REVIEW ARTICLE

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Benefit-Risk Assessment of Leflunomide

An Appraisal of Leflunomide in Rheumatoid Arthritis 10 Years After Licensing

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Contents

Abstract

Evidence is accumulating for the early sustained usage of disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis. Leflunomide was licensed for the treatment of rheumatoid arthritis in 1998. Postmarketing surveillance, case reports and observational studies have highlighted less common or unexpected adverse events. Therefore, it is appropriate that we review the benefit-risk profile of leflunomide after 10 years of widespread usage. A wide-based search of relevant literature was performed to formulate this assessment.

The improvements in rheumatoid arthritis shown by double-blind, randomized controlled trials (RCTs) of leflunomide have now been shown to be

maintained beyond 4 years in open-label extension studies. Leflunomide is comparable to methotrexate, but better than sulfasalazine at 24 months in only one study. However, tolerance in clinical practice research shows higher than expected withdrawal rates due to both toxicity and lack of efficacy when compared with methotrexate and placebo.

Adverse events reported include gastrointestinal upset, hypertension, headache, hepatotoxicity and hair loss, as well as predisposition to infection and peripheral neuropathy. The incidence of gastrointestinal adverse effects for leflunomide is similar to sulfasalazine but higher than those seen with methotrexate. Serious drug-induced hepatotoxicity leading to hospitalization is rare (0.02%), but isolated fatalities from liver failure have been documented. It is considered likely, but not yet proven, that there may be an increased incidence of weight loss and interstitial lung disease with leflunomide.

Leflunomide in combination with methotrexate or sulfasalazine is an effective regimen in RCTs utilizing placebo controls, but more research is needed to confirm its effectiveness in combination with other DMARDs, particularly biologicals.

The active metabolite of leflunomide is teratogenic in animal studies and is also found in breast milk. Therefore, contraception is advised in both males and females of child-bearing potential. There are genetic, pharmacokinetic and biochemical reasons to explain variation in both patient response and adverse event profile. Hence, blood and blood pressure monitoring are recommended and therapeutic drug monitoring should be considered in clinical nonresponders.

Leflunomide is an effective DMARD that sustains a clinical and radiological response comparable to sulfasalazine and methotrexate. However, adverse effects necessitate frequent monitoring. It should be used with caution in those of child-bearing potential and with pre-existing lung and liver disease.

Rheumatoid arthritis is a chronic autoimmune disease that manifests clinically as a symmetrical, peripheral polyarthropathy of both the large and small joints. Synovial inflammation leads to loss of cartilage, erosion of bone, and eventually joint destruction. The aim of disease-modifying antirheumatic drug (DMARD) treatment is not only to alleviate inflammatory symptoms but also to slow joint damage.

Current evidence-based guidelines advocate the early sustained use of DMARDs. Comparative studies of available DMARDs show comparable efficacy for sulfasalazine and methotrexate, the most frequently used DMARDs. The main difference between the two is in their toxicity profile. Hydroxychloroquine is less effective but has the advantage of fewer adverse effects.

Leflunomide is a new DMARD that resulted from a drug discovery programme, unlike many other DMARDs whose original use in rheumatoid arthritis arose more out of serendipity than science. The benefit of leflunomide in the control of rheumatoid arthritis symptoms was established in three double-blind, randomized controlled trials (RCTs).[1-3] These trials underpinned the US FDA and the UK Medicine and Healthcare products Regulatory Agency (MHRA) approval of the use of leflunomide in the control of rheumatoid arthritis symptoms in 1998.[4,5]

All double-blind RCTs are, out of necessity, conducted in highly selected populations under carefully controlled conditions and over a short period of time, often for life-long disorders. They are valuable in proving efficacy and identifying common drug adverse events. However, less frequent but potentially significant adverse events, as well as drug interactions, may take several years to become apparent.

Therefore, the aim of this review is to appraise the published literature on the efficacy of leflunomide 10 years after being licensed. We examine the mechanism of action, pharmacokinetics, drug-drug interactions and tolerance, as well as common and potential rare adverse effects of leflunomide.

