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Review Article

Pharmacology Section

Lesinurad, a Novel Uricosuric Drug for Allopurinol-Refractory Gout Patients

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ABSTRACT

Gout is the most common type of arthritis in developed countries that is often inadequately managed. Evidence regarding role of hyperuricaemia in poor outcomes in gout patients (e.g., disability, recurrent hospital admissions) with/without other chronic cardiometabolic comorbidities prompts the search of newer and more effective drugs. Current management of gout is limited to NSAIDS and intra-articular corticosteroids in acute gout and Allopurinol or Febuxostat with or without probenecid in chronic gout. Other drugs used as add-on therapy in refractory cases of gout who fail on monotherapy include benzbromarone and pegloticase but with limited role. Though these drugs have been available for several years, significant proportion of compliant patients fail to achieve consistent control of uric acid levels resulting in acute gout flares. Recent advances in the role of urate transporters in proximal tubules of kidney have resulted in the development of new generation uricosuric drugs including lesinurad. It is recently approved by US Food and Drug Administration (US FDA) and European Medicines Agency (EMA) in patients with uncontrolled gout along with Allopurinol or Febuxostat. Hopefully, it will contribute to fulfill the unmet goals in management of gout.

This review aims at exploring the current therapeutic strategies for the management of chronic gout patients as well as their limitations and the role of Lesinurad in patients who have failed on monotherapy. The published studies and poster presentations were identified by conducting a literature search from electronic database from 1980 till January 2017, using various medical subject headings and terminologies. These studies were screened and publications considered relevant to the topic were included in the study.

Keywords: Arthritis, Chronic gout, Selective uric acid reabsorption inhibitor

INTRODUCTION

Gout is the most prevalent arthritis in adults worldwide. It has high incidence of approximately 2.68 per 1000 person-years in developed countries especially US and UK, and the prevalence increases significantly with age [1-3]. It is a chronic inflammatory condition with ever-increasing prevalence due to increased longevity and changing lifestyle and is commonly associated with other chronic diseases such as diabetes mellitus, hypercholesterolaemia, obesity, cardiovascular diseases, hypertension and chronic kidney disease [4]. Despite of the availability of existing drugs for treatment of gout for several years, significant number of patients do not have adequate control of uric acid levels resulting in acute gout flares and recurrent hospital admissions, increased healthcare utilisation, disability and poor quality of life [5-8]. Hence, there is need of newer agents with better and sustained effect on serum Uric Acid (sUA) levels.

For this review, the studies were identified by conducting a literature search from electronic database from 1980 till January 2017 on Google Scholar, PubMed, the Cochrane Library, and ongoing trials registers at Clinical Trials (http://www.clinicaltrials.gov/in) for original and review articles, meta-analysis and systematic reviews. Other data sources included scientific abstracts, poster presentations from annual meetings, conferences American College of Rheumatology (ACR), US FDA and EMA. The search was made using various medical subject headings and terminologies such as lesinurad, monotherapy, add-on therapy, Selective Uric Acid Reabsorption Inhibitor (SURI) and gout. The articles were screened and those most relevant to the topic were included in the study.

Gout Pathophysiology, Current Treatment Scenario and its Limitations

Gout is clinically characterised by painful joint inflammation, most commonly in the first metatarsophalangeal joint, resulting from precipitation of Monosodium Urate (MSU) crystals in a joint space consequent to hyperuricaemia. Diminished renal clearance of uric acid is responsible for hyperuricaemia in at least 90% of patients with gout [9]. The aim of primary prevention and treatment of gout patients is to reduce the incidence of acute or recurrent attacks of pain and inflammation by lowering and maintaining serum urate levels below the limit of urate solubility (approximately 6.8 mg/dL) [10-13]. Urate-Lowering Therapy (ULT) represents the main pillar in the management of chronic gout. Xanthine Oxidase Inhibitors (XOIs) remain the first line treatment. Among these, allopurinol is recommended as the preferred agent by all guidelines but the ACR guidelines recommends Allopurinol or Febuxostat interchangeably. Uricosurics are second-line drugs in combination with XOIs when XOI monotherapy is not effective [10-13].

