Editorial

Leflunomide and the lung

Sir, LEF was licensed for the treatment of RA in the USA in 1998 and in the European Union a year later [1]. It rapidly gained a substantial share of the DMARD market in the West, with rheumatologists often prescribing LEF in preference to MTX for RA patients with established lung disease. However, following its launch in Japan in 2003, adverse pulmonary events were reported with accelerated interstitial lung disease (ILD) leading to several deaths [2, 3]. McCurry [4] detailed this development in 16 RA patients with a high associated mortality. Descriptions of acute LEF-induced pneumonitis, akin to MTX pneumonitis, continued to come from the East [5, 6], and in 2006, Suisa et al. [7] reported an apparent increased risk of acute lung disease in RA patients in North America treated with LEF, which disappeared once prior ILD and MTX treatment were excluded. However, the annual incidence of LEF lung disease in this Western population was relatively low at 0.08%, in comparison with Japan, where the manufacturers themselves disclosed an early incidence of ILD of 0.48% [8].

In this month’s issue, the Japanese Study Committee for LEF-induced Lung Injury describes the post-marketing surveillance strategy and its effect on the incidence of LEF-related lung disease in detail [8]. They prospectively examine more than 5000 patients who took LEF for RA over a 24-week period, and show an incidence of lung disease of 1.2%. The presence of prior ILD increases the odds ratio for risk of LEF lung disease by a factor of 8. Indeed, the authors found that >5% of all RA patients with ILD developed pneumonitis within 6 months of starting LEF. Their study clearly shows a marked reduction in incidence once patients with prior ILD are excluded from receiving the drug. However, LEF lung disease continued to develop in 0.7% of the Japanese patients with no evidence of prior ILD.

Along the same line, Chikura et al. [9] present a retrospective review of the literature on LEF pneumonitis and describe the outcome from 32 reported cases, evenly divided between the Far Eastern and Caucasian populations. They show that LEF pneumonitis typically occurs early in treatment, usually within 20 weeks of initiation of LEF and that the risk increases with loading doses of the drug. The overall case mortality (19%), independent of genetic background, significantly increases in those with prior ILD or MTX pneumonitis. The mean age of their patients is only 57 years, with more men than expected on the basis of female preponderance in RA. In addition, the authors also highlight the difficulty in defining LEF pneumonitis, and propose adopting the Searles and McKendry’s criteria, initially used to define MTX pneumonitis.

Overall annual incidence rates for LEF-induced pneumonitis in the Far East are 0.5–1.2% [8, 10], whereas the true incidence in the West is probably well under 0.1% [7, 11, 12]. LEF-induced lung disease seems to be more common than MTX pneumonitis in Japan, and also exceeds the reported incidence of MTX-induced lung disease in Western populations. Initial channelling of RA patients with ILD preferentially to LEF might not be the only factor contributing to this observation.

DMARD usage differs substantially in Japan compared with the West. In Japan, MTX is licensed for use only after failure of at least one other DMARD, and at a maximum dose of 8 mg/week. Licensed doses of other DMARDs, such as salazopyrin (maximum 1 g/day), are also lower than those in Western practice. Hence, the introduction of LEF in 2003 with a dosing schedule equivalent to that in the West, was hailed as a welcome advance. The subsequent high rates of reported lung disease may be partly due to the widespread uptake of LEF in Japan and to the use of relatively high doses of the drug.

The other possible explanation for the apparent excess of lung disease in Japanese and Korean patients might be genetic. Interest is increasing in the genetic profile of RA patients as a predictor for their subsequent response to treatment. Genetic profiling may also reveal important differences that might explain the apparent increased susceptibility of these patients to pneumonitis from LEF.

Sawada et al. [8] and Chikura et al. [9] concur in their recommendation that the presence of previous MTX pneumonitis should now be considered an absolute contraindication to the subsequent use of LEF. In addition, they suggest that LEF is best avoided in patients with prior ILD, which confers up to an 8-fold increase in risk of LEF pneumonitis. This risk is comparable with the 10-fold increase in risk of MTX pneumonitis in patients with significant ILD [13]. It seems that the use of LEF in patients with prior ILD should be avoided in those of Japanese or Korean origin, and used only as a last resort in Caucasians.

The use of a loading dose regime seems to increase the risk of lung disease, as does a history of smoking and low BMI (<40 kg). Clinicians should avoid using the loading dose schedule for LEF, which is associated with higher risk of pneumonitis, preferring a daily dose of 10–20 mg from the start of therapy. In patients with low body weight (<40 kg), it may prove prudent to limit the daily dose to 10 mg for the first 6 months. Age itself might not be an independent risk factor, but men appear to be at a slightly greater risk overall, possibly because underlying ILD in RA is more common in men [14].

Clinicians may wish to undertake prior assessment of pulmonary function tests in high-risk patients, especially those of Japanese or Korean origin. A gas transfer of <70% predicted suggests that further investigation to exclude ILD with high-resolution CT of the chest is indicated before commencement of LEF therapy. Such an approach has previously been shown to reduce the incidence of pneumonitis in patients scheduled to receive MTX [15].

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