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GUIDANCE

# Japanese guidance for use of biologics for psoriasis (the 2013 version)

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## ABSTRACT

**The clinical use of adalimumab and infliximab, human anti-tumor necrosis factor (TNF)-α monoclonal antibodies, for psoriasis began in January 2010. In January 2011, ustekinumab, a human anti-interleukin-12/23p40 (IL-12/23p40) monoclonal antibody, was newly approved as the third biologic with an indication for psoriasis. While all of these biologics are expected to exhibit excellent therapeutic effect for psoriasis and to contribute to the improvement of quality of life in patients, these drugs require careful safety measures to prevent adverse drug reactions, such as serious infections. The new guidance, an English version prepared by revising the *Japanese Guidance/Safety Manual for Use of Biologics for Psoriasis 2011* (in Japanese), is intended to provide up-to-date, evidence-based recommendations and safety measures on the use of biologics, and describes the optimal use of the three biologics, medical requirements for facilities for using biologics, details of safety measures against reactivation of tuberculosis and hepatitis B virus infection, and recommendable combination therapies with biologics.**

**Key words:** **adalimumab, biologics, guidance, infliximab, psoriasis, ustekinumab.**

## INTRODUCTION

The clinical use of adalimumab and infliximab, human anti-tumor necrosis factor (TNF)-α monoclonal antibodies, for psoriasis began in January 2010 when an additional indication for this disease was approved. In January 2011, ustekinumab, a human anti-interleukin-12/23p40 (IL-12/23p40) monoclonal antibody, was newly approved as the third biologic with an indication for psoriasis. While all of these biologics are expected to exhibit excellent therapeutic effect for psoriasis and to contribute to the improvement of quality of life (QOL) in patients, these drugs require careful safety measures to prevent adverse drug reactions, such as serious infections.

The *Japanese Guidance/Safety Manual for Use of Biologics for Psoriasis 2011* (in Japanese)[1] was established by revising the *Guidance/Safety Manual for Use of TNFα Antagonists for Psoriasis*[2] issued by the Biologics Review Committee of the Japanese Dermatological Association (JDA) in February 2010. The new guidance is intended to provide up-to-date, evidence-based recommendations and safety measures on the use of biologics, and describes the optimal use of the three biologics, medical requirements for facilities for using biologics, details of safety measures against reactivation of tuberculosis and hepatitis B, and recommendable combination therapies with biologics.

The main purpose of this guidance is to ensure that these biologics are safely and properly used by dermatologists in the treatment of psoriasis patients.

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## REQUIREMENTS FOR PHYSICIANS AND CLINICAL FACILITIES

A total of 525 accredited clinical facilities had been approved by JDA for the use of biologics as of the end of April 2013 (refer to the website of the JDA).[3] Establishing a support system for continuous long-term treatment based on the close collaboration between accredited hospitals and other hospitals or private clinics is essential for the convenience of patients who have difficulty in making regular and frequent visits to an accredited hospital for various reasons. Consequently, the following three requirements have been established:

1 Biologics should be used under the control, supervision and guidance of JDA board-certified dermatologists who are experienced in the diagnosis and treatment of psoriasis and are familiar with comorbidities associated with psoriasis, with knowledge of risks of biologics as well as the capability to manage adverse reactions. The safety profiles of biologics will need to be monitored periodically, and continuous caution should be exercised for ensuring the safety in long-term use.

2 Biologics should be used in clinical facilities (hospitals) that are capable of performing periodical indispensable examinations, emergency care for rapidly developing serious adverse reactions, and close collaboration with pulmonologists, radiologists, infectious disease specialists and other relevant specialists. Specifically, such hospitals include the major dermatology training institutions qualified by the JDA and facilities that are accredited by the Biologics Review Committee of the JDA and meet the above-mentioned requirements for the use of biologics. Hospitals in which attending dermatologists cannot gain cooperation from other specialists of their own hospitals during or after office hours will be approved on the condition that the written consent to cooperate is obtained from a nearby base hospital with full-time pulmonologists (refer to the website of the JDA for details).

3 In principle, the use of biologics in hospitals and private clinics is limited to maintenance therapy in patients for whom treatment has been initiated at one of the above-mentioned accredited hospitals and in whom remission has been achieved. For this purpose, new approval from the Biologics Review Committee is not required, but between-hospital or hospital–clinic cooperation with an accredited hospital must be properly maintained in daily medical practice. Emergency treatment should be performed at the accredited hospital, and it is recommended to conduct periodic follow up (e.g. blood test, imaging test and other tests every 6 months) at the accredited hospital in accordance with the hospital–clinic cooperation arrangement, even after the patient has been switched to maintenance therapy. To be able to introduce biologic therapies, hospitals and private clinics that do not meet the above conditions are required to: (i) have more than one full-time board-certified dermatologist; (ii) have participated in at least one clinical study for biologics; and (iii) be able to cooperate with nearby hospitals promptly and reliably in emergency situations. Accreditation is granted to hospitals and private clinics after the submitted documents have been closely reviewed and approved by the Biologics Review Committee of the JDA.

## ELIGIBLE PATIENTS FOR TREATMENT WITH BIOLOGICS

Biologics should be used for those patients listed below with careful considerations consisting of treatment factors (e.g. therapeutic characteristics, concomitant therapies), disease factors (e.g. disease type, severity, past illness, comorbidities), patient background (e.g. age, sex, treatment history, personality, wishes) and the degree of impairment in which the disease affects the patient's QOL, with close reference to the Important Precautions for Eligible Patients and the Safety Manual described later.

Psoriatic patients aged 16 years or older who are candidates for systemic therapy and meet any of the following criteria:

1 Patients with plaque-type psoriasis with or without psoriatic arthritis who meet either of the following criteria: (i) patients who have not adequately responded to any of standard systemic therapies including phototherapy, with rash covering at least 10% of the body surface area (BSA); and (ii) patients with refractory skin or joint symptoms that are intractable to standard systemic therapies, and significantly impair QOL.

2 Patients with generalized pustular psoriasis (GPP).
Treatment should be performed in accordance with the *Guideline for Diagnosis and Treatment of Generalized Pustular Psoriasis 2010*[4] issued by the JDA.

3 Patients with erythrodermic psoriasis.
Patient eligibility should be determined after consideration of response to previous treatments, comorbidities, general conditions and other factors.
(Only infliximab has been approved for pustular psoriasis and erythrodermic psoriasis.)

