Anti-TNF Biological Agents in Rheumatoid Arthritis and Other Inflammatory Diseases

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ABSTRACT
It is now evident that biological agents targeting on the tumor necrosis factor (TNF) have not only induce a substantial clinical response, but also inhibit the structural damage in patients with Rheumatoid Arthritis (RA). Upon the great success of anti-TNF biologicals as the therapeutic modalities of choice in the treatment of inflammatory disorders of unknown etiology, the details of TNF, and anti-TNF biological agents are extensively reviewed, particularly, focusing on those used against RA. So far, nearly one million patients are expected to expose to these agents worldwide. In Japan, chimeric monoclonal antibody to TNFα, infliximab has been approved for Crohn’s disease in 2002, RA in 2003, and TNF receptor 2-IgG Fc fusion protein, etanercept had just approved for RA in 2005. Full human anti-TNFα monoclonal antibody, adalimumab is now under clinical trials. Safety profiles of these agents, based on the exposure to one hundred million patients for up to ten years, are summarized. While the experiences using biological agents in Japan are rather limited, the unique circumstances in Asian countries should been taken into account. In this respect, the issues around the anti-TNF biologicals in Japan are finally discussed.

KEY WORDS
Monoclonal antibody, RA, Receptor antagonist, TNF

INTRODUCTION
Tumor necrosis factor (TNF) was first isolated in 1975, as a factor with the potential to kill tumor cell lines in vitro.¹ In addition, two other factors with similar physiological activity were identified, and designated as lymphotoxin α and β (LT-a, LT-b).²-⁴ TNFs are believed to play an important role in host defense against infections and tumor development.⁴,⁵ However, accumulating evidence has suggested that overproduction of TNFs is closely related to the pathogenesis of inflammatory disorders such as rheumatoid arthritis (RA), Crohn’s disease, and other inflammatory diseases.⁶,⁷ Subsequently, much effort has gone into the development of therapeutic agents, which target TNFs. These efforts have resulted in anti-TNF biological agents, which have shown dramatic improved outcomes in RA patients as well as in patients suffering from other inflammatory disorders of unknown etiology.⁸,⁹ These biological agents, which directly target the inflammatory cytokines have revolutionized our strategy in the management of such diseases.¹⁰

ACTION AND STRUCTURE OF TNFα
TNF binds to specific TNF receptors ubiquitously expressed on the surface of cells throughout the body, and has a long list of physiological actions.⁴,⁵ An excess amount of TNFα in the serum can alter the anticoagulant activity of the endothelial cells and rewul in the induction of hemorrhage, vasodilatation, and neutrophil activation, all prominent features of septic shock. On the other hand, a small but significant increase in the long term concentration of TNFα may evoke inflammatory responses, such as fever, anemia, body weight loss, and even osteoclast activation.⁷

Among tumor necrosis factors, TNFα and TNFβ
(a.k.a.: lymphotoxin α), and lymphotoxin β have been previously identified.⁴ These three molecules are generated from three distinct genes on the chromosome 3 and act as trimers, binding to receptors, which also consist of homotrimers.⁵ TNFα consists of heterotrimers of TNFα, TNFβ consists of homotrimers of TNFβ (LTα), and lymphotoxin B is a combined from of LT-α and LT-β1. TNFα and TNFβ can bind to two kinds of TNF receptors, namely TNF receptor I (p55) and TNF receptor II (p75). The unique heterotrimers, consisting of two molecules of LT-α and one molecule of LT-β binds to the third receptor, designated as LT-βR. It has long been thought that each of the receptor molecules exists independently, and assembly during ligand binding. This model is known as the “ligand-induced trimerization” model. Since signal transduction occurs independently, depending on the individual class of receptor,¹¹ it is widely accepted that a single receptor is primarily assembled as a trimer. This pre-ligand assembly model is now recognized as the correct process since a pre-ligand assembly domain (PLAD) has been identified.¹²

