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Leflunomide for the Treatment of Rheumatoid Arthritis in Clinical Practice

Incidence and Severity of Hepatotoxicity

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Abstract

Objective: Leflunomide is a novel disease modifying antirheumatic drug (DMARD). Because of reports on possible hepatotoxicity and adaptations in the recommendations for monitoring liver function during leflunomide treatment, we conducted a study to evaluate the incidence and severity of hepatotoxicity.

Methods: We included consecutive rheumatoid arthritis patients starting treatment with leflunomide in the region of Friesland (The Netherlands) between January 2000 and January 2002. During follow-up patient characteristics, disease characteristics, and clinical and laboratory data on liver functions were registered. Severity of hepatotoxicity was categorised using the National Cancer Institute Common Toxicity Criteria, as moderate (grade 2), severe (grade 3) or life threatening (grade 4).

Results: One hundred and one patients were followed for a median period of 10 months (range 0.5–12). Grade 2 or 3 elevations in any liver function blood test were recorded in a total of nine patients (8.9%). No grade 4 elevations were recorded. Four patients (4%) showed grade 2–3 aminotransferase elevations. Due to grade 2 hepatotoxicity one patient (1%) was withdrawn from leflunomide treatment, and one patient continued leflunomide at a reduced dose. In eight of nine patients with grade 2–3 liver function blood tests, these elevated liver function tests occurred within 6 months after starting leflunomide. None of the patients with grade 2 or 3 toxicity had a history of hepatic disease, eight patients concomitantly used potential hepatotoxic co-medication. Eight (8%) patients used leflunomide in combination with methotrexate, and one of these patients devel-

oped hepatotoxicity. No clinical signs of serious hepatotoxicity were recorded during follow-up.

Discussion: In 8.9% of the patients, grade 2 or 3 hepatotoxicity was recorded within the first year after the start of leflunomide therapy based on liver enzyme determinations. In the majority of the patients liver enzyme elevations occurred within the first 6 months of therapy and resolved during continued follow-up. None of the patients showed clinical signs of hepatotoxicity.

Conclusion: Under continued monitoring of liver functions hepatotoxicity during leflunomide use does not seem to be a major problem in our population.

Introduction

Leflunomide is an isoxazole-derived disease modifying antirheumatic drug (DMARD). Leflunomide is a prodrug that is converted in the gastrointestinal tract and plasma to its active metabolite A77 1726. The primary mechanism of action of A77 1726 is inhibition of the enzyme dihydroorotate dehydrogenase, a key enzyme in *de novo* pyrimidine synthesis. Activated T lymphocytes, which are believed to play a central role in the pathogenesis of rheumatoid arthritis (RA), depend on *de novo* pyrimidine synthesis for proliferation. Both the efficacy and safety of leflunomide have been demonstrated in several studies.[1-3]

Elevated liver function tests during treatment with leflunomide in patients with RA have been reported in randomised controlled trials studying leflunomide monotherapy in comparison with methotrexate or sulfasalazine.[1-3] After registration of leflunomide, the European Agency for the Evaluation of Medicinal Products (EMEA) in 2001 published a Public Assessment on rare, serious cases of hepatotoxicity during use of leflunomide. Reasons for the publication of this Public Assessment were 15 cases with fatal outcome and reported liver failure, liver toxicity, hepatitis, cholestatic jaundice or increased liver function tests over more than 100 000 patient-years of leflunomide exposure. In 10 of the 15 cases an hepatic event was not the immediate cause of death. The reported cases were complicated by associated factors possibly leading to poor outcome, such as pre-existing liver disease, pre-existing/concurrent illness or comorbidity (heart failure, infection/sepsis, pulmonary failure, pancreatitis) and other possibly hepatotoxic co-medication.

