Clinical expression of leflunomide-induced pneumonitis

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Objectives. To review all the current evidence of LEF-induced pneumonitis (LEIP) which will help rheumatologists recognize suspected cases of LEIP and to influence clinical guidelines.

Methods. Thirty-two reported cases of LEIP (13 males and 19 females) were identified from a literature search and classified using Searles and McKendry’s classification criteria. Their clinical characteristics were reviewed.

Results. All patients had a history of either exposure to MTX or interstitial lung disease (ILD) or both and all patients had RA. Most patients (82%) had LEIP within the first 20 weeks of initiation of LEF. All patients who had a loading dose LEF and most patients with ILD developed LEIP early (within 12 weeks of exposure). Case mortality was 19%. Two patients had previous MTX-induced pneumonitis (MTX-P) prior to initiation of LEF; both died from LEIP. There was a high mortality in the following groups of patients: diffuse alveolar damage (DAD) on histological examination, pre-existing ILD and ground glass shadowing on high resolution computerised tomography (HRCT). Treatment with cholestyramine did not appear to alter clinical outcome.

Conclusions. LEIP usually occurs within the first 20 weeks of initiation of LEF. Clinical features of patients who died were pre-existing ILD, ground glass shadowing on HRCT and DAD on histological examination, and these could be poor prognostic indicators. Patients need to be made aware of this rare complication. LEF should not be used in patients with previous MTX-P and should be used with caution in patients with ILD.

Key words: Leflunomide-induced pneumonitis, Hypersensitivity pneumonitis, Interstitial lung disease, Delayed hypersensitivity.

Background

LEF is an immunomodulatory drug and its active metabolite A77 1726 inhibits dehydroorotate dehydrogenase, an enzyme key to pyrimidine synthesis in activated T lymphocytes [1]. In randomized control trials, LEF was comparable with MTX in controlling joint symptoms and slowing radiological progression in patients with active RA [2, 3]. LEF is also effective in the treatment of other autoimmune conditions such as PsA [4], DM [5], JCA [6], sarcoidosis [7], Crohn’s disease [8] and WG [9]. LEF-induced pneumonitis (LEIP) is a rare but serious complication of LEF therapy. Since 2004, the awareness of LEIP has increased following an investigation by the Japanese Health Ministry after the death of five Japanese patients from LEIP [10] and the Committee on the Safety of Medicines (CSMs) also reported 17 cases in UK of which five were fatal. The current British Society for Rheumatology (BSR) guidelines on DMARD therapy [21] published recently are silent on providing clear guidance on the risk of LEIP. In this retrospective case series review, the clinical expression of LEIP is assessed and guidance on the possible risk factors of LEIP is provided.

Patients and methods

Thirty-two reported cases in English literature [12–20] of LEIP (13 males and 19 females) were identified from Pubmed (Medline), Proquest, Canahl and Embase databases using the following keywords and phrases: leflunomide, pneumonitis, leflunomide pneumonitis, interstitial lung disease (ILD), drug-induced pneumonitis, hypersensitivity pneumonitis and delayed hypersensitivity pneumonitis. The origins of cases were as follows: 10 were from Korea, 6 were from Japan, 1 was from UK, 1 from Germany and 14 were from Australia and New Zealand. Patients who had a clinical course suggestive of drug-induced pneumonitis, i.e. an acute respiratory illness following exposure to LEF in the absence of an infective cause, pulmonary interstitial infiltrates on radiological examination and appearances suggestive of hypersensitivity pneumonitis on histological examination (if available) were included in the study and patients who had an identifiable infective cause for their respiratory symptoms were excluded. Patients were classified using Searles and McKendry’s criteria [21]. Eleven patients (34%) were classified as definite, 11 (34%) as probable and 10 (29%) as possible LEIP. Demographic details, previous history of ILD, MTX exposure, treatment regimes and case mortality are shown in Table 1.

Statistical analysis

The results were analysed using chi-squared and Fisher’s exact tests.

Results

All patients had RA. Twenty-six patients (82%) presented with LEIP within the first 20 weeks of initiation of LEF therapy. Thirty-one patients (97%) had a history of MTX exposure. There were 13 patients (41%) on combination therapy (MTX and LEF). Four patients (13%) had loading doses of LEF and they all presented within 12 weeks of exposure to LEF. LEF and MTX were withdrawn in all cases. Steroids were given in 24 (75%) patients, 10 (31%) were treated with antibiotics, 7 (22%) received both steroids and antibiotics and 6 (19%) cases received neither. Patients who received cholestyramine were significantly more likely to have been treated with steroids as well compared with patients who did not receive cholestyramine (P = 0.01). There were six (19%) reported deaths and five of them were on combination therapies: two with MTX and three with oral steroids. Five of the six patients who died had LEIP <20 weeks of LEF exposure.

There were six patients with previous ILD. Two patients had previous MTX-induced pneumonitis (MTX-P) which had resolved prior to the initiation of LEF monotherapy; both presented with LEIP early (<12 weeks of LEF exposure) and both died from LEIP. Half of the patients who died following LEIP had either previous ILD or previous MTX-P. Five of the six patients with previous ILD were on LEF monotherapy. One out of four (25%) patients who had a loading dose of LEF died. There were four patients with other respiratory illnesses such as previous tuberculosis (TB) infection (three patients) and emphysema (one patient);
there were no deaths in this group. Mortality in Japanese and Korean patients was identical to Western patients (19% in both groups).

