

Pneumocystis jirovecii pneumonia: a rare but serious complication during TNF inhibitor treatment for rheumatoid arthritis in Japan

*“Strict pharmacovigilance programs performed in Japan disclosed that *Pneumocystis jirovecii* pneumonia is found in 0.2–0.4% of rheumatoid arthritis patients treated with TNF inhibitors.”*

KEYWORDS: *Pneumocystis jirovecii* pneumonia ■ rheumatoid arthritis ■ TNF inhibitors

Pneumocystis jirovecii pneumonia (PCP) is encountered in immunocompromised hosts such as patients with AIDS. Although rheumatoid arthritis (RA) patients receiving methotrexate and biologics, such as TNF inhibitors, are also known to be susceptible to PCP, its incidence in western countries is low and have not drawn much attention until the breakout in Japan. Strict pharmacovigilance programs performed in Japan disclosed that PCP is found in 0.2–0.4% of RA patients treated with TNF inhibitors [1–3]. Risk factors were identified by following clinical studies and chemoprophylaxis was proved to be successful to prevent PCP. Pharmacovigilance programs, therefore, shed a light on a rare, but serious adverse reaction, for example, PCP in Japanese RA patients.

Rare but serious adverse drug reactions cannot be found during clinical trials in which patients are selected with regards to age and comorbidities, and patients enrolled are limited in number. Furthermore, there is an ethnic difference or deviation in terms of frequency and severity of adverse drug reactions; PCP is a good example.

***Pneumocystis jirovecii* pneumonia**

Pneumocystis jirovecii is an ascomycetous fungus causing opportunistic infection known as PCP. The organism may colonize in immunocompromised hosts and PCP is the most prevalent opportunistic infection in patients with AIDS. RA patients receiving methotrexate and biologics such as TNF inhibitors are also known to be susceptible to PCP but their incidence in western countries did not draw much attention until its breakout in Japan.

TNF inhibitors & PCP

TNF inhibitors, for example infliximab, etanercept and adalimumab, have been approved in

Japan for RA patients and were subject to a strict postmarketing surveillance program as a condition of regulatory approval by the Ministry of Health, Labour and Welfare, Japan. The objectives of postmarketing surveillance are: to verify the safety profile of the target drug compared with the data obtained from the clinical trial; to investigate the incidence of serious adverse events which occur at 0.1% or more; and to identify the factors that may affect safety. All patients who received the target drug were enrolled in this program and prospectively monitored for all adverse events for a period of 6 months. As a result, PCP was found in 0.4% of 5000 patients treated with infliximab [1]. The same tendency was found in other TNF inhibitors, for example, 0.2% of 7091 patients with etanercept [2] and 0.3% of 3000 patients with adalimumab [3]. PCP occurred within 6 months in a majority of patients on TNF inhibitors, which suggests a strong causal relationship between development of PCP and use of TNF inhibitors.

Risk factors for developing PCP in patients with RA on TNF inhibitors

Our study identified risk factors for developing PCP in RA patients receiving infliximab by using COX proportional hazard regression analysis, for example, age over 65 years (hazard ratio: 3.77; 95% CI: 1.54–9.25), usage of prednisolone over 5 mg/day at the baseline (hazard ratio: 3.76; 95% CI: 1.37–10.3) and coexisting pulmonary disease (hazard ratio: 2.54; 95% CI: 1.00–6.46) [4]. Furthermore, cumulative probability of developing PCP was greatly enhanced in patients with more than two risk factors than in other patients. Similar findings were obtained with etanercept [5] and adalimumab [6]. However, PCP was successfully prevented by chemoprophylaxis using trimethoprim/sulfamethoxazole. The Japanese guidelines for the use of TNF inhibitors in RA



Nobuyuki Miyasaka

Author for correspondence:
Department of Medicine
& Rheumatology, Graduate School of
Medical & Dental Sciences, Tokyo
Medical & Dental University, Tokyo,
Japan
miya.rheu@tmd.ac.jp



Masayoshi Harigai

Department of Pharmacovigilance,
Graduate School of Medical & Dental
Sciences, Tokyo Medical & Dental
University, Tokyo, Japan

patients were therefore amended following our studies and recommended considering chemoprophylaxis in RA patients on biologics with these risk factors.

