Mod Rheumatol (2005) 15:4–8
DOI 10.1007/s10165-004-0357-7

MINIREVIEW

Nobuyuki Miyasaka · Tsutomu Takeuchi · Katsumi Eguchi

Official Japanese guidelines for the use of infliximab for rheumatoid arthritis

Abstract Differences in ethnic backgrounds as well as in medical and socioeconomic status often affect both the efficacy and adverse effects of medications. Recent data suggest an increased risk of opportunistic infections, especially tuberculosis (TB), among rheumatoid arthritis (RA) patients receiving infliximab, a chimeric monoclonal anti-tumor necrosis factor α (TNF-α) antibody. In this regard, the annual incidence of TB is approximately five times higher in Japan than in the United States. Furthermore, since Bacillus Calmette-Guérin vaccination is mandatory in childhood when the skin test for purified protein derivative (PPD) is negative, a high incidence of false-positive PPD skin tests is observed among the Japanese population. In addition, the upper limit of methotrexate dosage to be used for RA is lower in Japan. We have therefore established official guidelines for the proper use of infliximab in Japanese RA patients. In this review, an algorithm for the diagnosis and management of TB in RA is presented in an evidenced-based form.

Key words Guideline · Infliximab · Rheumatoid arthritis (RA) · Tuberculosis (TB) · Tumor necrosis factor α (TNF-α)

Introduction

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology. Synovial proliferation results in the destruction of both cartilage and bone, and tumor necrosis factor α (TNF-α) is thought to play a central role in this process. Infliximab is a human-murine chimeric anti-TNF-α monoclonal antibody with high affinity and specificity.[1] It forms stable complexes with the monomeric and trimeric forms of soluble TNF-α and with the transmembrane forms of TNF-α. Not only neutralizing soluble TNF-α, but also the cytolysis of macrophages and monocytes by binding to transmembrane TNF-α in vitro, might be relevant in its potent anti-inflammatory and immunosuppressive actions. Infliximab, when used with methotrexate (MTX) in rheumatoid arthritis (RA) patients, induces not only significant improvement in the signs and symptoms of RA but also substantial inhibition of progressive joint damage.[2,3] Infliximab was approved for RA in the United States in 1999.

In spite of its dramatic efficacy against RA, it has been noted that opportunistic infections, especially tuberculosis (TB), can occur among patients treated with infliximab. According to the report by Keane et al.,[4] the background rate of TB in RA patients is 6.2 cases per 100000 per year, whereas the estimated rate of TB among RA patients receiving infliximab therapy was 24.4 cases per 100000 in the United States. Although this report was confirmed by Wolfe et al.,[5] no cases of TB have occurred in persons with recent purified protein derivative (PPD) skin tests or prophylaxis. These findings reemphasize the importance of TNF-α in host immune response to *Mycobacterium tuberculosis*. In addition, infliximab administration is accompanied with severe acute infusion reactions in approximately 0.5% of patients because of the chimeric structure of the molecule. Given the differences in the medicosocial status of Japan and the high incidence of infusion reactions, the Ministry of Health, Labor, and Welfare of Japan has decided to conduct a special post-marketing survey of the initial 5000 patients treated with infliximab in Japan.

The potential problems of using infliximab in Japanese RA patients are as follows: (1) TB is approximately five times more prevalent in Japan than in the United States, (2) Bacillus Calmette-Guérin (BCG) vaccination given in childhood yields false-positive tests among Japanese so that

N. Miyasaka (✉)
Department of Medicine and Rheumatology, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Tel. +81-3-5803-5201; Fax: +81-3-5803-5998
e-mail: miya.rheu@tmd.ac.jp

T. Takeuchi
Second Department of Internal Medicine, Saitama Medical Center, Saitama Medical College, Kawagoe, Japan

K. Eguchi
First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

the PPD skin test may not be suitable for critically screening TB, (3) over 4% of TB patients are resistant to isoniazid (INH), (4) prophylactic use of INH can cause liver dysfunction in at least 10% of TB patients, and (5) infliximab can mask the clinical features of TB. These problems are discussed below.

Current situation of TB in Japan and the world

According to a report issued by the World Health Organization (WHO), there were 8.8 million new cases of TB in 2002, 3.9 million of which were smear-positive.[6] The global incidence of TB is growing at a rate of approximately 1.1% per year, and the number of cases at 2.4% per year.