The majority of TNFα is produced by a variety of cells including monocytes/macrophages, T cells, B cells, and keratinocytes.⁵ Upon stimulation, signals are transduced from the cell surface receptors into the cytoplasm,¹¹ ultimately leading to activation of the transcription factors and binding of the promotor region of the targeted genes which initiates final transcription of TNFα. Regulation of the stability of the messenger RNA (mRNA) for TNFα is controlled by stabilizing factors and destabilizing factors, which bind the AU-rich region located within the 3’ untranslated region (UTR) of mRNA. One of the stabilizing factors is HuR, while TIA-1 acts as a destabilizing factor. Thus TNFα is produced with the transmembrane domain is transported to the surface of the cell membrane, and expressed on the cell surface. When membrane proteases such as TNF-α Converting Enzyme (TACE) are activated in pathological conditions or MT-MMP in physiological conditions cleave TNF-α on the cell surface, the end result is the release of free TNF-α.⁵

### ROLE OF TNF-α IN THE PATHOGENESIS OF RA

Early experiments have demonstrated that RA synovial cells produced an excess amount of TNF-α in vitro, and anti-TNF-α monoclonal antibody inhibited not only TNF-α, but also subsequent production of IL-1, IL-6, and IL-8. These findings suggest that TNF-α is located upstream of the cytokine cascade.⁶ ⁷
To test the hypothesis that TNF-α plays a pivotal role in RA pathogenesis, TNF-α transgenic (tg) mice were generated. Results showed that erosive polyarticular arthritis developed in the TNF-α tg-mice, and blockade of TNF-α significantly reduced both the severity and even the development of arthritis, in addition to associated structural damage. Furthermore, it was demonstrated that the anti-TNF-α monoclonal antibody could ameliorate a collagen-induced type of arthritis. These results have provided evidence for a TNF blockade strategy, which has facilitated the development of a clinical application of this approach in the management of inflammatory arthritis.13

**BIOLOGICAL AGENTS INHIBITING THE ACTIVITY OF TNF-α**

Several strategies for the production of biological agents, designed to inhibit the activity of TNF-α have been adopted. There are two major categories of such agents: one is a monoclonal antibody, and another is a receptor-antagonist/receptor-Fc fusion protein. Table 1 shows the monoclonal antibodies such as, the chimeric monoclonal antibodies to TNF-α (clone cA2, inflixiamab : Remicade®),14 humanized mAb (CDP571),15 full human mAb (clone D2E7, adalimumab : Humira®),16 and the polyethylene glycol (PEG)-Fab fragment (CDP870). Receptor antagonist/receptor-Fc fusion proteins include, the TNF receptor II-Fc fusion protein (etanercept : Enbrel®), the TNF receptor I-Fc fusion protein (lenercept), and the PEG-TNF receptor 1.17 Infliximab, adalimumab, and etanercept have been approved for clinical use in the United States. Table 2 shows the approval status of these products worldwide. The first biological agents approved for the treatment of RA was etanercept in 1998, followed by infliximab in 1999 in the United States of America. In the year 2002, infliximab was approved for induction into the Japanese market for the treatment of Crohn’s disease, followed by approval for treatment of RA in 2003.

The indications for use of etanercept include RA, JIA,18,19 psoriatic arthritis,20 and ankylosing spondylitis,21,22 whereas those for infliximab are RA, Crohn’s disease,23,24 psoriatic arthritis,25 and ankylosing spondylitis.26-28

**EFFICACY OF THE BIOLOGICAL AGENTS**

Infliximab: This chimeric mAb consists of a variable region of mouse immunoglobulin (Ig), which binds to TNF-α with high affinity (Ka = 1.8 × 10⁹), and the Fc portion of human IgG1 (Table 1 & Fig. 1).

**SINGLE INFUSION TRIAL**

The first clinical trial of infliximab was carried out in severe RA patients who had not responded to conventional DMARDs. In this study a single infusion at 5–20 mg/kg clearly showed a striking improvement in the reduction of signs and symptoms.14 Due to the gradual decrease in the serum concentration of infliximab and total disappearance at 3–4 weeks post-infusion, the disease activity returned to the pretreatment level, suggesting that repeated infusions are required to control long-term disease activity.

