Focus

Leflunomide

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INTRODUCTION

Leflunomide is an isoxazole immuno-modulatory agent which belongs to DMARD (Disease Modifying Antirheumatic Drug) class of drugs. It is an inhibitor of pyrimidine synthesis and has antiproliferative and antiinflammatory actions. Leflunomide was licensed for use in rheumatoid arthritis in 1998 and psoriatic arthritis in 2004.

STRUCTURE AND METABOLISM

The chemical name of leflunomide is 5-methyl-N-[4-Triflueromethylphenyl]-5-methylisoxazole- 4-carboxamide. It is a pro-drug and following oral administration is converted to an active metabolite (A77 1726) in the gut wall, plasma and liver; and also to many minor metabolites (of which 4-trifluoromethyaniline is the most important). The parent compound is rarely detected in the plasma. It is the active metabolite A77 1726, which is responsible for all the *in vivo* activity of leflunomide.[1]

PHARMACOKINETICS

The oral bioavailability of leflunomide is 80% and peak plasma levels of active metabolite are reached 6–12 h after oral administration. The bioavailability of A77 1726 is not affected by high fat meal. As the active metabolite is 99% plasma protein bound, it has a low volume of distribution and hence, the time duration for the effect to start is between 8 and 12 weeks. A77 1726 undergoes enterohepatic circulation and biliary recycling and this may contribute to long elimination half-life (>2 weeks) of the active metabolite.[2]

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MECHANISM OF ACTION

Antiproliferative action

Activated lymphocytes require an eight-fold increase in ribonucleotide uridine monophosphate (rUMP) and other pyrimidine nucleotides to progress from G1 to S phase of cell cycle for proliferation and they must use the de novo pyrimidine synthesis.[1,2] A77 1726 (active metabolite) inhibits *dihydroorotate dehydrogenase*, an enzyme involved in de novo pyrimidine synthesis. Inhibition of this enzyme leads to decreased rUMP, decreased DNA and RNA synthesis, inhibition of T-cell proliferation and G1 cycle arrest [Figure 1].

The active metabolite also inhibits protein kinase activity and T-cell dependent B-cell formation of autoantibodies (IgG and IgA).[3]

Anti inflammatory action

A77 1726 interferes with T-cell production of

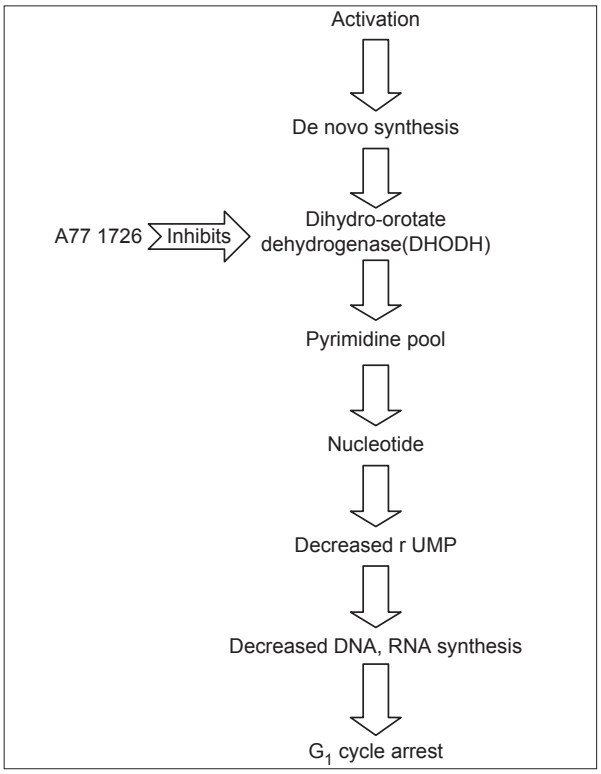

Figure 1: Schematic diagram showing the mechanism of action of leflunomide

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inflammatory cytokines by preventing activation and gene expression of nuclear factor (NF) κB required for expression of inflammatory cytokines.[4] It also increases the production of immunosuppressive TGF-β protein and inhibits the production of proinflammatory TNF-α and interleukin 1β.[2,4] A77 1726 has a direct effect on inhibition of COX-2 enzyme at the site of inflammation.[5]

DRUG INTERACTIONS

Side effects may occur when leflunomide is given concomitantly with hepatotoxic agents. This point also should be considered when leflunomide treatment is followed by drugs without a drug-elimination procedure, e.g. methotrexate.[6] The active metabolite of leflunomide, i.e. A77 1726 persists in the blood for two years after drug cessation, hence side effects may continue to develop several weeks after the drug is stopped. The resulting concomitant hepatotoxicity could be due to persistence of this active metabolite and simultaneous administration of methotrexate.