In Japan, the annual incidence of new TB infection in 2002 was 25.8 per 100000, or 4.6-fold higher than in the United States.[7] Although the incidence has been decreasing year by year, the proportion of the elderly population is increasing. Among 32828 newly registered TB patients in 2002, patients over 60 years of age comprise 58.4% and those over 70 years of age 41.5%, whereas the respective figures in 1996 are 53.2% and 31.7%. Fifty-three percent are positive for *M. tuberculosis* either in smear or culture. Pulmonary TB accounts for 81 and extrapulmonary for 19. There is a regional bias in the annual incidence of TB with percentages of patient increasing in urban areas: 74.4 per 100000 in Osaka city and 36.6 in Tokyo special district, but only 12.5 in Nagano Prefecture. In addition, 4.4% of isolated *M. tuberculosis* in culture is resistant to INH.

Purified protein derivative skin test

In Japan, 0.1cc of 3 tuberculin units of standardized PPD obtained from Aoyama B strain is injected intradermally into the volar surface of the forearm. Erythema, but not induration, is measured at 48h, and the diameter is recorded in millimeters. The cut-off criterion for positivity is 10mm in diameter. The size of induration, dual erythema, and presence of blisters and necrosis, if any, are also recorded. Those with diameters of more than 10mm, but not with induration or dual erythema, are evaluated to be 1+; those with induration, 2+; and those with induration, dual erythema, blisters and necrosis, 3+. The reason why erythema but not induration is measured is mainly due to the feasibility of measuring its diameter on the skin in the Japanese population. The PPD skin test has been performed in Japan at the time of entry to elementary school (6 years of age) and to junior high school (12 years of age) but this was abolished in 2003. Two-step testing is performed only in settings where tight TB screening is necessary, such as the employment of medical professionals. The PPD skin test is known to be influenced not only by exposure to TB but also by repeated PPD skin testing, which creates a booster phenomenon, and by other *Mycobacterium* infections such as *Mycobacterium avium* complex.

Bacillus Calmette-Guérin vaccination

Bacillus Calmette-Guérin vaccination has been given to those who show a negative PPD skin test in childhood. That is, the PPD skin test has been mainly used in Japan to evaluate whether BCG vaccination is necessary in childhood. Those who are negative in the PPD skin test even after BCG vaccination are subjected to revaccination. However, revaccination has not been used since 2003. Furthermore, the Japanese Government recommended that BCG vaccination should be performed to all infants by 1.5 years of age from 2004 without doing a PPD skin test. Although BCG vaccination might substantially contribute to decreasing the incidence of TB in Japan, it creates a false-positive reaction on the PPD skin test and makes it difficult to discriminate actual positivity due to TB from false positivity.

Difference in MTX dosage

The maximal dosage of MTX approved for use in Japan is 8mg/week. This dosage is based on a clinical trial conducted in Japan to determine the optimal dose, in which the efficacy of the 6 and 9mg/week groups was comparable, and was significantly better than that of the 2mg/week group.[8] Increased liver enzyme was observed at more than 9mg/week, although folic acid was not given during the trial. However, in the clinical setting, dosages of MTX in excess of 8mg/week are sometimes used if the physician deems it necessary. In such cases, informed consent is obtained from the patient.

Pneumocystis carinii pneumonia in MTX-treated RA patients

Pneumocystis carinii pneumonia (PCP) is a serious and potentially fatal infection often encountered in immunosuppressed patients such as those with acquired immunodeficiency syndrome (AIDS), cancer including hematological malignancies, and organ transplantation.[9] Patients with connective tissue diseases (CTD) are also at risk for PCP.[10] *Pneumocystis carinii* pneumonia affects 2.6%–4.3% of CTD patients with immunosuppressive treatments including corticosteroids.[11,12] Risk factors include the administration of high-dose corticosteroids or immunosuppressants, and low peripheral blood lymphocytes (PBL).[12] We have found that patients who developed PCP were significantly more intensively treated with corticosteroids and/or immunosuppressive agents and were more immunosuppressed than those who did not.[13] In our series of 124 patients who received more than 30mg/day of prednisolone, nine patients in the non-prophylaxis group ($n = 82$) developed PCP, whereas none in the prophylaxis group receiving one tablet of TMP/SMX (containing 80mg of trimethoprim and 400mg of sulfamethoxazole) ($n = 42$) developed PCP. *Pneumocystis carinii* pneumonia was diagnosed when the clinical and ra-

