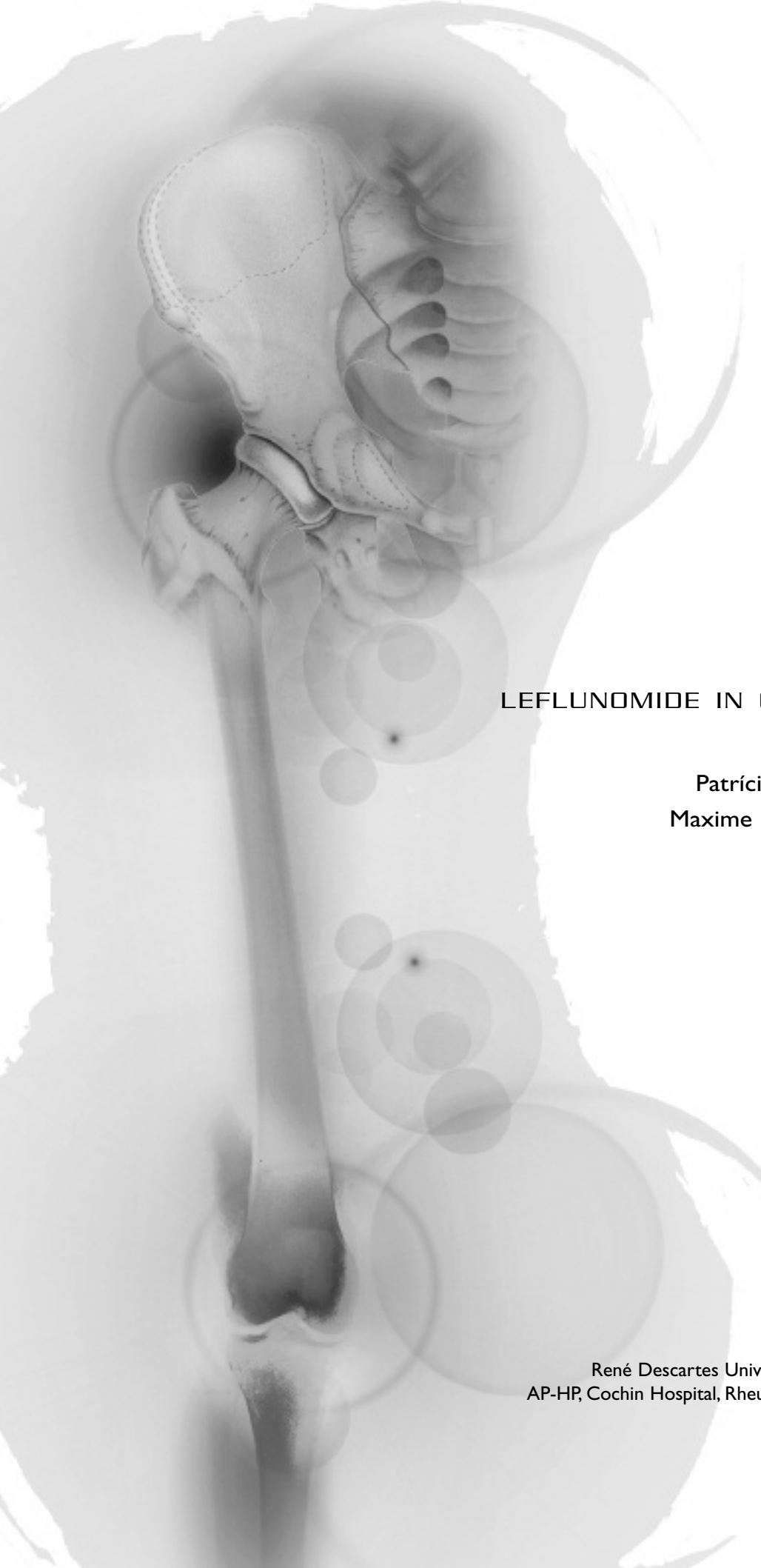

LEFLUNOMIDE IN CLINICAL PRACTICE

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ABSTRACT

Leflunomide (LEF) is a prodrug that is rapidly converted to its active metabolite A77 1726, that inhibits *the novo* pyrimidine nucleotide biosynthesis, mediated especially by the dihydroorotate dehidrogenase (DHODH).
DMARD properties were documented in rheumatoid arthritis with efficacy, safety and limiting of radiological progression demonstrated in multiple studies.
LEF has been also used in other autoimmune diseases, like Psoriatic Arthritis, Wegener granulomatosis, Systemic Lupus Erythematosus, Sarcoidosis and others.
This article reviews the place of LEF in clinical practice and outlines its potential applications beyond the officially recognized indication: rheumatoid arthritis (RA)

