

Management of Hyperuricemia with the Novel Urat-1 Inhibitor, Lesinurad: A Meta-Analysis

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Abstract:

Ameta-analysis on the pharmacokinetics, pharmacodynamics, safety, efficacy, dosing, administration and use of Lesinurad, a novel URAT1 inhibitor for the management of hyperuricemia and gout. Results of randomised phase 3 trials on lesinurad shows that it is superior to xanthine oxidase inhibitors (XOIs) alone, in lowering serum uric acid to the target levels. It was also found to have a tolerable safety profile compared to other antigout therapies. Lesinurad can be considered as a suitable add-on medication for patients in whom XO treatment alone is less effective in achieving target sUA levels.

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I. Introduction

Gout is a chronic rheumatological disorder characterised by an increase in serum uric acid (UA) levels, resulting in the deposition of monosodium urate crystals in the major joints and associated connective tissues, resulting in recurrent inflammatory arthritis and tophi formation(1). It affects a large population and its incidence is found to increase with time(2). Urate is the metabolic endpoint of purine. It is obtained from xanthine and hypoxanthine by the action of the enzyme xanthine oxidase. Urate is excreted primarily through kidneys. Hyperuricemia can occur either due to overproduction or underexcretion by the kidneys, the latter being more common(3). Uric acid levels within the body depends on the balance between its production and excretion, but in most patients insufficient renal excretion of urate, leads to hyperuricemia and eventually gout(1). Hyperuricemia, typically is defined as serum uric acid (sUA) levels > 6.8 mg/dL (> 400 µmol/L), caused mostly due to inadequate uric acid excretion(4). Risk factors for hyperuricemia and gout include old age, male gender, consumption of alcohol, postmenopausal females, renal failure, use of diuretics, genetic factors and certain drugs(5).

Depending on the mechanism of action, agents used to treat hyperuricemia are generally classified into three categories:

- Agents that reduce the production of uric acid such as xanthine oxidase inhibitors [XOIs],
- Agents that promote the excretion of uric acid such as probenecid,
- Agents that cause enzymatic degradation of excess uric acid in circulation such as pegloticase.(3).

Guidelines suggest maintenance of serum urate (UA) levels of 6.0 mg/dl or 5.0 mg/dl in patients with severe disease (6). Xanthine oxidase inhibitors (XOI's) are recommended as first-line therapy for hyperuricemia by inhibition of urate production(1). In certain cases treatment with a xanthine oxidase inhibitor (XOI) alone may not prove to be effective, in such instances a uricosuric agent can be co-administered(2).

Lesinurad, a novel selective urate anion reabsorption inhibitor has been approved in the US and Europe for the treatment of gout as an add-on agent along with a xanthine oxidase inhibitor for patients in whom the target serum uric acid levels are difficult to achieve(6). In a phase 3 clinical trial, treatment with lesinurad 200 and 400mg, in combination with febuxostat (80 mg was found to be more effective when compared with febuxostat alone. This combination showed reductions in gouty attacks at 12 months when tested at the highest dose (400mg), a dose that resulted in renal adverse effect. (7). In phase I and II trials, Lesinurad with allopurinol showed greater reductions in serum UA levels than allopurinol alone. In phase III trial-Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders (CLEAR1), lesinurad (200 mg or 400 mg orally, once daily) in combination with allopurinol has been studied (8).

MECHANISM OF ACTION:

Lesinurad inhibits uric acid transporter URAT1 which filters majority of uric acid from the renal tubular lumen and promotes its excretion. Lesinurad also inhibits OAT4, another uric acid transporter which is involved in diuretic-induced hyperuricemia (9). Lesinurad shows no interaction with the uric acid reabsorption transporter SLC2A9 (Glut9) (10).

PHARMACODYNAMICS:

In gouty patients, decrease in serum uric acid levels and increase in urinary uric acid excretion was seen to be dose-dependent (10). In healthy volunteers, lesinurad 200 mg lowered sUA levels but when lesinurad 200 mg was added to a xanthine oxidase inhibitor (i.e. febuxostat), a better reduction in sUA were observed (9). Also lesinurad when tested up to 1600 mg did not demonstrate an effect on the QTc interval (10).