## IMPORTANT PRECAUTIONS FOR ELIGIBLE PATIENTS

Before using biologics for plaque-type psoriasis without arthritis (psoriasis vulgaris), other systemic therapies should be considered, as a general rule. Biologics are therefore indicated in patients with plaque-type psoriasis if they: (i) have not adequately responded to therapies such as cyclosporine, etretinate, psoralen plus ultraviolet (UV)-A therapy and narrowband UV-B; (ii) cannot receive an adequate dose of those drugs or irradiation because of a previous history of adverse reactions; (iii) respond to the above therapies but are prone to have repeated relapses after dose reduction or discontinuation, which raises concerns about cumulative adverse reactions due to long-term use; or (iv) are difficult to treat because of comorbidities contraindicating these therapies.

Meanwhile, it is critical in patients with psoriatic arthritis, which causes progressive joint destruction, to suppress joint destruction before disability affects activities of daily living. It is therefore recommended to consider the use of biologics from an early stage of the disease. Clinical studies conducted in Japan and foreign countries have shown that ustekinumab improves joint symptoms in patients with psoriatic arthritis. As of today, however, ustekinumab has not been approved with the indication for the treatment of psoriatic arthritis in foreign countries due to lack of evidence for inhibitory effect on joint destruction.

### Plaque-type psoriasis with or without psoriatic arthritis (psoriasis vulgaris or psoriasis arthropathica)

Patients who have not adequately responded to standard systemic therapies, including phototherapy, with rash covering at least 10% of the BSA, or those with refractory skin or joint symptoms that are intractable to standard systemic therapies and significantly impair QOL.

It should be noted that the use of ustekinumab for psoriatic arthritis should be limited to patients with rash that either covers at least 10% of the BSA or is refractory enough to cause severe QOL impairment, namely, not simply having joint symptoms.

*Criteria for introducing systemic therapy.*

- Japanese clinical studies of adalimumab,[5] infliximab,[6] and ustekinumab[7] were conducted in patients with plaque-type psoriasis with or without psoriatic arthritis (psoriasis vulgaris or psoriasis arthropathica) who require systemic therapy including phototherapy, with plaque-type rash covering 10% or more of the BSA and with a Psoriasis Area and Severity Index (PASI) score of 12 or more. These criteria are virtually comparable to the definition of moderate and severe psoriasis in the USA and Europe.
- "The rule of 10s" (BSA ≥10%, PASI score ≥10 or Dermatology Life Quality Index [DLQI] score ≥10)[8] is a useful criterion for introducing systemic therapy and is used worldwide.

*QOL.*

- Because of the appearance and symptoms such as pruritus and arthralgia, patients with psoriasis have highly damaged QOL both psychologically and socially, with the extent of reduced QOL reported to be comparable to or severer than those of cancer, cardiac disease and diabetes mellitus. For this reason, treatment strategy with emphasis on QOL has been developed from patients' perspective in the USA[9,10] and Europe.[11–13] Psoriasis with a DLQI score of 10 or more is generally considered as having a severe disease due to highly damaged QOL. The DLQI score is regarded as a criterion required for the introduction of systemic therapy and considered independent of BSA and PASI scores. Cutaneous symptoms highly damaging QOL generally include refractory rash on the head and neck, palms and soles, and fingers including nails.
- Although QOL was not included in the inclusion criteria in any of the Japanese clinical studies, the median baseline DLQI score was 13.0 for infliximab, 8.0 for adalimumab and 10.0 for ustekinumab in those clinical studies.
- The Psoriasis Disability Index (PDI) is considered to be specific for psoriasis and useful for QOL assessment, in addition to the DLQI, which is used for dermatological diseases in general. The PDI was also used in clinical studies of ustekinumab conducted in Japan, and the median baseline score was 14.0.

*Joint symptoms.*

- Conventional therapies for psoriatic arthritis include non-steroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs and oral corticosteroids. Chronic progressive arthritis, which often accompanies psoriasis, is characterized by joint destruction and deformation similar to those observed with rheumatoid arthritis, and the progression of the disease entails further decline in QOL due to motor dysfunction. Thus, it is critical to suppress joint destruction before interference with the activities of daily living becomes manifest.
- Foreign clinical studies demonstrated that TNF-α inhibitors prevented the progression of joint destruction in patients with psoriatic arthritis. In the USA, it is therefore recommended to consider the use of TNF-α inhibitors for the treatment of moderate to severe psoriatic arthritis from an early stage. Meanwhile, ustekinumab showed improvements in disease activity (American College of Rheumatology score) and pain (on a visual analog scale) in a foreign phase 2 clinical study involving patients with psoriatic arthritis (it should be noted that the dosage regimens used in this study were different from those in Japanese studies).[11,12] However, the prevention of structural damage to the joints has not been evaluated, and a phase 3 clinical study to evaluate inhibitory effects on joint destruction is ongoing in foreign countries.
- The specific criteria for peripheral arthritis are: (i) three or more swollen joints; (ii) three or more painful joints; and (iii) C-reactive protein of 1.5 mg/dL or more. Patients who meet all of these criteria are to be treated with biologics. However, the use of biologics should also be considered in other patients who have destructive arthritis mutilans or joint symptoms of similar severity, accompanied by severe impairment of QOL.
- Biologics are indicated in patients with axial arthritis who have a Bath Ankylosing Spondylitis Disease Activity Index score of 4 or more.

*Selection criteria of biologics.*

- Adalimumab, infliximab and ustekinumab exhibited high response rates in patients with plaque-type psoriasis. The improvement rate in the PASI 75% response rate was 63–71% (after 16 weeks) for adalimumab, 69–80% (after 10 weeks) for infliximab and 60–67% (after 12 weeks) for ustekinumab.
- There are no established criteria for the selection of biologics for the treatment of plaque-type psoriasis. In the UK guidelines (2009),[11] ustekinumab, which is indicated only for psoriasis and not for rheumatoid arthritis or inflammatory bowel disease, is positioned as an option for patients who require biologic therapies but for whom TNF-α inhibitors are not effective or not applicable. In the US guidelines (2011),[10] however, the positioning of ustekinumab is similar to that of TNF-α inhibitors.
- The efficacy of adalimumab for plaque-type psoriasis is expected in patients with secondary failure (i.e. although treatment efficacy is seen for a certain period of time, it decreases and the disease condition becomes worse than that before the treatment) with infliximab, although the efficacy is decreased to some extent. In addition, the efficacy of ustekinumab is expected in patients who do not adequately respond to TNF-α inhibitors regardless of the pretreatment.
- The common view on psoriatic arthritis among foreign guidelines is that TNF-α inhibitors, which have been shown to prevent the progression of joint destruction regardless of the pretreatment, should be positioned as the first-line treatment, while ustekinumab should be positioned as a second-line treatment.