**REPEATED INFUSION WITHOUT MTX**

Clinical trials with repeated infusions of infliximab in RA patients has demonstrated that the intervals between infusions became shorter when infusions were repeated more than several times.29 It is assumed that the development of the human antibody to chimeric monoclonal antibody (HACA) was interfering with the infliximab activity,30 thereby shortening the
intervals of the infusion to maintain the efficacy.

**DOSE RANGING STUDY WITH OR WITHOUT MTX**

Exciting clinical evidence by Maini et al. has shown that low doses of infliximab such as 1 or 3 mg/kg in combination with MTX showed a clinical response comparable with that of high doses of infliximab (10 mg/kg) alone. The dose sparing effect of MTX could be attributed to immunosuppression of HACA production. Indeed, in the MTX/infliximab combination therapy, the frequency of HACA detected in the serum of the patients was significantly lower than in those patients treated with infliximab alone.

**COMPARISON STUDY BETWEEN MTX ALONE AND MTX+INFlixIMAB (ATTRACT)**

To prove the efficacy of infliximab and MTX combination therapy, the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis Concomitant Therapy (ATTRACT) study was conducted in 428 patients with severe RA, who did not respond to MTX with a dose of more than 12.5 mg/week. After 54 weeks, the patients treated with MTX + Placebo infusion showed only a 17% response, whereas all of the infliximab treated group showed a significant response, 56% of the patients achieving the ACR 20% response (Fig. 2). Surprisingly, the mean change in the modified Sharp score, which represents the semi-quantitative measure of bone and cartilage destruction, showed more than 7 in the placebo group (only MTX), while it was markedly suppressed to less than 1 in all the infliximab treated groups. These results suggest that infliximab in combination with MTX not only reduces the signs and symptoms of RA, but also strongly inhibits the radiographic progression of structural damage.

**JAPANESE TRIAL**

In Japan, a clinical trial with a similar design was carried out in three groups with MTX + placebo, MTX + infliximab (3 mg/kg), and MTX + infliximab (10 mg/kg) at 0, 2, and 6 weeks, and demonstrated a significantly better clinical response in the infliximab treated group. The ratio of patients treated with infliximab 3 mg/kg to the ACR20% responding criteria was 61% at 14 weeks. When the Japanese trial data was compared to the results observed in the ATTRACT study, the Japanese trial exhibited a slightly better result (AACC 20% [(that in MTX + infliximab) –
(that in MTX placebo)) at week 14: 34% in the Japanese trial vs the ATTRACTION study. One of the major distinctions between Western countries and Japan is the maximum dosage of MTX, which is 8 mg/week in Japan, raising the possibility that Japanese RA patients with a lower maximum doses of MTX would have milder disease activity than their Western counterparts, and thus demonstrating a better response to infliximab.

**COMPARISON OF MTX + PLACEBO, AND MTX + INFLEXIMAB IN EARLY RA**
MTX alone or two doses of infliximab (3 mg/kg, or 6 mg/kg) with MTX were compared in early active RA (less than 3 years after onset of RA) with poor prognostic factors. After 54 weeks, the combination of MTX and infliximab at any doses exhibited a significantly high ACR 20, 50, and 70% response, as well as a significantly smaller increases in the total sharp score, indicating that the effect of the combination therapy on early active RA is superior to that of MTX alone. The numbers of total and severe adverse events were comparable among the three treatment groups, supporting the idea that the combination therapy should be considered in the treatment of early active RA with a poor prognosis, where the radiographic structural damage is progressing rapidly, leading to a profound irreversible disability.

Etanercept: Etanercept is a genetically engineered protein consisting of two molecules of the extracellular domain of TNF receptor II (p75) and Fc fragment of IgG1 (Fig. 1 & Table 1).

**DOSE RANGING STUDY**
In an earlier study, the effects of placebo and etanercept 0.25 mg/m², 2 mg/m², and 16 mg/m² were compared in 180 RA patients, who had demonstrated a lack of efficacy to therapy with between one and four of the previous DMARDs. After 3 months of treatment, a significant reduction of disease activity was observed in the etanercept treated-group, and dose-related therapeutic effects were confirmed. In RA treated with 16 mg/m² of etanercept, 75% of the patients achieved the 20%ACR response, whereas the placebo group produced only 14% response.