PHARMACOKINETICS:

Absorption:

The absolute bioavailability of lesinurad is approximately 100% and it is rapidly absorbed after oral administration. Absorption was found to be altered in presence of food.

Distribution:

Lesinurad is extensively bound to plasma proteins (greater than 98%), mainly to albumin. The mean steady state volume of distribution of lesinurad was approximately 20 L on intravenous administration.

Elimination:

The elimination half-life ($t_{1/2}$) of lesinurad is approximately 5 hours and its total body clearance is approximately 6 L/hr.

Metabolism:

Lesinurad undergoes oxidative metabolism chiefly via the polymorphic cytochrome P450 CYP2C9 enzyme. It is to be used with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9.

Excretion:

Unchanged lesinurad excreted in urine accounted for approximately 30% of the dose (10).

SAFETY:

Lesinurad 200 mg was shown to have good patient tolerability in three randomized clinical trials. In CLEAR 1 and CLEAR 2 trials, the common adverse effects observed with lesinurad and allopurinol treatment were upper respiratory tract infection, hypertension, sinusitis, arthralgia, increased blood phosphokinase levels, increased blood creatinine levels, headache, and diarrhoea (11). In renal insufficiency, uric acid available for reabsorption via URAT1 will be less, and the effectiveness of lesinurad will be diminished (12). Renal adverse events, and increase in sCr concentration, were commonly seen in patients on lesinurad treatment alone (13). Lesinurad can cause an increase in renal UA excretion, resulting in microcrystallization of uric acid in the urinary system and could result in kidney stones or acute UA nephropathy. In CLEAR 1 and CLEAR 2 studies, the incidence of kidney stones during lesinurad therapy was less when used in combination with a xanthine oxidase inhibitor. The timing of lesinurad administration may also contribute to the low rate of nephrolithiasis, because once-daily dosing in the morning tends to increase urinary UA at a time when urine volume and urine pH are highest and thus reduces the potential for UA precipitation. A few kidney stones have been observed in CRYSTAL trial. Lesinurad was also found to cause increased incidence of CV diseases. The most common adverse effects observed in the lesinurad and febuxostat were nasopharyngitis, hypertension, serum creatinine elevation, headache, extremity pain, and back pain (1). Headache, influenza and worsening of reflux were common adverse events seen during treatment with lesinurad (11). Lesinurad, tested at supratherapeutic doses up to 1,600 mg, did not cause QT interval prolongation or cardiac arrhythmia in healthy volunteers (14).

The proportion of patients with treatment associated adverse events throughout the course of the study was found to be 72.5% in the febuxostat group, 82.1% in the lesinurad 200 mg plus febuxostat group, and 82.6% in the lesinurad 400 mg plus febuxostat group (6). The Adverse events reported in those taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol, was found to be 68.7%, 73.1%, and 77.6% respectively (8).

EFFICACY:

CLEAR 1 and CLEAR 2 trials showed that lesinurad in combination with allopurinol was superior to allopurinol alone in lowering serum uric acid levels (15). In both the trials, lesinurad when used in combination with allopurinol, met the target serum uric acid (sUA) level of <6.0 mg/dL (360 μ mol/L) within 6 months, compared to those treated with allopurinol alone (8). In CRYSTAL trial, lesinurad 200 mg in combination with febuxostat showed greater sUA lowering compared to febuxostat monotherapy (16). About one-third of patients treated with lesinurad monotherapy at 400 mg once daily achieved an sUA level <6.0 mg/dl at 6 months in a

multinational study (17).

Extended studies for efficacy assessments were conducted after 12 months. The main observation of the extension study was number of complete resolution of tophus at each monthly visit and overall. Also the number of patients with either complete or partial resolution of at least one target tophus at each visit and overall, and the mean change from the baseline values for all target tophi at each visit were observed (18).

