COMMENTARY

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Leflunomide in Combination Therapy for Rheumatoid Arthritis

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Alcorn et al.[1] have provided a welcome benefit-risk assessment of leflunomide use in the treatment of rheumatoid arthritis based on a review of the literature to 2008. The adverse reaction profile is discussed with specific reference to hepatotoxicity, interstitial lung disease (ILD), infection, peripheral neuropathy, weight loss and hypertension; however, there is more information about leflunomide use in combination therapy that should be considered.

Leflunomide has been widely used in Australia and New Zealand and has been monitored closely by the medicines regulators in each country. As Alcorn et al.[1] stated, there was early concern about leflunomide and hepatotoxicity that almost led to the withdrawal of leflunomide in the US. A regular comprehensive pharmacovigilance review of leflunomide conducted by the New Zealand Pharmacovigilance Centre and the regulator, Medsafe, was undertaken as it was considered a timely and proactive means of evaluating a newly introduced medicine intended for chronic use with an emerging profile of serious adverse reactions. The review, from 2006 to 2008, used national and international spontaneous reporting data, prescription data, literature review and review of international regulatory actions. The material gathered was considered by the New Zealand Medicines Adverse Reactions Committee and contributed to national decision making, information for prescribers and identification of emerging signals.

The adverse reaction profile of leflunomide as monotherapy that became apparent is similar to that found by Alcorn et al;[1] however, as the use of leflunomide in combination with other disease modifying anti-rheumatic drugs (DMARDs) increased, assessment of spontaneous reporting data and the literature provided further insights, particularly with regard to pneumonitis, pancytopenia and infection.

1. Pneumonitis

One of the earliest findings in the New Zealand Pharmacovigilance Centre database was a greater than expected number of reports of pneumonitis, a serious rapidly progressive form of ILD. This disorder can be life-threatening or fatal and is known to occur with methotrexate. Interrogation of the Australian Adverse Drug Reactions Unit (ADRU) database revealed similar reports and a case series from both countries was published.[2] Two index patients fulfilled the Searles and McKendry criteria[3] for hypersensitivity pneumonitis, and there was good evidence in the other reports for this diagnosis. ILD had been estimated to occur in <1 in 10 000 patients in clinical trials and early exposures.[4] Reports from Japan had indicated a much higher risk but it was suggested that there was confounding with co-prescribed medicines and underlying disease.[5,6] Using funding approval data from the national pharmaceutical funding agency (PHARMAC) as the denominator, the reporting rate in New Zealand was estimated to be between 1 in 150 and 1 in 600 users, similar to the estimated incidence in Japan. The reporting rate was lower in

Australia (1 in 1200 users), but in both countries, reporting of pneumonitis suggested an incidence well in excess of that found in clinical trials.[2]

ILD is a recognized complication of rheumatoid arthritis itself, and ILD, including pneumonitis, is a well documented adverse effect of methotrexate. One of the 14 patients in the series of reports from New Zealand and Australia had diagnosed pre-existing lung disease attributed to methotrexate, and 12 patients were concurrently taking methotrexate. It was therefore possible that the patients had developed methotrexate pneumonitis. Importantly, however, in nine patients, pneumonitis developed after leflunomide was added to methotrexate, usually within 12–20 weeks.[2] Five patients had taken methotrexate for more than 1 year. These observations suggest a role for leflunomide in the development of pneumonitis, and that this is more likely to occur in combination with methotrexate.

The study also recorded the seriousness of the reaction. Two patients died, one of whom had a history of methotrexate pneumonitis. Three patients required intensive care and assisted ventilation. Three patients, one of whom required assisted ventilation, improved after treatment with colestyramine to remove leflunomide.[2]

A nested case-control study derived from a large cohort of patients with rheumatoid arthritis in the US PharMetrics claims database[7] assessed the risk of serious ILD with leflunomide use and concluded that serious ILD only developed in patients who had previously been exposed to methotrexate and/or had pre-existing ILD, and that there was evidence that there was preferential channelling of patients with these clinical histories to leflunomide. However, this study did not address concomitant use of leflunomide and methotrexate. It is possible that the combination was unusual in the US.

2. Pancytopenia

In Australia, reports of pancytopenia attributed to leflunomide were first published in 2003 and 2004.[8,9] Subsequently, details of 11 spontaneous reports to the Australian national pharmacovigilance centre were published.[10] As with pneumonitis reports, the majority of patients (9/11) were also taking methotrexate. An important further similarity was that at the onset of pancytopenia, six of these patients had taken leflunomide for a shorter duration than methotrexate, a range of 6–78 weeks of combined therapy compared with a mean of 336 weeks for methotrexate in the five patients for whom specific duration data was supplied. Compared with clinical trials of leflunomide monotherapy where the incidence of pancytopenia was estimated to be <1 in 10 000 users, the reporting rate in Australia was estimated, using prescription data as the denominator, to be between 1 in 3698 and 1 in 4582 for leflunomide monotherapy and between 1 in 575 and 1 in 822 for combined leflunomide and methotrexate.[10]

