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REVIEW ARTICLE

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Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis

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Abstract Application of biological agents targeting tumor necrosis factor-α (TNF-α) caused a paradigm shift in the treatment of rheumatoid arthritis (RA). The introduction of infliximab in 2003 and etanercept in 2005 in Japan had a significant impact on both Japanese rheumatologists and RA patients, although serious adverse effects such as bacterial pneumonia, tuberculosis and *Pneumocystis jiroveci* pneumonia are significant concerns. Based on the data from post-marketing surveillance in Japan and accumulating evidence worldwide, the Internal Medicine Rheumatology Study Group of the Ministry of Health, Labor and Welfare (MHLW), Japan, has updated the guidelines for the use of anti-TNF-α agents for RA, which were subsequently approved by the Board of Japan College of Rheumatology (JCR). In the present revised guidelines, we combined the guidelines for use of each of infliximab and etanercept together with some modifications and precautions, paying special attention to serious adverse reactions. Although it is still controversial whether the use of TNF-α blocking agents per se increases the risk of infection or not, bacterial pneumonia, regardless of the pathogens, is the most frequent complications in RA. The risk factors associated with pneumonia identified in the post-marketing surveillance of infliximab in Japan are presented in this guideline. The diagnostic algorithm is also designed for early diagnosis and treatment of pulmonary lesions seen during the treatment of biological agents. Preventive measures and precautions against tuberculosis, another frequent and significant complication in Japan, are also described. Furthermore, risk factors for developing *Pneumocystis* pneumonia, which uniquely occurs at 30- to 50-fold frequency under TNF-α blockade therapy in Japan, are described here and its preventive measures are discussed. It is stressed that secondary-care rheumatologists should be better familiarized with the proper use of TNF-α blocking agents and be alert to any adverse events for a better management of RA patients.

Key words Adverse events · Etanercept · Infliximab · Rheumatoid arthritis · Treatment guidelines · Tumor necrosis factor-α antagonists

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Introduction

The introduction of biological agents resulted in a paradigm shift in the treatment of rheumatoid arthritis (RA). Infliximab, a chimeric anti-tumor necrosis factor (TNF)-α monoclonal antibody, was introduced in Japan in 2003 and etanercept, a recombinant soluble TNF-α receptor, in 2005. Although these agents are efficacious against RA, there is concern regarding the potential serious adverse effects of these drugs, especially infections and malignancies, in Japanese RA patients possibly because of genetic, environmental and socioeconomic differences. Therefore, specific guidelines for the proper use of these agents have been developed,[1,2] which were approved by the Japan College of Rheumatology (JCR). Strict pharmacovigilance has been advocated by Japanese pharmaceutical companies marketing these biological agents. All case report forms related to infliximab and etanercept were collected by these pharmaceutical firms in the first 2 years after their approval and their outcomes could be followed. By 2006, infliximab was prescribed for over 7000 and etanercept was for over 6000 Japanese patients with RA, and the profiles and frequency of the adverse events have been analyzed.[3,4] Based on such

analysis, and that of the reports and the guidelines established by other countries,[5–7] we, the Internal Medicine Rheumatology Study Group of the Ministry of Health, Labor and Welfare (MHLW), Japan, have updated the guidelines for the use of TNF-α antagonists in Japan by combining the guidelines for each of infliximab and etanercept (Table 1). These guidelines have been posted on the official website of the JCR.[8]

Eligible patients for TNF-α blocking agents

All patients must fulfill the American College of Rheumatology 1987 Classification criteria for the diagnosis of RA.[9] Biological agents are recommended for patients who show inadequate response to conventional treatment, a criterion similar to the previous guidelines.[1,2] Inadequate response of

Table 1. Treatment guidelines for the use of tumor necrosis factor (TNF)-α blocking agents

Currently, infliximab and etanercept are available for the treatment of rheumatoid arthritis in Japan (April, 2006)

A. Eligible patients for TNF-α blocking agents

Patients fulfilling the American College of Rheumatology 1987 Classification criteria for the diagnosis of rheumatoid arthritis (RA) and showing inadequate response to conventional treatment. Inadequate response of RA to previous treatment is defined as the presence of the following three clinical findings

- –Tender joints ≥6
- –Swollen joints ≥6
- –Erythrocyte sedimentation rate ≥28 mm/h or C-reactive protein ≥2.0 mg/dl

