REVISITING GOUT WITH NEW TREATMENT STRATEGY: LESINURAD.

*Dr. Kamalpreet Kaur, Amita Jindal, Nagma Bansal
India.

ABSTRACT
Arthritis can affect quality of life in an adverse way, and any new therapy generates a new hope for relief of pathology of this joint disorder to which hippocrates termed as ‘Podagra’. Apart from therapeutic options available outcome has been shown to improve by this new drug LESINUARD which is mainly a transporter inhibitor and helps regulate the serum uric acid levels.

KEYWORDS: Arthritis, Serum uric acid, Xanthine Oxidase Inhibitor, Lesinurad.

INTRODUCTION
Hippocrates termed gout as “the unwalkable disease” and observed that podagra (acute onset pain, erythema and swelling of the first metatarsophalangeal joint) was related to affluent lifestyle and termed it as “arthritis of the rich”. In last two decades this most common crystal arthropathy has shown an increase in the incidence globally because of multiple factors like increased life expectancy, widespread use of hyperuricemic drugs like diuretics and aspirin, epidemic of obesity and metabolic syndrome, dietary trends (fructose /soft drinks). Dietary consumption of meat and seafood. increased alcohol consumption the number of cases have almost doubled.

Epidemiology
Various studies in India have quoted variable incidences with a high urban prevalence than rural and high uric acid level is associated with laboratory and anthropometric parameters of metabolic syndrome.
Patho-physiology of gout

In most cases diagnosis is based on clinical presentation, which includes severe pain developing within hours, tenderness, warmth, swelling and erythema, e. g. in the first metatarsophalangeal or metacarpophalangeal joint. Frequently, gout flares up following rich meals and alcohol consumption, in the middle of the night. It is caused by the inflammatory reaction that arises in response to the deposition of Mono sodium urate (MSU) crystals into the joints of patients with hyperuricemia. The pathology involved is cited in the figure below:

<table>
<thead>
<tr>
<th>Overproduction of urate (10%) OR  underexcretion of urate (90%), (often in combination).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia  (common pathogenic factor in the development of gout).</td>
</tr>
<tr>
<td>Leads to MSU Crystallization (depends on temperature and pH).</td>
</tr>
<tr>
<td>MSU crystals further initiate, amplify and sustain an intense inflammatory response.</td>
</tr>
<tr>
<td>Formation of tophi which consist of MSU crystals in a matrix of lipids, protein, and mucopolysaccharides</td>
</tr>
<tr>
<td>Microtrauma facilitates crystal interaction with synovial cell lining and residential inflammatory cells, leading to an acute gouty flare.</td>
</tr>
<tr>
<td>Flares of gouty arthritis may also contribute to bone damage.</td>
</tr>
<tr>
<td>Clinical presentation</td>
</tr>
</tbody>
</table>

**Figure 1: Pathogenesis of gouty flare.**

**Treatment Milestones:** Treatment options of acute gout.

**Colchicine** – It is the ideal drug in patients where the diagnosis of gout is not confirmed. It acts by inhibiting the action of neutrophils. It retards the adhesiveness and motility of neutrophils and prevents chemotaxis. It also downregulates TNF-α receptors and inhibits mast cell histamine release.\(^9\)
**NSAIDs** – The FDA has approved naproxen, Indomethacin and Sulindac.[10] for the treatment of acute gout. However, analgesic and anti-inflammatory doses of other NSAIDs may be as effective. Although prevention of acute attacks can be achieved by regular NSAIDs or colchicines.[11] this does not tackle the underlying hyperuricaemia. The main mechanism of crystal-induced inflammation is interleukin 1β (IL-1β) which strengthens the relevance of targeting IL-1β in patients with crystal-induced arthritis.[12]

**IL-1 Traps/inhibitors:** Drugs like Anakinra,[13] Riloncept, Canakinumab,[14] and appear to be effective in reducing pain and signs of inflammation in randomized controlled trials.