Administration of cholestyramine or active charcoal causes decreased levels of active metabolite. This interaction is used in drug washout procedure in cases of serious adverse effects or reproductive issues (discussed in later section).[7]

The concomitant or sequential use (without the recommended leflunomide washout period or procedure) of oral retinoids, e.g. acetretin, NSAIDs known to induce hepatotoxicity may potentiate the risk of liver injury associated with leflunomide. Following concomitant administration of a single dose of leflunomide to patients receiving multiple doses of rifampin, A77 1726 peak levels are increased.[7] Leflunomide is a weak inhibitor of cytochrome P450. The co-administration of leflunomide with tolbutamide causes an increase in tissue concentration of tolbutamide and hence should be avoided.

CONTRAINDICATIONS

Leflunomide is contraindicated in the following patient groups:

1. Patients with known hypersensitivity to drug.[7]
2. Pregnant women or women of child-bearing age group not using reliable contraceptive method. Women on treatment should not become pregnant before 2 years of completion of therapy.[8]
3. Patients with pre-existing liver or renal disease.[9]
4. Patients with severe immunodeficiency or bone marrow dysplasia.
5. Active infections (Bacterial, viral or fungal).
6. Avoided in combination with hepatotoxic drugs such as methotrexate, acetretin, NSAIDs and alcohol.

INDICATIONS FOR USE

1. Rheumatoid arthritis[2,7,10]
2. Psoriatic arthritis[2,7,15]
3. SLE[11]
4. Wegener's granulomatosis[12]
5. Crohn's disease[13]
6. Takayasu's arteritis[14]
7. Ankylosing spondylitis[14,15]
8. Sarcoidosis[16]
9. Felty's syndrome
10. Bullous pemphigoid
11. Polyoma BK virus nephropathy
12. Juvenile rheumatoid arthritis (FDA Approval Pending)

DRUG MONITORING

Test	Frequency
Complete blood count	At baseline visit, then monthly for 6 months and every 6–8 weeks thereafter[7]
ALT, AST monitoring	At baseline visit, then monthly for 6 months and every 6–8 weeks thereafter
Hepatic transaminases, serum creatinine, serum albumin	At baseline visit and every 6-8 weeks thereafter
HBV and HCV serology	Baseline visit

DOSAGE OF LEFLUNOMIDE

Leflunomide is available in tablets of 10, 20 and 100 mg.[7,8,10] Oral loading dose of 100 mg daily for 3 days is given to rapidly reach a steady drug level. The initial loading dose is followed by maintenance dose of:

(i) 10–20 mg daily for rheumatoid arthritis
(ii) 20 mg daily for psoriatic arthritis

Total duration of treatment is from 1 to 2 years.[2]

SIDE EFFECTS

1. Most common side effect of leflunomide is diarrhea. Other gastro-intestinal side effects are colitis, cholelithiasis, esophagitis and aphthous stomatitis.[7-17]
2. Liver toxicity - Most cases of liver toxicity are seen within 6 months of treatment when multiple risk factors are present (hepatotoxin, previous

liver diseases). Manifestation of liver toxicity ranges from mild jaundice to severe permanent hepatitis, severe liver necrosis and liver cirrhosis.
3. Myelosuppression - Anemia, leukopenia and thrombocytopenia.
4. Skin - Life-threatening Stevens Johnson syndrome or Toxic epidermal necrolysis, acne eruptions, hair discoloration, alopecia, maculopapular rash and nail discoloration seen in less than 1% patients.
5. Respiratory infection with *Pneumocystis jiroveci* and aspergillus which manifests as non-reversible asthma and dyspnea.
6. Others - Other side effects are CVS (angina, palpitation), CNS (anxiety, depression and insomnia). Few cases of anaphylaxis have also been reported.

LEFLUNOMIDE ELIMINATION AND WASHOUT

This is recommended to achieve nondetectable plasma levels of leflunomide after stopping treatment.[7,8] The aim of washout procedure is to bring plasma level of leflunomide to less than 0.02 mg/l or 0.02μg/ml. The drug elimination procedure is indicated in:

(i) Female patients who plan to start a family
(ii) Worsening of respiratory symptoms or onset of new symptoms
(iii) Patients with renal insufficiency
(iv) In cases of adverse cutaneous drug reactions to leflunomide
(v) Simultaneous administration of drugs with hepatotoxic potential

Procedure of drug washout

Cholestyramine 8 g three times daily for 11 days (The 11 days need not be consecutive unless urgent reduction of plasma level is needed).[17] Verification of plasma level of the drug should be done by two separate tests done 14 days apart. If the plasma level is more than 0.02 mg/L, additional cholestyramine treatment should be considered.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube 50 mg every 6 h for 24 h, in addition to the cholestyramine dose that can be given for rapid reduction of plasma levels.

In cases of cutaneous adverse reactions, leflunomide must be stopped. Depending on the severity, systemic steroids can be instituted along with other supportive measures. Oral cholestyramine 4 gm tid may be given as it is expected to help in the excretion of leflunomide by interfering with biliary secretion and reabsorption of leflunomide.[17]

Leflunomide has a beneficial effect when used in setting of nephrotoxicity; however, there are no controlled trials of leflunomide use in the setting of rheumatoid or psoriatic arthritis with nephrotoxicity. Physicians should use the drug with regular monitoring of renal parameters and stop the drug at the earliest sign of renal abnormality.[18]

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