Keywords: Leflunomide; Clinical trials; Rheumatic diseases

RESUMO

A Leflunomida (LEF) é uma pró-droga que é rapidamente convertida no seu metabolito activo, o A77 1726, que inibe a síntese de novo dos nucleotidos de pirimidina. Esta acção é mediada fundamentalmente pela enzima dihidroorotato desidrogenase.

As suas propriedades de fármaco modificador de doença foram comprovadas na Artrite Reumatóide, nomeadamente a sua eficácia, segurança e limitação da progressão radiológica.

A LEF foi também utilizada em outras patologias autoimunes como a Artrite Psoriática, a Granulomatose de Wegener, o Lúpus Eritematoso Sistémico, a Sarcoidose e outras.

Neste artigo os autores reviram o papel da LEF na prática clínica e salientam as possíveis utilizações, assim como o seu papel na indicação oficialmente reconhecida: Artrite Reumatóide.

Palavras-Chave: Leflunomida; Ensaios clínicos; Doenças reumáticas

LEFLUNOMIDE IN CLINICAL PRACTICE

Patrícia Pinto, Maxime Dougados*

Introduction

Leflunomide (N- (4-trifluoromethylphenyl) – 5 – methylisoxazol - 4 – carboxamide) is a selective inhibitor of *de nov*o pyrimidine nucleotide biosynthesis by blocking the rate limiting enzyme dihydroorotate dehidrogenase (DHODH), thereby preventing DNA synthesis. T cells preferentially use this enzyme in pyrimidine synthesis.[1]

It is a prodrug that is metabolized in the gut wall and liver to the active metabolite A77 1726.[1]

Leflunomide (LEF) was reported to inhibit the production of tumour necrosis factor, interleukin 1, reactive oxygen radicals and matrix metalloproteinase 3 (MMP-3) by human synovial cells, in vivo and vitro.[2,3]

This article reviews the place of LEF in clinical practice and outlines its potential applications beyond its officially recognized indication: rheumatoid arthritis.

Leflunomide in Rheumatoid Arthritis (RA)

In Rheumatoid Arthritis LEF has been shown to fulfil the Outcome Measures in Arthritis Clinical Trials (OMERACT) definition of a disease modifying anti-rheumatic drug (DMARD): reducing the signs and symptoms of active inflammation; inhibiting structural damage; and improving physical function. It has been shown to improve functional ability as early as 4 weeks after the start of treatment, with a sustained long term efficacy for up to 40 weeks. It has proved to be effective in early and late disease, regardless of whether patients have received other disease modifying anti rheumatic drugs (DMARD) previously.[4-16]

Leflunomide in Monotherapy

Leflunomide *versus* placebo

The randomized clinical trial (RCT), by Mladenovic *et al*, comparing three different doses of LEF with placebo at 24 weeks showed that patients in the LEF group were two times more likely to reach ACR20 criteria at 6 months than patients in the placebo group (60% of LEF patients versus 27% of placebo patients) and at 12 months (53% versus 26%). Similarly, an ACR50 was seen in 29% and 34% of LEF patients, and 11% and 8% of placebo- treated patients at the same time points.[4]

Kalden *et al*, reported that LEF-treated patients showed a significant improvement in disability, assessed by the mean Health Assessment Questionnaire (HAQ) score which decreased at 12 months by 0.37 compared with an increase of the placebo HAQ scores of 0.06.[7]

LEF significantly delayed radiographic changes of hand joints as measured by Sharp /van der Heijde modified score (1.9units/year *versus* 7.5units/ /year), as well as improved functional ability and health status[15].