**Glucocorticoids** – Prednisolone is effective in gout flares. Alternatively, short course (3 to 5 days) of intravenous methylprednisolone or triamcinolone intramuscularly is equally effective. Intra-articular methylprednisolone depot preparation is also effective.[15]

**Treatment of chronic gout**
A major goal in managing gout is long-term reduction of serum urate concentrations to clearly sub saturating levels; such reduction, if maintained over time, will prevent or reverse the formation and deposition of urate crystals.[16, 17]

**Allopurinol, a Xanthine oxidase inhibitor,** is the most commonly prescribed of the Urate-lowering agents. The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day, titrated to serum urate and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency.[18-19]

**Febuxostat:** It is a non-purine analogue, and thus does not block the other metabolites of purine and have no effect on pyrimidine metabolism. All these help to alleviate allopurinol toxicities. Various trials have established the efficacy of febuxostat 40 mg to 80 mg daily.[20] In a study of subjects with renal impairment, the serum urate–lowering effect of febuxostat was unaltered.[21]

**Rasburicase:** Uricolytic and a recombinant fungal enzyme was used in tumour lysis syndrome. It has a half-life of 24 hours, and is highly immunogenic.
**Pegloticase:** A uricolytic Pegylated uricase is now available. It is given 8 mg every 2 weeks and is effective in severe chronic tophaceous gout as well as refractory hyperuricemia due to tumour lysis.\(^{[22]}\)

**Approach to the management and the new molecule Lesinurad**

Management approaches to hyperuricemia in gout include not only xanthine oxidase inhibitor (XOI) monotherapy and uricase therapy for refractory disease, but also renal urate transporter (URAT1) inhibitors (probenecid and benz bromarone) in monotherapy or in combination with XO inhibition. Drug–drug interactions limit probenecid use and increase the complexity of dosing in combination with other therapies. Benz bromarone use similarly is limited because of but highly hepatotoxicity.\(^{[23]}\) Other drugs with mild-to-moderate URAT1 inhibition activity, such as the lipid-lowering agent, fenofibrate, and the angiotensin receptor blocker, losartan, have been studied for the treatment of hyperuricemia and gout.\(^{[24]}\) but there remains an important clinical need for potent and selective drugs required to achieve appropriate serum uric acid (sUA). The sUA targets recommended by the American College of Rheumatology (ACR) and European Union League Against Rheumatism (EULAR) are sUA < 6 mg/dL for all patients and sUA < 5 mg/dL for patients with greater disease severity, such as those with tophaceous gout.\(^{[25]}\) Effective and convenient treatment options are clearly needed for those patients who do not achieve sUA targets on available ULTs and require further sUA lowering to control their disease. A new solution to this problem may be provided by LESINURAD which is a selective uric acid reabsorption inhibitor that inhibits the renal uric acid transporter (URAT1) and is recently approved in its 200-mg dose orally by the US Food and Drug Administration and developed by Ardea Biosciences and is indicated in combination with an XOI for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.\(^{[26]}\)

**Mechanism of action** The urate transporters URAT1 and OAT4 are all genetically associated with sUA and promote the reabsorption of uric acid from the kidney proximal tubule. The clinical effect of increasing fractional excretion of uric acid by Lesinurad is consistent with inhibition of organic anion transporter (OAT4) and URAT1 (Figure 2) Lesinurad-mediated equi-potent inhibition of these transporters is consistent with increasing urinary uric acid excretion and its OAT4 activity in particular may counteract diuretic-induced hyperuricemia. Although lesinurad inhibits URAT1, OAT1 and OAT3 at a similar potency, lesinurad does not inhibit OAT1 or OAT3 in vivo. URAT1 is also the primary target of the other
antihyperuricemic agents, benzbromarone and probenecid. Lesinurad has a higher potency for URAT1 compared with probenecid

Figure 2: A schematic diagram of site action of lesinurad.

![Diagram of site action of lesinurad](image)

**OAT4**: Organic anion transporter. **URAT1**: Uric acid transporter 1.

Urate transporter-1 (URAT1) is located in the apical membrane of proximal tubular cells in human kidneys and transports urate from lumen to proximal tubular cells in exchange for anions in order to maintain electrical balance.

Clinical trials in healthy volunteers indicate that a single dose of lesinurad increases fractional excretion of uric acid (FEUA), in an exposure-dependent manner and that lesinurad treatment significantly reduces serum uric acid (sUA).\[^{27}\] A similar study by Miner et al.\[^{28}\] defined the mechanism of action by evaluating sUA levels, fractional excretion of uric acid (FEUA), lesinurad plasma levels and urinary excretion of lesinurad were measured in healthy volunteers treated with lesinurad. After 6 hours, a single 200-mg dose of lesinurad elevated FEUA 3.6-fold (p<0.001) and reduced sUA levels by 33 % (p<0.001). The FDA approval is based on data from three pivotal Phase III studies, CLEAR1, CLEAR2 and CRYSTAL, which represent the largest clinical trial data set of gout patients (n=1,537 total) treated with combination urate lowering therapy.

