs. An anti–tuberculosis drug, isoniazid, is given to patients suspected of having latent tuberculosis infection. Prophylaxis of pneumocystis pneumonia should also be considered in high–risk patients. The results of post–marketing surveys for TNF inhibitors have demonstrated that the respective prevalences of serious infections overall, pneumonia, pneumocystis pneumonia and tuberculosis, were 1.0–4.0 %, 0.3–2.2 %, 0.1–4.4 % and 0.03–0.3 %. The prevalence of serious infections was similar in patients treated with tocilizumab, and less frequent with abatacept. It is noted that tocilizumab may delay detection of the signs of infections and increase infection severity by masking fever and C-reactive protein (CRP) elevation. Risk factors for serious infections have shown to include age above...

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65 years, co-existence of lung disease, glucocorticoid use (over 5 mg per day of prednisolone) and impaired body functions. It is still controversial whether bDMARDs increase the risk of malignancies, and there have been a number of negative studies on this issue. Infusion reaction, a particular side effect of bDMARDs, is generally mild but sometimes severe in patients treated with the chimeric antibodies. Although treatment of rheumatoid vasculitis with bDMARDs is commonly accepted, they may conversely cause vasculitis. Inhibition of TNF often induces autoantibody production as well.

**Spondyloarthritis**

Spondyloarthritis (SpA) is a group of disorders that includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), the arthritis and spondylitis that may accompany inflammatory bowel diseases, and undifferentiated SpA. They have common clinical features: axial spondylitis, peripheral arthritis, enthesitis and extra-articular manifestations such as uveitis. AS is a prototype of SpA that is strongly associated with the HLA-B27 gene, and tends to affect younger individuals. The vertebrae in AS patients are characterized radiographically by bone erosion of vertebral edges and subsequent new bone formation that causes ankylosis. While non-steroidal anti-inflammatory drugs (NSAIDs) are more effective for axial disease in AS than for mechanical back pain, both methotrexate and salazosulfapyridine show no significant effect on inflammatory back pain in AS. Two anti-TNF-α antibodies, infliximab and adalimumab, are used for active AS patients with inadequate responses to NSAIDs, and are clinically effective in 60-70% of these individuals. However, the effects of anti-TNF-α antibodies on radiographic progression in AS is still controversial. Anti-TNF-α antibodies are also used for refractory psoriasis and PsA. Anti-IL-17 antibodies have been approved for psoriasis, and are being evaluated in clinical trials in patients with AS. Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, is also effective for psoriasis and PsA, suggesting that the IL-17/IL-23 axis is crucial in the pathogenesis of SpA. Despite their efficacy against RA, tocilizumab and abatacept do not decrease disease activity in AS.

**Systemic vasculitis and Behçet’s disease**

Granulomatosis with polyangiitis (GPA; formerly Wegener’s granulomatosis) and microscopic polyangiitis (MPA) are ANCA–associated vasculitides (AAVs) that primarily affect capillaries, venules or arterioles. GPA, and also severe MPA, is treated with the combination of cyclophosphamide and high-dose glucocorticoids for remission induction. Since cyclophosphamide has considerable cellular toxicity, less toxic immunosuppressants such as azathioprine or methotrexate should be used instead after remission. Although most patients with GPA successfully achieve clinical remission with initial induction therapy, more than half relapse. Rituximab, a chimeric monoclonal antibody to CD20, is as effective as cyclophosphamide in inducing remission, both in newly diagnosed and relapsed cases. CD20 is expressed on the surface of B cells (from pre-B cells to mature B cells), and administration of rituximab completely eliminates B cells in peripheral blood. It is suggested that depletion of B cells contributes to prevention of memory B cell–induced immune activation and subsequent autoantibody production. On the other hand, the efficacy of TNF inhibitors in AAVs is very limited.

Takayasu’s arteritis and giant cell arteritis affect large-sized vessels, and in general are initially treated with glucocorticoids alone. However, patients often relapse as glucocorticoids are tapered. It has been reported that IL-6 inhibition was effective in these large vessel vasculitides. A clinical trial of tocilizumab in patients with TA is now underway.

Behçet’s disease (BD) is an inflammatory disease characterized by recurrent oral aphthous ulcers and other clinical manifestations such as genital ulcers, uveitis, gastrointestinal ulcers and involvement of the central nervous and vascular systems. Most of these clinical manifestations are thought to be due to vasculitis, and vessels of all sizes on both the arterial and venous sides can be involved. Glucocorticoids, colchicine, cyclosporine and other immunosuppressants are used to treat BD. In refractory disease with uveitis, intestinal Behçet’s and other manifestations, anti-TNF-α antibodies
have been demonstrated to improve symptoms and achieve sustained disease control.

**Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause organ-specific and nonspecific manifestations. Although immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, tacrolimus and mycophenolate mofetil are concomitantly used with glucocorticoids in the treatment of SLE, long-term glucocorticoid use is required in most patients and relapses occur often. Because of its clinical heterogeneity, it is not feasible to precisely assess the disease activity of SLE, which may increase the difficulty of SLE clinical trials. Several observational studies found that rituximab was effective in patients with SLE, including refractory cases, but randomized clinical trials have failed to demonstrate its efficacy. Belimumab, a neutralizing monoclonal antibody to a B cell survival factor, B lymphocyte stimulator (BlyS) (also called B cell-activating factor: BAFF), is approved for SLE only in the United States. However, the use of belimumab is recommended mainly in limited cases with active musculoskeletal or cutaneous disease that are unresponsive to standard therapy. No significant efficacy has been observed in ongoing clinical trials of epratuzumab, an anti-CD22 monoclonal antibody that blocks another target, or abatacept, which inhibits T cell activation. A pathogenic role of interferon (IFN)-α has been suggested in SLE due to the observation of increased expression of type I interferon–induced genes in blood and involved tissues in patients with SLE, correlation between serum interferon levels and SLE clinical activity, and development of SLE in patients undergoing IFNα treatment. Sifalimumab, an anti–IFNα monoclonal antibody, is undergoing clinical trials.

**Adult-onset Still’s disease**

Adult-onset Still’s disease (AOSD) is an inflammatory disorder characterized by daily spiking fevers, arthritis and an evanescent salmon-colored rash. In addition to NSAIDs and glucocorticoids, biologics have been recently used in severe or refractory cases. TNF inhibitors tend to be used concomitantly with methotrexate in patients with severe arthritis. On the other hand, tocilizumab, an IL-6 inhibitor, is preferred in patients with life-threatening systemic inflammation. It should be noted that IL-6 inhibition may cause exacerbation of macrophage activation syndrome. IL-1 inhibitors may be selected instead of IL-6 inhibitors, but their use is entirely off-label.

This article reviewed the recent use of biologics in adult rheumatic diseases. Although these drugs are costly and may cause side effects such as serious infections, they are playing an increasingly standard role in the treatment of RA and SpA. Furthermore, they are extremely beneficial in some patients with other rheumatic diseases that are severe and/or refractory. Approval of additional indications may contribute to more effective disease control and allow patients to avoid long-term exposure to glucocorticoids and other toxic drugs. Tofacitinib, a Janus kinase inhibitor that prevents the production of multiple cytokines, was recently approved in RA patients mainly with an inadequate response to bDMARDs. Bispecific antibodies that simultaneously block two different targets may be developed in the near future, however their safety should be ensured. Biologic agents have contributed to resolving the mechanisms of rheumatic diseases in both clinical and research settings. More effective biological agents with new target molecules should be developed in the near future.

**References**


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