### Generalized pustular psoriasis (GPP)

No randomized double-blind clinical studies on biologics have been conducted in patients with GPP because of a limited number of patients. However, reports have shown that patients with GPP responded to TNF-α inhibitors, and infliximab has been approved with an indication for GPP in Japan. To ensure the safety of TNF-α inhibitors in patients with GPP, it is necessary to collect and analyze the data of treated patients across the country. The diagnosis of GPP should follow the criteria stipulated in the *Guideline for the Diagnosis and Treatment of Generalized Pustular Psoriasis* issued by the JDA (2010 edition).[4] Palmoplantar pustulosis, subcorneal pustular dermatosis and acute generalized exanthematous pustulosis are not included in GPP and not indicated for biologic therapy.

### Erythrodermic psoriasis

No randomized double-blind clinical studies on biologics have been conducted in patients with erythrodermic psoriasis because of a limited number of patients. However, reports have shown that patients with erythrodermic psoriasis responded to adalimumab and ustekinumab, as well as infliximab, which has the only indication for erythrodermic psoriasis in Japan.

## DOSAGE AND ADMINISTRATION

*Adalimumab*

The usual adult dose for s.c. injection is 80 mg of adalimumab at week 0 (initial administration), followed by 40 mg every 2 weeks from week 2. If the patient shows inadequate response, the dose can be increased to a dose of 80 mg.

*Infliximab*

Infliximab, at 5 mg/kg bodyweight, is i.v. infused slowly over 2 h or longer. The drug is infused at 2 and 6 weeks after the initial infusion, followed by every 8 weeks. At week 14 and after, 1-h infusion is allowed only if no infusion reactions occur throughout the first three infusions.

*Ustekinumab*

Generally, a dose of 45 mg of ustekinumab is s.c. injected. The drug is injected at week 0 (initial administration) and at 4 weeks, followed by every 12 weeks. If the patient shows inadequate response, the dose can be increased to a dose of 90 mg.

## PRECAUTIONS FOR DOSE AND MODE OF ADMINISTRATION

### Dose adjustment

*Adalimumab.* The effect of adalimumab is usually obtained within 4–16 weeks after the initiation of treatment. If the effect is not obtained within 16 weeks, the continuation of the treatment should be considered carefully, including the dose increase from 40 to 80 mg. If symptoms are aggravated after 4 weeks or more, the dose may be increased.

*Infliximab.* The dose can be adjusted according to bodyweight because infliximab is administrated i.v. at a dose of 5 mg/kg of bodyweight. Unlike in the treatment of rheumatoid arthritis, however, the dose escalation or shortening of treatment intervals due to the decreased effect is not currently allowed in the treatment of psoriasis (clinical studies are ongoing).

*Ustekinumab.* When treatment effect of ustekinumab is not obtained within 28 weeks of the initiation of administration, change of treatment plan, including the dose increase from 45 to 90 mg, should be considered. If treatment effect is not obtained after the dose has been increased, whether to continue the treatment should be carefully considered.

### Administration site

It is recommended to change the injection site of adalimumab and ustekinumab each time. Do not inject the drug into skin with any abnormality (e.g. wound, rash, redness, induration) including psoriatic eruption or sensitive skin.

### Self-injection

- Adalimumab is a convenient drug in that it can be self-injected and can meet various needs of patients. However, considerable care should be taken when using it. The physician should carefully examine the rationale for its use and give proper education and training to the patients before introduction of self-injection. Self-injection should be performed under the supervision and guidance of the physician after the patient has been confirmed to understand the risks of self-injection and the actions to be taken, and to be able to self-administrate the drug correctly. If adverse reactions including infections are suspected after the initiation of self-injection, or if a situation arises that precludes the continuation of self-injection, the patient should be instructed to discontinue self-injection immediately, and appropriate measures, such as careful monitoring under the supervision of the physician, should be taken.
- Ustekinumab, like adalimumab, is administrated s.c., but self-injection is not approved.

### Administration (infusion) reaction

- Administration of infliximab may cause serious infusion reactions, such as anaphylactoid reaction. With due consideration to this possibility, it is necessary to establish the environment that allows the medical institution to give urgent treatment to the patient immediately, namely, the environment that allows airway management at the bedside while receiving treatment with oxygen, epinephrine and corticosteroid. In a Japanese post-marketing surveillance of adverse events following administration of infliximab to patients with rheumatoid arthritis, the frequency of serious infusion reaction was significantly higher in patients in whom infliximab administration was resumed after an interval of 2 years or more after treatment with the drug in the clinical study. Therefore, particularly careful preparation is essential before resuming the administration after a long-term interruption or washout.
- Thus, the following drugs should be administrated in accordance with the following protocol to prevent infusion reactions to infliximab in patients who have had infusion reactions previously and those who require re-administration after a long-term interruption.
  From 1 week before infusion to the day of infusion, histamine H1 receptor antagonist should be administrated p.o. (histamine H2 receptor antagonists may be co-administrated).
  One and a half hours before the initiation of infusion, diphenhydramine 25–50 mg should be administrated p.o. (other antihistamines may be used).
  Acetaminophen 650 mg should be administrated p.o.
- In patients who have had serious infusion reaction, oral corticosteroid (prednisolone 20 mg/day) should be administrated for 3 days, from 1 day before through 1 day after the infusion. Alternatively, hydrocortisone (100 mg) or methylprednisolone (20–40 mg) should be infused at 20 min before infusion of infliximab.

## CONTRAINDICATIONS

1 Patients with serious infection such as active tuberculosis. If a patient has serious infection, the priority should be given to an appropriate treatment for the infection. Virus tests, such as tests for hepatitis B virus (HBV) and hepatitis C virus (HCV), should be performed as necessary before administration of biologics. Although there have been no reports on ustekinumab, administration of TNF-α inhibitors is reported to cause HBV activation and aggravation of hepatitis B; therefore, biologics should not be administrated to patients with HBV infection. Consensus has not been reached on adverse effects of biologics in patients with HCV infection; however, patients should be tested for HCV infection before biologic therapy and, if administration is necessitated in HCV-positive patients, they should be carefully followed up.

2 Patients with congestive heart failure of class III or above by the functional classification of the New York Heart Association (NYHA, 1964): class I, asymptomatic heart disease with no limitation of subjective physical activity; class II, slight limitation of subjective physical activity due to heart disease (usual physical exercise causes symptoms such as fatigue, dyspnea, palpitation and angina); class III, marked limitation in activity due to symptoms that occur even during less-than-ordinary activity; class IV, symptoms experienced even while at rest (even the mildest physical exercise aggravates symptoms). In patients of NYHA class II or below, risks versus benefits of the use of biologics should be carefully considered, and the treated patients should be closely followed up.

3 Patients currently undergoing treatment for malignant tumor.

4 Patients with previous or current demyelinating disease (e.g. multiple sclerosis). It is known that TNF-α inhibitors may cause relapse or exacerbation of the symptoms of existing demyelinating diseases. Clinical studies of ustekinumab in patients with multiple sclerosis were conducted in foreign countries. In these studies, no relapse or exacerbation of symptoms of multiple sclerosis was noted, although no differences in efficacy were found as compared with placebo.

