THERAPY

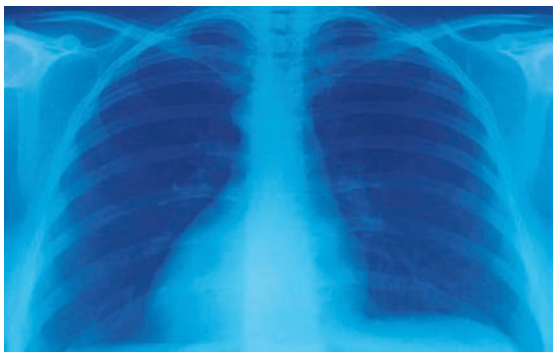
The threat of leflunomide-induced lung disease

Pulmonary adverse events (PAEs) are rare but serious complications of leflunomide therapy. The results of two recent studies add to our knowledge of the prevalence, risk factors and clinical features of leflunomide-induced lung disease, and could influence guidelines for the use of this DMARD in patients with rheumatoid arthritis (RA).

A Japanese study has identified several risk factors for leflunomide-related interstitial lung disease (ILD) on the basis of data from 5,054 patients with RA. "There is a unique post-marketing surveillance system in Japan for newly approved anti-rheumatic drugs, in which strict pharmacovigilance has been advocated by Japanese pharmaceutical companies," explains Shigeko Inokuma, who led the study on behalf of the Japan College of Rheumatology. "Since leflunomide was put on the market in September 2003, all patients with RA starting leflunomide therapy were pre-registered, and were monitored for 24 weeks."

Overall, 61 of the 5,084 patients (1.2%) in the cohort developed ILD. Multivariate analysis identified pre-existing ILD, cigarette smoking, low body weight (<40 kg) and the use of a loading dose as independent risk factors for leflunomide-induced ILD. "Pre-existing ILD was the most important risk factor for leflunomide-induced ILD, with an odds ratio of 8.17," says Inokuma.

The incidence of ILD in the cohort decreased over time, as fewer patients with pre-existing ILD were prescribed the drug following the issue of a safety notice in January 2004. Although not mentioned in the safety notice, the use of a loading dose also declined.



In a separate study, a UK-based group reviewed the clinical characteristics of 32 published cases (including 6 from Japan) of leflunomide-induced pneumonitis in patients with RA. The investigators were prompted to undertake the retrospective review after finding a dearth of information in the literature and clinical guidelines.

Confirming the Japanese group's observations, they found that pre-existing ILD is an important risk factor for leflunomide-induced PAEs. In addition, says lead author Batsi Chikura, "this is the first study to show variations in the clinical expression of leflunomide-induced pneumonitis." From the results, some of this variation could be indicative of prognosis. "The clinical features of patients who died were pre-existing ILD, ground glass opacities on high-resolution CT and diffuse alveolar damage on histological examination," says Chikura.

Lung disease usually appeared within 20 weeks of the start of leflunomide therapy, although the timing was influenced by several factors. Patients who received a loading dose and those with pre-existing ILD presented early (within 12 weeks), and the appearance of ground glass shadowing on high-resolution CT was associated with earlier onset than a honeycombing pattern.

As well as the clinical features already mentioned, mortality was also linked to a history of methotrexate-induced pneumonitis. A comparison of the clinical and laboratory features of survivors and non-survivors in the Japanese cohort should further elucidate those factors predictive of survival in leflunomide-induced disease.

Although leflunomide-induced PAEs are infrequent, clinicians should be aware of the characteristics of these life-threatening complications.

Sarah Price

Original articles Sawada, T. *et al.* Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. *Rheumatology (Oxford)* doi:10.1093/rheumatology/kep052
Chikura, B. *et al.* Clinical expression of leflunomide-induced pneumonitis. *Rheumatology (Oxford)* doi:10.1093/rheumatology/kep050