During management of chronic gout, it is observed that XOI monotherapy fails to sufficiently lower serum urate to target level in a substantial subset of adherent patients along with decrease in total renal uric acid elimination [9,14,15]. Moreover, there is a risk of fatal hypersensitivity reaction with XOI in certain high-risk population including females, advanced age, renal impairment, presence of HLA B* 5801 genotype [16]. Recombinant uricase are newer drugs as add-on to the first-line drugs when monotherapy fails. High cost of uric acid degrading pegloticase infusion therapy in addition to infusion related adverse events and formation of neutralising anti-pegloticase antibodies make it unsuitable for majority of patients in developing countries like India [17-19]. Thus, there is unmet need to improve efficacy of oral urate-lowering therapy particularly in those patients failing on XOI with or without probenecid. The goal of emerging urate-lowering therapies is to address the unsatisfactory control of serum uric acid in patients with symptomatic hyperuricaemia. It aims at sustained efficacy and better tolerability by reduction in the risk of adverse events compared to traditional agents especially in elderly patients with comorbidities.

Uricosurics are drugs which increase renal urate excretion by competitive inhibition of Organic Anion Transporters (OATs) responsible for reabsorption of filtered uric acid in the lumen of proximal tubular cells. These uric acid transporters include URAT1, GLUT9 mainly and/or OAT1, 3, 4. The two main agents of this class are probenecid and benzbromarone whereas sulfinpyrazone has very restricted use. The literature search supports that probenecid and benzbromarone significantly lower uric acid, with magnitude of effect comparable to allopurinol, but with substantial Adverse Events (AE) for both agents, including severe hepatotoxicity with benzbromarone and increased risk of urolithiasis with probenecid [9,20-23]. In contrast to Benzbromarone, Lesinurad and Probenecid showed no mitochondrial toxicity. Peroxisome Proliferator-Activated Receptor gamma (PPARγ) activation which is associated with increased cardiovascular risk is also shown by Benzbromarone but not by Lesinurad and Probenecid in clinically used doses [9]. However, short half-life of probenecid necessitates its higher dose frequencies up to four times daily. Moreover, probenecid is prone to drug–drug interactions as it alters the Pharmacokinetics (PK) of a wide variety of other drugs through inhibition of OAT1 and OAT3 (OAT1/SLC22A6 and OAT3/SLC22A8) [24,25]. Since, clinical trials of probenecid have shown that relatively higher percentage of patients achieve lower sUA goal when used add-on to allopurinol than as monotherapy in patients of chronic gout, it is still reserved as an option for those who cannot tolerate allopurinol or cannot reach target sUA on monotherapy with XOI.

LESINURAD

History of Development

The Lesinurad prodrug (RDEA806) is a non-nucleoside reverse transcriptase inhibitor discovered to have significant hypouricaemic properties in clinical trials for treatment of HIV patients. It was then chosen for clinical trials in hyperuricaemia patients and results found it to be an effective uricosuric in patients of gout especially those who have failed on XOI monotherapy [26,27]. Lesinurad is a small molecule with a structure unrelated to previously known uricosuric agents [9].

Mechanism of Action

Lesinurad (RDEA594) is a SURI which increases urate excretion by acting as Uric Acid Transporter (URAT1) and OAT4 inhibitor at proximal renal tubules with IC50 values of 7.3 and 3.7 μM, respectively. URAT1 encoded by SLC22A12 is responsible for bulk reabsorption of filtered uric acid from lumen of proximal renal tubules whereas OAT4 is associated with diuretic-induced hyperuricaemia. Unlike probenecid, lesinurad did not inhibit OAT1 or OAT3 in the clinical setting leading to fewer drug interactions [9]. Also, lesinurad does not inhibit the uric acid reabsorption by newly discovered uric acid transporter SLC2A9 (also known as GLUT9) located on basolateral membrane of the proximal tubule cell on the basolateral membrane of the proximal tubule cell and ABCG2 encoded apical membrane transporter involved in urate secretion [9,23,27]. Compared to benzbromarone, lesinurad has low mitochondrial toxicity and PPARγ induction translating clinically to lower risk of hepatotoxicity and adverse cardiovascular events [9].

