

CONCISE REPORT

Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan

T Yamada, A Nakajima, E Inoue, E Tanaka, M Hara, T Tomatsu, N Kamatani, H Yamanaka



Ann Rheum Dis 2006;65:1661–1663. doi: 10.1136/ard.2005.047274

Objective: To determine the risk for tuberculosis infection in patients with rheumatoid arthritis before the anti-cytokine era in Japan.

Patients and methods: A database of a single-institute-based large observational cohort study for rheumatoid arthritis at the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, was analysed. Information on the history of tuberculosis infection was collected by patient self-reporting during April and October 2003. The age-adjusted incidence rate and relative risk for tuberculosis infection were investigated.

Results: Among 5044 patients with rheumatoid arthritis, 483 (9.6%) patients claimed to have a history of tuberculosis infection before October 2002. The frequency of history of tuberculosis increased according to the age of the patient. Four cases of new-onset tuberculosis were identified among 5544 patients with rheumatoid arthritis during 1 year. The age-adjusted incidence of tuberculosis was 42.4/100 000 patients. The relative risk for tuberculosis was 3.21 (95% confidence interval (CI) 1.21 to 8.55), and that of men and women was 10.59 (95% CI 3.42 to 32.78) and 1.41 (95% CI 0.2 to 10), respectively.

Conclusion: There was an increased risk of tuberculosis infection in Japanese patients with rheumatoid arthritis, especially in male patients before the introduction of anti-tumour necrosis factor treatment. These data should form the basis for the risk management of anti-cytokine treatment in Japan.

The introduction of biological agents against tumour necrosis factor α (TNF α)^{1,2} represents a major advance in the treatment of rheumatoid arthritis. On the other hand, an increased occurrence of tuberculosis is one of the major concerns.^{3,4} TNF α has a key role in suppressing mycobacterial infections,⁵ and the emergence of active tuberculosis infection is reported soon after the introduction of infliximab.³ In Spain, the incidence of tuberculosis increased in patients with rheumatoid arthritis after the introduction of anti-TNF agents. In Japan, the incidence of tuberculosis in the general population is high compared with that evident in the US⁶ or UK,⁷ and is comparable with that in Spain.⁸ Therefore, the increase in tuberculosis after the introduction of anti-TNF agents is of grave concern. However, there has been no systematic investigation of the incidence of tuberculosis in patients with rheumatoid arthritis in Japan so far, and this is required to facilitate accurate interpretation of the current problem.

We have established a large observational cohort survey of patients with rheumatoid arthritis from 2000 in our institute. By using the database in this cohort, we investigated the

prevalence and incidence of tuberculosis infection among Japanese patients with rheumatoid arthritis just before the launch of biological anti-TNF agents in Japan.

PATIENTS AND METHODS

This report relates to two studies analysing a large observational cohort study for rheumatoid arthritis at the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, that started in October 2000. A survey is conducted every 6 months on all patients with rheumatoid arthritis treated at the institute, who have given informed consent. Three major domains are included in this survey system: (1) the doctor's evaluation (swollen and tender joints, the level of disease activity on a visual analogue scale), (2) the patient's evaluation (pain and general health on a visual analogue scale and the Stanford Health Assessment Questionnaire Functional Index (disability)) at each survey, and (3) the patient's report of events (infection, hospitalisation, operation, drugs, etc), which occurred within the previous 6 months, and laboratory data. Patients were instructed to complete the questionnaire at home and to mail the completed forms within 2 weeks in a pre-addressed and pre-stamped envelope. The questionnaires were mailed to patients who failed to join the subsequent survey, to obtain the information.

In study 1, the history (before October 2002) of tuberculosis was collected at the sixth survey conducted in April 2003, when the active screening programme regarding tuberculosis was started. Questions asked were: "Have you ever had tuberculosis? If so, were you treated? If you had extra-pulmonary tuberculosis, please specify the organ." The number of patients with a history of tuberculosis was based on the patient's self-report.

In study 2, information on the recent onset (within 6 months) of tuberculosis was collected in the questionnaire by the question: "Have you ever had tuberculosis within this 6 months?" at two consecutive surveys in April 2003 (sixth survey) and October 2003 (seventh survey). The diagnosis of a patient with a recent onset of tuberculosis was validated by medical records or by information provided by corresponding hospitals. The age-adjusted incidence rate and relative risk of our cohort data in 1 year from October 2002 to September 2003 were standardised on the basis of the database officially reported from The Research Institute of Tuberculosis Japan Anti-Tuberculosis Association (<http://www.jata.or.jp/rit/rj/stoukei02.htm>).