Diagnosis of PCP

The incidence of PCP in Japanese RA patients receiving TNF inhibitors is therefore approximately 10–20-fold greater than that of western countries [7]. Prospective and strict postmarketing surveillance programs may influence the results, but this could be explained by differences of ethnicity, patient demographics and treatment profile. In addition, we not only used microscopic evidence of *Pneumocystis jirovecii* as definite diagnosis, but also employed positive PCR for *Pneumocystis jirovecii* DNA or increased serum 1,3- β -D-glucan levels with therapeutic response to standard treatment for PCP as a presumptive diagnosis [8]. β -D-glucan, the major component of fungi cell walls, has been recognized as a useful serum marker for PCP [9]. The difference of methodology in making diagnosis of PCP may also contribute a higher incidence of PCP in Japan.

Conclusion & future perspective

These postmarketing surveillance programs performed in Japan clearly showed that PCP may occur early in the course of TNF inhibitors in patients with RA. In-hospital mortality of patients with RA who had PCP was reported to be 30.8% in the USA [10]. Careful monitoring, early

diagnosis and proper management are essential to provide a better prognosis for these patients. These programs are prospective in study design, although they are limited to 6 months, and provide clinical evidence of the highest quality in the use of TNF inhibitors for RA patients in daily practice. The pathogenesis of the high frequency of PCP in Japanese RA patients remains to be solved in the future.

Financial & competing interests disclosure

N Miyasaka has received research grants from Abbvie Japan Co. Ltd, Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd, Daiichi-Sankyo Co. Ltd, Eisai Co. Ltd, Mitsubishi Tanabe Pharma Co., Novartis Pharma KK, Ltd., Takeda Pharmaceutical Co. Ltd and Teijin Pharma Ltd, and has received consulting fees or honorarium from Abbott Japan Co. Ltd., Bristol-Myers Squibb, Janssen Pharmaceutical KK and Otsuka Pharmaceutical Co. Ltd. M Harigai has received research grants from Abbvie Japan Co. Ltd, Astellas Pharma Inc., Bristol-Myers Squibb KK, Chugai Pharmaceutical Co. Ltd, Eisai Co. Ltd, Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi-Aventis KK, Santen Pharmaceutical Co. Ltd and Takeda Pharmaceutical Co. Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Takeuchi T, Tatsuki Y, Nogami Y *et al.* Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 67, 189–194 (2008).
- 2 Koike T, Harigai M, Inokuma S *et al.* Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. *J. Rheumatol.* 36, 898–906 (2009).
- 3 Koike T, Harigai M, Ishiguro N *et al.* Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3000 patients. *Mod. Rheumatol.* 22, 498–508 (2012).
- 4 Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. *N. Engl. J. Med.* 357, 1874–1875 (2007).
- 5 Tanaka M, Sakai R, Koike R *et al.* *Pneumocystis jirovecii* pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. *Mod. Rheumatol.* 22, 849–858 (2012).
- 6 Watanabe K, Sakai R, Koike R *et al.* Clinical characteristics and risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case-control study of 17 patients. *Mod. Rheumatol.* doi:10.1007/s10165-012-0796-5 (2012) (Epub ahead of print).
- 7 Koike R, Takeuchi T, Eguchi K, Miyasaka N. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. *Mod. Rheumatol.* 17, 451–458 (2007).
- 8 Komano Y, Harigai M, Koike R *et al.* *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. *Arthritis Rheum.* 61, 305–312 (2009).
- 9 Tasaka S, Hasegawa N, Kobayashi S *et al.* Serum indicators for the diagnosis of *Pneumocystis* pneumonia. *Chest* 131, 1173–1180 (2007).
- 10 Louie GH, Wang Z, Ward MM. Trends in hospitalizations for *Pneumocystis jirovecii* pneumonia among patients with rheumatoid arthritis in the US: 1996–2007. *Arthritis Rheum.* 62, 3826–3829 (2010).