Leflunomide *versus* sulphasalazine

In a study performed by Smolen *et al*, 358 patients were randomly assigned to LEF (100 mg daily on days 1-3, then 20 mg daily), placebo or sulphasalazine (SLZ, 0.5 g daily, titrated progressively to 2.0 g daily at week 4). There were no statistically significant differences between LEF and SLZ in most of the clinical outcomes: tender and swollen joints, investigator and patient overall assessments.[11,12] However, LEF did better than SLZ in the ACR20 response rate, at 24 months (48% vs 44%).[6]

There was a significant difference between the LEF and SLZ groups regarding CRP (51% versus 32% reduction), while the improvement in ESR was significantly better in SSZ-treated group than in the LEF group (33% reduction versus 13%).

Improvement in functional ability as assessed by changes in the Health Assessment Questionnaire (HAQ) scores was observed in both groups at 6, 12 and 24 months, with a greater reduction in the LEF group (44%, 50% and 59%) than in the SSZ group (30%, 45% and 39%).[7]

The radiographic effect of LEF administration

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was not statistically significantly different from that of SSZ administration at 6 months and 12 months.[12]

Leflunomide *versus* methotrexate

The efficacy and safety of LEF treatment compared with methotrexate (MTX) treatment was assessed in three major RCT.[8,9,10]

The Strand *et al* 52 weeks trial, with 482 patients, showed that the ACR 20 rates in the LEF and MTX treatment groups were statistically equivalent (41% *vs.* 35%).[9] However, MTX treatment resulted in significantly more improvement in the four primary clinical efficacy end-points (tender and swollen joints, physician and patient global assessment) than LEF in the first year of treatment, although this distinction was not significant after 2 years of treatment.[10] These differences in outcome were not observed in the trial conducted by Emery *et al*.[8] This discrepancy of results could be explained by differences in the recruitment of patients and by the use of folate supplement. Patients in the Stand *et al* trial had longer disease duration than those in the Emery *et al* trial (mean disease duration of 6.5-7.0 vs 3.7-3.8, respectively). Secondly, the use of folate supplementation was mandatory in the Strand *et al* trial but was taken by less than 10% of the subjects in the Emery *et al* trial. Folate supplement may decrease the efficacy as well the toxicity of MTX.[5,13]

It was reported that the time to reach ACR20 response was shorter in patients receiving LEF than in MTX-treated patients (74±80 days *versus* 101±92, $p<0.05$).[8,9,10]

In the above described RCT patients in both treatment groups showed little or no progression of radiographic damage. Neither erosion or joint space narrowing scores were significantly different[12,13].

In another study, in which a subset of patients

Table I. Studies of leflunomide efficacy in RA treatment

Study	Year	nº of subjects	Type	Interventions	Duration	Outcome measures
Mladenovic	1995	206	Double blind RCT	LEF 100 mg/day for 1 day then 25 mg/day; placebo	24 week	ACR20 Paulus criteria Adverse events
Smolen	1999	357	Double blind RCT	LEF 100 mg/day for 3 days then 20mg/day; SSZ 2g/day placebo	24 weeks	ACR20, ACR50, Paulus criteria, X-ray, adverse events
Scott (year 2 extension of Smolen study	2001	197 (6-12mo) 146 (12-24mo)	Double blind RCT	LEF 20 mg/day; SSZ 2g/day	18 months	ACR20, ACR50, ACR 70, X-ray, function, adverse events
Strand	1999	482	Double blind RCT	LEF 100 mg/day for 1 day then 20 mg/day; MTX 7.5-15mg/wk Placebo	12 months	ACR20, ACR50, ACR70, X-ray
Emery	2000	999	Double blind RCT	LEF 100 mg/day for 1 day then 20 mg/day; MTX 7.5-15mg/wk	12 months	ACR20 and Paulus criteria, X-ray adverse events
Cohen (year 2 extension of Strand study)	2001	199	Double blind RCT	LEF 10-20 mg/day; MTX 15-20mg/wk with folate	12 months	ACR20, ACR50, ACR70, X-ray, function and HRQOL, adverse events
Sharp	2000	Smolen Strand e Emery studies	Combined analysis progression	Evaluation of radiographic		radiographs of the hands and feet of 3 RCT

initially treated with LEF or MTX for 12 weeks, were submitted to dynamic gadolinium-enhanced magnetic resonance imaging (DEMRI) with a comparison at baseline and at 16 weeks, it was reported that despite indistinguishable in terms of ACR response, the initial rate of synovial and maximal signal intensity enhancement showed significant improvement in LEF-treated patients and a slight deterioration in the MTX group.[15]

