Leflunomide: A novel disease modifying anti-rheumatic drug

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Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis affecting approximately 0.5 to 1% of the population. It follows a progressive course with evidence of structural joint damage occurring as early as 4 weeks after the onset of symptoms and usually gets fully established by 2 years in untreated patients. Based on this observation, current treatment guidelines emphasize the early use of disease-modifying anti-rheumatic drugs (DMARDs), a class of therapeutic agents that have the potential to minimize or prevent joint damage. However, most of the current DMARDs show loss of efficacy with time and/or development of serious adverse effects. There is therefore a need for newer DMARDs with better efficacy and a better safety profile. Leflunomide (active metabolite A77 1726) is one such new drug with novel immunomodulatory and anti-inflammatory properties that has shown promising results in terms of efficacy and safety for the treatment of this crippling autoimmune disease and is a welcome addition to the roster of anti-rheumatoid drugs.

Chemical structure

Leflunomide, an isoxazole derivative, is a prodrug that is rapidly and almost completely metabolized after absorption to its active metabolite A77 1726 (open ring metabolite- malononitrilamide).

The overall reaction involves the opening of the five-membered ring, forming cyanide and a hydroxyl group. This occurs quickly in the gut walls and liver.

**Mechanism of Action**

A77 1726 has several mechanisms of action as listed below:

1) Primary immunomodulating action - Inhibition of de novo pyrimidine synthesis

Activated lymphocytes in RA require an eightfold increase in their levels of ribonucleotide uridine monophosphate (rUMP) and other pyrimidine ribonucleotides in order to progress from G₁ to the S phase of the cell cycle for proliferation and they must use de novo synthesis of pyrimidines. A77 1726 acts reversibly on the critical mitochondrial rate-limiting enzyme dihydrourate dehydrogenase (DHODH) required for the de novo synthesis of rUMP. Inhibition of this enzyme leads to decreased rUMP, decreased DNA and RNA synthesis, inhibition of T cell proliferation and G₁ cell cycle arrest. T cell-dependent B cell formation of autoantibodies, including IgA and IgG isotypes, is also inhibited by A77 1726.

2) Anti-inflammatory actions-

- A77 1726 inhibits the activation and gene expression of nuclear factor (NF) κB required for the activation of genes

Inhibition of DHODH leads to decreased rUMP synthesis resulting finally in the arrest in G₁ phase of cell cycle

![Figure 1: Chemical stucture of leflunomide and its active metabolite](image1)

![Figure 2: Cellular mechanism of immunomodulating action of A77 1726](image2)
for various inflammatory cytokines and metalloproteinases.\textsuperscript{6}

- A77 1726 increases the production of immunosuppressive transforming growth factor-\(\beta\) protein (TGF-\(\beta\)) and inhibits the production of pro-inflammatory cytokines TNF-\(\alpha\) and interleukin 1\(\beta\).\textsuperscript{4}
- Direct inhibition of COX-2 enzyme at sites of inflammation.\textsuperscript{7}

**Pharmacokinetics\textsuperscript{4}**

After oral administration leflunomide is rapidly metabolised to its major active form A77 1726 in the gut wall, plasma and in the liver. The parent compound is rarely detected in the plasma. Peak plasma levels of A77 1726 are reached 6-12 h after oral administration of leflunomide. Bioavailability of A77 1726 is unaffected by high fat meal. It has a low volume of distribution as it is >99\% protein-bound. A77 1726 undergoes entero-hepatic circulation and biliary recycling may contribute to its long elimination half-life (~ 2 weeks). A77 1726 is further metabolised and excreted in the urine as an oxalic acid derivative and in the unchanged form in faeces.

**Drug interactions**

There is limited data regarding drug interactions with leflunomide. In vivo drug interaction studies have demonstrated a lack of a significant drug interaction between leflunomide and methotrexate.\textsuperscript{5,10} Levels of leflunomide are increased after multiple dosing with rifampin.\textsuperscript{5} A77 1726 inhibits CYP2C9 that metabolises many NSAIDS. However, no clinically relevant interactions were observed in clinical trials in patients receiving leflunomide with NSAIDS, which are so frequently used in RA treatment.\textsuperscript{5} No interactions have been documented with oral contraceptives that were used by several subjects in the clinical trials.

**Comparison of Efficacy, Safety and Tolerability with established DMARDs**

The clinical efficacy and slowing of radiological progression in active RA with leflunomide monotherapy as compared to placebo, methotrexate (MTX) and sulphasalazine (SSZ) has been evaluated in 6 large, double-blind, randomised controlled trials. A brief overview of these trials and the outcomes measured are shown in the table.