Dosage and Administration

Lesinurad is recommended by FDA in dose of 200 mg once daily orally with XOI either allopurinol or febuxostat in patients with Creatinine Clearance (CrCL) of 60 mL/minute or greater who have failed to achieve or maintain the target serum uric acid levels on allopurinol monotherapy in dose of ≥300 mg. It is not recommended for treatment of asymptomatic hyperuricaemia, severe renal impairment with CrCL <60 mL/minute, or severe hepatic impairment [28,29].

Pharmacodynamics

In gout patients, lesinurad lowers serum uric acid levels by increasing renal clearance and Fractional Excretion of Uric Acid (FEUA) in dose-dependent manner. It has a higher potency for URAT1 compared with probenecid. Lesinurad at doses up to 1600 mg did not demonstrate an effect on cardiac repolarisation or the QTc interval in normal healthy subjects and gout patients [29-31].

Pharmacokinetics

The drug has a bioavailability of 100% and reaches maximum plasma concentration (Cmax) within one to four hours. Volume of distribution is 20 L following intravenous dosing. Lesinurad is extensively plasma protein bound (up to 98%), binds mainly to albumin. Plasma protein binding of lesinurad is not significantly altered in patients with renal or hepatic impairment [29]. The drug is primarily metabolised by CYP2C9 enzyme. Since, CYP2C9 is known to have genetic polymorphisms, patients who are poor CYP2C9 metabolisers will have higher concentration of lesinurad. Thus, the drug is to be used with caution in CYP2C9 poor metabolisers and in patients taking CYP2C9 inhibitors. Metabolites are not known to contribute to the uric acid lowering effects. The elimination half-life (t½) of lesinurad was approximately five hours and total clearance is 6 litre/hour [29]. Lesinurad does not accumulate following multiple doses [30]. Lesinurad is excreted approximately 32% in urine over seven days following administration of radiolabelled dose. Unchanged lesinurad in urine accounted for approximately 30% of the dose [26]. No clinically significant difference in PK of lesinurad was found due to gender, race or ethnicity in population PK analysis [32]. Also, when administered with XOI, no clinically relevant changes in the PK of Lesinurad or the XOIs Febuxostat or Allopurinol have been detected in patients with gout [31].

Important clinical differences between Lesinurad and Probenecid are due to high plasma protein binding of Lesinurad of up to 98% leading to plasma-free concentrations that are insufficient to inhibit OAT1 in vivo [9]. Thus, the in vivo clinical effects of Lesinurad show inhibition of both URAT1 and OAT4 (unlike Benzbromarone, which inhibits only URAT1) but no inhibition of OAT1 and OAT3 (unlike probenecid which inhibits URAT1, OAT4, OAT1, and OAT3) [9,33].

Drug Interactions

Lesinurad is a substrate for CYP2C9, OAT1 and OAT3 but primarily metabolised by CYP2C9 enzyme. Since, CYP2C9 is known to show genetic polymorphisms, higher plasma concentration of lesinurad is reported in subjects who are poor CYP2C9 metabolisers (up to 1.8 fold higher concentration than in normal individuals) or those taking moderate inhibitors of CYP2C9 (e.g., fluconazole, amiodarone); warranting cautious use of lesinurad in these subjects. Lesinurad exposure is decreased when Lesinurad is coadministered with moderate inducers of CYP2C9 (e.g., Rifampin, Carbamazepine), which may decrease the therapeutic effect of the drug. Aspirin at doses of 325 mg or less per day used for cardiovascular protection does not decrease the efficacy of Lesinurad and can be safely coadministered with Lesinurad though higher doses that may decrease the efficacy of Lesinurad in combination with allopurinol [29].

In vitro assays indicate that Lesinurad is an inducer of CYPs in the order CYP3A >CYP2C8 >CYP2C9 >CYP2C19 >CYP2B6 and an inhibitor of CYP2C8 and CYP2C9 [34,35]. However, in vivo studies show induction of CYP3A but no apparent induction of CYP2C8 and CYP2C9 based on co-exposure effects on sildenafil, amlodipine, repaglinide and tolbutamide [36].