## PRECAUTIONS AND SAFETY MANUAL FOR PATIENTS WHO ARE PRONE TO DEVELOP ADVERSE REACTIONS

The essential test items at screening are the interview, tuberculin test and chest imaging test (it is recommended to perform both X-ray radiography and computed tomography [CT] scan; if this is not possible, CT scan is recommended). In addition, it is recommended to perform an interferon (IFN)-γ release assay (QuantiFERON test or T-SPOT). Overall assessment should be

made on the basis of all these screening results and discussion with a pulmonologist, radiologist or infection specialists as necessary to comprehensively examine the presence or absence of respiratory infection including pulmonary tuberculosis (see 2 below).[14]

If hepatitis B surface (HBs) antigen is negative but either an antibody against HBs or hepatitis B core (HBc) is positive in patients infected with HBV, there could be a risk of developing severe hepatitis due to the reactivation of HBV. It is therefore recommended to perform tests for not only HBs antigen but also HBs antibody and HBc antibody at screening (see 3 below).[15,16]

Table 1 lists the tests that should be performed and questions that should be asked before the initiation of treatment with biologics, and Table 2 lists those that should be performed periodically after the initiation. Figure 1 shows preventive measures against tuberculosis during the treatment with biologics. Figure 2 shows those against immunosuppressive therapy-induced reactivation of HBV infection. Figure 3 shows a flowchart of measures to be taken against pyrexia, coughing and dyspnea that may occur during the treatment.

Particular attention should be paid to the following patients during the treatment with biologics.

**1** Patients with infection or with suspected infection.

- Biologics attenuate immunoreactions, possibly affecting normal immune response. Therefore, the priority should be given to the treatment of infection, and the use of biologics should be postponed until the infection is adequately controlled. When the patient has chronic infection, such as non-tuberculous mycobacterial infection, treatment with biologics may be taken into consideration with careful judgment by the attending physician and consent of the patient, if benefits for the patient outweigh risks. In such cases with chronic infectious complications, however, it is essential that the attending physician collaborates closely with an expert physician well versed in the infection.
- Due caution should be exercised against bacterial, fungal, protozoan and viral infection during the treatment with biologics. Appropriate examinations should be performed as necessary. If symptoms such as pyrexia, cough or dyspnea occur, measures should be taken by assuming bacterial pneumonia, tuberculosis or *Pneumocystis* pneumonia (see Fig. 3). Prophylactic administration of a sulfamethoxazole–trimethoprim (ST) combination should be considered for patients with risk factors for serious infections, such as those who are elderly, have a pulmonary disease or are receiving systemic administration of corticosteroid to treat complications.
- There are no reports of live vaccine-induced infection in patients on biologics. However, because possibility of such a risk cannot be ruled out, live vaccine should not be administrated to patients on biologics.

**2** Patients with a previous history of tuberculosis, patients with a shadow that corresponds to old pulmonary tuberculosis in chest images (e.g. calcification, stripes, pleural thickening), patients with a positive tuberculin test (major axis of redness ≥10 mm) and patients with a positive IFN-γ release assay (QuantiFERON test or T-SPOT).

- Biologics may reactivate latent tuberculosis. In patients with a high risk of tuberculosis, oral isoniazid (INH; 300 mg/day as a general rule, 5 mg/kg per day for low weight patients) should be prophylactically administrated usually for 6 months starting from 3 weeks before the initiation of treatment with biologics. In cases that are complicated by diabetes mellitus or are suspected to be immunocompromised, INH should be administrated for 9 months. The possibility cannot be completely ruled out that tuberculosis may be manifested even after the end of prophylactic treatment. Therefore, chest X-ray examination and IFN-γ release assay (QuantiFERON test or T-SPOT) should be performed periodically (e.g. every 8–16 weeks) and re-administration of INH should be considered as necessary.[14]
- Due attention should be paid to the occurrence of tubercular symptoms during the treatment with biologics. Chest imaging tests should be performed periodically (e.g. chest X-ray radiography every 6 months) and QuantiFERON test or T-SPOT also should be performed if necessary. Tuberculin conversion or respiratory symptoms are supposed to occur approximately 8 weeks after infection. Both QuantiFERON test and T-SPOT are sensitive and useful for rapid evaluation of the reactivation of tuberculosis in patients under treatment.
- Active tuberculosis may occur after the initiation of treatment with biologics, even in patients who are negative for tuberculin test or IFN-γ release assay at screening. Therefore, due attention should be paid to the occurrence of tuberculosis as long as patients continue to receive biologic therapies.
- The possibility of extrapulmonary tuberculosis should also be kept in mind, and it is recommended to promptly collaborate with a pulmonologist, radiologist and/or infection specialist.

**3** Patients infected with hepatitis B virus (including HBs antibody-positive or HBc antibody-positive patients).

- Hepatitis B surface antigen-negative and HBs antibody- or HBc antibody-positive patients were thought to have previously had HBV infection that is healed clinically. However, reports have shown that, in these patients with previous HBV infection, HBV-DNA replication continues for a long time, albeit at a low level, in the liver and mononuclear cells in the peripheral blood, and that severe hepatitis can develop due to reactivation of the virus after transplantation or by the use of potent immunosuppressants. Based on these backgrounds, a report on *Prevention of Immunosuppressive Therapy- or Chemotherapy-induced Reactivation of Hepatitis B Virus Infection*[15] was issued in 2009, and it has been integrated in *Guidelines for the Management of Hepatitis B Virus Infection*[16] in

**Table 1.** Check list before initiation of biologics (at screening)

(□:**must**)

**< Informed Consent>**

- □ Explanation and agreement of biologics administration date: / /
- □ Explained by _____
- □ Biologics administration start at / /
- □ Emergency contact details (Phone & mail address) 1 _____
- □ Emergency contact details (Phone & mail address) 2 _____

**< Pre-treatment tests >**

**Blood tests/ Urinalysis**

- □ WBC ( /μL)
- □ Lymphocyte ( /μL)
- □ CRP ( mg/dL)
- □ liver function test ( )
- □ β-D-glucan ( pg/mL)
- □ KL-6 ( U/mL)
- □ ANA (antinuclear antibody) ( )
- □ Urinalysis ( )

**Infection**

- □ HBs antigen ( negative ・ positive )
- □ HBs antibody ( negative ・ positive )
- □ HBc antibody ( negative ・ positive )
- □ HBV- DNA, quantitative (if any HBV test is positive) ( below detection ・ above detection )
- □ HCV antibody ( negative ・ positive )
- □ HIV antibody ( negative ・ positive )
- □ HTLV-1 antibody ( negative ・ positive )