Leflunomide in Combination Therapy

Incomplete response to DMARD monotherapy in RA is frequently observed. Antirheumatic drugs used in combination therapy should have complementary biological effects, non-additive toxicity, an acceptable dosing schedule, a rapid onset of action and should be cost-effective.[16]

According to the opinion of an International Rheumatology Expert Panel *(Kalden J, Smolen J, Emery P, Riel P, Dougados M, Strand C and Breedveld F)* who met in Paris in May 2003 LEF can be used in combination therapy: 61% of the Expert Panel would use LEF with MTX, 71% with SLZ, 43% with infliximab, 33% with adalimumab, 19% with etanercept and 38% with anakinra.[16]

Most studies of LEF in combination with DMARDs therapy and biological agents have been conducted in patients who have failed treatment with MTX.

Combination with non steroidal anti-inflammatory drugs

The active metabolite of leflunomide inhibits P450 cytochrome which is necessary for non steroidal ant inflammatory drugs (NSAID) metabolism, however published clinical trials suggest that NSAID can be safely used with LEF. There are no clinical studies that specifically assessed the combination of COX-2 selective NSAID and LEF.

Combination with methotrexate

This combination is based in their complementary mechanisms of action: inhibition of pyrimidine and purine biosynthesis respectively.

In the one-year open-label pilot study that was conducted in 30 patients with active RA despite at least 6 months of MTX, LEF was added with a loading dose of 100 mg for two days and a maintenance dose of 10 mg/day that was increased if necessary to 20 mg/day. An ACR 20 response at year one was achieved in 53% of the patients and 3 withdrew due to adverse events.[17]

In a 24 week, double-blind RCT, LEF was added to patients with active disease despite MTX treatment (at least 15 mg/day or 10-15 mg/week if this was the maximum tolerated dose). Patients continued MTX and were randomized to either LEF 10 mg/day increased to 20 mg/day at week 8 if necessary (130 patients) or matching placebo (133 patients). At week 24 a better efficacy was shown for LEF plus MTX combination versus LEF plus placebo (ACR20 response at endpoint achieved by 46% of the LEF treated patients versus 19.5% in the placebo group).[18]

Patients already receiving this combination continued therapy and those in the MTX plus placebo group were switched to MTX plus LEF for a further 24 weeks of open-label therapy. The benefits were documented by significant improvements in ACR20, ACR50 and ACR70 response rates (Table II).[19]

Improvement in physical function in the LEF group showed a mean HAQ-DI change of -0.52 at week 24 that was maintained at week 48 (-0.54). In patients that switched from placebo to LEF there was a further improvement (-0.15 *vs.* -0.33).[19]

The frequency of adverse effects after adding LEF were similar to those reported in the LEF monotherapy studies. Elevated liver enzymes, diarrhoea and nausea were less frequent after adding leflunomide without a loading dose than after adding leflunomide with a loading dose.[19]

Elevated liver enzymes that occurred in patients with combination therapy normalized after reduction or discontinuation of LEF.[19]

The use of a loading dose (100 mg during the first 3 days of therapy) may be associated with more frequent side effects.[16]

Combination with sulphasalazine

SLZ combined with LEF versus SLZ treatment was essayed in the second double-blind phase of the RELIEF study (***R**heumatoid **A**rthritis **E**valuation of **L**eflunomide: Further insights into the **Eff**icacy)*. This 48 weeks study had two phases:

The first phase evaluated the efficacy and safety of LEF in a 24-week open-label cohort.[20]

In the second phase of the study, patients who were good or moderate responders to LEF treatment continued LEF for an additional 24-week period in a second open-label phase. Patients who did not adequately respond to LEF entered a dou-