Lesinurad is an inhibitor of OATP1B1, OCT1, OAT1, and OAT3 as per in vitro assays. However, in vivo drug interaction studies show that lesinurad is not an inhibitor of these transporters and does not affect atorvastatin (substrate of OATP1B1) or Metformin (substrate of OCT1). Also, Lesinurad does not decrease the renal clearance and diuretic activity of furosemide (substrate of OAT1/3) which is in stark contrast to Probenecid, which alters the PK and renal excretion of Furosemide as Probenecid is an inhibitor of OAT1 and OAT3, thereby limiting its use due to clinically significant OAT1/

OAT3-dependent drug-drug interactions [9,21,33,35-36].

Safety and Tolerability

Clinical trials showed that lesinurad 200 mg in combination with a XOI was associated with an increased incidence of serum creatinine elevations, which were reversible by the end of study period. Rarely, elevation of serum creatinine levels 1.5 to 2 times the pre-treatment values or acute renal failures were reported with lesinurad in doses of ≥400 mg as monotherapy. Other adverse effects reported include headache, gastroesophageal reflux disease and influenza [28]. Some risk of cardiovascular events and non-fatal myocardial infarctions was seen in patients treated with lesinurad as compared to placebo but a causal relationship to lesinurad could not be established [28,29]. Contrary to it, lesinurad was shown to be cardiovascular safe in a recent study even in supratherapeutic doses upto 1600 mg having no significant effect on the QT interval in healthy male or female subjects [30].

Precautions

Gout flare prophylaxis is recommended when starting lesinurad as gout flares may occur after initiation of the drug due to mobilisation of urate from tissue deposits consequent to changing serum uric acid levels. It should be ensured that patients stay well-hydrated [e.g., 2 liters (68 oz) of liquid per day] in order to reduce the risk of nephrotoxicity. Lesinurad should not be initiated in patients with a CrCL <60 mL/minute. Hence, assessment of renal function is recommended prior to initiation of lesinurad therapy and periodically thereafter. More frequent renal function monitoring is recommended in patients with a CrCL below 60 mL/minute or with elevation of serum creatinine levels 1.5 to 2 times the pre-treatment values [29]. Lesinurad should be discontinued when CrCL is persistently less than 45 mL/minute or serum creatinine is elevated to ≥2 times the pre-treatment value or in patients reporting symptoms of acute uric acid nephropathy [28].

Contraindications

The use of lesinurad is contraindicated in severe renal impairment (CrCL less than 30 mL/minute), end stage renal disease, kidney transplant recipients, or patients on dialysis or intolerant to colchicine, tumour lysis syndrome or Lesch-Nyhan syndrome [27].

Use in Special Populations

There are no available human data on use of lesinurad in pregnant women, lactating mother, paediatric population or young adults under 18 years of age. No dose adjustment is necessary in patients with mild or moderate renal impairment (CrCL of 45 mL/minute or greater), mild or moderate hepatic impairment (Child-Pugh classes A and B) or in elderly. Lesinurad has not been studied in patients with severe renal or hepatic impairment and is therefore not recommended in these patients [26,37].