Twenty-four patients had high-resolution computerised tomography (HRCT) done during the episode of pneumonitis and the main findings are summarized in Table 2. The main findings on HRCT were ground glass shadowing, bilateral reticular/interstitial shadowing and honeycombing. Consolidation was reported in one case. Fourteen patients had ground glass opacities; they presented early (median duration 12 weeks), three (21%) were on combination treatment (LEF and MTX), and five of the six deaths were in this group. Five patients had mainly bilateral reticular/interstitial shadowing; they presented early (median duration 12 weeks) and there were no deaths in this group. Four patients had predominantly honeycombing; all had previous MTX exposure, none was on combination therapy, none had previous history of ILD and most of them presented with LEIP after more than a year (median duration of 74 weeks) of treatment with LEF. Histological examination was performed in six cases (three autopsies, two thoracic routes and one unspecified route). The main histological findings were diffuse alveolar damage (DAD) in three cases and interstitial pneumonia in the rest. All three cases with DAD died.

Discussion

This is the first study to show variations in the clinical expression of LEIP. The question as to whether LEIP is a myth or reality [22] is a foregone conclusion. The temporal relationship between initiation of LEF and onset of pneumonitis makes the diagnosis of LEIP likely. Most of the patients with LEIP had previous MTX exposure which is not surprising because LEF is mostly used as second line therapy to MTX; however, LEIP has been reported in patients without previous MTX exposure [18]. Three of the six patients who died had predominantly DAD on histological examination. Our observations are supported by Sakai et al. [23] who reported similar findings of a high mortality in patients with DAD appearances. Lung biopsies are potentially useful in LEIP in that the finding of DAD (which could be a poor prognostic marker) may lead to aggressive therapy, i.e. high dose steroids and close monitoring, possibly in a high dependency unit in view of a high mortality in this group. However, sampling bias cannot be excluded in that some patients with DAD who did not have lung biopsies done may have survived.

Two patients, who had previous MTX-P which had completely resolved and then started on LEF monotherapy, both had early onset LEIP and both died following LEIP. Saravanan and Kelly [24] in their review article published in this journal in 2006 suggested that it is safe to use LEF in previous MTX-P cases. Although the numbers in this study are small and the conclusion could be better drawn after a case-control study, it appears that previous MTX-P carries a high risk for LEIP (100% mortality in this study) and our advice will be either to avoid or to use LEF with caution in patients with a history of MTX-P. The occurrence of pneumonitis in these two patients with two completely different drugs brings into question whether or not there is a genetic basis for hypersensitivity pneumonitis, i.e. some patients are genetically predisposed to hypersensitivity pneumonitis than others. LEIP is five times more common in Japan and Korea (0.5%) than the West [25]. Japanese and Korean populations who are genetically similar have similar rates of LEIP. This provides indirect evidence of a genetic role in LEF hypersensitivity pneumonitis. Genetic polymorphism associated with MTX metabolism has been shown to influence toxicities of MTX [26, 27], however, there are no studies that have demonstrated such genetic polymorphism in LEIP. Future studies are needed to investigate the genetic basis of hypersensitivity pneumonitis.

Half of the patients with previous ILD died from LEIP and five of the six patients who died had ground glass opacities on HRCT. Pre-existing ILD and ground glass shadowing could be poor prognostic markers. In this study, mortality was not influenced by whether patients received cholestyramine or not. Our findings bring into question whether cholestyramine has an influence in the clinical course of LEIP taking into account the nature of the pathophysiology of LEIP, i.e. an idiosyncratic hypersensitivity reaction. However, a channelling bias cannot be excluded in that those patients who had severe disease were probably more likely to be given cholestyramine compared with those with disease of a lesser severity. Case mortality rate in our case series was 19% and this is similar to MTX-P which is estimated to be between 17 and 30% [28–31]. Savage et al. [13] in their case series from New Zealand and Australia reported a case mortality of 14%.

Combination of LEF and MTX has been found to be effective in treatment of RA. Both drugs can induce pneumonitis either as monotherapy or in combination. LEIP and MTX-P are in most cases indistinguishable. Some of the cases of LEIP could be MTX-P. Currently there are no established clinical features that can help distinguish LEIP from MTX-P. LEIP is only recently described and so far published studies and case reports on LEIP use either Kremer et al.’s [29] or Searles et al.’s [21] diagnostic criteria. Both diagnostic criteria are based on clinical, radiological and histological features which are suggestive of drug-induced hypersensitivity reaction and the requirement to exclude infection is universal. Both criteria would be adaptable to any drug-induced hypersensitivity pneumonitis. This is very much in keeping with the recent British Thoracic Society’s views on diagnosis in ILD being multidisciplinary as it is not possible to make a diagnosis on one feature alone. There are three established diagnostic criteria for MTX-P: Carson et al.’s [32], Kremer et al.’s [33] and Searles et al.’s [34] criteria. As yet none of these diagnostic criteria have ever been validated, primarily because no gold standard investigation exists to validate the diagnostic criteria against. We do not know how well they perform for either MTX-P or LEIP and this is a potential source of weakness of all studies on drug-induced pneumonitis.

We recently published a paper on MTX-P [35], and using our findings we have observed some differences in presentation between MTX-P and LEIP. LEIP symptoms tend to appear acutely (median duration of 3 days and the range was 1–10 days), in contrast to our previous study which showed that MTX-P symptoms appear subacutely (median duration 14 days and range 1–56 days) [35]. MTX-P usually occurs within the first
LEF-induced pneumonitis

In patients with previous ILD, LEF should either be avoided or used with caution. Clinicians need to alert patients to this rare but serious complication of LEF therapy.

Rheumatology key messages

- LEF usually occurs within 20 weeks of exposure to LEF.
- LEF should be either avoided or used with caution in patients with previous MTX-P.
- Either avoid or use LEF with caution in patients with pre-existing ILD.

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References