A systematic review and meta-analysis of the above 6 trials by Oshir et al\textsuperscript{15} concludes that

- Comparison with Placebo: The pooled estimates of the clinical efficacy of leflunomide shows it to be significantly better than placebo at 6 and 12 months in all the clinical outcomes. Progression of radiological changes was also significantly slower in the leflunomide-treated group than the placebo group. Adverse events in the leflunomide-treated group that were significantly increased as compared to placebo and included alopecia, gastrointestinal symptoms and elevated liver function tests.
- Comparison with MTX and SSZ: Its efficacy was comparable with MTX and SSZ for most of the clinical outcomes, except leflunomide did better than SSZ in improving the ACR20 response rate at 24 months.\textsuperscript{14} The delay in radiological progression with leflunomide was comparable with MTX and SSZ at 6 and 12 months of treatment. However, at 24 months, leflunomide delayed joint erosions at a significant rate compared to SSZ. Withdrawal rates and adverse events in the leflunomide group were not different from SSZ or MTX. [ACR20, ACR 50, ACR 70: Proportion of patients showing a 20\%, 50\%, 70\% improvement respectively from baseline levels in the number of tender and swollen joints, as well as 20\%, 50\%, 70\% improvement respectively in 3 of the following 5 criteria -

Table 1: Efficacy of Leflunomide (LEF) in randomised, double-blind, multicentric trials in adult patients with active RA.

<table>
<thead>
<tr>
<th>Trial and Duration</th>
<th>Study type</th>
<th>Outcomes measured</th>
<th>Overall efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mladenovic\textsuperscript{9}, 1995, 24 wks</td>
<td>Comparison with Placebo (PL)</td>
<td>ACR core set of disease activity measures*, ACR20 and Paulus criteria, Adverse events</td>
<td>LEF 25 &gt; PL</td>
</tr>
<tr>
<td>Strand\textsuperscript{11}, 1999, 12 months</td>
<td>Comparison with MTX</td>
<td>ACR core set of disease activity measures, ACR20, ACR50, ACR70, ACR success, X-ray changes- Sharp scores, Adverse events</td>
<td>LEF &gt; PL</td>
</tr>
<tr>
<td>Emery\textsuperscript{11}, 2000, 52 wks</td>
<td>Comparison with MTX</td>
<td>ACR core set of disease activity measures, ACR20 and Paulus criteria, X-ray changes- Sharp scores, Adverse events</td>
<td>LEF = MTX</td>
</tr>
<tr>
<td>Cohen\textsuperscript{12}, 2001, 12 months (Year 2 extension of Strand study)</td>
<td>Comparison with MTX</td>
<td>ACR20, ACR50, ACR70, ACR core set of disease activity measures, X-ray changes- Modified Sharp scores, Function and HRQOL, Adverse events</td>
<td>LEF = MTX</td>
</tr>
<tr>
<td>Smolen\textsuperscript{10}, 1999, 24 wks</td>
<td>Comparison with SSZ</td>
<td>ACR core set of disease activity measures, ACR20, ACR50, Paulus criteria, X-ray changes- Sharp scores, Adverse events</td>
<td>LEF &gt; PL</td>
</tr>
<tr>
<td>Scott\textsuperscript{14}, 2001, 2 years (Year 2 extension of Smolen study)</td>
<td>Comparison with SSZ</td>
<td>ACR core set of disease activity measures, ACR20, ACR50, ACR70, X-ray changes- Larsen scores, Function and Adverse events</td>
<td>LEF &gt; SSZ</td>
</tr>
</tbody>
</table>

HRQOL: health-related quality of life, *Number of tender and swollen joints, patient and physician global assessments of disease activity, functional status, pain, ESR.
physician global assessment, patient global assessment, pain intensity assessment, physical disability and CRP or ESR level)

**Efficacy and safety in combination with MTX**

A recent randomised, double-blind, placebo-controlled trial by Kremer et al.,\(^{10}\) showed statistically significant efficacy in the ACR20 response rate and functional disability when compared with the placebo-MTX combination for patients with active RA despite stable doses of MTX. The combination of the two anti-metabolites was well tolerated and can be used safely with appropriate liver enzyme and haematological monitoring. No significant differences in the adverse effects were seen when compared with the placebo-MTX group.

**Long-term efficacy and safety of leflunomide**

A 5-year open-labelled, non-controlled extension study by Kalden et al.,\(^{13}\) demonstrated that the early efficacy of leflunomide [ACR20, ACR50, ACR70 response rates and health assessment questionnaire (HAQ) scores] seen at 1 year in patients with RA was maintained for up to 5 years. The long-term safety profile was no different from previous trials. No new adverse events were observed and liver functions were normal in the majority of patients throughout the study. The subjects included in this extension study were those who had completed full 24 months of leflunomide treatment in the previous 2 Phase III trials.\(^{11,13}\)

**Adverse Drug Effects**

The major adverse events reported in the clinical trials included gastrointestinal symptoms (diarrhoea, dyspepsia, nausea, abdominal pain, oral ulcers), elevated liver function tests, skin rash/allergic reactions, alopecia, infections, weight loss and hypertension.\(^{15}\) Only GI symptoms, alopecia, and hypertension were found to be significantly more in the leflunomide group as compared to MTX.\(^{15}\) Adverse events were similar when comparing leflunomide and SSZ.\(^{15}\) New onset hypertension as a side-effect of leflunomide therapy has been demonstrated in a prospective trial by Rozman et al.,\(^{18}\) highlighting the need for regular measurement of blood pressure during leflunomide treatment. A rise in the systolic blood pressure was noted after 4 weeks of initiating treatment with leflunomide. By contrast, the rise in diastolic pressure appeared later.