Table 1 : Proportion of patients who achieved target serum uric acid levels (5)(19)

Anti-hyperuricemic agent	Percentage of patients who achieved target sUA levels
Allopurinol (300 mg)	30% -70 %
Allopurinol (600 mg)	69% - 78%
Allopurinol (300 mg) + Lesinurad (200 mg)	54% - 63%
Allopurinol (300 mg) + Lesinurad (400 mg)	59% - 78%
Febuxostat (80 mg)	47% - 67%
Febuxostat (40 mg)	56%
Febuxostat (80 mg) + Lesinurad (200 mg)	56%
Febuxostat (80 mg) + Lesinurad (400 mg)	76%-100%

DOSING AND THERAPEUTIC USE:

Lesinurad, with a Xanthine Oxidase Inhibitor, is indicated for the treatment of hyperuricemia in gout patients. The recommended dose of lesinurad is 200 mg once daily. It is to be taken in the morning along with food and water, and patients must be counselled to take plenty of fluids as it affects the pharmacokinetics of the drug. Lesinurad must be taken in the morning along with the XO. If a dose of XO is missed, then lesinurad also must not be taken. Acute gouty attacks may be observed on initiation of lesinurad, resulting from the mobilization of urate from tissue deposits. Therefore, during first few months following initiation of lesinurad therapy, prophylaxis of gout attacks with colchicine or a nonsteroidal anti-inflammatory drug (NSAID) is recommended (1).

II. Discussion

Patients with very high serum uric acid levels who are on initial treatment might not reach the target levels even with appropriate dose titration. Patients may need more frequent monitoring of serum uric acid and early addition of a uricosuric agent probably at the time of initiation of therapy (20). Because of the inability of existing antigout agents in achieving target SUA levels and adverse effects associated with them, newer therapies are being explored. The fact that under-excretion of uric acid is a leading cause of hyperuricemia, urate transport proteins such as the human uric acid transporter 1 (URAT1) and the fructose transporter SLC2A9 are being targeted for treatment of hyperuricemia (3).

Lesinurad is a selective inhibitor of UA transport protein URAT 1, that has been approved as an add-on treatment for gout in combination with a XO. This drug is an orally available small molecule with a structure that is different from other known uricosuric agents. It acts by promoting the excretion of uric acid seen in patients with gout (21). Lesinurad, when used in combination with a Xanthine Oxidase Inhibitors (Allopurinol or Febuxostat), targets both production and excretion of UA providing a dual approach to lowering uric acid (16).

Lesinurad was found to be well tolerated in CLEAR 1, CLEAR 2, and CRYSTAL trials. The safety profile of the lesinurad 200 mg orally once daily was similar to that of allopurinol or febuxostat alone, except for elevations in serum creatinine levels. Because of the increased risk of adverse renal events monotherapy with lesinurad is not recommended.

The three studies showed greater achievement of serum UA targets with lesinurad 200 mg plus a XO compared with each XO alone. Twelve months was insufficient to observe significant differences in reduction of gouty flares and tophi and so subsequent extension studies were done to evaluate long-term efficacy and safety with combination therapy (1).

Lesinurad, 200 mg is recommended to be taken with food and water in the morning, resulting in higher excretion of uric acid at night when urine gets more concentrated. Therefore, patients should be advised to take plenty of fluids during treatment with lesinurad. Baseline renal function should be assessed prior to initiation of lesinurad treatment. No dosage adjustment is needed for patients with renal impairment, but lesinurad should be discontinued if serum creatinine falls below 45 ml/min and contraindicated if creatinine falls below 30 ml/min (22).

Further long-term studies are needed to evaluate the long-term efficacy and safety of lesinurad in a larger population and in patients with declined renal function (23).

III. Conclusion

Lesinurad in combination with a Xanthine Oxidase Inhibitor was more efficacious and safer compared to XOI monotherapy. Reduction in the serum UA concentration below 6 or 5 mg/dL was achieved with this combination. Further, Lesinurad was found to have better safety profile in comparison to other agents available for the treatment of gout. It also has lesser chance of drug interactions as with other uricosurics like probenecid. Therefore, Lesinurad can be considered as an additional treatment option for patients in whom XOI monotherapy is less effective.

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