B. Inclusion criteria

Patients showing inadequate control despite treatment for at least 3 months with standard doses of conventional disease-modifying-anti-rheumatic-drugs (DMARDs) rated in the Diagnostic Manual and Evidence-Based Treatment Guidelines developed by the study group of the Ministry of Health, Labor and Welfare (MHLW), Japan[a]

It is recommended that patients should have the following in order to avoid potential opportunistic infections:

- –Leukocyte count ≥4000/mm^3
- –Peripheral blood lymphocyte count ≥1000/mm^3
- –Serum or plasma (1→3)-β-D-glucan: negative

[a] For infliximab, conventional DMARD means methotrexate (MTX) administration at 6–8 mg/week. For etanercept, conventional DMARD means MTX, bucillamine, or sulfasalazine, recommended as level A by MHLW

C. Exclusion criteria

1. Current infection
   - –Hepatitis B virus (HBV) reactivation has been reported in patients with chronic HBV infection receiving anti-TNF-α agents. The effect of TNF-α antagonists on hepatitis C virus (HCV) infection remains unclear. When TNF-α antagonists are used for treatment, it is recommended to examine the carriage of HBV or HCV and monitor liver function
   - –Because non-tuberculous mycobacterium (NTM) is an opportunistic pathogen resistant to most drugs, it is currently recommended that TNF-α antagonists be avoided in patients with history of NTM infection
2. Past history of serious infections in the last 6 months
3. Abnormal shadows on chest radiographs suggestive of old pulmonary tuberculosis (TB) or tuberculosis pleuritis
4. History of pulmonary or extrapulmonary TB
5. Past history of *Pneumocystis* pneumonia (PCP)
6. Congestive heart failure
7. Malignancy or demyelinating disease

D. Dosage and usage of TNF-α antagonists

1. Infliximab[b]
   - –Administer 3 mg/kg body weight by two-hour drip infusion
   - –Booster administration must be followed at 2 and 6 weeks after the first injection. Maintenance treatment is provided every 8 weeks
2. Etanercept
   - –Administer subcutaneously at a dose of 10 to 25 mg twice weekly
   - –Reduction of the dose or the frequency of injection might be considered for low-weight patients or those with comorbidities because the approved dose has been set to international standard physique
   - –Self-injection of etanercept is allowed for adherent patients showing adequate response to the drug after providing detailed instructions by a health professional

[b] Infliximab is approved for administration only with MTX at 6 or 8 mg/week. MTX co-administration has increased the efficacy of infliximab in RA and prevented the production of neutralizing antibodies (HACA); these antibodies do not only decrease effectiveness but could induce severe infusion reaction

E. Cautions

1. According to the post marketing surveillance (PMS) of TNF-α antagonists in Japan and other countries, infectious diseases are the most frequent of all the serious adverse events. To prevent TB or other opportunistic infections, practitioners are recommended to attend the following
   - –Obtain chest radiographs on the same day, which should be read by a pulmonologist, TB specialist, or radiologist
   - –According to PMS of infliximab in Japan, old age (over 65 years of age), diabetes mellitus, and coexisting pulmonary diseases correlate with the frequency of pneumonia. Administration of TNF-α antagonists to patients with any of the above risk factors should be considered carefully and the patients followed frequently
   - –Treat opportunistic infections; comprehensive TB screening should be conducted including an in-depth patient history, chest radiographs (chest CT whenever possible) and a purified protein derivative (PPD) skin test, or with a PPD skin test positive (redness of at least 20 mm in diameter or the presence of induration), prophylactic treatment with isoniazide at 300 mg/day should be considered
   - –Because cases of PCP are identified frequently in Japan (22 cases in 5000 registrants) during infliximab treatment, PCP should be considered as a possible diagnosis in RA patient with pneumonia (refer to Fig. 1)