diographic presentation was strongly suggestive of PCP and when microbiologic confirmation of *P. carinii* in respiratory samples was made or there was a response to treatment only with agents active against *P. carinii*. All the patients diagnosed with PCP had the following four features strongly suggestive of PCP: (1) clinical manifestation including pyrexia, dry cough, and dyspnea, (2) hypoxemia ($PaO_2 < 80$ torr) and/or increased A-aDO_2 (>15 mmHg),[14] (3) diffuse alveolar infiltrates or interstitial infiltrates on chest X-ray as well as on computed tomography of the thorax, and (4) increase of serum β-D-glucan level.[15] We also found that PBL counts 4 weeks after the institution of PSL in the patients who developed PCP were significantly lower than those in the other patients (476 ± 350 vs 1229 ± 1.019, mean ± SD, $P < 0.004$). Since we occasionally but infrequently experience PCP in MTX-treated RA patients and have experienced a case of PCP during the clinical trial of infliximab in Japan, we are extremely cautious regarding the possibility of PCP developing as a complication during treatment with infliximab in combination with MTX in Japanese RA patients.

Treatment guidelines for using infliximab (Fig. 1)

We have therefore created guidelines for the use of infliximab to safely treat Japanese RA patients according to our data described above. The guidelines were initially established by the Study Group of Rheumatoid Arthritis, Ministry of Health, Labor, and Welfare, Japan (principal investigators; Nobuyuki Miyasaka, MD, Tsutomu Takeuchi, MD, and Katsumi Eguchi, MD), and were later officially approved by the Japan College of Rheumatology.

Inclusion criteria

Inclusion criteria are active RA with at least six swollen and tender joints with concomitant usage of methotrexate of over 6 mg/week. Patients must have either C-reactive protein >2.0 mg/dl or erythrocyte sedimentation rate >28 mm/h. Patients also are required to have more than 4000/mm^3 of white blood cells and more than 1000/mm^3 of peripheral blood lymphocytes in addition to negative β-D-glucan in sera, to avoid possible opportunistic infections including TB and *P. carinii*.

Exclusion criteria

Patients having concurrent infection or histories of serious infection for the last 6 months are excluded from the study. Patients who have chest X-ray findings indicative of old TB (pleural thickening, fibrotic scarring shadows, calcified shadows of more than 5 mm in diameter), a history of TB, extrapulmonary TB and PCP, congestive heart failure, malignancy, and demyelinating disease are also excluded from this study. However, if the physician thinks that the

A. Inclusion criteria

1. Disease activity
   Active RA patients with concomitant usage of methotrexate (MTX) of over 6 mg/week for more than three months who fulfill following conditions.
   1) tender joints ≧ 6
   2) swollen joints ≧ 6
   3) ESR ≧ 28 mm/hr or CRP ≧ 2.0 mg/dl
2. Laboratory data
   1) WBC ≧ 4,000/mm^3
   2) peripheral blood lymphocytes ≧ 1,000/mm^3
   3) serum β-D glucan: negative

B. Exclusion criteria

1. Ongoing infection
2. Past history of serious infection for the last six months
3. Abnormal shadows in chest radiographs suggestive of old pulmonary tuberculosis (TB) or tuberculous pleuritis (fibrotic scarring shadows, calcified shadows of more than 5 mm in diameter, pleural thickening)
4. History of pulmonary and extrapulmonary TB*
5. History of *Pneumocysits carinii* pneumonia
6. Congestive heart failure
7. Malignancy
8. Demyelinating disease

* If the physician thinks that the advantage of infliximab treatment outweighs its safety in patients with latent TB infection, prophylactic treatment of isoniazid (INH, 0.3 mg/day) is recommended.

Fig. 1. Treatment guidelines for using infliximab to rheumatoid arthritis patients in Japan

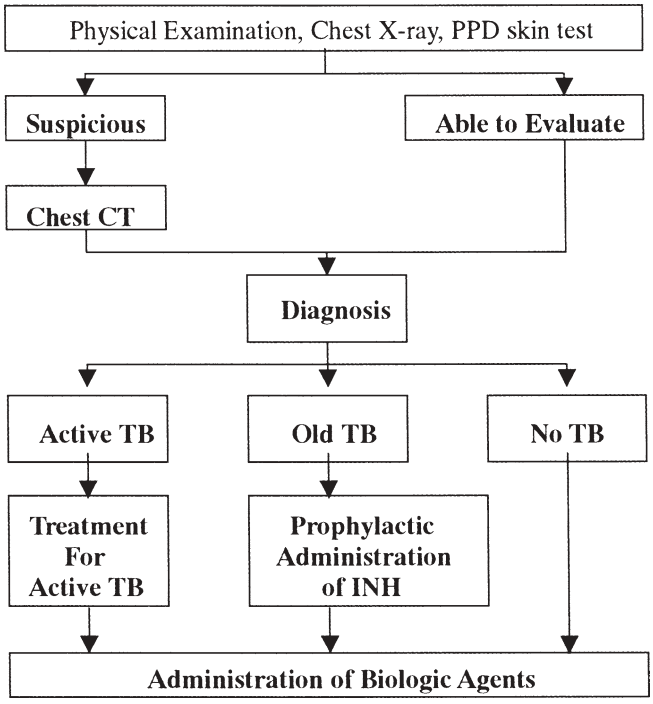

Fig. 2. Algorithm for the diagnosis and management of tuberculosis in patients with rheumatoid arthritis on biologic agents

advantage of infliximab treatment outweighs its safety in patients with latent TB infection, prophylactic treatment of INH (0.3 mg/day) is recommended.