RESULTS

In study 1, among 5044 patients with rheumatoid arthritis (870 men and 4174 women), 484 (9.6%) patients claimed to have a history of tuberculosis infection before October 2002. Men ($n=117$, 13.3%) exhibited a significantly higher

Abbreviations: TNF, tumour necrosis factor

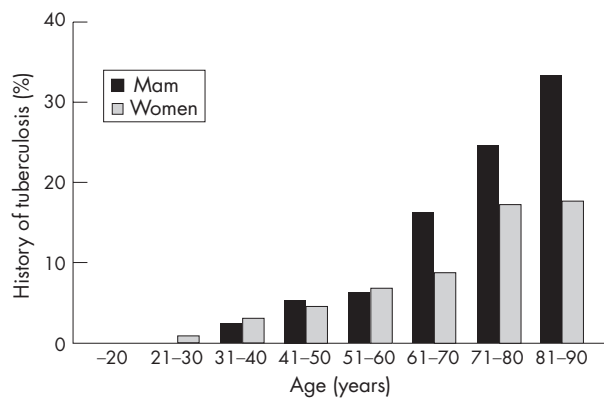


Figure 1 The percentage of history of tuberculosis in patients with rheumatoid arthritis in each age range. Men had a higher percentage of histories of tuberculosis than women. The numbers of each generation were as follows: age <21 years (2 men; 12 women), 21–30 years (18 men; 32 women), 31–40 years (42 men; 318 women), 41–50 years (91 men; 539 women), 51–60 years (225 men; 1215 women), 61–70 years (232 men; 1098 women), 71–80 years (135 men; 465 women), >80 years (11 men; 56 women).

frequency of a history of tuberculosis than women ($n = 367$, 8.8%; $p < 0.001$). Pulmonary tuberculosis affected 454 patients and extrapulmonary tuberculosis affected 52 patients. Twenty two patients had both pulmonary and extrapulmonary disease. The locations of extrapulmonary organs were bones/joints in 10, pleurae and bronchi in 10, cervical lymph nodes in 9, kidney in 6, skin in 5, peritoneum in 4, intestine in 3, eye in 3, uterus in 2 and disseminated in 1 patient. One of the patients had both disseminated and bone tuberculosis. Figure 1 shows the percentage of the history of tuberculosis of men and women in each age range. The percentage increased with age of the patient, and men had a higher percentage of history of tuberculosis than women. No significant difference was found between the groups of patients with or without a history of tuberculosis with regard to the percentage of patients receiving treatment with steroids or disease-modifying antirheumatic drugs.

In study 2, during the period between October 2002 and September 2003, four patients (3 men and 1 woman) with recent-onset tuberculosis were identified among 5544 (970 men, and 4574 women) patients with rheumatoid arthritis who enrolled in one or both surveys in April 2003 or October 2003. Four patients had received treatment with low-dose prednisolone (5–10 mg/day) and two patients had received methotrexate (4–6 mg/week). One patient died from acute interstitial pneumonia during the treatment of lung tuberculosis, and the other three patients recovered.

The age-adjusted incidence rate of tuberculosis was 42.4/100 000 patients (4836 patient-years) in patients with rheumatoid arthritis, whereas the incidence rate was 25.8/100 000 patients in the Japanese general population (table 1). In men, the incidence rate was 173.4/100 000 patients in patients with rheumatoid arthritis, whereas it was 34.2/100 000 in the general Japanese male population. In women, the incidence rate was 13.1/100 000 in patients with rheumatoid arthritis whereas it was 17.7/100 000 in the general Japanese female population. The relative risk for tuberculosis in our population with rheumatoid arthritis was 3.21 (95% confidence interval (CI) 1.21 to 8.55) whereas that of male and female patients was 10.59 (95% CI 3.42 to 32.78) and 1.41 (95% CI 0.2 to 10), respectively (table 1).

DISCUSSION

This is the first report of a large observational cohort study regarding the incidence of tuberculosis in Japanese patients with rheumatoid arthritis, and presumably the last report just before the dawn of the era of novel biological agents. Our study is not multi-institutional but is based on a single institution and may, thus, not be representative of the general situation in Japan. However, the large number of patients in this study ($n = 5044$) actually accounts for approximately 1% of the population with rheumatoid arthritis in Japan; therefore, our results probably reflect at least the current status of tuberculosis infection in Japanese patients with rheumatoid arthritis.