**Tuberculosis (TB)**

- □ Tuberculin skin test / PPD
  injection site ( )
  injection (date: / ) judgment (date: / )
- □ judgment ( negative ・ positive + / ++ / +++ )
  redness ( × mm) induration (no・yes)
  bulla (no・yes) double redness (no・yes) necrosis (no・yes)
- □ QuantiFERON test (QFT) ( )
- □ T-SPOT ( )

**Imaging procedure**

- □ chest X ray ( )
- □ chest CT ( )

**< Questionnaire about medical history >**

- □ allergic to any biologics _____ (no・yes)
- □ allergic to _____ (no・yes)
- □ infection _____ (no・yes)
- □ malignancy _____ (no・yes)
- □ demyelinating disease (including family) (no・yes)
- □ diabetes mellitus (DM) (no・yes)
- □ congestive heart failure (CHF) (no・yes)
- □ interstitial pneumonia (IP) (no・yes)
- □ active TB (no・yes)
- □ contact with TB-patients (family・office) (no・yes)
- □ infected with TB (no・yes)
- □ treatment history for TB (no・yes)
- □ any other pulmonary disease _____ (no・yes)
- □ pregnancy (no・yes)
- □ vaccination against _____ (no・yes)
- □ phototherapy ( J/cm$^2$/ times/ years) (no・yes)
- □ cyclosporine ( mg/day for years) (no・yes)

**Table 2.** Check list after initiation of biologics (for monitoring)

**< After 1 month >**

- ☐ chest X ray (　　)
- ☐ chest CT（as necessary） (　　)
- ☐ β-D-glucan (　　pg/mL)
- ☐ CRP (　　mg/dL)
- ☐ WBC (　　/μL)
- ☐ liver function test (　　)
- ☐ other blood tests/urinalysis (　　)

（in case HBs antibody or HBc antibody was positive）

- ☐ HBs antibody titer (　　)
- ☐ HBV-DNA, quantitative (below detection・above detection)

**< After 3 months >**

- ☐ chest X ray (　　)
- ☐ chest CT（as necessary） (　　)
- ☐ β-D-glucan (　　pg/mL)
- ☐ CRP (　　mg/dL)
- ☐ WBC (　　/μL)
- ☐ liver function test (　　)
- ☐ other blood tests/urinalysis (　　)

（in case HBs antibody or HBc antibody was positive）

- ☐ HBs antibody titer (　　)
- ☐ HBV-DNA, quantitative (below detection・above detection)

**< After 6 months >**

- ☐ chest X ray (　　)
- ☐ chest CT（as necessary） (　　)
- ☐ β-D-glucan (　　pg/mL)
- ☐ KL-6 (　　U/mL)
- ☐ CRP (　　mg/dL)
- ☐ WBC (　　/μL)
- ☐ liver function test (　　)
- ☐ ANA (antinuclear antibody) (　　)
- ☐ QuantiFERON test (QFT) (　　)
- ☐ T-SPOT (　　)
- ☐ other blood tests/urinalysis (　　)

（in case HBs antibody or HBc antibody was positive）

- ☐ HBs antibody titer (　　)
- ☐ HBV-DNA, quantitative (below detection・above detection)

**< After 12 months >**

- ☐ chest X ray (　　)
- ☐ chest CT（as necessary） (　　)
- ☐ β-D-glucan (　　pg/mL)
- ☐ KL-6 (　　U/mL)
- ☐ CRP (　　mg/dL)
- ☐ WBC (　　/μL)
- ☐ liver function test (　　)
- ☐ ANA (antinuclear antibody) (　　)
- ☐ QuantiFERON test (QFT) (　　)
- ☐ T-SPOT (　　)
- ☐ other blood tests/urinalysis (　　)

（in case HBs antibody or HBc antibody was positive）

- ☐ HBs antibody titer (　　)
- ☐ HBV-DNA, quantitative (below detection・above detection)

Thereafter, it is preferable to conduct clinical tests every half a year. In cases HBs antibody or HBs antibody was positive, more frequent inspection is recommended

If the antinuclear antibody was positive, the anti-dsDNA antibody should also be measured.

If the patient complains of symptoms, such as fever, cough, or shortness of breath, respiratory tract infection or interstitial pneumonia should be suspected, and the diagnosis should be made according to the flowchart on diagnostic algorithm for pneumonia during biologic therapy (Figure 3).