Table 1. *Continued*

2. Be ready for serious infusion reactions (including anaphylactic shock) that may occur during infliximab administration
   –Preparation for emergency treatment: airway maintenance, oxygen inhalation, subcutaneous epinephrine, and intravenous corticosteroid have to be available at bedside
   –Be cautious when re-administering infliximab after a long period of discontinuation, because analysis of the Japanese PMS database indicates frequent encounter of serious infusion reactions after long drug holidays of infliximab (especially over 2 years)
3. Surgery should be delayed until a sufficient time had elapsed from the last administration of TNF-α antagonists (recommend to keep 2–4 weeks for etanercept or 4 weeks for infliximab with long half-life), because it is not clear whether or not TNF-α blockade interferes with the healing of wounds and prevention of postoperative infection. Treatment with TNF-α antagonists could be resumed after complete healing of the surgical wound and in the absence of any postoperative infection
4. The regular prescription of anti-TNF-α agents by child-bearing or lactating woman cannot be advocated because these drugs can transfer to the placenta and milk and their safety on embryos, fetuses and neonates has not yet been confirmed. Lactation should be avoided for longer than 6 months from last administration of infliximab. Although there is no evidence that anti-TNF-α agents are toxic for children or can induce mutagenesis, discontinuation of treatment and careful follow-up are recommended when a patient inadvertently become pregnant during anti-TNF-α therapy
5. There is a great concern regarding the possible carcinogenic effects of TNF-α antagonists, but this issue remains controversial. Prescribing TNF-α antagonists for patients with pre-cancerous lesions (leukoplakia of the esophagus, dysplasia of corpus uteri, or adenoma of the colon) or past history of neoplasm should be done with caution or monitored carefully by a specialist

RA to previous treatment is defined as the presence of at least six tender joints and swollen joints and either a C-reactive protein (CRP) level of at least 2.0 mg/dl or erythrocyte sedimentation rate (ESR) of at least 28 mm/h.

Inclusion criteria

Infliximab can be used for RA patients who show inadequate response to methotrexate (MTX) of more than 6 mg/week for more than 3 months. Etanercept is indicated for those patients whose RA is inadequately controlled despite treatment for at least 3 months with the standard doses of one of the disease modifying antirheumatic drugs (DMARDs) (MTX, bucillamine, or sulfasalazine), which are rated as "recommendation A level" in the Diagnostic Manual and Evidence-Based Treatment Guidelines[10] developed by the study group of the MHLW. However, it has to be pointed out that there is no sufficient evidence for the efficacy of combination therapy with etanercept and either bucillamine, sulfasalazine, or other DMARDs at present. Leflunomide, another DMARD rated as recommendation A, is not included in the present guidelines because the post-marketing surveillance (PMS) of this drug is still underway and its safety remains to be determined in Japan.[11,12]

To avoid potential opportunistic infections, it is recommended that patients should have a peripheral blood leukocyte count of 4000/mm^3 or more, peripheral lymphocyte count of 1000/mm^3 or more, and a negative test for blood (1→3)-β-D-glucan. These criteria are based on the findings that reduced cellular immunity may be responsible for the development of opportunistic infections such as tuberculosis and *Pneumocystis jiroveci* pneumonia (*Pneumocystis* pneumonia; PCP) and that patients with low lymphocyte count are susceptible to these infections[13]. Serum or plasma (1→3)-β-D-glucan is a useful and snap marker of fungal infection,[14] especially PCP,[15,16] widely used by most Japanese practitioners.

Exclusion criteria

Current infection

Biological agents are contraindicated in patients with ongoing infections. The use of TNF-α antagonists should be delayed until a full improvement of acute infections. In particular, it is recommended to delay such treatment as long as 6 months after recovery from serious or life-threatening infection (e.g., sepsis, systemic disseminated infections).

There is controversy regarding the effect of TNF-α antagonists on chronic or asymptomatic infections; e.g., hepatitis B, hepatitis C, and human immunodeficiency virus (HIV).[7] Hepatitis B virus (HBV) infection is common among Japanese population and its reactivation has been reported in patients with chronic HBV infection receiving TNF-α antagonists.[17] It is therefore advisable that TNF-α antagonists should be avoided in patients with HBV infection.[17] However, when the potential benefits of treatment might exceed the risk, it has been recommended recently that patients carrying HBV should be pre-treated with lamivudine.[17] In contrast, the effect of TNF-α antagonists on hepatitis C virus (HCV) infection remains unclear. When TNF-α antagonists are administered, it is recommended to monitor liver function in association with HBV or HCV burden.