**PLACEBO-CONTROLLED TRAIL (PLACEBO, 10 MG, 25 MG)**
Thereafter, a randomized placebo-controlled trail using fixed etanercept doses such as 10 mg and 25 mg twice a week for 24 weeks was designed and carried out in 234 patients with active RA for 6 months. Results showed a profound reduction of all the core set variables in the etanercept group, and the 20%ACR response was 59% in the etanercept treated-group (25 mg twice a week), and only 11% in the placebo group (Fig. 2).

**ADD-ON STUDY TO MTX**
A further study was carried out to examine the efficacy of Etanercept in patients with inadequate response to a stable dose of MTX. In the group treated with etanercept 25 mg twice a week, the 20%ACR response rate was 71%, while placebo produced a 27% response, indicating that etanercept is also exhibiting a significant benefit in RA with MTX inadequate responders (Fig. 2).

**COMPARISON OF MTX AND ETANERCEPT IN EARLY RA**
To test the efficacy of etanercept in early RA, a direct comparison between etanercept and MTX was carried out in 632 patients, diagnosed as having RA for no more than 3 years and no prior treatment with MTX. The patients were divided into three groups consisting of MTX \( (n = 217) \), 10 mg etanercept \( (n = 208) \), and 25 mg etanercept \( (n = 207) \). MTX was started with a weekly dose of 7.5 mg, followed by an increase up to 15 mg/wk at week 4, and 20 mg/wk at week 8 with folic acid supplementation (1 mg/day). After the second dose escalation, the mean dose of MTX was only 19 mg/week, because 15% of the patients needed to reduce the dose due to adverse events. After 24 weeks, patients treated with 25 mg of etanercept showed a more rapid improvement, more ACR20%, 50%, and 70% response rates over MTX treated patients.

**COMPARISON OF MTX, ETANERCEPT, AND MTX + ETANERCEPT IN EARLY RA (TEMPO STUDY)**
In 682 early active RA (less than 3 years), patients treated with MTX+etanercept showed a significant high ACR70% response and high clinical remission rate according to the DAS definition, in addition to a significantly low mean sharp score below zero, compared with the groups on MTX and etanercept alone. These remarkable results indicate that the combination can achieve remission in a much higher proportion in early active RA patients with a poor prognostic profile than MTX alone or even etanercept alone, and furthermore it may arrest or even repair the structural damage.

Adalimumab: Adamimumab is a full human monoclonal antibody of IgG1, which binds to TNF-α with
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Table 3  Incidence of tuberculosis in patients with anti-TNF biologics\textsuperscript{52}

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of pts</td>
<td>200,000</td>
<td>150,000</td>
<td>2,500</td>
</tr>
<tr>
<td>pts * year</td>
<td>230,000 pts * yr</td>
<td>230,000 pts * yr</td>
<td>4,900 pts * yr</td>
</tr>
<tr>
<td>number of Tb</td>
<td>172</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>areas used</td>
<td>USA</td>
<td>non-USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>areas developed</td>
<td>USA</td>
<td>non-USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>onset after infusion</td>
<td>75%: within 6 week</td>
<td>1 - 22 months (Median 11.2)</td>
<td>3 - 8 month</td>
</tr>
<tr>
<td>extra-pulmonary/miliary</td>
<td>45%</td>
<td>50%</td>
<td>40%</td>
</tr>
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high affinity (Kd = 6 \times 10^{-10}M). The antibody with the clone name of D2E7 is made by the phage display method with amino acid sequencing from the human germline (Table 1 & Fig. 1).

**COMPARISON OF PLACEBO AND SEVERAL DOSAGES OF ADALIMUMAB**

Two hundred and eighty-four active RA patients, who had not responded to DMARDs, were randomly assigned to receive weekly subcutaneous injections of adalimumab (20 mg, 40 mg, or 80 mg) or placebo without concomitant DMARDs for 12 weeks. Adalimumab significantly improved the signs and symptoms of RA with significant better ACR20\% response rates (20, 40, 80 mg for 50.7\%, 57.1\%, and 54.2\%, respectively, versus 10.0\% for placebo)\textsuperscript{16} (Fig. 2).