Screening of TB (Fig. 2)

Intensive history taking and physical examination

Patients are asked whether they have had a history of TB or exposure to TB patients. They are screened for symptoms consistent with active TB, such as cough, sputum, or fever. It should be emphasized that signs and symptoms of TB can be masked by the use of infliximab, and therefore an extensive physical examination should be performed.

Purified protein derivative skin test

The PPD skin test is mandatory for all patients enrolled in this study and is performed before the initial infusion. If it is strongly positive (>2+), continuous use of INH (0.3 g/day) for 9 months, beginning one month prior to the initial infusion, is recommended.

Chest radiography and chest computed tomography (CT)

Chest radiography is also mandatory for all patients before the initiation of infliximab therapy. If the chest radiograph shows any findings suggestive of old TB, chest CT is recommended. Prophylactic use of isoniazid (INH) should be initiated in patients showing chest radiographs indicative of old pulmonary TB or tuberculous pleuritis. In the case of active TB, patients should be treated with a full course of anti-TB drugs for a sufficient period of time before starting infliximab. Physicians are simultaneously required to be capable of reading chest radiographs, evaluating them on the same day of clinical examination, and properly treating opportunistic infections including TB.

Treatment protocol

Intravenous infusion of infliximab (3 mg/kg) at weeks 0, 2, and 6 was performed, followed by subsequent infusions every 8 weeks. Intravenous infusion is initiated at a slow rate (15 ml/h) for the first 15 min and increased to 50 ml/h over a period of 2 h. The signs and symptoms of the patient are monitored throughout the infusion. Vital signs are closely monitored every 10 min during infusion with an automated manometer.

Management of infusion reactions

Physicians need to prepare for serious infusion reactions that may possibly occur during infliximab administration.[16] When mild to moderate infusion reactions occur, it is recommended to slow the infusion rate to 10 ml/h or stop infusion, if necessary. Further, p.o. or i.v. diphenhydramine (25–50 mg) and p.o. acetaminophen (650 mg) are administered. When wheezing is audible, i.v. hydrocortisone (100 mg) is given.

For severe acute reactions such as dyspnea with wheezing, significant discomfort, severe urticaria, or hypotension below 40 points of systolic blood pressure, s.c. epinephrine ([1:1000] 0.1–0.5 ml) is given and can be repeated every 5 min for three doses followed by i.v. methylprednisolone (50–100 mg) if necessary. The airway should be maintained with oxygen inhalation, and the patient should be transferred to the emergency room in case of anaphylaxis.

Assessment of the guidelines

As of July 11, 2004, 3011 cases were enrolled in this study and all of their case report forms were collected. The details of the study will be published elsewhere (Takeuchi T et al. Postmarketing survey of infliximab in 3000 cases of Japanese rheumatoid arthritis patients, in preparation). Briefly, TB was seen in nine patients, six of whom were observed in the initial 1000 cases, followed by two patients in the next 1000 cases, and one patient in the remaining 1000. Six of the cases were pulmonary and two extrapulmonary. None of the patients was under prophylactic use of INH. However, in six cases the chest radiographs turned out to be abnormal when retrospectively assessed by pulmonologists, although initial readings by attending physicians were assessed to be normal. Furthermore, three of these patients were strongly positive for the PPD skin test, and one had a history of TB. False-negative PPD skin tests were seen in two patients who had abnormal findings suggestive of old TB on chest radiographs.

Pneumocystis carinii pneumonia was observed in six patients (0.2%), none of whom was undergoing prophylactic

use of TMP/SMX. Serious infusion reactions were observed in six patients (0.3%), but all were successfully treated.