Nontuberculous mycobacterium (NTM) is an opportunistic pathogen resistant to most drugs. A few cases of NTM infection in patients on TNF blockade therapy have been published as case reports[18–20] and have appeared in the U.S. Food and Drug Administration (FDA) documents.[21] It is currently recommended that TNF-α antagonists should be avoided in patients with history of NTM infection.

Abnormal shadow on chest radiography suggestive of old pulmonary tuberculosis (TB), tuberculosis pleuritis, or definite past history of TB without completion of chemotherapy

When patients have past histories of TB by interviews, or abnormal radiographic findings, they must be excluded from treatment with TNF-α or advised to receive chemoprophylaxis.

Past history of *Pneumocystis* pneumonia (PCP)

PCP is one of the serious adverse complications observed during TNF-α blocking treatment in the post-marketing surveillance (PMS) in Japan.[3,4] Thus, patients with past history of PCP should be excluded from such therapy because of its possible continuous and latent infection. In HIV patients, an episode of PCP can be one of the risk factors[22] for further suffering.

Congestive heart failure (CHF)

TNF-α antagonists should be avoided in patients with CHF above the New York Heart Association (NYHA) III grade, because of high number of deaths reported in the clinical trials in patients with CHF.[23,24] However, based on the PMS data in Japan, there are no reports of severe heart failure or related death.

Malignancy or demyelinating disease

The early clinical trial of TNF-α blocking agents against multiple sclerosis (MS) reported a significant increase in the number of patients with flare or exacerbation in the treatment group.[25] Furthermore, some patients with neurological events suggestive of demyelination have been reported in Western countries following administration of either infliximab or etanercept;[26,27] however, TNF-α antagonists do not seem to increase the frequency of MS.[26] It is nevertheless recommended that patients with a history of MS should avoid such treatment.[27]

Since TNF-α blocking agents can potentially exacerbate pre-existing cancer due to the biological activity of TNF-α,[28] they are contraindicated in patients with active malignancy.

Dosage and usage of biological agents

The dosages of both infliximab and etanercept are similar to those recommended in the previous guidelines.[1,2] Infliximab should be administered intravenously at 3 mg/kg by drip infusion for 2 h. Booster administration must be followed at 2 and 6 weeks after the first injection. Maintenance treatment is provided every 8 weeks. Six to 8 mg/week of MTX should be given simultaneously with infliximab. Methotrexate does not only act in synergy with infliximab to produce efficient antirheumatic effect but also inhibits the production of human antichimeric antibodies (HACA).[29] In Japan, the dosage and interval of infliximab are strictly fixed and increment of dosage or shortening of interval is not allowed.

Etanercept is administered subcutaneously at a dose of 10 to 25 mg twice weekly. Treatment may begin with 25 mg once weekly in patients with low body weight or those with comorbidities. Self-injection of etanercept is allowed after providing detailed instructions after 4 weeks of commencement of etanercept to patients who show adequate response to the drug. Etanercept may be used as monotherapy as was applied previously in clinical trials in Japan. However, the TEMPO study reported that the combination of etanercept and MTX provides greater effect.[30] The combination of etanercept with MTX should be thus considered in patients with highly active disease.

Corticosteroids should be tapered after significant response to the biological agents is noted since long-term use of corticosteroids may increase the risk of serious adverse effects such as infection.[31,32]

Potential and serious adverse effects during TNF-α blockade therapy

Infections

According to the PMS of TNF-α blocking agents in Japan and other countries, infectious diseases are the most frequent of all the serious adverse events.[3,4,33–36] The risk factors of bacterial pneumonia are old age (over 65-years of age), diabetes mellitus, and coexisting pulmonary diseases.[3] Administration of TNF-α blocking agent to patients with any of the above risk factors should be considered carefully and followed frequently with multiple prophylactic measures (e.g., mouth cleaning, prevention of dysphagia, and vaccination against influenza and pneumococci). When patients under TNF-α blocking therapy develop symptoms suggestive of respiratory infection such as fever, cough, and dyspnea, physicians should obtain chest radiographs on the same day that should be read by a pulmonologist or radiologist. Treatment of RA with TNF-α blocking agents should be executed by specialists with experience in the field, who can diagnose and treat infectious diseases appropriately. Those who prescribe TNF-α antagonists should be acquainted with the diagnosis and treatment of opportunistic infections; comprehensive TB screening should be conducted including an in-depth patient history, chest radiographs (chest computed tomography (CT) whenever possible) and a purified protein derivative (PPD) skin test. When PPD skin test is positive (redness of at least 20 mm in diameter or the presence of induration), prophylactic treatment with isoniazide at 300 mg/day should be considered. Strict recommendation of chemoprophylaxis in the original guidelines has reduced the inci-