**MTX ADD-ON TRIAL (ARMADA STUDY)**

Two hundred and seventy-one active RA patients were randomly assigned to four treatment arms of placebo + MTX, 20 mg, 40 mg, and 80 mg of adalimumab every other week over 24 weeks.\textsuperscript{43} The patients were active even though a sufficient dose of MTX (12.5 - 25 mg \(\text{kg}^{-1}\) \text{wk}^{-1} or 10 mg if intolerant to higher doses) was administered for at least 6 months. All of the adalimumab treated groups showed a significantly higher ACR20\% and 50\% response rate than that in the placebo group (Fig. 2).\textsuperscript{43} Furthermore, the ACR70\% rate in the 40 mg and 80 mg groups was significantly higher than in the placebo group. These results suggest a rapid and sustained improvement over 24 weeks compared with MTX alone, although the effect on radiographic progression was not documented in this trial.

Summary of the three anti-TNF biologics (Fig. 2): The efficacy of the above three agents in the advanced RA patients who have had an inadequate response to MTX appears to be comparable, demonstrating approximately 60\% of ACR20, 40\% of ACR50, and 20\% of ACR70.\textsuperscript{44} As illustrated in the 2002 update version of the ACR guideline for the management of RA, the biological agents are now positioned as an-chor drugs.\textsuperscript{45} Based on these results in early active RA patients, evolving evidence of dramatic efficacy, which could pave the way for a hypothesis for the use of combination of biologic agents with MTX directed at arresting the disease in the early course RA patients with a poor prognostic profile, is within the window of opportunity in the foreseeable future.\textsuperscript{46}

**SAFETY**

Generally, biological agents are well tolerated, and safe in most patients. Frequent, but less severe side effects with standard management have been reported. While infliximab has been used in over 500,000 patients and etanercept in 200,000 patients worldwide, few, but severe adverse events have accumulated. The individual events are listed as follows.

**INFUSION INJECTION REACTIONS**

Infliximab has been associated with infusion reactions, which are rare severe events such as life-threatening anaphylaxis reactions. The lower the dose of MTX or infliximab, the higher the rate of HACA production.\textsuperscript{47} In previous studies in Western countries, the minimum dose of MTX against HACA production was 7.5 mg \(\text{kg}^{-1}\) \text{wk}^{-1} and that of infliximab was 3 mg/kg. In clinical trials in Western countries, the frequency of infusion reactions has been reported to be around 5\%\textsuperscript{48} while that of placebo infusion was 2.0\%. The patients with infusion reactions leading to withdrawal accounted for 2.5\%, and those with serious infusion reactions were 0.8\% - 3.0\%. In Western countries at a dose of more than 7.5 mg \(\text{kg}^{-1}\) \text{wk}^{-1}, HACA can be detected in up to 10\% even with the concomitant usage of MTX. There was a concern that the frequency of infusion reaction and HACA production would be higher in Japan, since the average dose of MTX used in Japan has been much lower than that in Western countries. However, the frequency of infusion reaction and HACA production was comparable between Western countries and Japan, suggesting that the minimal weekly MTX dose of 6 mg in the Japanese clinical trial would have an immunosuppres-sant effect similar to those doses used in Western
serious infection was comparable between the genetically significant difference. The frequency of serious infection between patients treated with MTX alone and that with MTX + infliximab was almost the same. Similarly, the rate of infection in etanercept-treated patients was 50–60%, which was similar to those in the control population. Again, the risk for serious infection was comparable between the general population and etanercept treated patients. However, the incidence of severe infections in patients treated with anti-TNF biologicals in the clinical setting, though not clinical trials, has been reported to be high with less signs and symptoms. Mycobacterium tuberculosis had been reported in three patients in major clinical trials including ATTRACT, ACCENT, and PROMPT.