3. Leflunomide and Methotrexate Combination Therapy

The concomitant use of methotrexate in reports of pneumonitis and pancytopenia raised the question of whether this reflected the general prescribing pattern for leflunomide. However, in the New Zealand and Australian databases, only 38% and 32.5% of patients, respectively, in reports of all types of adverse reactions to leflunomide were also taking methotrexate.[2,10] Two estimates based on analyses of national prescribing data suggested that approximately one-third of Australian patients who had prescriptions dispensed for leflunomide also had prescriptions dispensed concurrently for methotrexate.[10] Separate data from a survey of Australian rheumatologists suggested that 55% of their patients taking leflunomide were also taking methotrexate.[10] This compares with 86% of patients with pneumonitis and 82% of patients with pancytopenia in the two published case series.[2,10]

The comparative durations of use of methotrexate and leflunomide recorded in some reports of pneumonitis and pancytopenia suggest a causal role for the combination of leflunomide and methotrexate. These observations have led to a search of the literature for a possible interaction between these medicines. The first published study of combined leflunomide and methotrexate

treatment for rheumatoid arthritis included a pharmacokinetic study in a subset of 12 patients.[11] No difference in the pharmacokinetic parameters of methotrexate was found over a period of 24 weeks after leflunomide was added to stable weekly methotrexate treatment; however, patients took the lowest recommended daily dose of leflunomide (10 mg) for the first 12 weeks and it was not stated how many, if any, increased to 20 mg daily after 12 weeks, as was permitted in the study protocol. Thus, it is not known if there is a pharmacokinetic interaction at the standard daily leflunomide dose of 20 mg.

In 2004, Breedveld et al.[12] referred to a number of publications providing evidence that methotrexate is transported by the efflux transporter breast cancer resistance protein (BCRP, also known as ABCG2). This group provided further evidence by investigating the reason for increased methotrexate toxicity with benzimidazoles. Methotrexate clearance was significantly reduced in BRCP knockout mice and in wild-type mice pre-treated with pantoprazole. Further *in vitro* analysis confirmed that pantoprazole reduced methotrexate clearance by predominantly inhibiting the hepatobiliary excretion of methotrexate by BCRP.[12] In vesicular and cellular transport assays published in 2009,[13] leflunomide and its active metabolite A771726 inhibited BCRP-mediated cellular efflux of methotrexate. These observations support the possibility that leflunomide may increase methotrexate concentrations, and thus toxicity, in susceptible patients.

4. Infection

Alcorn et al.[1] quoted the New Zealand study describing a rheumatology department audit of infection associated with leflunomide coupled with national spontaneous reports.[14] The rate of serious infection in the audited patients was 3.3/100 patient-years. There were no data to compare this rate with other DMARDs; however, an important observation was that 15 of the total 18 patients presented in the study were also taking corticosteroids and the majority of these were also taking at least one other DMARD. Infections were sometimes profound and included sepsis, mycotic aneurysm and disseminated herpes zoster.

5. Discussion

Combination DMARD therapy in the treatment of rheumatoid arthritis has been found to be more effective than monotherapy in a number of studies and this is now the accepted approach to treating serious forms of this disorder. Nevertheless, pre-approval clinical trials of leflunomide were of monotherapy. McEwen et al.[10] pointed out that at the time of approval of leflunomide by the European Medicines Agency the combination of leflunomide and methotrexate had only been trialled in 30 patients[11] and a recommendation was made that the combination of leflunomide with another DMARD (e.g. methotrexate), particularly in long-term treatment, was not advisable because of the lack of information about associated risk.[15] One further published, randomized, placebo-controlled, double-blind study of 263 patients showed the effectiveness of the leflunomide/methotrexate combination in patients who were not responding to methotrexate monotherapy.[16]

It might be argued that patients with rheumatoid arthritis severe enough to meet funding criteria for leflunomide in New Zealand and Australia, particularly when it was first marketed in these countries, were already at increased risk of infection and ILD, and for this reason the evidence of a causal association with leflunomide is not conclusive; however, the published observations point to a temporal relationship for the emergence of pancytopenia and pneumonitis after leflunomide was added to methotrexate. The observations also serve to emphasize the importance of close monitoring of patients taking combined leflunomide and methotrexate therapy, especially for lung function, blood dyscrasias and the hepatic effects described elsewhere,[2,10,11] and of informing patients of warning symptoms. This is especially so as the prompt use of colestyramine to remove leflunomide may avert life-threatening illness or persisting disability. The very high proportion of patients with serious infection also taking corticosteroids indicates the importance of

decreasing the corticosteroid dose as far as possible as the DMARDs become effective, and reviewing the need for each of these medicines.

The adverse reaction experience reported as use of the combination increased in Australia and New Zealand should be considered when assessing the risks and benefits of leflunomide.

The observations described also demonstrate the importance of timely pharmacovigilance review as the pattern of use of a medicine changes. In this context, as well as signalling previously unrecognized adverse reactions, well documented spontaneous reports, together with usage data, can provide valuable supplementary information about a suspected reaction when there are only a small number of published case reports or limited clinical trial data.

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