1. Literature Search

We searched the medical literature electronically using Embase and MEDLINE for articles on leflunomide published in English between 1966 and 2008. Additional references were identified using reference lists of published articles. Textbooks and prescribing guidelines on rheumatoid arthritis were also consulted. An advanced search was performed using the terms 'leflunomide', 'rheumatoid arthritis', 'risk-benefit', 'safety' and 'adverse reactions' in isolation and combination. Double-blind RCTs identified by this method were used to establish efficacy and to identify adverse events. Case reports, non-randomized cohort studies and observational studies were included to understand rare adverse events and patient tolerance.

2. Mechanism of Action of Leflunomide

Leflunomide is considered a cytostatic rather than cytotoxic agent. Two mechanisms of action have been proposed: the reversible inhibition of dihydrooroatase dehydrogenase (DHODH), a key enzyme in pyrimidine synthesis, as well as the inhibition of tyrosine kinases.[6]

Nonactivated T cells meet their metabolic requirements for nucleic acid synthesis primarily via salvage pathways. On the other hand, rapidly dividing T lymphocytes require *de novo* synthesis of purine and pyrimidine. DHODH is required for uridine monophosphate (UMP) synthesis, a precursor of pyrimidine nucleotides. Lymphocytes treated with teriflunomide, the active metabolite of leflunomide (also known as A771726), are arrested after stimulation rather than progressing through to mitosis.[7,8] The plasma concentrations of active metabolite required to interfere with tyrosine kinases are much higher than those necessary for DHODH inhibition, but adequate concentrations for tyrosine kinase inhibition are achieved in the plasma of rheumatoid arthritis patients treated with standard doses of leflunomide.[9]

In synovial tissue studies leflunomide decreased macrophage numbers, intercellular adhesion molecule (ICAM)-1 and metalloproteinases, all of which are known to be involved in rheumatoid synovitis.[10,11] Falls in levels of metalloproteinases, interleukin (IL)-6 and IL-10 following treatment with leflunomide, correlate with clinical benefit.[11] Effects on IL-2 have also been shown.[12] Neutrophils in synovial fluid and peripheral blood of leflunomide-treated rheumatoid arthritis patients show reduction in numbers and decreased chemotaxis.[13] Inhibition of immunoglobulin synthesis,[14,15] nuclear factor-κ-B, cyclooxygenase activity[16] and effects on growth factor B1 have also been described.[12]

3. Pharmacology and Pharmacokinetics of Leflunomide

Leflunomide, an isoxazole derivative, is structurally very different from other DMARDs. It has a molecular weight of 270 Da. On oral administration, leflunomide is rapidly converted to its active metabolite teriflunomide during first-pass metabolism in the gut wall and liver.[17] It is highly protein bound in plasma (99%) and excreted in both the urine and faeces to similar degrees.

Leflunomide has a long elimination half-life of 15–18 days, which is most likely due to enterohepatic circulation and biliary recycling.[18] For this reason, oral colestyramine or activated charcoal can be used to rapidly decrease plasma concentrations of active metabolite and facilitate drug elimination.[19]

A loading dose of 100 mg once daily for 3 days was administered in many of the earlier trials to reach steady state quickly because of the long half-life. However, this has become less favoured in clinical practice because of gastrointestinal adverse effects and headache. Discontinuation was twice as likely if leflunomide 100 mg was administered over 3 days compared with other dosing regimens.[20] Emerging evidence of variation in pharmacokinetics may explain the differences in dose response between individuals.[21]

Several studies have investigated the most appropriate therapeutic regimen. Once weekly dosing, a daily loading dose of 100 mg over 3 days with subsequent 20 mg maintenance dose, and 10 mg once daily have all been investigated.[1,22-24]

Pharmacokinetic studies show that patients with rheumatoid arthritis have an increased plasma free fraction compared with healthy volunteers.[6,18] There can also be marked pharmacokinetic differences between individual patients with rheumatoid arthritis.[21] In fact, a steady-state plasma concentration of leflunomide of >13 mg/dL was a better predictor of treatment success than the oral dose.[25] It has been suggested that nonresponders have their teriflunomide steady-state concentration measured to allow dose adjustments or withdrawal if poor response is suspected.[26] Recent evidence suggests that the breast cancer resistance protein (BCRP) efflux transporter may interact with leflunomide and teriflunomide *in vitro*.[27] As this receptor is important in the absorption and excretion of drugs, it may contribute in part to variations seen in pharmacokinetics and the poor response of some individuals to leflunomide.