Table II. ACR responses in patients receiving double-blind MTX + LEF and MTX + placebo (PLA) (from week 0 to 24) who were then switched to MTX + LEF (open-label from week 24 up to week 48).[17,18]

Study Duration	24 weeks		48 weeks	
Type of treatment	LEF/MTX	PLA/MTX	LEF/MTX	PLA switched to LEF/MTX
Nº patients	263 patients		192 patients	
	130 patients	133 patients	96 patients	96 patients
ACR20	59.4	25	55.2	57.3
ACR50	25.4	6	35.4	28.1
ACR70	9.2	2.3	16.7	11.5

ble-blind phase. This study compared the efficacy and safety of adding SLZ to LEF with switching from LEF to SLZ alone.

Of the 968 patients treated in the first open-label phase, 806 completed 24 weeks of LEF treatment and 778 continued in the second phase of the trial. Only 106 out of 778 were classified as inadequate responders according to the DAS 28 criteria and therefore entered the double-blind phase.

Of these 106 patients 50 were randomized to SLZ and 56 to LEF plus SLZ. A higher percentage of patients treated with LEF and SSZ (30%) were DAS28 responders as compared with those receiving placebo and SSZ (20%), but this difference did not reach statistical significance (p=0.081). Comparable numbers of patients in each treatment group were ACR 20 responders (25%/24%, p=0.543), however, only patients with the combination treatment (LEF+ SSZ) achieved ACR 50% response (9%).

The combination of LEF plus SSZ had a similar safety profile to that of SSZ alone, with a comparable incidence of adverse events reported in both groups.[20,21]

Combination with infliximab

This combination therapy has been evaluated in retrospective and prospective studies.

In an open-label, multicenter retrospective study, Hansen *et al,* investigated 88 patients (63 women, average age: 53 years, disease duration: 10.3 years), most of whom had mild to moderate disease. Patients received LEF and infliximab for a mean duration of 6.6 months, with a total exposure of 581 patients-months. Thirty four percent of the patients experienced adverse events, which were serious in 6 patients. Efficacy was shown by improvement in swollen and tender joint counts of 64% and 67%, respectively, and pain evaluated in a visual analogue scale improved by 57%. C reactive protein levels decreased by 45% and erythrocyte sedimentation rate (ESR) decreased by 39%.[22]

Godinho *et al,* studied 17 patients (7 women, median age of 57.6 years) with active RA and previous DMARD failures, 13 of whom had been treated for a minimum of 3 months with LEF before starting infliximab. In the remaining four, the two drugs were started simultaneously. Thirteen patients experienced adverse events. There was a decrease in the mean DAS score from 5.94 ± 0.88 to 4.34 ± 1.25.[23]

A retrospective study of 45 patients was performed by Ortiz, *et al,* in Spain (35 patients were women, mean age of 57). In 28 patients, infliximab was added to the previous treatment with LEF, and in the remaining 38% cases LEF was added to ongoing infliximab. This study compared infliximab and LEF combinations with triple therapy with infliximab, LEF and MTX. No difference in the discontinuation rate due to adverse events was observed for patients on bi-therapy or tri-therapy.[24]

In a 32-week open-label study, 20 patients (18 women, median age of 55 years) with active RA despite previous multiple DMARD treatments received LEF (100 mg for 3 days and than 20 mg once daily) and Infliximab (3 mg/kg) that was administered at 2, 4, 8 and 16 weeks after the start of concomitant LEF treatment. All patients reported side effects and 11 withdrew before the end of the study due to adverse events. An ACR 20 response was achieved by 80% of the patients that were able to continue the treatment.[24]

Struppler *et al,* studied 6 patients with RA and insufficient response to MTX; they received 20 mg/day of LEF and infliximab for 22 weeks. No

subject withdrew from the treatment and the average DAS 28 decreased from 6.4 to 5.1.[24]

A prospective open-label study followed for up to 60 days 40 patients who had failed to respond to LEF monotherapy and to whom infliximab treatment was added. There was a high rate of treatment discontinuation with 10 patients stopping for inefficacy and 17 due to adverse events.[24]

