Pneumocystis Jirovecii Pneumonia in Japanese Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Pooled Analysis of 3 Agents

To the Editor:

Pneumocystis jirovecii pneumonia (PCP) is an infectious fungal disease caused by *P. jirovecii*, which has attracted the attention of physicians treating patients with human immunodeficiency virus infection[1], as well as those with connective tissue diseases, malignancies, and organ transplantation[2].

In patients with rheumatoid arthritis (RA), PCP used to be an uncommon infectious disease, but the number of case reports of PCP in patients with RA has increased since the introduction of low-dose methotrexate as an anchor drug for RA in the 1980s[3]. Moreover, with the introduction of anti-tumor necrosis factor (TNF) therapy, a further increase of incidence of PCP in patients with RA has been noticed, especially in Japan where strict postmarketing surveillance (PMS) programs have been conducted for patients with RA treated with TNF inhibitors[4,5,6]. The numbers of patients with RA with PCP in these PMS programs who were treated with infliximab (IFX), etanercept (ETN), or adalimumab (ADA) were 22 (0.4%) out of 5000[4], 25 (0.18%) out of 13,894[5], and 25 (0.33%) out of 7469 patients[6], respectively. Notably, these incidence rates of PCP in Japan are higher than the corresponding figure (0.01%) reported from the United States. Therefore, we previously analyzed the clinical characteristics and risk factors for PCP in patients with RA in Japan treated with these 3 TNF inhibitors[7,8,9,10]. In most cases, PCP developed rapidly with respiratory failure, and *P. jirovecii* organisms could not be detected microscopically, requiring for diagnosis the PCR test for *P. jirovecii* DNA or the measurement of plasma or serum 1, 3-β-D-glucan levels. Only some of the cases were in an immunocompromised state, showing a remarkable decrease in concentrations of serum immunoglobulins and the number of peripheral blood lymphocytes. Some of the risk factors for PCP were common to IFX and ETN, but others differed among the 3 TNF inhibitors[8,9,10]. It is possible that small sample size, patient background, the launch time of each drug, distinct mechanism of action among TNF inhibitors, or other unmeasured factors resulted in these differences in risk factors for PCP among the drugs. We therefore merged and analyzed the data of our previous studies to identify risk factors for development of PCP common to these 3 TNF inhibitors. Details of the designs and the methods of our previous studies were published elsewhere[8,9,10].

In our previous studies, we accumulated a total of 53 patients with RA who developed PCP under treatment with 1 of the 3 TNF inhibitors: IFX in 21 cases, ETN in 15 cases, and ADA in 17 cases. Of these, 51 patients who developed PCP within 12 months after commencement of a TNF inhibitor (the PCP group) were analyzed. For a control group, 265 patients with RA who did not develop PCP within 12 months after the beginning of a TNF inhibitor (the non-PCP group) were randomly selected from a consecutive series of patients with RA in the hospitals that participated in these studies.

To characterize the PCP group, we compared demographics, comorbidities, laboratory data, and concomitant drugs between the PCP and the non-PCP groups at the time of initiation of treatment with TNF inhibitors (Table 1). Compared with patients of the non-PCP group, patients of the PCP group were significantly older, had a lower percentage of women, had a higher prevalence of comorbid pulmonary disease and diabetes mellitus, and were treated with a higher daily dose of prednisolone. None of the 51 patients were receiving chemoprophylaxis for PCP at the time of PCP diagnosis. All of the patients received therapeutic doses of trimethoprim/sulfamethoxazole, except for 1 who received pentamidine isethionate. One case in an ETN study[9] and 3 cases in an ADA study[10] died after developing PCP.

A multivariate Cox proportional hazard analysis yielded HR and 95% CI for the following risk factors: older age (per 10-yr increment), 1.8 (1.4–2.5); presence of comorbid pulmonary disease, 3.1 (1.8–5.3); comorbid diabetes mellitus, 2.9 (1.5–5.8); and daily dose of prednisolone ≥ 5 mg, 2.7 (1.5–5.0). The cumulative probability for developing PCP was calculated using the Kaplan-Meier method (Figure 1). Patients with 3 or more of these risk factors had a significantly higher risk for PCP than those with 2, 1, or no risk factors ($p < 0.001$ for all comparisons by the log-rank test). Patients with 2 risk factors had a significantly higher risk for PCP than those with 1 or no risk factors ($p = 0.045$ and $p < 0.001$, respectively). Patients with 1 risk factor had a significantly higher risk for PCP than those with no risk factors ($p = 0.008$).

Table 1. Baseline clinical characteristics of patients with RA treated with TNF inhibitors. Values are mean ± SD or % unless otherwise specified.