4. Drug Interactions

Several studies have investigated drug interactions between leflunomide and anti-rheumatic as well as other medications. Teriflunomide inhibits cytochrome P450 (CYP) 2C9 *in vitro*. Caution should therefore be exercised with drugs metabolized via CYP, such as warfarin and phenytoin. Warfarin does not affect protein binding of teriflunomide *in vitro*,[8,28] but there are now over 300 reports of raised international normalized ratio (INR) in patients taking leflunomide with warfarin.[29]

Teriflunomide increases the free fractions of diclofenac and ibuprofen[14] but there is no interaction between methotrexate (10–25 mg/wk) and leflunomide (standard dosage regimen). Oral leflunomide (loading dose for 3 days and then 20 mg/day) had no pharmacokinetic interaction with the triphasic contraceptive pill (n = 32).[28] Multiple doses of rifampicin (rifampin) increased the peak active metabolite concentrations of leflunomide 100 mg by around 40%.[28]

Smoking increases leflunomide clearance and this may be of particular relevance as several studies have shown smoking to adversely influence the severity of rheumatoid arthritis.[30,31]

5. Efficacy of Leflunomide in Rheumatoid Arthritis

Six papers published the results of four double-blind RCTs of leflunomide in rheumatoid arthritis.[1-3,32-34] The study designs and efficacy are shown in table I. Three of the original trials were placebo-controlled.[1-3] All studies are broadly comparable in disease duration, leflunomide dosage and sample size, and all were of between 6 and 24 months' duration (table I).

5.1 Disease Activity

The American College of Rheumatology (ACR) response criteria for the main randomized controlled studies are shown in table I. Using the ACR response criteria, leflunomide shows clear advantage over placebo. It appeared to be better than methotrexate in two of three comparative trials.[2,32] However, in a meta-analysis, Osiri and colleagues[35] showed that there was no statistically significant difference between leflunomide, methotrexate or sulfasalazine apart from between leflunomide and sulfasalazine at 24 months. The ACR 50 response for leflunomide was 34% compared with 23% for methotrexate at 12 months and 56% compared with 43% after a 12-month trial extension. The ACR 50 for leflunomide evaluated against sulfasalazine was 33% compared with 30% at 6 months and then 52% compared with 25%, respectively, at 24 months.

5.2 Functional Scores

The level of functional disability in rheumatoid arthritis is a predictor of future morbidity and mortality[36] and is an important secondary outcome measure when investigating drug efficacy. The health assessment questionnaire (HAQ) is a validated measure of function in rheumatoid arthritis.[37] The modified HAQ is based on a shorter subset of questions, and the functional disability index charts the degree of difficulty

Table I. Description of study design and efficacy of double-blind, randomized controlled trials of leflunomide in rheumatoid arthritis

Study (y)	No. of subjects	Study design	Mean disease duration (y)	Drug dosages	Comparative drugs	ACR response 20, 50, 70 (%)	Duration of follow-up (mo)	Study site
Mladenovic et al.[1] (1995)	402	Double-blind, randomized, placebo-controlled	8.3	LEF 5 mg/10 mg/25 mg vs PL	LEF (5 mg) LEF (10 mg) LEF (25 mg) PL	30, NR, NR 50, NR, NR 60, NR, NR 32, NR, NR	6	Yugoslavia, Croatia, Slovenia
Strand et al.[2] (1999)	482	Double-blind, randomized, placebo-controlled	7 6.5 6.9	LEF 100 mg/day for 3 days then 20 mg/day; MTX 7.5–15 mg/wk; PL	LEF MTX PL	52, 34, 20 46, 23, 9 26, 8, 4	12	USA, Canada
Cohen et al.[32] (2001)	199	Double-blind, randomized	5.9 6.7	LEF 10–20 mg/day; MTX 15–20 mg/day	LEF MTX	79, 56, 26 67, 43, 20	12 (extension of study above)	USA, Canada
Smolen et al.[3] (1999)	358	Double-blind, randomized, placebo-controlled	7.6 7.4 5.7	LEF 100 mg/day for 3 days then 20 mg/day; SASP 2 g/day; PL	LEF SASP PL	55, 33, NR 56, 30, NR 29, 14, NR	6	Europe, Australia, New Zealand, South Africa
Scott et al.[33] (2001)	168	Double-blind, randomized	7 6 5	LEF 20 mg/day SASP 2 g/day	LEF SASP PL/SASP	82, 52, 25 60, 25, 17 NR, NR, NR	24 (follow-up of study above)	Europe, Australia, New Zealand, South Africa
Emery et al.[34] (2000)	999	Double-blind, randomized	3.5–3.8	LEF 100 mg/day for 3 days then 20 mg/day; MTX 7.5–15 mg/wk	LEF MTX	50, NR, NR 65, NR, NR	24	Europe, Australia, New Zealand