In a German open-label, 30-week trial, 72 patients, with moderate to severe disease and at least 16 weeks of inadequate response to LEF monotherapy, received infliximab at weeks 0, 2, 6, 14, and 22. From baseline to week 30 mean DAS 28 score decreased from 6.8 to 4.8 and 19.4% and 46.3% of the subjects were rated as good or moderate EULAR responders, respectively. The mean HAQ score also decreased from 1.65 to 1.21. Thirteen of the 72 patients withdrew due to adverse.[24]

In a recent prospective study 162 RA patients started infliximab therapy, 57 in the LEF group (already taking LEF or that had began it within 6 months of starting infliximab) and 105 in the non-LEF group. No statistically significant differences in baseline characteristics were observed between groups. Maximum follow-up time was 46 months for both groups. No differences in drug survival, disease activity or adverse events were observed between groups.[25]

Combination with etanercept

In a study with 11 RA patients with moderate to severe disease and at least 16 weeks of inadequate treatment with LEF monotherapy, etanercept (25 mg twice a week) was added. Eight patients attained ACR 20 response. Serious adverse events were observed in 2 patients.[24]

Combination with adalimumab

The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) evaluated safety and efficacy of adalimumab when given with standard DMARD therapy in patients with active RA. This 24-week trial included 636 patients (78.4% women, mean age of 55.4 years) which received either 40 mg (318 patients) or placebo (318 patients), while continuing their standard DMARD therapy (13.4% were receiving LEF). The authors reported no statistically significant difference between DMARD/Adalimumab and DMARD/placebo.[26] But a secondary analysis performed for the US Food and Drug Administration reported a higher rate of adverse events in patients receiving LEF and adalimumab.[24]

Adverse events of leflunomide in monotherapy or in combination therapy

In postmarketing surveillance the incidence and the comparison of adverse drug reactions during LEF treatment were consistent with the safety profile of LEF reported in phase II and III clinical trials.[27-29]

The Expert Panel meeting that was held in Paris in 2003 considered that adverse events associated with LEF were manageable (95% participants).[29]

In clinical trials LEF had a tolerability profile intermediate between that of MTX and SSZ, in terms of withdrawal rates and infections.[28]

The most common adverse events resulting in treatment withdrawals were diarrhoea, elevated liver enzymes, alopecia and cutaneous rash.

Diarrhoea is a frequent side effect, usually mild or moderate, that is solved in 98% of cases following symptomatic treatment.[29]

Elevated liver enzymes and hepatic dysfunction are known undesirable effects of LEF. In the trial led by Emery *et al*[14] the cumulative incidence of hepatic enzyme elevation (three times the normal upper limit) was higher with MTX (17%), followed by LEF (5%), SSZ (4%) and placebo (1%).[8] The Strand *et al* study evidenced similar prevalence of elevated liver enzymes.[9] It has been reported that the incidence of hepatic failure was 14/100.000 patients-year, no higher than that observed by other DMARDs. Recent studies showed that the total number of spontaneous reports of hepatic events is declining.[30]

Alopecia is a common transitory side effect of LEF (≤ 10% of patients) thought to be dose dependent. To try to solve this problem, 56 % of the members of an Expert Panel would reduce the dose, if this option would be compatible with the severity of RA. As an alternative the Expert Panel propose the use of topical lotions which can also be of some benefit.[29]

One of the **cutaneous reactions** more frequently reported is rash, usually mild or moderate, which resolves spontaneously in 90% of cases. LEF can be continued with symptomatic anti-allergic medications. There were no cases of Stevens Johnson syndrome and toxic epidermal necrolysis associated with the use of LEF in the retrospective cohort study (40 594 patients) based on data from the Aetna-US Healthcare claims database. Isolated pruritus is rare. Mucosal ulcers have been described and treatment should be stopped if they persist or worsen.[28]

Hypertension has been mentioned as a common side effect of treatment. New onset hypertension occurred in 3.7% and 2.1% of patients in two phase III studies.[8,9] In a small study, evaluating 30 patients, hypertension was detected using standardised conditions of blood pressure. A statistically significant increase in systolic blood pressure was already apparent after 2-4 weeks of treatment. By contrast, increase in diastolic blood pressure appeared later. As heart rate also increased during LEF treatment it was assumed that hypertension was due to an increased sympathetic load.[31] Therefore it is recommended to closely monitor blood pressure before starting LEF, and regularly throughout treatment

The **pulmonary events** reported include respiratory infections and drug induced pneumonitis.

