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New Drug Update

Lesinurad: a novel therapeutic option in the pharmacotherapy of gout

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ABSTRACT

Gout is characterized by painful joint inflammation, most commonly in the first metatarsophalangeal joint, resulting from precipitation of monosodium urate crystals in a joint space. Current therapies for chronic gout include mainly allopurinol and febuxostat. Inspite of the availability of these medications for several years, a significant number of patients do not have adequate control of uric acid levels resulting in acute gout flares. Lesinurad is the most recent drug molecule approved by US FDA & EMA for the treatment of gout in patients with uncontrolled gout along with allopurinol. Lesinurad prevents reabsorption of uric acid from the renal tubules, resulting in uricosuria. The efficacy of the lesinurad was demonstrated in three randomized phase 3 controlled clinical trials where the drug was primarily evaluated in the setting of background therapy with allopurinol or febuxostat. There is a definite risk of nephrotoxicity with monotherapy and when the drug is used in patients who have inadequate renal function. The drug does appear to be relatively safe, though the inconclusive cardiovascular safety of the drug has prompted the regulatory agency to mandate post marketing trials to evaluate the safety of this molecule. Nevertheless, lesinurad does appear to have a lot of promise as a front line drug molecule in the control of hyperuricemia.

Keywords: Allopurinol, Gout, Hyperuricemia, Lesinurad, Renal function

INTRODUCTION

Gout is characterized by painful joint inflammation, most commonly in the first metatarsophalangeal joint, resulting from precipitation of monosodium urate crystals in a joint space.[1] The chronic inflammation seen in gout can lead to chronic pain, joint destruction and deformities and decrements in function and quality of life, among patients who receive treatment.[2] Uric acid largely exists as urate (the ionized form, pKa is 5.8) at neutral pH and it is the end product of purine metabolism in humans. High serum levels of urate (hyperuricaemia) are causative in gout and urolithiasis.[3] Gout occurs due to the risk factors such as high protein intake, purine rich foods and consumption of alcohol.[4,5]Allopurinol is the drug of choice for hyperuricemia and has been in the market for several decades. However the drug is not devoid of its unique set of problems. Patients taking allopurinol are at a risk of developing a fatal hypersensitivity reaction and certain populations are at a greater predilection to develop this event such as female gender, advanced age, renal impairment, presence of HLA B* 5801 genotype.[6] Lesinurad is a novel drug that was approved by the US FDA in 2015 for the treatment of hyperuricemia associated with gout.[7] We have attempted a brief review on the mechanism of action, efficacy, safety, pharmacokinetics and current status of the lesinurad in the treatment of gout.

MECHANISM OF ACTION

Uric acid transporter 1 (URAT 1) is present in the proximal convoluted tubule of the kidney that accounts for the bulk of the filtered uric acid from the lumen of the

renal tubules. Lesinurad binds to the URAT 1 and results in inhibition of uric acid reabsorption by the kidneys resulting in uricosuria and lowering of serum uric acid.[7]

EFFICACY

The efficacy of the lesinurad drug has been evaluated by three pivotal, multinational; phase 3 studies [CLEAR 1 and CLEAR 2, CRYSTAL].[8,9] The CLEAR 1 and 2 study included patients with uncontrolled gout. In both of these studies, patients were randomized to receive lesinurad 200 mg or 400 mg or placebo. There was distinctly greater proportion of patients who achieved the target lowering of less than 6 mg/dl among those taking the 400 mg dosage when compared with placebo. Similar results were seen in the CRYSTAL study which was performed among patients with tophaceous gout (Table 1). There was no difference in the number of gout flares in the six month period following stoppage of investigational drug. Lesinurad did not have any significant effect on the reduction of the number of tophi in the CRYSTAL study. Health related quality of life remain unchanged between the study groups. In the LIGHT study which assessed lesinurad monotherapy among subjects intolerant to Allopurinol, about one third of participants treated with 400 mg lesinurad showed a reduction of serum uric acid less than 6 mg/dl.[10]

Table 1: Summary of results of phase 3 trials of lesinurad in subjects with gout.

Name of study (year)	Population	Sample size	Study groups	Background therapy	Primary end point	Results (percentage of patients who achieved primary end point)
CLEAR 1	Uncontrolled gout with serum uric acid less than 6 mg/dl	603	Lesinurad 200 mg Lesinurad 400 mg Placebo	Allopurinol 300-900 mg/d	Proportion of patients with serum uric acid <6 mg/dl by month six	Group 1- 54.2% Group 2- 59.2% Group 3- 27.9%
CLEAR 2	Uncontrolled gout with serum uric acid less than 6 mg/dl	610	Lesinurad 200 mg Lesinurad 400 mg Placebo	Allopurinol 300-900 mg/d	Proportion of patients with serum uric acid <6 mg/dl by month six	Group 1- 55.4% Group 2- 66.5% Group 3- 23.3%
CRYSTAL	Uncontrolled Tophaceous gout with serum uric acid less than 5 mg/dl	324	Lesinurad 200 mg Lesinurad 400 mg Placebo	Febuxostat 80 mg	Proportion of patients with serum uric acid <5 mg/dl by month six	Group 1- 56.6% Group 2- 76.1% Group 3- 46.8%

SAFETY

Headache, influenza and worsening of reflux were common adverse events seen among lesinurad users. There were instances of worsening serum creatinine in a small proportion of patients with lesinurad and that resolved before completion of study without dosage adjustment. Major adverse cardiovascular events were observed with an incidence of 1.36 per 100 patient years and 2.71 for lesinurad 200 and 400 mg respectively. Nevertheless a causal relationship between the drug and MACE remains to be established.[11]

PHARMACOKINETICS

The drug has a bio availability of 100% and reaches Cmax within 1-4hrs. Drug is extensively bound to albumin. Volume distribution is 20 L. Mean half-life is approximately 5 hrs and total clearance is 6 lt/ hr. The drug is primarly metabolised by CYP2C9 enzyme. Since CYP2C9 is known to have genetic polymorphisms, patients who are poor CYP2C9 metabolisers will have higher concentration of lesinurad.[12]

CURRENT STATUS OF DRUG

The US Food and Drug Administration (FDA) have approved lesinurad (*Zurampic*, AstraZeneca) 200 mg once daily to treat gout-associated hyperuricemia, in combination with a xanthine oxidase inhibitor (XOI).[13] The drug was also approved in the European market for the same indication. Trials are underway with a fixed dose combination of lesinurad and allopurinol to confirm its bioavailability. As there has been sufficient concerns on its cardiovascular and renal safety post marketing extension studies are underway to explore the safety of this molecule.[14] The drug is to be avoided in patients with a creatinine clearance of less than 60 ml/min.

CONCLUSION

The approval of lesinurad is certainly a shot in the arm for all physicians who treat patients with gout as it provides them a much needed alternative particularly in that subset of patients who continue to have persistently elevated uric acid levels resulting in painful tophi. The results of phase 3 trials have given sufficient ground for the drug's approval by the regulatory bodies. Nevertheless the long term safety of this molecule through post marketing surveillance would help us understand the molecule better.[14]

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