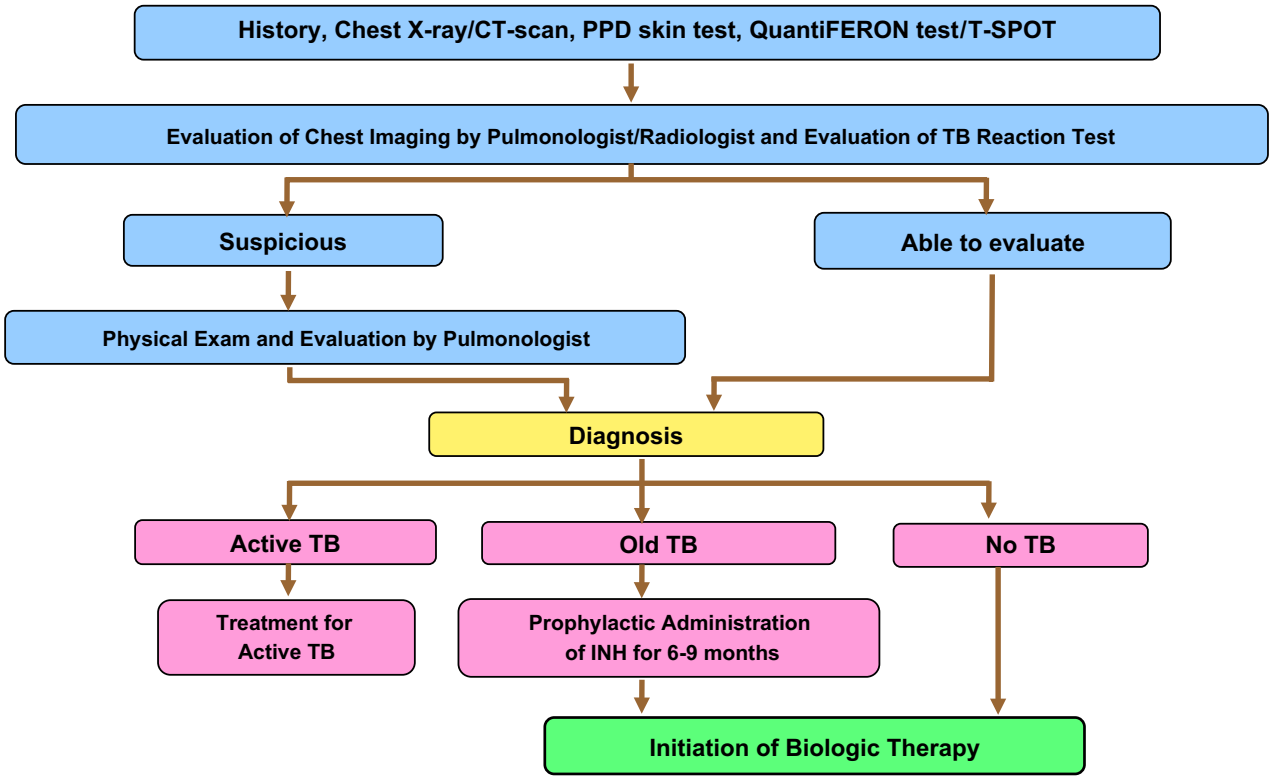



**Figure 1.** Algorithm for diagnosis and management of tuberculosis on biologic therapy. CT, computed tomography; PPD, purified protein derivative; TB, tuberculosis.

2013. The guideline now recommends that all patients undergoing immunosuppressive therapy and chemotherapy receive tests for not only HBs antigen but also HBs and HBc antibodies. It is therefore recommended that patients who require treatment with drugs that may bring immunosuppression, such as biologics, are tested for both HBs antibody and HBc antibody at screening in accordance with this guideline.

– If either HBs antibody or HBc antibody is positive, quantitative measurement of HBV-DNA should be performed. If the HBV-DNA level is above the detection sensitivity (e.g. 2.1 log copies/ml), the patient should be referred to a hepatologist (gastroenterologist) and the treatment with nucleic acid analogs should be considered. If the HBV-DNA level is below the detection sensitivity, treatment with biologics can be started; however, even after the initiation of biologic therapy, hepatic functions and HBV-DNA level should be monitored periodically (if HBs antibody is positive, it is useful to follow the change with time in the antibody titer because the antibody titer decreases when HBV is reactivated). If the HBV-DNA level becomes above the detection sensitivity during biologic therapy (HBs antigen also becomes positive at this time), whether to continue or discontinue the biologic therapy should be carefully decided with a hepatologist, and the treatment with nucleic acid analogs should be initiated (see Fig. 2).

**4** Patients who have signs suggestive of or have a family history of a demyelinating disease.

– Tumor necrosis factor-α inhibitors may cause relapse, aggravation or development of a demyelinating disease. Advisability of using TNF-α inhibitors should be carefully considered on the basis of risks versus benefits through neurological examination and diagnostic imaging, and patients should also be observed carefully after the initiation of treatment.
– Although no results obtained thus far from clinical studies suggest that ustekinumab has an effect on the development of demyelinating diseases, adequate follow up is recommended after the initiation of treatment with ustekinumab.

**5** Patients with a previous or current serious hematological disease (e.g. pancytopenia, aplastic anemia).

– Tumor necrosis factor-α inhibitor-associated hematological adverse events including serious cytopenia (e.g. thrombocytopenia, leukopenia) have been reported, albeit rarely.
Patients should be instructed to seek medical advice immediately if they experience any signs or symptoms suggestive of blood dyscrasia (e.g. persistent fever, subcutaneous hemorrhage, bleeding, pallor).

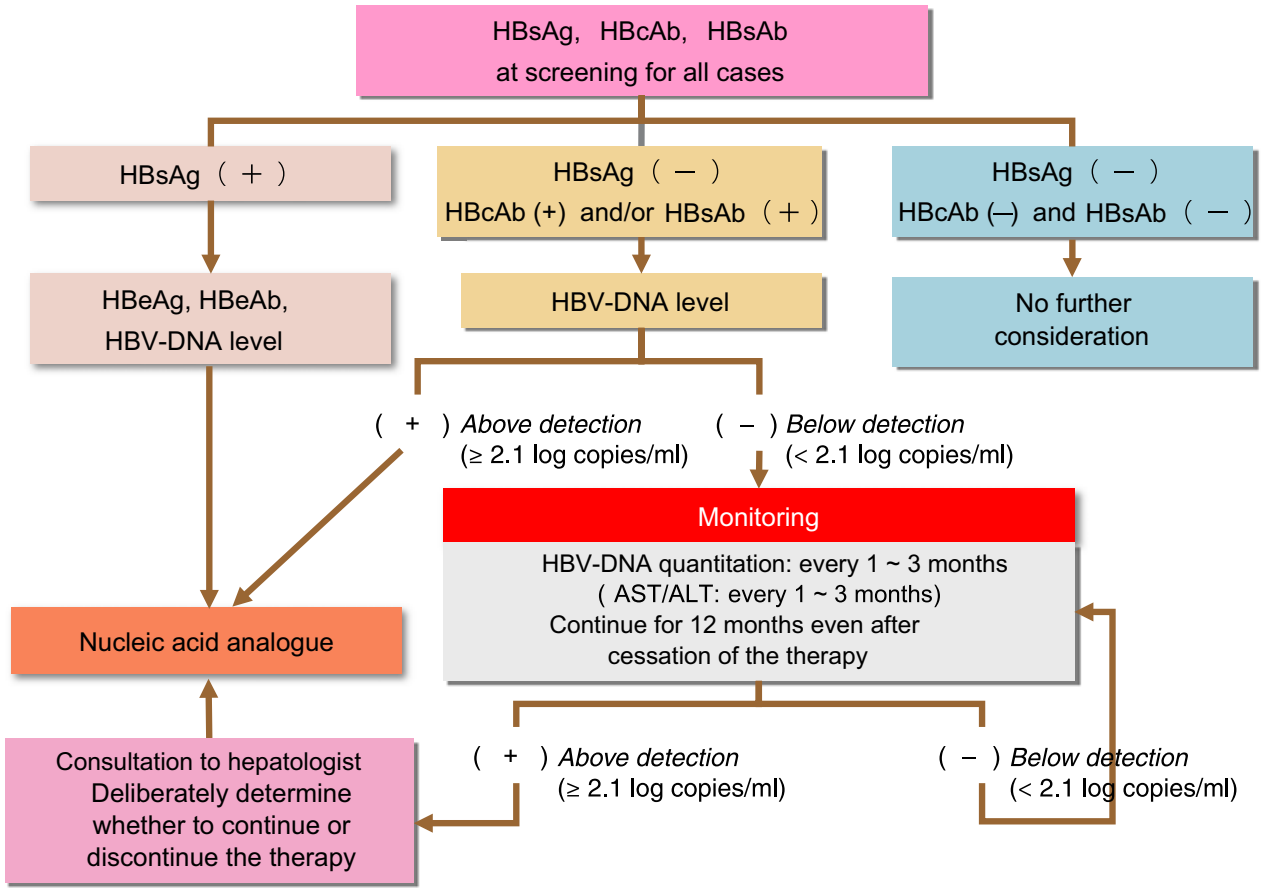



**Figure 2.** Prevention and management of immunosuppressive therapy- or chemotherapy-induced reactivation of HBV infection. HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e-antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- The use of biologics should be discontinued in patients with evident blood abnormality.