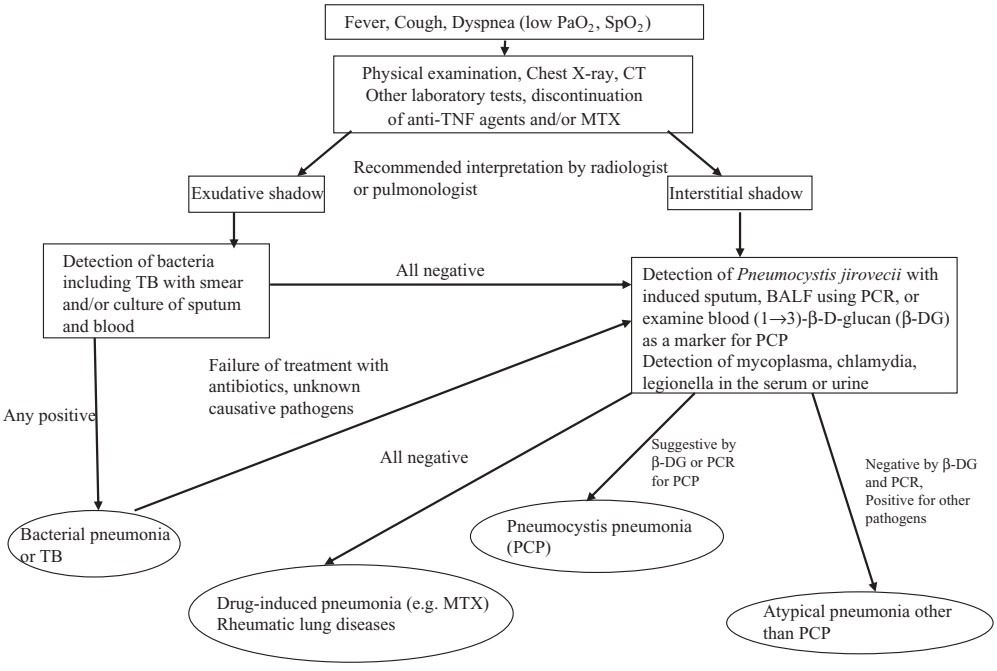

Fig. 1. Diagnostic algorithm of pneumonia during anti-tumor necrosis factor therapy. *BALF*, bronchoalveolar lavage fluid, *PCR*, polymerase chain reaction; *PCP*, *Pneumocystis* pneumonia

dence of new cases of TB among infliximab users. Eleven patients within the first 2000 infliximab users developed TB whereas only two patients were reported in the second 2000 registrants.[3] Among the 5519 registrations on etanercept, 10 patients who did not receive prophylaxis developed TB.[4] Although there are concerns that excessive chemoprophylaxis might increase multidrug resistant TB, prophylaxis with isoniazide (INH) is currently effective[37] and recommended for high-risk patients according to the guidelines.[38,39]

Pneumocystis pneumonia (PCP), one of the important opportunistic infections in immunocompromised hosts caused by *P. jiroveci*, has been reported to cause sporadic infection in patients with RA, especially after introduction of MTX to the treatment.[40] There are few cases of PCP reported in patients treated with TNF-α antagonists from Western countries.[41] The PMS data in Japan identify 22 patients among 5000 registrants treated with infliximab who developed PCP;[3] and thus the incidence is 30-fold that in the United States.[21] It is possible that this complication could be specific to Japanese patients and case series analysis is currently underway in Japan. When monitoring Japanese RA patients, it is necessary to keep in mind that PCP might be one of the serious complications, especially in those patients treated with TNF-α blocking agents. Serum (1→3)-β-D-glucan, which is a useful marker of fungal infection[14] and approved only in Japan, has been proved useful for early and non-invasive diagnosis of PCP.[15,16] It is therefore recommended to examine serum (1→3)-β-D-glucan levels in RA patients at the time of introducing TNF-blocking agents (see section on Inclusion criteria).