**CLEAR 1 And CLEAR 2 Trials**

The CLEAR 1 and CLEAR 2 studies (Combining Lesinurad with Allopurinol in Inadequate Responders) evaluated lesinurad 200 mg and 400 mg QD compared with placebo as add-on
therapy to allopurinol in patients who had not achieved sUA target levels while on a physician-determined medically appropriate dose of allopurinol. In both the trials, lesinurad when used in combination with allopurinol, met the primary endpoint in both studies with approximately twice as many patients achieving the serum uric acid (sUA) goal of <6.0mg/dL (360 µmol/L) by month 6, compared to those treated with allopurinol alone.[29]

**CRYSTAL Trial**

CRYSTAL was a pivotal Phase III study that evaluated the efficacy and safety of a once daily dose of lesinurad in combination with febuxostat 80mg compared to febuxostat 80mg alone in gout patients with tophi (visible deposits of urate crystals in joints and skin). Patients were administered febuxostat 80mg orally once daily for 3 weeks before randomisation. In CRYSTAL, results showed lesinurad 200mg in combination with febuxostat demonstrated greater (nominal p<0.05) sUA lowering to the target for tophaceous gout of <5.0mg/dL (300 µmol/L) compared to febuxostat alone at all months except at the time of the primary endpoint, month 6 (56.6% vs. 46.8%, non significant). In the subgroup of patients with baseline sUA ≥5.0mg/dL (300 µmol/L) (i.e. those above recommended sUA treatment target for tophaceous gout on febuxostat alone), lesinurad 200mg in combination with febuxostat resulted in more subjects reaching target sUA of <5.0mg/dL (300 µmol/L) compared to febuxostat alone at sixth month.[30]

**Pharmacokinetics**

Lesinurad has rapid oral absorption and is highly plasma protein bound. Approximately, half of the oral dose is cleared via CYP2C9 metabolisms; 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.[31]

**Safety**

Single oral doses of lesinurad were well tolerated in the bioavailability study as well. In all the three studies mentioned above there were no significant findings on laboratory examination in the three studies, other than the decrease in sUA. The results for some parameters, including serum creatinine, were outside the appropriate reference ranges, but the findings were generally transient and occurred at isolated time points only. No findings were considered to be of clinical importance at any dose level.[29]
The tabulated form of all the drugs used in gout is shown in table 1.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>HALF LIFE</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colchicine</td>
<td>Oral: 0.6 -1.2mg followed by 0.2 mg every 1-2 hrs. Maximum dose upto 6 mg. I.V. 1-2 mg then 0.5 mg every 6 hrs. Maximum dose upto 4 mg</td>
<td>26 hrs</td>
<td>GIT symptoms</td>
</tr>
<tr>
<td></td>
<td>I.V. 1-2 mg then 0.5 mg every 6 hrs. Maximum dose upto 4 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>25-50 mg 4 times daily</td>
<td>4.5 hrs</td>
<td>GIT and CNS side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>20 mg I.V BD followed by tapering doses over few weeks</td>
<td>2-4 hrs</td>
<td>Mood changes, hyperglycemia, increase BP and fluid retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Start with 100 mg OD. Maintenance dose of 300 mg/ day. Maximum 600 mg/day</td>
<td>2 hrs</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febuxostat</td>
<td>40-80 mg OD</td>
<td>5-8 hrs</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasburicase</td>
<td>0.15 -0.2 mg/kg as a single daily dose for 5 days</td>
<td>18 hrs</td>
<td>Nausea, vomiting, stomach pain, diarrhea, constipation, fever, sore throat, mild rash or swelling in hands and feet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegloticase</td>
<td>8 mg as iv infusion every 2 weeks</td>
<td>10-12 days</td>
<td>Nausea, vomiting, sore throat, stuffy nose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesinurad</td>
<td>200 mg OD</td>
<td>5 hrs</td>
<td>Renal and cardiovascular side effects</td>
</tr>
</tbody>
</table>

CONCLUSION
Availability of a new therapy always offers an opportunity for us to revisit the treatment strategies to improve outcome in this highly treatable disease. The dual mechanism of regulating production and excretion of this new agent, Lesinurad, when used in combination with an Xanthine Oxidase Inhibitors (Allopurinol or Febuxostat), targets both aspects of SUA regulation (production and excretion) providing a dual mechanism approach to more effectively lower uric acid and a new hope for gout patients.

REFERENCES
16. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of