Variables	PCP Group, n = 51	Non-PCP Group, n = 265	p
Characteristics			
Age, yrs	65.5 ± 9.5	55.2 ± 12.7	< 0.001†
Female	68.6	84.2	0.009‡
Disease duration, yrs	10.8 ± 8.7	9.3 ± 8.3	0.203†
Comorbid pulmonary disease	47.1	14.3	< 0.001‡
Diabetes mellitus	23.5	6.8	0.001‡
Laboratory data			
White blood cells < 4000/μl	2.0	0.8	0.402‡
Lymphocytes < 1000/μl	32.6	23.8	0.222‡
Serum IgG, mg/dl	1370 ± 386	1552 ± 497	0.064†
Concomitant treatment			
MTX	90.2	76.2	0.026‡
MTX dosage, mg/week	8.2 ± 2.9	8.3 ± 2.3	0.447†
MTX dosage > 8 mg/week	23.5	20.4	0.612‡
Oral corticosteroids	86.3	66.0	0.004‡
PSL-equivalent dosage of corticosteroids, mg/day	9.3 ± 9.9	6.0 ± 3.2	0.008†
PSL-equivalent dosage of corticosteroid ≥ 5 mg/day	70.6	47.5	0.003‡

† p values were calculated using the Mann-Whitney U test. ‡ p values were calculated using the chi-square test. Comorbid pulmonary disease = interstitial pneumonia, bronchiectasis, follicular bronchiolitis, chronic obstructive pulmonary diseases, chronic bronchitis, bronchial asthma, middle lobe syndrome, old pulmonary tuberculosis, old pleuritis, pneumoconiosis. RA: rheumatoid arthritis; TNF: tumor necrosis factor; PCP: *Pneumocystis jirovecii* pneumonia; IgG: immunoglobulin G; MTX: methotrexate; PSL: prednisolone.

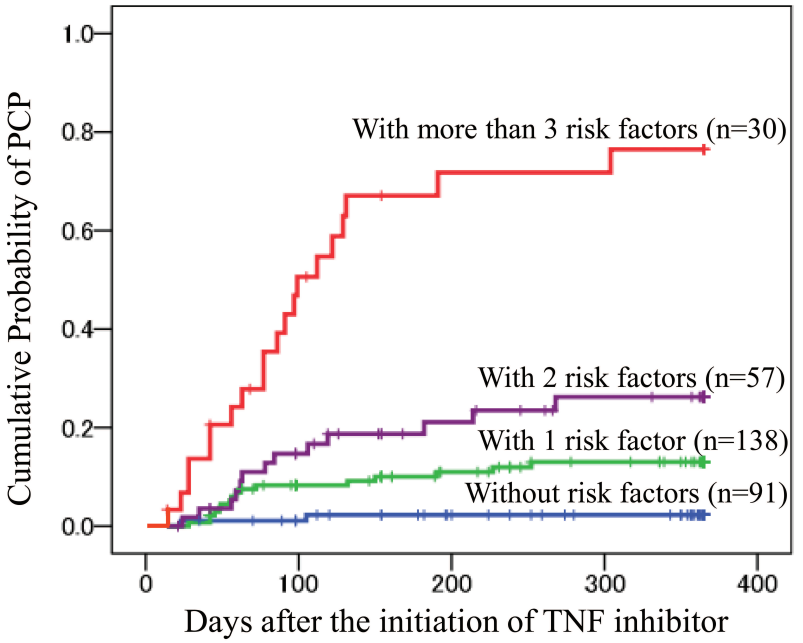

Figure 1. Cumulative probability for developing PCP under treatment with TNF inhibitors by number of risk factors. The cumulative probability was calculated using the Kaplan-Meier method. The differences in cumulative probability among the groups were examined using the log-rank test. Patients with 3 or more risk factors had a significantly higher risk for PCP than those with 2, 1, or no risk factors ($p < 0.001$ for all comparisons by the log-rank test). Patients with 2 risk factors had a significantly higher risk for PCP than those with 1 or no risk factors ($p = 0.045$ and $p < 0.001$, respectively). Patients with 1 risk factor had a significantly higher risk for PCP than those with no risk factors ($p = 0.008$). PCP: *Pneumocystis jirovecii* pneumonia; TNF: tumor necrosis factor.

We were able to identify common and more robust risk factors for the development of PCP by combining the data of PCP developed during treatment with any 1 of the 3 TNF inhibitors. Although prophylaxis success must be demonstrated in randomized controlled trials, we consider that it is important to screen for these risk factors based on this analysis and consider diligent prophylaxis before starting a TNF inhibitor.

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