The discussion on potential hepatotoxicity of leflunomide led to adaptations in the Summary of Product Characteristics and the package leaflet stressing the importance of monitoring of liver functions. The current recommendations are that alanine aminotransferase (ALT) must be checked before initiation and for at least at monthly intervals during the first 6 months of treatment and every 8 weeks thereafter. For ALT elevations between 2- and 3-fold the upper limit of normal (ULN) values (as defined by the local laboratory), dose reductions from 20mg to 10mg may be considered and monitoring must be performed weekly. If ALT elevations $>2 \times$ ULN persist or if ALT of $>3 \times$ ULN are present, leflunomide must be discontinued and washout initiated.

Observational cohort studies performed after registration of a novel medication regimen can help to establish the efficacy and safety of leflunomide in a setting similar to daily clinical practice. Therefore, to gain insight in the timing, frequency and severity of elevated liver enzymes or clinical hepatotoxicity and to aid in clinical decision-making, we conducted a study on the incidence and severity of hepatotoxicity during leflunomide treatment in a cohort of RA patients in a setting of 'care-as-usual'.

Methods

Patients and Inclusion Criteria

All consecutive RA patients who were prescribed leflunomide *de novo* by their rheumatologist in the outpatient departments of rheumatology in Friesland (in the northern part of The Netherlands, covering approximately 600 000 inhabitants in four hospitals) from January 2000 to January 2002 were included. The human research committee approved the study, and written informed consent was received from all subjects in the study. Patients were followed for a period of 12 months from the start of leflunomide therapy, baring withdrawal or death. The standard data set consisted of patient characteristics, disease characteristics, parameters of disease activity (DAS_{28}),[4] and laboratory data on liver function.

Intensity of follow-up of the patients during this study was not different from non-study patients in our outpatient departments of rheumatology, reflecting 'care-as-usual'. Patients visited the rheumatologist every 4–8 weeks for the first 6 months after initiation of leflunomide therapy. Depending on the judgement of the rheumatologist the frequency of visits after 6 months was reduced to at least every 6 months. With laboratory controls, including hepatic enzyme determination, every 8 weeks.

During visits, a routine interview and physical examination including collection of DAS_{28} parameters took place. In the case of problems the outpatient department of rheumatology could be reached by telephone. Every telephone contact was registered in the outpatient medical records.

During follow-up visits patients were asked about any adverse events. When an adverse event or an abnormal biochemical parameter was encountered and judged by the rheumatologist or patient as possibly related to leflunomide use, then the adverse event was recorded in the study database. All liver enzyme determinations and elevations were included in the analysis regardless of causality.

Medication

Leflunomide was prescribed by the participating rheumatologists on the basis of good clinical practice for their individual patients in a dosage as recommended by the manufacturer: starting with a loading dose of 100mg daily for 3 days, followed by 20mg daily.

Clinical and Outcome Measures

Clinical data on hepatotoxicity (hepatitis, jaundice, (pre)coma hepaticum) were collected from outpatient and hospital medical records. Since the reports on hepatotoxicity of leflunomide involved both hepatocellular injury and cholestatic adverse events, laboratory data on the enzyme activities of ALT, aspartate aminotransferase (AST) as well as alkaline phosphatase (AP), γ-glutamyl transpeptidase (γ-GT) and total bilirubin (TB) were collected. With respect to the moment of occurrence of the hepatotoxicity event, four time frames were defined, based on the start of leflunomide treatment:

- period I consisted of the time from 6 months prior to the start of leflunomide until the start of leflunomide (for this period data were collected by retrospective chart review);
- period II consisted of the time period during leflunomide treatment from 1 week to 1 month;
- period III consisted of the time period during leflunomide treatment from 1–6 months;
- period IV consisted of the time period during leflunomide treatment from 6–12 months.