Less frequently seen adverse events\(^{8}\) include urinary tract infections, respiratory tract infections and bronchitis, and minor musculoskeletal problems (backache, tenosynovitis, myalgias). There have been rare reports of sepsis, leukopenia, pancytopenia,\(^{8}\) serious skin reactions (Stevens-Johnsons syndrome,\(^{8}\) toxic epidermal necrolysis\(^{8}\) and erythema multiforme-like drug eruption\(^{9}\)) and interstitial lung disease\(^{9}\) in patients receiving leflunomide alone.

**Dosage and administration**

Leflunomide therapy is initiated orally with a **loading dose** of 100 mg/day administered once daily for 3 days to hasten attainment of the steady state concentration (Css), and **maintenance** dose of 20 mg/day. If the dose of 20 mg/day is not well tolerated then the dosage is decreased to 10 mg/day. Dosages more than 20 mg/day are not recommended.

Recent open-labelled trials\(^{20,21}\) with weekly 100 mg Leflunomide showed the same efficacy and less toxicity than the conventional daily dosage of leflunomide. Another important benefit was a reduction in the monthly cost of Leflunomide treatment. These findings with a weekly dosage of leflunomide are encouraging but more comparative and blinded trials are required to confirm the same.

**Monitoring**

Patients taking leflunomide should have a complete haemogram and ALT (SGPT), monitored at baseline and monthly for 6 months following initiation of therapy, if stable every 6 to 8 weeks thereafter. In addition, if leflunomide and MTX are given concomitantly, American College of Rheumatology (ACR) guidelines for monitoring methotrexate-induced liver toxicity must be followed.

**Contra-indications**

There is no data regarding the safety of leflunomide in children with JRA and it is not recommended for patients < 18 yrs of age. It is contraindicated in those with hepatic insufficiency. Caution needs to be exercised in patients with chronic renal insufficiency as plasma levels of A77 1726 are increased with impaired kidney function.

**Reproductive Adverse effects**

Leflunomide is contraindicated in pregnant females and those not on reliable contraception because of demonstrated teratogenic effects in mice. Although male-mediated fetotoxic effects are not known, men wishing to have a child should avoid the drug. Women/men on leflunomide and wanting to have a child should undergo drug elimination procedure and ensure non-detectable plasma levels (<0.02 mg/L or 0.02 µg/mL).\(^{8}\)

**Drug elimination procedure**

If there are indications to stop the drug on account of adverse reactions, overdosage or reproductive issues, the following is undertaken to achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 µg/mL):

1) Administer cholestyramine 8 g 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.) Verify plasma levels less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

2) Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 gm every 6 hours for 24 hours) in addition to the above, if rapid lowering of the drug levels is indicated.
Role of leflunomide in the management of rheumatoid arthritis

The efficacy and safety of leflunomide as monotherapy is comparable to that of first-line DMARDS—MTX and SSZ. However, rheumatologists have differing opinions regarding the exact place of leflunomide in the hierarchy of DMARDS for RA. Presently, leflunomide is considered for use in the following clinical situations—

1) As monotherapy in place of MTX or SSZ when the latter drugs are poorly tolerated or contraindicated.

2) Refractory RA patients—In combination (add-on therapy) with MTX for patients with persistent active RA despite recommended doses of MTX.

Further studies and longer follow-up periods are required before it can be advocated as first-line therapy for use in combination with other DMARDS.

Constraints of Leflunomide therapy with respect to Indian patients

1) High cost of therapy as compared to established DMARDS.

2) Lack of facilities to monitor blood levels during drug elimination procedures when indicated.

Other potential indications for Leflunomide

Leflunomide as an immunomodulator is being evaluated for use in patients with systemic lupus erythematosus, Wegener’s granulomatosis, Crohn’s disease, and solid tumours.

Conclusion

Leflunomide, a new DMARD with novel immunomodulatory and anti-inflammatory properties, has been added to the armamentarium against RA after more than 10 years of use of established DMARDS. It has shown equivalent efficacy, safety and tolerability when compared with the existing first-line DMARDS—SSZ and MTX—in controlled clinical trials. With extended experience in routine clinical practice, it may be a first choice when starting DMARD treatment for this progressive and disabling disease. There are also encouraging results with weekly leflunomide therapy which, if confirmed with large-scale blinded trials, may result in lesser cost of therapy, less side-effects and better compliance without loss of efficacy.

References

1. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radio-