**6** Patients with a previous history or treatment history of malignancies or with a precancerous lesion.

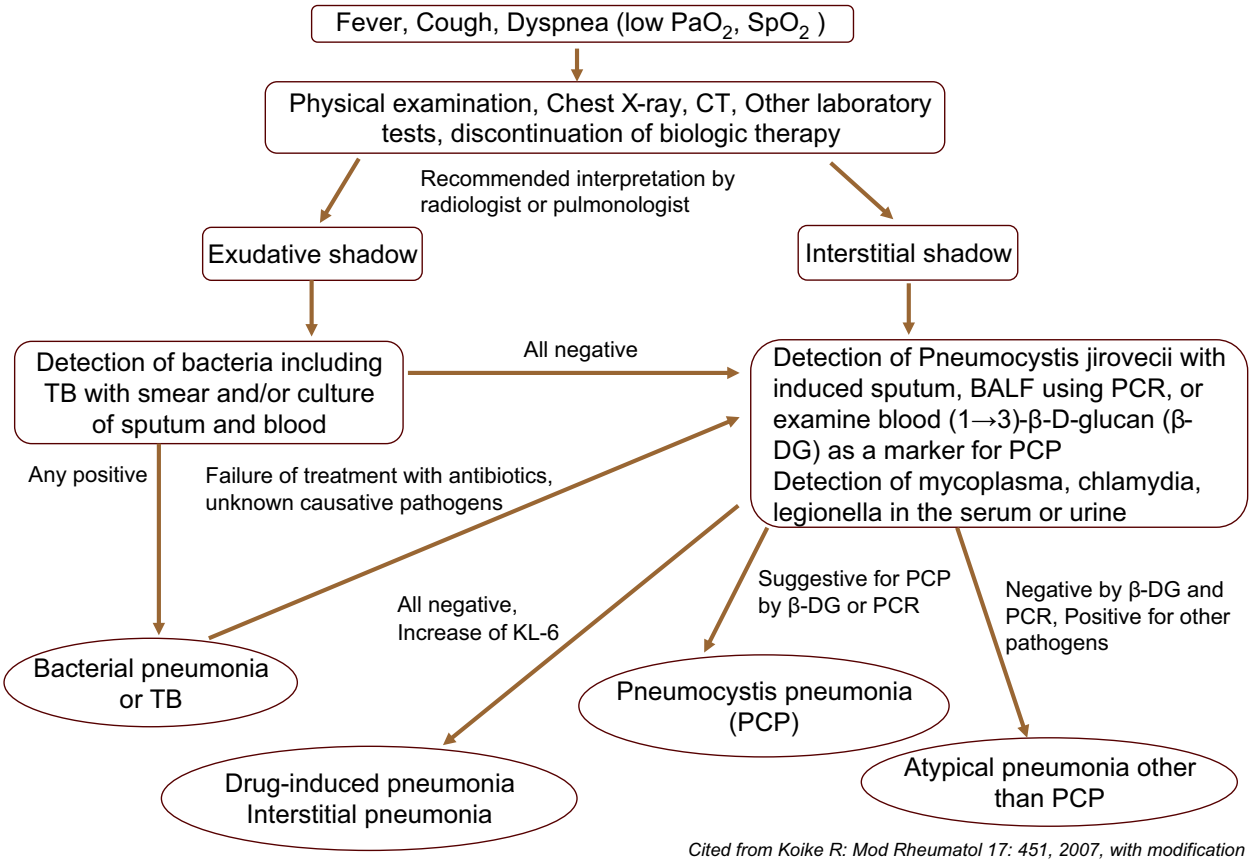
- There is a concern about the possibility that biologics may increase the frequency of malignant tumor judging from its mechanism of action although no conclusion has been reached at the moment because of insufficient data available. Therefore, risks versus benefits of biologic therapies should be evaluated carefully in patients who have a previous history or treatment history of malignant tumor or have a precancerous lesion (e.g. lesions in the esophagus, uterine cervix, colon). Due attention should be paid to the occurrence of new malignancies during the treatment with biologics.
- In the UK guidelines,[11] biologic treatment is allowed if 5 years have passed after extirpative surgery of malignant tumors and if it is confirmed that there has been no relapse or metastasis.
- It is pointed out that there is an increased risk of the occurrence of skin cancer in patients who have been frequently treated with UV therapy over a long time. If biologics are used after a long-term UV therapy, it is recommended to constantly observe the patient closely for the occurrence of skin cancer.

**7** Patients with congenital or acquired immunodeficiency syndrome or with compromised immune function caused by the use of other systemic immunosuppressants.

- Biologics attenuate immunoreactions, possibly affecting normal immune response. Biologics may increase the risk of infection if the immune function is reduced by the use of other systemic immunosuppressants. Therefore, the advisability of using biologics should be carefully considered on the basis of risks versus benefits, and patients should also be observed carefully after the initiation of treatment.

**8** Elderly patients.

- Because of a limited number of patients aged 65 years or older (elderly patients) who were enrolled in clinical studies involving patients with psoriasis, no conclusion has been reached on the tendency of serious adverse




*Cited from Koike R: Mod Rheumatol 17: 451, 2007, with modification*

**Figure 3.** Diagnostic algorithm for pneumonia during biologic therapy. CT, computed tomography; MTX, methotrexate; PCR, polymerase chain reaction; TB, tuberculosis; TNF, tumor necrosis factor.

events in elderly patients (≥65 years) and in non-elderly patients (<65 years). However, an increasing tendency of the incidence of serious adverse events in the elderly was seen in clinical studies in patients with rheumatoid arthritis. In consideration of generally reduced physiological functions including immune function in the elderly, it is therefore necessary to closely observe patients and to pay attention to adverse reactions such as infection when biologics are used in elderly patients.

– Influenza vaccine should be administrated whenever possible to prevent respiratory infection. The administration of pneumococcal vaccine should also be considered.

Note: Reports have shown that treatment with TNF-α inhibitors does not affect the production of neutralizing antibodies in response to influenza vaccine administration.

**9** Children.

– Because safety of biologics in children has not been established, the drugs should not be used in children, as a general rule. However, cases of pediatric GPP treated with infliximab have been reported. When no other systemic therapies can be used during the acute aggravation phase accompanied by systemic symptoms, the use of TNF-α inhibitors, such as infliximab, may be a useful option for emergency treatment. In using TNF-α inhibitors in such situations, it is recommended to refer to the *Guideline for Diagnosis and Treatment of Generalized Pustular Psoriasis 2010*[4] issued by the JDA, and to switch to other non-biologic drugs after symptoms have improved, whenever possible.

