Review Article

Lesinurad: A significant advancement or just another addition to existing therapies of gout?

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ABSTRACT

Gout is a metabolic disorder that usually presents as recurrent episodes of acute arthritis due to deposition of crystals in joints and cartilages. Despite the availability of several drugs for gout, its management is still less than adequate. There is always a search for newer, safer, and more potent urate-lowering therapies for treating patients inadequately controlled with available drugs. Lesinurad in combination with a xanthine oxidase inhibitor provides an effective mode of therapy in the management of hyperuricemia associated with gout. Lesinurad is a selective uric acid transporter 1 (URAT1) inhibitor. URAT1 is responsible for the majority of uric acid absorption from kidneys to the circulation. Lesinurad was granted marketing approval based on three randomized, double-blind, placebo-controlled; phase III clinical trials. It is devoid of interaction with organic anion transporters (OATs) such as OAT1 and 3, responsible for drug–drug interactions, an undesirable property associated with probenecid. On-going research is more focused on reducing inflammation consequent to deposition of crystals rather than production and excretion of urate. Various targets are being explored, and interleukin-1 beta inhibition seems to be one of the most promising approaches.

Key words: Hyperuricemia, lesinurad, uric acid transporter 1, xanthine oxidase inhibitor

INTRODUCTION

Gout is a metabolic disorder wherein fundamental biochemical abnormality is hyperuricemia.[1] It clinically presents as recurrent episodes of acute arthritis due to deposition of monosodium urate crystals in joints and cartilage.[2] The crystallization of uric acid depends on several factors such as temperature, pH, concentration of cations, the level of articular dehydration, and the presence of such nucleating agents as nonaggregated proteoglycans, insoluble collagens, and chondroitin sulfate.[3] In comparison to its hypoxanthine and xanthine precursors, uric acid is relatively insoluble. Low temperature favors crystal deposition making peripheral regions of the body more susceptible.[4] Urate crystals through toll-like receptor pathway lead to activation of the NALP3 inflammasome with the release of proinflammatory cytokines including interleukin-1 beta (IL-1β) and tumor necrosis factor (TNF)-α. These cytokines, in turn, cause endothelial activation and attraction of neutrophils to the site of inflammation.[5-7]

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Urate is the end product of purine metabolism. It is produced 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.

The recommended serum uric acid (SUA) target to durably improve the signs and symptoms of gout is <6 mg/dL.[8-10] However, a target of SUA <5 mg/dL is recommended for greater disease severity, such as patients with tophaceous gout.[8,9]

Agents used to treat hyperuricemia can be grouped into three categories based on their mechanism of action: Drugs that decrease uric acid production (xanthine oxidase inhibitors [XOIs]; allopurinol and febuxostat); drugs that increase urinary uric acid excretion (probenecid); and drugs that enzymatically degrade excess circulating uric acid (pegloticase).

Newer targets for treating gout have been persistently explored because none of the currently used drugs can be called ideal. This is primarily because of ineffectiveness in achieving target SUA levels and adverse effects associated with available therapies. Considering under-excretion of uric acid as major cause of hyperuricemia, in recent years important urate transport proteins such as the human uric acid transporter 1 (URAT1) and the fructose transporter SLC2A9 have been characterized.[11,12] Lesinurad, a newer drug to treat chronic refractory gout by targeting the URAT1 transporter, has been approved recently by the US Food and Drug Administration in combination with an XOI.[13] It has also been currently approved by the European Commission for marketing authorization throughout the European Union in February 2016.[14]

PHARMACOLOGICAL BASIS FOR USE OF LESINURAD IN PATIENTS OF GOUT

Urate homeostasis depends on the balance between production, complex processes of secretion and reabsorption in the kidney tubule as well as excretion in the intestine. It is estimated that approximately 30% of urate excretion is by the intestine and 70% by renal mechanisms.[15] URAT1 is a 12-transmembrane domain containing protein found in the apical membrane of proximal tubular epithelial cells and transports urate in exchange for Cl – or organic anions. The antiuricosuric agents lactate, pyrazinoate, and nicotinate can serve as a substrate for the antiporter activity of URAT1 to increase urate reabsorption. On the other hand, URAT1 is inhibited by the classical uricosuric agents benzbromarone, probenecid, and losartan.[16-18] Uric acid is freely filtered in the kidney at the glomerulus and enters the proximal tubule where more than 90% is reabsorbed back into the bloodstream through URAT1.[19]

Any uric acid that is not reabsorbed moves to the distal part of the nephron and is excreted in the urine. In the majority of patients with gout, hyperuricemia is caused by inefficient renal excretion of uric acid.[20] Lesinurad is a selective uric acid reabsorption inhibitor that inhibits the URAT1; thus, increases uric acid excretion. Lesinurad also inhibits organic anion transporter 4 (OAT4), an URAT1 involved in diuretic-induced hyperuricemia.[21]

XOIs such as allopurinol and febuxostat act by reducing the production of uric acid, primarily in the liver and intestine. Targeting both excretion and production of uric acid provide a dual mechanism approach to effectively lower SUA levels. This combination approach is considered ideal for those who do not achieve SUA targets on a XOI alone, and in patients with uncontrolled gout as evident by continuing disease activity.[8,9]

Lesinurad has rapid oral absorption and is highly plasma protein bound. Approximately, half of the oral dose is cleared via CYP2C9 metabolisms;[22] therefore, caution is required when it is administered with moderate CYP2C9 inhibitors (e.g., fluconazole, amiodarone). Lesinurad has no relevant effect on anionic or cationic transporters such as OAT1 and OAT3 which are mainly responsible for drug–drug interactions associated with probenecid.[22]

CLINICAL TRIALS

The regulatory approval of lesinurad is based on three randomized, double-blind, placebo-controlled; phase III clinical trials - CLEAR 1, CLEAR 2, and CRYSTAL.