Pneumonia occurring in RA patients treated with TNF-α antagonists should be diagnosed, its cause identified, and be treated promptly and aggressively. The algorithm for the differential diagnosis of pneumonia is presented in Fig. 1.

Infusion reaction against infliximab

Because serious infusion reactions including anaphylactic shock may occur during infliximab administration, preparations for emergency treatment, i.e., airway maintenance, oxygen inhalation, subcutaneous epinephrine, and intravenous corticosteroid, have to be available at bedside. However, mild infusion reactions that can be managed adequately should not be a hindrance to further administration of infliximab to patients.[42] Analysis of the Japanese PMS database indicates that frequent encounter of serious infusion reactions after long drug holidays of infliximab, especially over 2 years,[3] and thus one has to be cautious when readministering infliximab after a long period of discontinuation.

Interestingly, although increased incidence of delayed infusion reactions to infliximab after a long period of discontinuation in patients with Crohn's disease has been already reported by the FDA,[43,44] acute infusion reactions under RA treatment at similar situation have been reported especially in Japan.[45] The underlying pathogenic mechanisms of these reactions await further research.

Surgery

It is still not clear whether or not TNF-α blockade interferes with the healing of wounds. However, several studies have reported that perioperative adverse events, especially postoperative infection, might increase in RA patients under

TNF-α blockade therapy.[46] It is advised that surgery should be delayed until a sufficient time had elapsed from the last administration of TNF-α antagonists, taking into consideration the biological half-life of the drugs (infliximab: 7.7–9.5 days,[47] etanercept: 102 ± 30 h[48]).

After surgery, treatment with TNF-α antagonists could be resumed after complete healing of the surgical wound and in the absence of any infection. It is recommended that patients who undergo artificial joint replacement surgery, e.g., knee or hip artificial joint, should be followed-up carefully over a period of 6 months to ensure lack of infection, according to the guidelines of the British Society of Rheumatology.[7]

Pregnancy and lactation

Tumor necrosis factor-α blocking agents can pass the placenta and milk to the fetus and newborn but their safety remains unknown. At present, although TNF-α antagonists are categorized as class B or C with regard to the risk for pregnancy by the FDA,[49] their regular use during pregnancy cannot be advocated. Lactation should be avoided for longer than 6 months from last administration of infliximab.

On the other hand, several anecdotal reports[50,51] suggested the safety of TNF-α antagonists during childbirth. Moreover, the prescription of TNF-α blocking agents before or at conception does not seem to increase the risk of adverse pregnancies or congenital malformations.[52] However, at present, discontinuation of treatment and careful follow-up are recommended when a patient inadvertently becomes pregnant during TNF-α blocking therapy. International collaborative effort to collect information about pregnancy outcomes in patients on TNF-α blocking agents is needed.[53]

Malignancy

There is a great concern among rheumatologists and other specialties regarding the possible carcinogenic effects of anti-TNF-α therapy. This issue, however, remains controversial because there are contradictory reports supporting both an increase[54–57] and no change in malignancies[58–60] with the use of TNF-α blocking agents. Prior to the introduction of TNF-α antagonists, increased risk of malignant lymphoma was reported in RA patients[61–64] and such risk correlated with the RA disease activity.[55,65,66] Furthermore, MTX has been implicated in the pathogenesis of certain types of malignant lymphoma positive for Epstein–Barr virus.[67,68] A multiple risk factor analysis using a large cohort may answer this question in the future.

Prescription of TNF-α blocking agents for patients with concurrent cancer is contraindicated. Leukoplakia of the squamous epithelium, cervical dysplasia, and adenoma of the colon are recognized as precancerous lesions. Prescribing TNF-α antagonists for patients with precancerous lesions or past history of neoplasm should be done with caution or monitored carefully by a specialist.

Summary

We updated the guidelines for the use of TNF-α blocking agents for RA patients. In this edition, we combined both the guidelines for infliximab and etanercept and added other issues related to infection, surgery, pregnancy, lactation, and malignancy. Based on the PMS database in Japan, the most frequent and important adverse event is infection, especially *Pneumocystis* pneumonia in RA patients. There is a need for further research into the link, if any, between TNF-α antagonists and carcinogenesis. It is essential that physicians are aware of both the benefits and risks of these agents and should be involved in pharmacovigilance so as to deliver a safe and proper treatment with TNF-α blocking agents.

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