**10** During pregnancy, delivery or lactation.

– Infliximab and ustekinumab have been shown to pass the placenta and be excreted into breast milk in animals (not confirmed with adalimumab), and the safety of these drugs in fetuses and infants has not been established. Pregnancy and breast-feeding should therefore be avoided during the treatment with biologics. Until now, however, there have been few reports suggesting toxicity or teratogenicity in offsprings in animal experiments or treatment experiences in humans. In case of unintended exposure to a fetus, it is therefore recommended to immediately discontinue the use of biologics in the mother and to closely follow up the course.

**11** Patients undergoing operation.

- Biologics may affect postoperative wound healing and prevention of infection. Therefore, it is recommended to perform surgical operation at least 2 weeks after the last administration of adalimumab, 4 weeks after that of infliximab, and 8 weeks after that of ustekinumab. After the operation, administration of biologics may be resumed if it is confirmed that the wound has been healed and that there is no complication by infection.

Note 1: The use of TNF-α inhibitors should be discontinued if lupus-like syndrome develops, and antinuclear and anti-dsDNA antibodies become positive (TNF-α inhibitors may cause the positive conversion of antinuclear and anti-dsDNA antibodies and the occurrence of symptoms suggestive of lupus-like syndrome). Although no reports have shown that ustekinumab induces the development of lupus-like syndrome, it is difficult to properly evaluate ustekinumab for this point because treatment experiences are not yet sufficient and the frequency of the positive conversion of those antibodies remains unclear.

Note 2: Reports have shown cases of fatal progressive multifocal leukoencephalopathy (PML) caused by other biologic preparations, such as natalizumab (anti-α4 integrin antibody used for multiple sclerosis), rituximab (anti-CD20 antibody for malignant lymphoma) and efalizumab (anti-CD11a antibody for psoriasis that had been used in foreign countries, but was withdrawn in 2009).

Although TNF-α inhibitors are unlikely to cause PML, precautions will be warranted. The disease starts with an initial symptom of staggering gait, which is followed by inarticulate speech and forgetfulness, and, if advanced, results in impaired consciousness. Similar findings have been reported in patients with HIV and in patients on multiple immunosuppressants including cyclosporine. These findings suggest the associations of the disease with persistent immunosuppressed conditions. In addition, reversible posterior leukoencephalopathy syndrome was reported with treatment with ustekinumab in foreign countries, although causality is not clear.

## COMBINATION THERAPY WITH BIOLOGICS

### Combination with topical therapy

- In Japanese clinical studies, no clinically significant adverse reactions were seen when biologics were administrated in combination with topical corticosteroids or with active vitamin $D_3$ for topical use. However, attention should be paid to adverse reactions and skin infection if topical drugs are co-administrated with biologics.

### Combination with systemic therapy

- The efficacy and safety of biologics used in combination with other systemic therapy or systemic UV therapy have not been established. If combination therapy is necessitated, risks versus benefits should be carefully evaluated, and patients should be closely followed up after the initiation of combination therapy.
- In addition to the risk of leukoencephalopathy, cyclosporine further deteriorates immunocompromised conditions, thereby increasing the risk of complications by serious infections. Therefore, as a general rule, cyclosporine should not be co-administrated with biologics. When patients were switched from cyclosporine to biologic therapy in Japanese clinical studies with infliximab,[17] PASI scores were decreased rapidly without worsening of psoriasis, even when cyclosporine was withdrawn immediately before switching, and there were no noteworthy safety problems. However, it is generally true that the relapse of symptoms is a concern when cyclosporine is switched to biologics. In this setting, combined use of cyclosporine with a biologic for a few weeks is considered to be one of the useful means to switch the drugs smoothly, and the US guideline[10] describes a similar, relatively short-duration combination therapy. Likewise, the European guideline[11,12] places the combined use of adalimumab and cyclosporine, for example, at a similar position as that of the combined use of adalimumab and methotrexate, which means that combination of these systemic drugs is not necessarily limited. However, when drugs are administrated in combination, it is necessary to consider the patient's age and other background factors carefully, to explain about the risks of infections thoroughly to patients, and to monitor the course carefully.
- Acitretin, a retinoid drug not marketed in Japan, has been reported to be co-administrated with biologics in foreign countries without any clinically significant adverse reactions. However, it is recommended to carefully evaluate the risks versus benefits when using etretinate, a retinoid drug that is commercially available in Japan, in combination with biologics.
- Methotrexate is widely used in foreign countries. In the US guideline for the treatment with methotrexate, liver biopsy is recommended for long-term treatment with methotrexate. In Japan, where methotrexate is not indicated for plaque-type psoriasis or psoriatic arthritis, however, there is no safety manual corresponding to the treatment with methotrexate in the US guideline. Infliximab is stipulated to be used in combination with methotrexate for the treatment of rheumatoid arthritis, when methotrexate alone is not effective. In addition, combined use of infliximab and methotrexate has been shown to be more effective than the use of infliximab alone for rheumatoid arthritis. However, no studies to evaluate the efficacy of combined use of infliximab and methotrexate have been conducted for the treatment of plaque-type psoriasis with or without psoriatic arthritis.

## CONFLICT OF INTEREST

M. O., T. T., A. O., A. M., M. K. and H. N. have served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used

for the treatment of psoriasis including AbbVie (formerly Abbott), Eisai, Mitsubishi-Tanabe, Janssen, Novartis, Eli Lilly, MSD, Kyowa-Kirin, Leo, Maruho, Torii and Teijin. S. S. has served similarly for AbbVie, Eisai, Mitsubishi-Tanabe, Janssen, Novartis, Eli Lilly, Kyowa-Kirin, Maruho, Torii and Teijin. H. T. (Takahashi) has served similarly for AbbVie, Eisai, Mitsubishi-Tanabe, Janssen, Novartis, Kyowa-Kirin and Maruho. T. E. has served similarly for AbbVie, Eisai, Mitsubishi-Tanabe, Janssen, Novartis, Kyowa-Kirin, Leo and Maruho. A. I. has served similarly for Eisai, Mitsubishi-Tanabe, Janssen, Novartis, MSD, Kyowa-Kirin and Maruho. H. T. (Torii) has served similarly for AbbVie, Eisai, Mitsubishi-Tanabe, Janssen, Eli Lilly and Kyowa-Kirin. A. A. and O. N. have served similarly for AbbVie, Eisai, Mitsubishi-Tanabe, Janssen, Novartis, Kyowa-Kirin and Maruho.

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