In the case of more than one known laboratory value for one parameter in a specific period the value most deviating from the ULN was recorded in the database. Laboratory values on liver enzyme activities were categorised according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [see table I]. Primary outcome measures, with general NCI-CTC definitions, were grade 2 (moderate adverse event), grade 3 (severe and undesirable adverse event) or grade 4 (life-threatening or disabling adverse event) toxicity according to NCI-

Table I. National Cancer Institute Common Toxicity Criteria (NCI-CTC) toxicity categories for liver enzyme elevations

	Toxicity grade (NCI-CTC)				
	0	1	2	3	4
Description[a]	WNL	≤2.5 × ULN	>2.5–≤5 × ULN	>5–≤20 × ULN	>20 × ULN
Description for TB	WNL		<1.5 × ULN	≥1.5–<3 × ULN	≥ 3 × ULN
Clinical relevance of hepatotoxicity	None	Mild	Moderate	Severe	Life-threatening/ disabling

a Description of NCI-CTC categories for ALT, AST, AP and γ-GT.

ALT = alanine aminotransferase; **AP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **TB** = total bilirubin; **ULN** = upper limit of normal value; **WNL** = within normal limit; **γ-GT** = γ-glutamyl transpeptidase.

CTC. The ULN of a given liver enzyme activity is defined as the mean of the distribution + 2 standard deviations (SD) of a presumably representative healthy population. It has to be taken into account that, by definition, 2.5% of healthy individuals will have an abnormal elevation of a given liver chemistry test.[5] For this reason, and the minor clinical relevance of grade 1 enzyme activity elevations (NCI-CTC description: mild adverse event), we scored only grade 2, 3 or 4 liver enzyme elevations.

For patients with grade 2–4 elevations of liver enzyme activities in any time period during leflunomide treatment (II-IV) the medical records were screened for pre-existent hepatic disease, or potential hepatotoxic co-medication. Co-medication was regarded as potentially hepatotoxic when liver toxicity was mentioned in *Meyler's Side Effects of Drugs*.[6] Alcohol intake was not recorded during the study.

Table II. Patient characteristics

Demographic characteristics	
No. of patients	101
Age (y)	
mean (SD)	65.1 (12.9)
range	27–89
Female (%)	65
Rheumatoid factor positive (%)	77
Duration of RA (y)	
mean (SD)	10.3 (11.9)
range	0.1–60
Clinical characteristics	
Previous DMARD treatment (%)	82
Number of previous DMARDs	
mean ± SD	1.7 (1.4)
range	0–6
Concomitant systemic corticosteroids (no. [%])	
none	55 (54)
<7.5mg prednisone equivalents daily	29 (29)
≥7.5mg prednisone equivalents daily	17 (17)

DMARD = disease-modifying antirheumatic drug; **SD** = standard deviation.

As AP and γ-GT may behave as acute phase proteins and therefore may result from an active inflammatory process, the correlation between DAS_{28} and AP or γ-GT activities was calculated.

Statistical Analyses

Access database software (Microsoft Corp.) was used for data collection and selection. SPSS 10.0 for Windows was used for the descriptive statistics.

Results

During the study period, clinical and laboratory data on hepatotoxicity are recorded for 101 patients who began leflunomide therapy with a median follow-up of 10 (range 0.5–12) months (see table II). Due to the variable follow-up (i.e. not all patients had liver enzyme levels determined in all periods) and withdrawal of leflunomide during treatment for some subjects, the number of patients for whom liver function blood tests could be evaluated for periods I, II, III and IV were 101, 68, 81 and 55, respectively.

Of the 101 patients enrolled over the 2 years of the study, a total of 38 patients (38%) withdrew from leflunomide treatment. Reasons for withdrawal were given as: adverse drug reactions (n = 23; 23%; 22 of these withdrawals were due to non-

hepatic events and one due to grade 2 elevations of liver enzymes), inefficacy (n = 5; 5%), a combination of inadequate efficacy and adverse drug reactions (n = 7; 7%) or other reasons (n = 3; 3%).

In total, 997 liver function blood tests were recorded during the 2-year study period, with 316, 190, 290 and 201 test results in periods I, II, III and IV, respectively. Throughout the 2-year study period no clinical signs of severe hepatotoxicity were registered.

During period I, before start of leflunomide treatment, no patients had grade 2 or 3 ALT or AST level elevations and three patients had grade 2 or 3 AP and/or γ-GT level elevations. None of these latter patients showed further elevation in AP or γ-GT-levels during follow-up.