Clinical Trials

As shown in [Table/Fig-1], Phase I open-label ascending-dose

Clinical Trial Name	Phase of trial	Study Duration	Sample Size	Test group	Standard comparator	Primary end point	Results/outcome (% of patients achieving primary end point)	Adverse effects	Reference
	I	Six weeks	34 in single ascending dose (SAD), 32 in multiple ascending dose (MAD)	Lesinurad monotherapy SAD group-lesinurad doses from 5 mg to 600 mg (5, 25, 100, 200 400, 600 mg) MAD group-lesinurad doses from 100 mg to 400 mg (100, 200, 400 mg).	Placebo	Median percent change from baseline in serum uric acid, Increases in urinary excretion of uric acid and reductions in serum uric acid, area under the plasma concentration–time curve (AUC), urinary excretion of unchanged lesinurad.	Reductions in serum uric acid and increases in urinary excretion of uric acid, AUC, increased in a dose-dependent manner. No apparent accumulation following multiple doses.	No significant differences in adverse effects between the groups Lesinurad was generally safe and well tolerated. All AEs were mild in severity and resolved without treatment.	Shen Z et al., [26].
	IIa	Four weeks or one month	208	Lesinurad 200 mg or 400 mg or 600 mg+Allopurinol.	Allopurinol 300-900 mg+placebo	Percentage of patients with s. uric acid <6 mg/dL at four weeks	63%, 73.8% and 79.2% versus 25%	No significant differences in adverse effects between the groups.	Perez-Ruiz F et al., Sundy J et al. [38-40].
	IIb	44 weeks or 11 months	126	Lesinurad 200 mg or 400 mg+Allopurinol	Allopurinol 300-900 mg+placebo	Percentage of patients with s. uric acid <6 mg/dL at 44 weeks	78% versus 56%	No significant differences in adverse effects between the groups.	Perez-Ruiz F et al., Sundy J et al. [38-40].
CLEAR-1	III	12 months	603	Lesinurad 200 mg or 400 mg+Allopurinol	Allopurinol 300-900 mg+placebo	Percentage of patients with s. uric acid <6 mg/dL at six months	54.2% and 59.2% respectively versus 27.9%	Elevations of serum creatinine (SCr) to upto two times of the baseline level in 6% pt's with resolution of to baseline values by the end of the study without need to discontinue medication in all in 200 mg group and 85% pt's of 400 mg group Episodic AKI without gross urolithiasis in some pt's of 400 mg group.	Saag KG et al., [41].
CLEAR-2	III	12 months	610	Lesinurad 200 mg or 400 mg+Allopurinol	Allopurinol 300-900 mg+placebo	Percentage of patients with s. uric acid <6 mg/dL at six months.	55.4% and 66.5% respectively versus 23.3%	Elevations of serum creatinine (SCr) to upto two times of the baseline level in mostly in lesinurad 400 mg group with resolution of to baseline values in all.	Bardin T et al., [42].

Clinical Trial Name	Phase of trial	Study Duration	Sample Size	Test group	Standard comparator	Primary end point	Results/outcome (% of patients achieving primary end point)	Adverse effects	Reference
LIGHT	III	Six months	214	Lesinurad 400 mg monotherapy	Placebo	Percentage of patients with s. uric acid <6 mg/dL.	29.9% versus 1.9%	Elevations of serum creatinine (SCr) to upto two times of the baseline level 8.4% pt's with resolution of to baseline values in <50% pt's treated with lesinurad.	Tausche AK et al., [44].
CRYSTAL	III	Six months	324	Lesinurad 200 mg or 400 mg+Febuxostat 80 mg	Febuxostat 80 mg+placebo	Percentage of patients with s. uric acid <5 mg/dL Resolution of ≥1 tophus or decrease in tophus area.	56.6% and 76.1% respectively versus 46.8%	Elevations of serum creatinine (SCr) to upto two times of the baseline level mostly in lesinurad 400 mg group with resolution of to baseline values in all.	Dalbeth N et al., [45].

[Table/Fig-1]: Comparison of lesinurad as monotherapy, combination therapy in different clinical trials.

three weeks study in healthy adult males having sUA >5 mg/dL with CrCl >80 mL/minute comparing PK, pharmacodynamics, bioavailability and safety of lesinurad in doses between 5 mg and 600 mg in single ascending dose (n=34), multiple ascending dose (n=30) and bioavailability studies (n=8) showed that lesinurad is safe and well-tolerated as sUA concentrations decreased significantly with lesinurad in dose-dependent manner with sustained effect. There was no accumulation of lesinurad and no effect of food on its bioavailability and extent of absorption [38].

Phase IIa and IIb double-blind dose-finding trials of four weeks and 44 weeks duration respectively in patients of hyperuricaemia with sUA ≥6 mg/dL on more than two occasions more than two weeks apart despite of six weeks or more of allopurinol with CrCl >60 ml/minute showed that lesinurad was significantly more effective than placebo with no significant difference in incident AEs between the groups except for elevation of serum creatinine in 400 mg group which returned to baseline by the end of study [38-40].