We found a 3.2-fold increased risk of tuberculosis in patients with rheumatoid arthritis and a 10-fold increased risk in men, but no increase in women with rheumatoid arthritis. Owing to a follow-up system for patients who have dropped out from the subsequent survey, this increased risk is not considered to be overevaluated. In addition, the relative risk in men with rheumatoid arthritis is high, regardless of the higher incidence rate of the general male population in Japan. Thus, our study indicated that Japanese male patients with rheumatoid arthritis have a higher risk of tuberculosis even without the use of TNF inhibitors.

It is generally believed that autoimmune rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis,¹³ may be associated with an increased risk of tuberculosis. The increased risk may be attributed to the immunological dysfunction caused by the disease itself, as well as treatment with immunosuppressive agents. However, the reports on the risk of tuberculosis in patients with rheumatoid arthritis are controversial. The incidence of tuberculosis was not increased by conventional immunosuppressive treatment in the general population in the US⁹ (table 1). On the other hand, an increased relative risk for tuberculosis in patients with rheumatoid arthritis in Sweden (2)¹⁰ and Spain (3.68) before the anti-TNF era has been

Table 1 Comparison of the risk of tuberculosis in patients with rheumatoid arthritis and patients with rheumatoid arthritis treated with anti-TNF

	Rheumatoid arthritis			
	General population	Incidence rate (per 100 000 people)	Relative risk (95% CI)	Rheumatoid arthritis after introduction of anti-TNF
US	6.4 (1999) ⁶	6.2 (1998–9) ⁹		52.5 (2000–2) ⁹
Germany	8.5 (2001) ⁷			
UK	10.1 (2001) ⁷			
Sweden			2.0 (1.2–3.4) ¹⁰	
Spain	21 (2000) ⁸	134 (1990–2000) ¹¹	3.68 (2.36 to 5.92) ¹¹	1893 (2000) ¹² 1113 (2001) ¹²
Japan	25.8 (2002)	42.4 (2002)	3.21 (1.21 to 8.55)	
Men	34.2	173.4	10.6 (3.42 to 32.78)	
Women	17.7	13.1	1.48 (0.20 to 10.00)	

TNF, tumour necrosis factor.

reported. In our report, the magnitude of the relative risk (3.21) for tuberculosis in Japanese patients with rheumatoid arthritis was similar to that in Spain. In Spain, increased incidence of tuberculosis occurred after initiation of anti-TNF treatment. However, by the adequate use of guidelines for the treatment with biological agents, especially for the prevention of tuberculosis established in 2001, the incidence of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF agents was successfully reduced.^{12–14} Therefore, the acknowledgement of the important association between anti-TNF treatment and tuberculosis, as well as the rigorous implementation of guidelines for the use of anti-TNF agents will help protect patients with rheumatoid arthritis from the risk of developing tuberculosis infection as a result of anti-TNF treatment.

Authors' affiliations

T Yamada, A Nakajima, E Inoue, E Tanaka, M Hara, T Tomatsu, N Kamatani, H Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Competing interests: None declared.

Correspondence to: Dr T Yamada, Institute of Rheumatology, Tokyo Women's Medical University, 10–22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan; tyamada@ior.twmu.ac.jp

Accepted 31 January 2006

Published Online First 12 July 2006

REFERENCES

- Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;**343**:1594–602.
- Maini RN, Breedveld FC, Kalden JR, Smolen JS, Frust D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004;**50**:1051–65.
- Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwertman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
- Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. *J Rheumatol* 2002;**29**(Suppl 65):33–8.
- 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. *Lancet Infect Dis* 2003;**3**:148–55.
- Centers for Disease Control and Prevention (CDC). *Reported tuberculosis in the United States, 2000*. Atlanta, GA: US Department of Health and Human Services, CDC, 2001.
- World Health Organisation. *Global tuberculosis control, WHO Report*. Geneva: WHO, 2003:171.
- Sociedad Espanola de Salud Publica (SESPAS). 2002 SESPAS report: investing in health. In: Cabases JM, Vilalbi JR, Aibar C, eds. *Priorities for public health in Spain*. Granada, Spain: Escuela Andaluza de Salud Publica, 2002:21–42.
- Walte F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum* 2004;**50**:372–9.
- Askling J, Forell CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 2005;**52**:1986–92.
- Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. *J Rheumatol* 2003;**30**:1436–9.
- Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, on behalf of the BIOBADASER Group. 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**:2122–7.
- Bouza E, Moya JG, Munoz P. Infections in systemic lupus erythematosus and rheumatoid arthritis. *Infect Dis Clin North Am* 2001;**25**:1900–7.
- Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;**52**:1766–72.