ACR = American College of Rheumatology; **LEF** = leflunomide; **MTX** = methotrexate; **NR** = not reported; **PL** = placebo; **SASP** = sulfasalazine.

patients have with performing specified tasks. Both these measures are less sensitive to change than the standard HAQ.[38]

Table II shows that each comparative study between leflunomide and placebo found a significant statistical improvement in HAQ.[1-3,33] Improvements in HAQ were seen at 6, 12 and 24 months. Methotrexate resulted in a greater improvement in HAQ compared with leflunomide in the larger study at 24 months.[34] However, in another slightly smaller but comparable study leflunomide was better at 12 months than methotrexate.[2] Leflunomide was better at 6 months than sulfasalazine in the only study making this comparison.[3]

5.3 Radiographic Progression

Joint damage occurs early in the rheumatoid arthritis disease process[39] and is characterized radiologically by joint space narrowing, periarticular bone erosion and eventually secondary degeneration. Structural damage in rheumatoid arthritis studies is quantified by either the original Sharp score,[40] the van der Heijde modification of the Sharp score,[39] or the Larsen method.[41] Five of the six key papers documented radiographic outcomes,[2,3,32-34] three reported radiological outcome using the Larsen scores,[3,33,34] one a Sharp score[2] and the other the van der Heijde modification of the Sharp score system.[32]

When compared with placebo, leflunomide-treated patients had better 6-month Larsen scores.[3,33] In these two studies, sulfasalazine and leflunomide were comparable in terms of radiographic progression. Disease progression was similar between methotrexate and leflunomide in the first year of treatment, but radiological progression was less in the methotrexate group using Larsen scores.[34] However, Cohen et al.[32] found that there was no significant difference using the van der Heijde modification of the Sharp score at 2 years when comparing methotrexate and leflunomide.

5.4 Leflunomide Follow-Up Beyond 2 Years in Clinical Trials

Kalden et al.[42] reported on disease and functional activity of 214 patients treated with

Table II. Comparison of standard health assessment questionnaire (HAQ)[a] scores from six papers detailing randomized controlled trials of leflunomide in rheumatoid arthritis

Study (y)	Timepoint of change in HAQ (mo)	Type of HAQ compared	Change in HAQ				Statistical comparison
			LEF (n)	MTX (n)	SASP (n)	PL (n)	
Mladenovic et al.[1] (1995)	6	HAQ	−13.6 (101)	NA	NA	−8.1 (102)	Significant statistical difference between LEF vs PL
Strand et al.[2] (1999)	12	MHAQ	−0.3 (182)	−0.2 (180)	NA	0.1 (118)	Significant statistical difference between LEF and MTX vs PL
Cohen et al.[32] (2001)	12	HAQ DI	−0.6 (98)	−0.37 (101)	NA	NA	Significant statistical difference between LEF vs MTX ($p < 0.05$)
Smolen et al.[3] (1999)	6	HAQ	−0.5 (130)	NA	−0.29 (132)	−0.04 (91)	Significant statistical difference between LEF and MTX vs PL Significant statistical difference between LEF vs SASP ($p < 0.03$)
Scott et al.[33] (2001)	24	HAQ	−0.65 (52)	NA	−0.36 (45)	−0.2 (21)	Statistical difference between LEF and SASP vs PL
Emery et al.[34] (2000)	24	HAQ	−0.45 (252)	−0.5 (278)	NA	NA	Statistical difference between MTX vs LEF ($p < 0.05$)

a Derived from the Stanford Health Assessment Questionnaire.[37]

HAQ = Health Assessment Questionnaire; **HAQ DI** = HAQ Disability Index; **LEF** = leflunomide; **MHAQ** = modified HAQ; **MTX** = methotrexate; **NA** = not applicable; **PL** = placebo; **SASP** = sulfasalazine.

leflunomide for a mean of 4.6 years (maximum 5.8 years). The ACR response rates showed that improvement was maintained for 4 years.[42] Van der Heijde and colleagues[43] reported on x-ray data on patients treated with leflunomide for 3–5 years. The mean annual progression at baseline was 7.9 units/year (Sharp score), which fell to 1.9 units per year after sustained treatment with leflunomide (n = 128).