Promising results in the phase II trials encouraged many phase III trials namely CLEAR-1, CLEAR-2, LIGHT and CRYSTAL of 6-12 months duration comparing the efficacy and safety of lesinurad 200 mg and 400 mg as add-on to XOI (allopurinol in all except febuxostat in CRYSTAL trial) versus placebo in patients of hyperuricaemia with sUA >6 mg/dL with inadequate response to a stable dose of allopurinol of at least 300 mg (or 200 mg for moderate renal impairment) or contraindication to XOI. Most of the patients had gout diagnosis for ≥12 years with at least two gout flares in the prior 12 months and mild to moderate renal impairment with CrCl >45 mL/minute. The primary outcome was percentage of patients achieving sUA <6 mg/dL at the end of six months. Secondary outcome was percentage of patients achieving sUA <5 mg/dL and/or complete resolution of ≥2 tophi or decrease in tophus area or rates of gout flares. The results of all these trials showed that lesinurad was safe and more efficacious than placebo in terms of significantly higher percentage of patients achieving primary outcome with no significant difference in AE as compared to placebo group except for rise of serum creatinine to up to twice the baseline reading with lesinurad (mostly in 400 mg group) with return to baseline levels in all by the end of study. There were no major AE leading to discontinuation of the drug except for episodic Acute Kidney Injury (AKI) without gross urolithiasis seen in few patients of lesinurad 400 mg group in CLEAR trials. Also, secondary outcomes were achieved by significantly higher proportion of patients in lesinurad group in all these trials [41-44]. The results of LIGHT trial comparing lesinurad 400 mg monotherapy versus placebo however differed from other trials in terms of significantly less proportion of patients achieving the primary outcome and higher percentage of patients showing rise of serum creatinine to up to twice the baseline level with return to baseline in less than half of the patients by the end of study [44].

The clinical trials of lesinurad (randomised, multicentre, placebo-controlled) are summarised in [Table/Fig-1].

Current Status of Drug

Lesinurad is currently approved by US FDA and EMA 200 mg once daily to treat gout-associated hyperuricaemia, in combination with a XOI who have failed to achieve or maintain the target serum uric acid levels on XOI monotherapy. The drug is to be avoided in patients with a creatinine clearance of less than 45 mL/minute [9,29].

DISCUSSION

Despite of high prevalence and significant impact of inadequate management on productivity and quality of life, therapeutic options for gout are sparse. This has led to a suboptimal patient care and poor health outcomes.

Xanthine Oxidase Inhibitors (XOIs) are first-line therapy in patients of chronic gout but allopurinol fails to lower serum urate to target level in a substantial subset of adherent patients. Although, Febuxostat has emerged as a good option, its availability is still limited because of it's high cost and health insurance coverage considerations. Also, Pegloticase use is limited by infusion reactions, high cost, and/or the formation of neutralising anti-pegloticase antibodies. Uricosurics use is limited in renal impairment due significant adverse effects like urolithiasis and substantial drug interactions with probenecid and severe hepatotoxicity with Benzbromarone. Lesinurad is novel selective uricosuric that overcomes the above limitations and is effective in patients with inadequate response on XOI monotherapy. All uricosurics are ineffective in renal damage and themselves carry increased risk of precipitation of urate stones. The safety of lesinurad in patients with moderate to severe renal impairment and other comorbidities is still not known. More efforts are needed to elucidate them and development of drugs that lessen the sUA levels with no/minimal risk of urolithiasis and other renal adverse events.

CONCLUSION

Results of lesinurad from phase II and III trials are encouraging. When compared to existing drugs for treatment of gout, it has emerged as novel therapeutic alternative for gout patients who have failed on XOI monotherapy. Combination therapy of Lesinurad with XOI clearly represents a future treatment option for patients of tophaceous gout on XOI who warrant additional therapy due to incomplete resolution of symptoms or intolerance to XOI. Hopefully, when introduced in clinical setting, Lesinurad in combination regimes will help to achieve the unmet goals in management of chronic gout.

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