Respiratory infections were the most commonly reported pulmonary events but had the lowest incidence rate when compared to other therapies. The incidence rate of respiratory infections in patients treated with the combination of LEF plus MTX was not statistically different from other treatment options.[27] **Drug induced pneumonitis** was as frequent as with other DMARDs.[32,33]

Use in Other Autoimmune Diseases

The role of T cells is relevant in the pathogenesis of most autoimmune diseases. As previously highlighted, LEF can modulate these cells, therefore constituting a potential alternative to failure or intolerance of other ongoing drugs.

Within rheumatic diseases, evidence is accumulating for an effective role in the treatment of **Psoriatic Arthritis**. In a double-blind placebo-controlled study LEF treatment led to a significant reduction in Psoriatic Arthritis Response Criteria (PsARC) compared to placebo over 24 weeks; 56 of 95 LEF-treated patients and 27 of 91 placebo-treated patients were classified as responders by the PsARC.[39] The adverse event profile was similar to the one that was seen in other RA trials. A significant improvement was also reported on cutaneous psoriasis; however these studies included less than 20 patients.[34-36]

Other data are emerging in other closely related diseases such as **Ankylosing Spondilitis**. An open-label study including 20 patients with ankylosing spondylitis refractory to NSAIDS showed that LEF was only effective in peripheral disease, without axial symptoms improvement.[37]

There are some anecdotal observations that suggest the efficacy of LEF in other rheumatic diseases. In **Systemic Lupus Erythematosus (SLE)** LEF was reported to be effective and safe in 18 SLE patients after 2-3 months of therapy.[38] In a recent small double-blind, placebo controlled study with 12 SLE patients with mild to moderate disease activity LEF was more effective than placebo in decreasing SLEDAI.[39]

In **Wegener granulomatosis** a phase II, single-centre, open-label study treated patients with LEF after the induction of complete (n = 4) or partial (n = 16) remission by cyclophosphamide/prednisolone combination therapy. LEF treatment was initiated at 20 mg/day and increased to 30 mg/day after 12 weeks and, in patients with partial remission, up to 40 mg/day after 24 weeks. Concomitant low-dose prednisolone (less than 10 mg/day) was allowed during the study.

During the treatment period of up to 2.5 years (median 1.75 years, range 1-2.5 years), one patient had a major relapse and required retreatment with cyclophosphamide/prednisolone. Eight patients had minor relapses that were successfully treated by dose increases up to 40 mg/day of LEF. Side effects were comparable to those seen with the standard dose.[40]

In longstanding **Polyarticular Juvenile Idiopathic Arthritis patients** who had failed to respond or were intolerant to MTX therapy LEF appear to have a sustained positive effect (24 months).[41] Successful use in **Sarcoidosis**.[42] **Atrophic dermatitis and Pemphigus** has also been reported. Each of these indications awaits further confirmation of efficacy and tolerability in large controlled trials.

Conclusion

LEF inhibits pyrimidine synthesis which is required for proliferation of activated autoimmune CD 4+ T cells.

Clinical efficacy, inhibition of structural damage, improvement of physical function and safety in RA patients were demonstrated in phase II and III trials. This determined its use in RA patients, as an alternative or combined with MTX or SSZ. The use of LEF in combination with biologic treatments lacks solid evidence, with the possible exception of its combination with infliximab.[43]

Economical analysis of RA treatment showed

that the use of LEF is more cost-effective for the average RA patient who has failed MTX than switching to or combining with biological therapy.[44]

Adverse events most frequently associated with LEF, like elevated liver enzymes, diarrhoea, alopecia, cutaneous disease, are mainly transitory and mild. Infection rate was comparable to other DMARDs. Hepatic enzymes and blood pressure should always be monitored before starting and regularly throughout treatment.

In other autoimmune diseases there are some encouraging results that can broaden the use of this drug, particularly in psoriatic arthritis and Wegener granulomatosis.

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