6. Tolerability in Clinical Practice

The duration of use of a drug in routine practice can provide useful insights into long-term patient tolerance. Several observational studies showed higher than historically expected withdrawal rates for leflunomide. In a Dutch cohort more than half of the patients withdrew from leflunomide treatment, many due to adverse drug reactions (29%) within the first year of a treatment.[44] American researchers found that 42% of individuals discontinued treatment, with 63% terminating therapy in the first 6 months[20]. In this study, discontinuation was twice as likely if the higher loading dose was used.[20] The discontinuation rates for methotrexate and leflunomide were comparable, with the median time to discontinuation being 14 and 15 months, respectively. However, when survival rates are charted using Kaplan-Meier analysis from a database of more than 1000 patients, methotrexate showed improved long-term retention compared with sulfasalazine and leflunomide.[45]

7. Adverse Drug Reactions

Comparing leflunomide treatment with placebo or another DMARD, the most common adverse effects were gastrointestinal (diarrhoea, dyspepsia, nausea/vomiting, abdominal pain, oral ulcers), abnormal liver function tests (LFTs), drug eruptions, alopecia, infections, weight loss and

hypertension.[35,46,47] The rates of gastrointestinal adverse effects for leflunomide were similar to those with sulfasalazine but higher than those with methotrexate; however, a recent review found no statistical difference in the frequency of serious adverse events between sulfasalazine, methotrexate and leflunomide.[48]

7.1 Liver Function

Four of five of the original double-blind RCTs of leflunomide documented abnormal LFTs twice or more than the upper limit of normal (ULN) [ALT > AST]. The frequency of abnormal LFTs varied from 2.2% to 19% of patients.[3,32-34] Scott et al.[33] found that rises in transaminases were minor and transient and no patients were withdrawn as a result. Raised liver enzymes that were up to three times the ULN occurred with similar frequency between the leflunomide, sulfasalazine and methotrexate groups.[46] One study showed methotrexate to have a higher withdrawal rate due to hepatotoxicity compared with leflunomide.[34]

In 2001, the European Medicines Agency published a report of 15 cases of fatal liver toxicity in patients treated with leflunomide.[49] However, when further analysed, an hepatic event was not the cause of death in ten of these patients.[50] In the US, the FDA was also unsuccessfully petitioned to withdraw the drug in 2002.[51,52] Two cohorts from insurance claim databases comprising more than 42 000 individuals receiving leflunomide between 1998 and 2001 found 4.9 serious hepatic events per 10 000 per year.[53] A study of 101 patients was specifically undertaken to assess liver function over a median of 10 months (0.5–12 months).[50] Nine percent had ALT levels two or three times normal, one patient withdrew due to hepatotoxicity and one continued on a decreased dose. None of the patients had pre-existing liver disease. The study was limited in that there were no LFT results in half the individuals at endpoint.

The potential hepatotoxicity of leflunomide led to a change in the drug information, emphasizing the need to monitor liver function. The current monitoring guidelines suggest that LFTs should be checked prior to starting the drug and then monthly for the initial 6 months. Once leflunomide is established, LFTs are required every 8 weeks. An increase in ALT between two to three times the ULN laboratory range requires dose reduction, and LFTs should be checked weekly. If ALT remains twice the ULN or exceeds three times the ULN, treatment should be discontinued and washout with colestyramine undertaken. Leflunomide should not be used in patients with pre-existing liver disease. Serious drug-induced hepatotoxicity leading to hospitalization remains rare (0.02%).[47,52]

A recent case report found an association between CYP2CP*3 allele homozygosity and biopsy proven leflunomide-induced hepatitis.[54] But most recently, prevention of paracetamol (acetaminophen)-induced hepatoxicity by inhibition of N-acetyl p-benzoquinone imine (NAPQI) bioactivation by teriflunomide has been proposed.[55] Physicians should thus be aware that there may be a genetic predisposition to hepatotoxicity, which may be compounded by variability in serum drug concentrations.