Discussion

We have established official guidelines for the use of infliximab in combination with MTX to treat Japanese RA patients and have simultaneously developed an algorithm for the diagnosis and management of TB. Approval was given by the Japan College of Rheumatology in 2003. Nine cases of TB were observed in this study, and six of them occurred during the first 1000 cases. However, if the above guidelines had been strictly followed by the treating physicians, these TB cases might have been prevented. Strict enforcement of the guidelines after the experience of the initial 1000 cases prevented the subsequent occurrence of TB at the same frequency. In this respect, Spain is in the same situation as Japan, with the incidence of TB higher than in other west European countries and the United States. However, Spain overcame this situation by establishing official guidelines and recommendations, and succeeded in dramatically reducing new cases of TB among patients receiving infliximab treatment.[17]

RA patients taking corticosteroids or MTX are often anergic, but this study had only two cases of false-negative PPD skin tests. Even though a high incidence of false-positive PPD skin tests is expected owing to BCG vaccination in childhood, the PPD skin test was useful in screening latent TB, and chest radiography combined with chest CT was effective in detecting latent TB infection in the lung.

An increased risk of TB in patients with RA has been reported in Mexico[18] but not in the United States.[5] No epidemiological studies on the risk of TB in RA patients have been carried out in Japan; however, this type of study is essential. In any event, our study again demonstrated that TNF-α is essential in host immune response to *M. tuberculosis*.[19,20]

The guidelines should be revised in the near future by more closely analyzing the upcoming results of the post-marketing survey in Japan. Enrollment of the 5000 cases initially planned for the post-marketing survey will be completed by the end of 2004.

Finally, recognition of the potential risk of opportunistic infections in RA patients treated with infliximab in combination with MTX by medical professionals is strongly required, and close monitoring of these patients for the signs and symptoms of complicated diseases such as TB and PCP will enable physicians to safely treat RA patients with infliximab.

Acknowledgments This work was supported by a Grant from the Ministry of Health, Labor, and Welfare, Japan.

References

1. Maini RN, Breedveld F, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–63.
2. Maini RN, St Clair EW, Breedveld FC, Furst DE, Kalden JR, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932–9.
3. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedfveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med, 2000;343:1594–62.
4. Keane JK, Gershon S, Rharm D, Wise RP, Mirabile-Levens E, Kasznica J, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med 2001;345:1098–104.
5. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50:372–379.
6. World Health Oraganization. WHO report. Global tuberculosis control – surveillance, planning, financing. http//www.who.int/tb/publications/global-report/2004/en
7. Ministry of Health, Labor, and Welfare, Japan. Report (in Japanese). http://www.jata.or.jp/rit/rj/03toukei.jtml
8. Kashiwazaki S, Ichikawa Y, Sugawara S, Nagaya I, Kawai S, Hakota M, et al. Determination of the clinical optimal dose of L-377 (methotrexate capsule) for the treatment of rheumatoid arthritis (in Japanese). Ensho 1996;16:437–8.
9. Hughes WT, Feldman S, Aur RJA, Verzosa MS, Hustu HO, Simone JV. Intensity of immunosuppressive therapy and the incidence of *Pneumocystis carinii* pneumonitis. Cancer 1995;36:2004–9.
10. Liam CK, Wang F. *Pneumocystis carinii* pneumonia in patients with systemic lupus erythematosus. Lupus 1992;1:379–85.
11. Godeau B, Coutant-Perronne V, Le Thi Huong D, Guillevin L, Magadur G, De Bandt M, et al. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol 1994;21:246–51.
12. Kadoya A, Okada J, Iikuni Y, Kondo H. Risk factors for *Pneumocystis carinii* pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. J Rheumatol 1996;23:1186–8.
13. Ogawa J, Hariga MI, Nagasaka N, Nakamura T, Miyasaka N. Prediction of and prophylaxis against *Pneumocystis carinii* pneumonia in patients with connective tissue diseases undergoing high-dose corticosteroid therapy. Mod Rheumatol; in press.
14. Bergin CJ, Wirth RL, Berry GJ, Castellino RA. *Pneumocystis carinii* pneumonia: CT and HRCT observations. J Comput Assist Tomogr, 1990;14:756–9.
15. Yasuoka A, Tachikawa N, Shimada K, Kimura S, Oka S. (1–3) β-D-glucan as a quantitative serological marker for *Pneumocystis carinii* pneumonia. Clin Diagn Lab Immunol 1996;3:197–9.
16. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003;98:1315–24.
17. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk. A multicenter active-surveillance report. Arthritis Rheum 2003;48:2122–27.
18. Carmona L, Hernandez-Garcia C, Vadillp C, Pato E, Balsa A, Gonzalez-Alvaro I**,** et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:1436–9.
19. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lance Infect Dis 2003;3:148–55.
20. Ehlers S. Role of tumour necrosis factor (TNF) in host defence against tuberculosis: implications for immunotherapies targeting TNF. Ann Rheum Dis 2003;62(suppl II):ii37–42.