In total, during follow-up nine patients (8.9%; 95% CI 3.2, 14.6) showed grade 2–3 elevations in liver enzyme activities (see table III). Of these, the maximal deviations from ULN seen were grade 3 elevations for three patients and grade 2 elevations for six patients. None of the patients with grade 3 elevations withdrew from leflunomide therapy because of hepatotoxicity. One of these patients showed spontaneous regression of ALT elevations in period III (grade 2) and period IV (grade 1); for two patients with grade 3 γ-GT elevations, these elevations were present throughout complete follow-up. Abdominal ultrasound scans were performed for two of the three patients with grade 3 elevations, showing no evidence for pathology. No liver biopsies were performed for any of the patients with grade 3 elevations. No grade 4 toxicity was recorded.

Concerning the potential risk factors accounted for, none of these patients with grade 2 or 3 elevations had a history of hepatic disease or excessive alcohol consumption. Eight of the nine patients with grade 2–3 elevations of liver enzyme activities have been treated with other potentially hepatotoxic comedication concomitantly (six with diclofenac, one with methotrexate and one with flucloxacillin).

During the 2-year study period, eight (8%) patients used leflunomide in combination with methotrexate. One of these patients developed grade 2 liver enzyme elevations (AP and γ-GT) during combination therapy, which reverted to normal values under continued combination treatment without dose reduction.

Table III. Characteristics of patients with grade 2 or 3 liver enzyme elevations

Patient	Follow-up duration (mo)	Liver enzyme determinations					Remark
		total[a]	abnormal[b]	enzyme	highest NCI-CTC category	period	
1	12	7	1	γ-GT	3	IV	
2	12	12	6	AP (3×) γ-GT (3×)	3	II	
3	12	16	2	ALT (2×)	3	III	
4	3	6	1	γ-GT	2	II	Death, unrelated to treatment
5	12	10	2	ALT/AST	2	III	
6	12	6	1	γ-GT	2	III	
7	12	10	2	ALT/AP	2	III	
8	3	9	1	ALT	2	III	Withdrawn; hepatotoxicity
9	2	7	1	AP	2	II	Withdrawn; mouth ulcerations

a Total number of liver enzyme determinations.

b Total number of grade 2 or 3 elevations for each patient.

ALT = alanine aminotransferase; **AP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **NCI-CTC** = National Cancer Institute Common Toxicity Criteria; **γ-GT** = γ-glutamyl transpeptidase.

For two patients (2%) the prescription of leflunomide was altered. For one patient the daily leflunomide dose was reduced from 20mg to 10mg in period III, due to grade 1 level elevations of ALT and AST. Transferase activities normalised after dose reduction, but leflunomide was withdrawn due to insufficient efficacy after 8 months on therapy. For the other patient leflunomide was withdrawn on the basis of grade 2 ALT elevations in period III.

Neither AP nor γ-GT values correlated with DAS_{28} scores, showing correlation coefficients of 0.002 and 0.06, respectively.

Discussion

In previous, large, randomised controlled trials of leflunomide abnormal plasma liver enzyme levels have been recorded for patients treated with leflunomide. Emery et al.[1] reported abnormal plasma liver enzyme levels in 5.4% of patients in their study during the first year of treatment. Strand et al.[2] reported aminotransferase level elevations for 14.8% of patients taking leflunomide, all of which were reversible under continued treatment or after treatment withdrawal. The current surveillance of RA patients taking leflunomide in The Netherlands gives a valuable estimate of the incidence of hepatotoxicity under conditions of 'care-as-usual' and strict monitoring of liver function tests. In our population the occurrence of grade 2–3 liver enzyme elevations is 8.9%. The incidence of grade 2–3 aminotransferase level elevations during leflunomide treatment is 4%. The grade 2–3 elevations of liver enzyme function activities that are recorded in our study, regress to normal during ongoing leflunomide treatment for all except one patient.