However, a post-marketing survey revealed that the incidence of tuberculosis would be high in RA patients treated with MTX + infliximab, particularly in Europe. Until August 23, 2002, 277 cases had been reported to the FDA Arthritis, # Arthritis., # , while infliximab was used in 365,201 with the relative risk of around 7% in the general population. Seventy-five percent of these patients developed tuberculosis within the first 6 weeks (3 infusions), and the incidence was higher in endemic regions, suggesting that its appearance was due to reactivation of latent tuberculosis. Although the incidence of tuberculosis in RA patients treated with etanercept appeared to be at the upper limit of the normal controls. It is reported that the risk can be seen in patients treated with adalimumab (Table 3). Since infliximab and adalimumab are believed to lyse TNF-expressing macrophages (Fig. 1), which play an indispensable role in host defense against Mycobacterium infection, the incidence may be higher in patients treated with infliximab and adalimumab. Given the observation that the onset is 11 months after starting etanercept, we need to pay close attention to the incidence of tuberculosis in the long-term treatment of patients treated with all of the biological agents including etanercept. Considering the relative high risk for tuberculosis, the PPD skin test has been recommended to rule out latent tuberculosis infection. Following implementation of this screening, the incidence of tuberculosis in patients being treated with anti-TNF biologicals was reportedly even lower than in prior studies. Given the high incidence of tuberculosis in Japan, with 30 out of 100,000 in 2001, which is one of the highest among most of the industrialized nations, where it is less than 10/100,000, it can be assumed that the estimated increased risk of tuberculosis in Japan is up to 7 × 30/100,000. In this respect, guidelines for the prescription of infliximab in Japan have been proposed by the study group of Ministry of health, labor, and welfare (MHLW) at 2003, and have been used in Japan for a post-marketing survey of all RA cases. Six cases of tuberculosis have been reported in the initial one thousand cases for six months observation. In addition, six cases of Pneumocystis carinii pneumonia were reported. Although those patients were treated with successful resolution of the condition, we need to pay attention to other opportunistic infections such as those caused by fungi including P. carinii in addition to mycobacterial infection, and look at the simi-
even if it does develop. Group and it is not a severe life-threatening disease has not been significantly elevated in the treatment considered. However, the incidence of the disease increased risk for developing SLE had been seriously suggested a significant positive clinical response. On the chronic inflammatory demyelinating diseases with these diseases. Curiously, a recent clinical trial on the chronic inflammatory demyelinating diseases suggests a significant positive clinical response. The changed cytokine environment, which is largely skewed by anti-TNF biologicals, is believed to account for the change in the profile of autoantibody production and the phenotype of the autoimmune diseases.

The institution which can carry out an emergency treatment: Keep air-way, Oxygen, Epinephrine, Corticosteroids, etc.

**Table 5** Japanese Guidelines for the use of infliximab of RA proposed by study group of RA, MHLW.

**Indications:**
Active RA despite previous treatment with MTX (Rheumatixx) (≥3 months with MTX ≥6 mg/w). The following 3 items are satisfied.
1. ≥6 painful joints
2. ≥6 swollen joints
3. CRP ≥20 mg/L or ESR ≥28 mm/hr

As a patient who has low risk of opportunistic infections. The following 3 items should be satisfied.
1. WBC, ≥4000/mm³
2. Total lymphocyte count, ≥1000/mm³
3. β-D-glucan negative

**Contraindications:**
1. Active infectious disease
2. History of a serious infection during the past 6 months
3. Chest X-rays showing old TB (e.g. Calcification shade ≥5 mm)
4. Latent TB. When the cases where benefit outweigh risks, medication of Remicade is considered after treatment of TB.
5. History of ex-pulmonary TB, Carinii pneumonia
6. Congestive heart failure
7. Malignant tumor, demyelinating disease

**Cautions:**
A. Following items are important, because for screening of Infection (TB, opportunistic infections) and side effects.
1. Chest X-rays can be taken within the same day. And it can be read by Pulmonologist or Radiologist.
2. Opportunistic infective disease can be treated. Evaluate risk through an interview, tuberculin test, chest X-ray, and chest CT scan etc.