7.2 Infection

The possibility that leflunomide leads to predisposition to infection has been investigated. The rates of post-operative infection in a small cohort of patients receiving leflunomide or another DMARD were found to be similar.[56] Nevertheless, a retrospective case-note review evaluating the rates of severe infection found that there was a higher risk of infection in patients receiving leflunomide treatment, particularly when it was given in combination with methotrexate and prednisolone.[57] Opportunistic infections such as *Pneumocystis carnii* pneumonia have also been reported.[58]

7.3 Peripheral Neuropathy

Leflunomide has also been associated with an apparent increase in the symptoms suggestive of a peripheral neuropathy but there was no correlation between symptoms and neurophysiological studies.[59] Neurophysiological measurements were only performed in the first 6 months; however,

it may be a long-term or idiosyncratic adverse effect of leflunomide.

7.4 Interstitial Lung Disease

Case reports of interstitial lung disease (ILD) associated with leflunomide use have recently been published.[60-65] A case series of severe ILD in Japanese patients receiving leflunomide, with five subsequent deaths, was published in 2004 and 2005.[60-62] Suissa and colleagues[63] retrospectively reviewed the incidence of ILD using large databases that included pharmaceutical, clinical and hospitalization data from Western patients (n = 62 734). Despite the limitations of retrospective cohort studies, the risk of ILD seemed to be increased by leflunomide. It was postulated that this increased risk may be in part due to a selection bias. Patients with a history of ILD and/or previous methotrexate exposure had an increased risk of ILD with leflunomide. It has been suggested that the incidence and severity of ILD is higher in Eastern Asian than Western populations. Two subsequent smaller studies in Korea and Japan did not show any additional ILD-related deaths.[64,65]

7.5 Weight Loss

In one of the initial phase II trials, weight loss was found to be more frequent in leflunomide-treated individuals than those receiving placebo.[1,66] In this trial, the significance of the weight loss was not clear.[66] Subsequent phase III trials showed no significant differences in weight between the active drug and placebo arms of the trial. Weight loss was not more common in leflunomide-treated patients when methotrexate, sulfasalazine and leflunomide were compared in a Cochrane review.[35] A subsequent case report suggests that leflunomide causes substantial weight loss in the absence of any other identifiable cause.[67]

7.6 Pregnancy, Breastfeeding and Male Fertility

The active metabolite of leflunomide is teratogenic in animal studies. Leflunomide caused dysplastic bone formation in rabbits, as well as hydrocephalus and developmental eye defects in rats.[17] The manufacturers recommend performing pregnancy testing prior to commencing therapy in women of childbearing age. A reliable method of contraception should also be advised throughout the course of treatment. Female patients are recommended to wait 2 years after treatment before conceiving. A washout procedure with activated charcoal or colestyramine should be performed to promote drug elimination. To date, very limited information is available on the effect of leflunomide on male fertility or the potential of male-related fetal toxicity. Present recommendations advocate that males should stop treatment with leflunomide and wait 3 months prior to conception. Two levels of active metabolite <0.02 mg/L in serum 14 days apart are thought to confer a low risk of fetal toxicity.[8,18,19] Leflunomide should be avoided during breastfeeding as animal studies have shown it to be present in breast milk.[18]

7.7 Overview of Safety Profile

Ten years after the initial licensing of leflunomide, its full safety profile in rheumatological practice is becoming clear. Postmarketing surveillance rates for 80 000 patient years on leflunomide report that adverse reaction rates are consistent with toxicity rates seen in original RCTs.[68] Several small studies have reported on adverse effects that were not evident in the initial RCTs. Care should be taken in those with pre-existing lung and liver disease, and the possible effects on weight, blood pressure and peripheral sensation should be considered. Review of patient cohorts show that withdrawal rates may be higher than those for other DMARDs, and may be greater than originally anticipated from original studies.

8. Leflunomide in Combination

8.1 Disease-Modifying Anti-Rheumatic Drugs

A systematic review of the use of DMARD therapy in rheumatoid arthritis shows that the combination of methotrexate, sulfasalazine and hydroxychloroquine is one of the most effective

nonbiological treatment strategies.[69] The majority of larger studies have investigated leflunomide in combination with either methotrexate or sulfasalazine.