Some remarks on the present study have to be made. First, the absence of clinical signs of severe hepatotoxicity and/or grade 4 liver enzyme elevations in our study does not mean that these events cannot occur. Based on our population size the upper limit of the 95% CI of the probability of these events occurring is 2.95%.

Second, the present data do not allow comparison with hepatotoxicity during treatment with DMARDs other than leflunomide. In the setting of 'care-as-usual', this comparison cannot be made since the place of leflunomide in the treatment strategy of RA is different from the place of alternative DMARDs, such as methotrexate or sulfasalazine. This results in treatment of populations with different characteristics and potential confounding of treatment safety results. Despite this consideration, the results of the study by Cannon et al.[7] do not show evidence of an increased risk of hepatotoxicity for patients receiving leflunomide compared with other DMARDs. The study by Wolfe[8] however, although not statistically significant, suggests that the rates of hepatic adverse events attributed to leflunomide and methotrexate were higher than those attributed to other DMARDs. Randomised, controlled trials offer direct comparison of hepatic safety of leflunomide versus other DMARDs in populations with comparable characteristics. Abnormal plasma liver enzyme levels during 12 months follow-up were reported for 5.4% and 16.3% of patients receiving leflunomide and methotrexate, respectively, in a randomised trial of these two agents in patients with RA.[1] In another randomised trial, aminotransferase level elevations are reported in 14.8% and 11.5% of patients treated with leflunomide and methotrexate, respectively, during 12 months of follow-up.[2] In their recently published systematic review of controlled clinical trials Osiri et al.[9] concluded that elevated liver function tests were not significantly different for the leflunomide-treated patients than for those treated with methotrexate or sulfasalazine.

Third, the duration of follow-up in our study, similar to the randomised controlled trials,[1-3] is restricted to a maximum of 12 months. A part of the population could not be followed up to this point. Thirty-eight percent of the patients withdrew from leflunomide therapy before 12 months for reasons other than hepatotoxicity, and liver function tests were not available for the complete 12-month period for all patients. Early withdrawal and incomplete-

ness of follow-up leads to 55 of 101 patients for which data on liver enzymes were available after 6 months of follow-up. Furthermore, hepatotoxicity occurring after a period of 12 months was not recorded in the present study. Eight of the nine patients with grade 2–3 liver enzyme elevations in the present study experienced liver enzyme elevations within 6 months after start of leflunomide treatment. In three randomised, controlled trials,[1-3] ALT elevations >3 × ULN occurred within 9 months after the start of leflunomide treatment in 18 of 23 patients (78%). Two-year follow-up data from these trial populations show no late toxicity or unexpected adverse events after longer duration of leflunomide treatment.[10,11] This suggests that the potential underestimation of liver enzyme activity elevations due to too short follow-up will be minimal.

Fourth, in eight of the nine patients with liver enzyme elevations potentially hepatotoxic co-medication is used. Hepatotoxicity due to these co-medications or due to a combination of these co-medications with leflunomide cannot be excluded.

Lastly, only 8% of the study patients used leflunomide in combination with methotrexate. Therefore, results of this study are not applicable for extrapolation to populations using leflunomide in combination therapy. Several studies report on the incidence of elevated liver enzyme activities in patients treated with leflunomide alone or in combination with methotrexate.[12-14] Kremer et al. conclude that combination treatment of leflunomide and methotrexate can be used safely with appropriate monitoring of liver enzyme activity.[13] The combination of disease modifying anti-rheumatic drugs in the treatment of RA may become more important, but information on the place of combination therapy in the treatment paradigm and the preferred combinations still is scarce.[15] Leflunomide monotherapy in RA will therefore remain an important treatment option, leaving the need for extensive data on safety and efficacy from studies in settings of 'care-as-usual'.

Conclusion

This study presents a critical evaluation and risk assessment on the incidence of hepatotoxicity during leflunomide use in an outpatient setting of 'care-as-usual'. Hepatotoxicity during leflunomide treatment does not seem to present a major problem, under conditions of strict monitoring of liver function.

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