B. The caution and preparation for an infusion reaction (including anaphylactic reactions) is required.

**AUTOIMMUNITY**
It has been reported that infliximab and etanercept can induce production of anti-nuclear antibodies and anti-DNA antibodies, although the titer of the antibodies remains low. In the earlier studies, the increased risk for developing SLE had been seriously considered. However, the incidence of the disease has not been significantly elevated in the treatment group and it is not a severe life-threatening disease even if it does develop. On the other hand, the risk for demyelinating diseases such as multiple sclerosis and optic neuritis appears to be high, and TNF blockade therapy is contra-indicated in patients with these diseases. Curiously, a recent clinical trial on the chronic inflammatory demyelinating diseases suggests a significant positive clinical response. The changed cytokine environment, which is largely skewed by anti-TNF biologicals, is believed to account for the change in the profile of autoantibody production and the phenotype of the autoimmune diseases.

**MALIGNACIES**
As mentioned above, TNF-α has been identified as a factor inducing tumor cell lysis in vitro. Thus, one may wonder whether a blockade of TNF-α would result in an increase in the incidence of malignancy. So far the incidence of non-hematological malignancies has been demonstrated to be comparable with the general population, while that of malignant lymphoma may be higher in patients treated with anti-TNF biologicals. Agent due to evidence that the incidence is higher in RA, more active disease, and MTX users, the risk is not simply attributed to biological agentes alone. We still need to follow up the incidence carefully over an extended period.

**CONGESTIVE HEART DISEASES**
Since it has been proposed that TNF-α has a role in the pathogenesis of heart failure, clinical trials of infliximab and etanercept have been conducted for patients with congestive heart failure. In contrast to the earlier expectation, the mortality rate in patients using higher amounts of infliximab has become evidently higher than that of the placebo group, and no significant benefit was reported in the etanercept
treatment group. These results indicate that anti-TNF biological agents are not appropriate for the patients with congestive heart failure.

**ANTI-TNF THERAPY IN OTHER DISEASES (TABLE 4)**

Following the great success of anti-TNF biological agents as the therapeutic modalities of choice in the treatment of inflammatory disorders of unknown etiology, their possible application in the treatment of other diseases is now being explored, including in a long list of diseases such as Wegener’s granulomatosis and other types of vasculitis, sarcoidosis, amyloidosis, polymyalgia rheumatica, adult Still’s disease, ulcerative colitis graft vs host disease, myelodysplastic syndromes, multiple myeloma, interstitial pneumonitis, Behcet’s disease, polymyositis, dermatomyositis, systemic sclerosis, and even SLE.

**FUTURE PERSPECTIVES**

It is now clear that the usefulness of anti-TNF biological agents in combination with MTX or other biological agents lies not only in inducing clinical remission but also arresting structural damage in early RA. These results have led to the introduction of a new strategy whereby powerful combination therapy is applied to early RA as an induction regimen. To take advantage of this strategy, we need both to be able to identify patients who have a poor prognosis and to have access appropriate powerful treatment regimens. In this regard, remission can be expected to be induced in 40% of patients with MTX+anti-TNF biological agents, implying the presence of both responders and non-responders to the regimen. It has been demonstrated that ~308 polymorphism at the promoter region of TNF-α could be a predictive marker for responders to TNF blockade therapy, while others reported results to the contrary. Similar approaches are used in Crohn’s disease.

Given that we can now have biological agents targeting TNF, IL-1 and IL-6 as cytokines, CD20, and CTLA-4 as cell surface structures, it is necessary to predict the responders to each biological agents before treatment or after early inhibition of biological agents, so that we can avoid toxicity of the drugs in non-responders, and provide efficient treatment to the right patients. Comprehensive profiling of the mRNA expression strategy has recently been started to identify and predict possible responder candidates. If we can identify the prediction markers, then tailor-made therapy using several biological agents may soon be a clinical reality. Finally, issues of correct treatment dose and duration for use of anti-TNF biological agents in these inflammatory disorders remains to be considered.

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