8.2 Methotrexate

Leflunomide inhibits pyrimidine, and methotrexate inhibits primarily purine biosynthesis. A small open-label trial of 30 patients who had active rheumatoid arthritis, despite 6 months of methotrexate therapy, were administered additional leflunomide to assess the effects on disease activity. The combination was well tolerated and 53% of subjects achieved an ACR 20% improvement according to the ACR criteria.[70] In a larger study, 263 patients were randomized to receive leflunomide and methotrexate or methotrexate and placebo. A greater proportion of patients in the combination group achieved an ACR 20 response than those receiving methotrexate and placebo (46.2% vs 19.5%). Leflunomide was then added to the placebo group and after 6 months similar response rates were comparable to the original combination group.[71,72] At 16 weeks Cohen and colleagues[73] added methotrexate to nonresponders receiving leflunomide and, in this study, this converted nonresponders to responders. The responders to leflunomide maintained their response to 40 weeks.[73] Apart from the latter study, adverse event profiles were similar in monotherapy and combination groups and the rates of LFT abnormalities were higher in the methotrexate and leflunomide combination arm.[73] Radiographic progression was similar at 2 years for both drugs.[48]

8.3 Sulfasalazine

In the RELIEF (Rheumatoid arthritis Evaluation of Leflunomide further Insights into its EFficacy) study,[74] individuals initially received leflunomide for 6 months; those with an inadequate response according to the DAS28 (disease activity) score were randomized to sulfasalazine and leflunomide or switched from leflunomide to sulfasalazine with placebo. There were 56 and 50 subjects in each treatment arm. The combination of sulfasalazine and leflunomide had significantly more ACR 50 responders than placebo plus sulfasalazine. This would seem to indicate that the addition of sulfasalazine to leflunomide was better than changing from leflunomide to sulfasalazine. Discontinuation due to toxicity was more frequent in the combination group. No other unexpected adverse effects were encountered.[73] Radiographical changes were again similar for both sulfasalazine and leflunomide.[48]

8.4 Biological Therapy

Leflunomide has also been investigated in combination with biological agents. These are agents used in rheumatoid arthritis and other inflammatory diseases to target inflammatory mediators such as cytokines, including tumour necrosis factor-α and various interleukins. Nine studies were found and all combined infliximab with leflunomide in rheumatoid arthritis.[75-83] All studies were small in number, with three studies having 20 or fewer patients and only two having a sample size >100. Studies used different measures of efficacy, including change in the DAS28 score and swollen and tender joint counts. In a prospective study of 40 patients, Bingham and colleagues[82] showed that 49% achieved an ACR 20 improvement at 24 months and 42% at 48 months. The combination was found to be effective, but no study had a placebo arm. Adverse event profiles were in keeping with the known risks of each drug.

9. Conclusions

The double-blind RCTs outlined in this review have shown that leflunomide is effective in relieving the symptoms of rheumatoid arthritis and reducing radiological progression for up to 2 years. Treatment with leflunomide results in a similar ACR response to that of sulfasalazine and methotrexate. Subsequent open-label extensions of double-blind RCTs have shown that the effects on disease activity and radiographical progression are sustained for up to 4 years.

The adverse event profile of leflunomide is similar to sulfasalazine in many respects, but rates of gastrointestinal adverse effects, mild skin reactions,

alopecia and hypertension are more frequent than for methotrexate. Ten years of post-licence marketing surveillance finds that the rates of the initial adverse effects remain similar to those in the original RCTs.

There may be increased risk of ILD, weight loss and severe infection associated with leflunomide use, but further investigation is required to confirm this. Severe hepatatoxicity remains of concern but is rare.

One of three studies of leflunomide in combination with methotrexate showed an increased frequency of abnormal LFTs. Sulfasalazine in combination with leflunomide was also effective. More studies are needed to ascertain the effect of leflunomide in combination with biological therapies.

Significant drawbacks include leflunomide's adverse effect profile, teratogenicity and long half-life. It should therefore be considered for use during childbearing years only after serious patient and physician consideration and with extreme caution in those with pre-existing or previous ILD or liver disease.

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