Two replicate studies (CLEAR 1, CLEAR 2) evaluated lesinurad (200 or 400 mg oral, once daily) in combination with allopurinol versus allopurinol + placebo in subjects with gout aged 18–85 years. Subjects were required to be on stable allopurinol doses ≥300 mg (≥200 mg for moderate renal impairment), have SUA ≥6.5 mg/dL at screening, and history of ≥2 gout flares in the prior 12 months. The primary endpoint was the proportion of subjects meeting SUA target of <6.0 mg/dL by 6 months. Lesinurad (200 or 400 mg) in combination with allopurinol achieved SUA target at 6 months by ~2–2.5-fold compared to allopurinol alone.[23]

Similarly, the CRYSTAL[24] study evaluated lesinurad in combination with febuxostat against febuxostat monotherapy in patients with tophaceous gout. Not only the combination therapy resulted in the higher proportion of patients achieving SUA <5 mg/dL at 6 months but also achieved greater tophus area resolution.

DOES LESINURAD HAS AN EDGE OVER EXISTING URICOSURICS?

- OAT1 and OAT3 are organic transporters involved in the movement of uric acid through the basolateral membrane

to the circulation. Many drugs such as tenofovir and emtricitabine, reverse transcriptase inhibitors depend on OAT1 and OAT3 for clearance through kidneys. Existing urate lowering drugs such as probenecid and benzbromarone inhibit OAT1 and OAT3 thus posing a significant problem of drug–drug interactions. Lesinurad devoid of interaction with OAT1 or OAT3, is a major breakthrough in solving this hurdle of clinically relevant drug–drug interactions[25]

- It has been shown in animal[26] as well as clinical[27] studies that no unfavorable pharmacokinetic interaction or interference with urinary excretion exists between lesinurad and XOIs such as allopurinol or oxypurinol and febuxostat. Coadministration of lesinurad and XOIs thus could safely be used to accelerate urate reduction in gout patients
- Continued use of allopurinol at suboptimal doses in patients with renal insufficiency could worsen renal failure, or sometimes may precipitate fatal hypersensitivity syndrome.[28] Under-dosing for fear of side-effects is clearly a hindrance in achieving therapeutic goal. Combining lesinurad at a fixed dose of 200 mg/day with XOIs helps in controlling hyperuricemia more effectively. Evidence is available that effective treatment of hyperuricemia may improve renal functions. Introduction of lesinurad has effectively addressed the issue of allopurinol under dosing
- It also inhibits OAT4, a URAT1 involved in diuretic-induced hyperuricemia. In future, it might be indicated to prevent hyperuricemia usually associated with prolonged diuretic (loop or thiazides) therapy.

THERAPIES IN PIPELINE

Further research for the management of gout is directed towards limiting the inflammatory events that are initiated by the deposition of urate crystals. Various specific targets in the inflammatory pathway of gout are:

- NALP3 inflammasome and IL-1β[5-7]
- Complement C5b-9 membrane attack complex,[29] agonism of phagocyte melanocortin receptor 3 (shown to be a direct peripheral target of adrenocorticotropic hormone), the chemokines CXC1 and CXCL8, TNF-α.[30]

Among above targets, IL-1β neutralization appears to play a central role in the control of inflammatory events. Both animal[31] and clinical[32] studies have demonstrated the effect of IL-1β inhibition by anakinra in gout. Based on the above findings, biologics against IL-1β such as canakinumab and rilonacept were evaluated for its effect in patients of acute gout or those who were intolerant to existing therapies. Both the agents demonstrated a significant improvement in the patients' symptoms such as gout flares, and pain as compared to placebo or corticosteroids.[25] Further clinical trials on a large scale with IL-1β inhibitors will help in establishing their role in patients of gout.

CONCLUSION

Apprehensions and confusions about how to use existing drugs in the management of gout is a perpetual issue, and merely addition of new drugs is not sufficient to resolve these misconceptions. Availability of a new therapy always offers an opportunity for us to revisit the treatment strategies to improve outcome in this highly treatable disease. Concerns clearly warrant additional treatment options for patients with gout who are unable to achieve and sustain recommended SUA levels with currently available therapies. Lesinurad inhibits URAT1, increases uric acid excretion and thereby lowers SUA. Lesinurad, when used in combination with an XOIs (allopurinol or febuxostat), targets both aspects of SUA regulation (production and excretion) providing a dual mechanism approach to more effectively lower SUA.

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Conflicts of interest

There are no conflicts of interest.

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