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## **Pharmacological overview for therapy of gout and hyperuricemia**

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**Abstract**--Hyperuricemia & gout are disease conditions marked by over production and reduced excretion of uric acid. These conditions are linked with unhealthy lifestyle, Hypertension, Diabetes Mellitus, Metabolic syndrome, Cardiovascular & Chronic renal disease. Thus controlling & monitoring uric acid level becomes important. Development in the technology have led to greater insights into the pathophysiology of gout & hyperuricemia. Now we have a better understanding of involvement of interleukin 1 $\beta$  in inflammatory process of gout. Thus with better understanding newer therapeutic targets are being explored for treatment of gout & hyperuricemia. The armamentarium of drugs being used in therapy of acute gout here been expanded with recent addition by interleukin-1 inhibitors especially for refractory patients and patients with comorbidities. As these new therapies are evolving we need to focus on improving the use of Allopurinol through patient education and training of physicians in order to minimize development of Allopurinol hypersensitivity syndrome (AHS). Further pretesting of Human leukocyte Antigen- B (HLA-B\*5801\*) should be considered in Asian population. Febuxostat being critically new drug needs cautious approach, proper education of patients and Adverse Drug Reaction (ADR) reporting. With entry of Pegloticase there is a new class of drug added for treating hyperuricemia. Pegloticase has shown benefit in clinical trials. However, it has potential of inciting immunogenicity

leading to loss of efficacy and potential for infusion reactions. One approach to decrease the immunogenicity of Pegloticase is to use concept of immunosuppression.

**Keywords**---inflammatory arthritis, urate lowering drugs, uricosuric drugs, urate synthesis inhibitors, uric acid.

## **Introduction**

Gout is a chronic, painful, crippling type of inflammatory arthritis. It occurs due to by elevated concentration of serum uric acid (sUA), which leads to hyperuricemia (sUA >6.8 mg/dL) [1]. Constantly raised levels of sUA results in monosodium urate (MSU) crystal deposition in joints and soft tissues, which triggers acute and chronic inflammation [2]. Hyperuricemia is defined as serum urate concentration higher or equal to 6.8mg/dl at physiological temperatures 37°C and neutral pH [1]. Hyperuricemia is widespread and occurs due to unfit lifestyle consisting of unhealthy diet, with excess of purine nucleotide, protein, alcohol and carbohydrate intake. Hyperuricemia is the biochemical state which is cardinal to the development of gout. [2]

## **Aim**

The aim of this review is to give overview of contemporary and new therapeutic strategies which are focused at improving the present therapy of hyperuricemia and Gout.

## **Literature survey and problem definition**

A literature search was performed by the authors with keywords such as Gout, Hyperurecemia, inflammatory arthritis in India and world in search engines of google, pubmed and web of science and the references included are from year 2000 to 2020. Gout is the most common inflammatory arthritis in men above 50yrs of age. In western world it affects approximately 1-2% of adult men [3]. Gout develops in ratio of 10:1 in men vs women and seldom occurs in premenopausal women [2]. In India the incidence of gout is not clearly known [3]. According to a study in Bhigwan village of India the prevalence of gout was found to be 0.12% as per International League of Nations Against Rheumatism, community oriented program for control of rheumatic diseases (ILAR COPCORD) [3]. Multiple factors like increased life expectancy, prevalence of hypertension and rampant use of diuretics and low dose aspirin, increased prevalence of obesity and metabolic syndrome have led to increased incidence of Gout. One of the studies carried out in India showed high prevalence of hyperuricemia in patients of diabetes type 2, hypertension and in patients with co-morbidities [4]. Hyperuricemia and Gout are associated with chronic diseases such as hypertension, diabetes mellitus, and metabolic syndrome, cardiovascular and chronic renal diseases. Thus controlling and monitoring uric acid levels becomes vital [5].

### **Physiology of uric acid metabolism**

Uric acid is an end product of degradation of purine compounds. Its formation occurs due to catabolism of deoxyribonucleotides and purine nucleotides. Endogenous production accounts for two-third of total body urate, while remaining one-third is accounted by dietary purines. Uric acid is a weak acid, pKa (5.75-10.3). At physiological pH of 7.40 uric acid remains in ionized form as monosodium urate in blood and as potassium, ammonium and calcium urate in urine [1, 6]. In urinary tract, where pH can fall to 5.7, uric acid stone formation is favoured. The normal range of uric acid is based on the solubility limit of urate in body fluids. The solubility of monosodium urate, in connective tissue is approximately 7mg/dl and this solubility gradually declines progressively at cooler temperature such as those in peripheral joints [6]. The enzymes involved in uric acid pathway are Purine nucleotide phosphorylase, xanthine oxidase. Hypoxanthine and xanthine are intermediary outcomes of this metabolic pathway [1]. In most mammals' enzyme uricase (urate oxidase) is a unique enzyme which oxidises uric acid to allantoin. Allantoin being highly soluble in water, does not accumulate in form of crystals and is excreted unchanged through urine. Thus urate oxidase is very effective in lowering uric acid levels in mammals. But the enzyme urate oxidase is not functional in humans [1, 6]. This leads to development of hyperuricemia in humans which further leads to uric acid crystal accumulation in human tissues and urinary tract. Uric acid is known to demonstrate antioxidant activity, and studies have shown protective role of uric acid in eliciting type 2 immune response leading to protective role in infections on one hand but on the other side hyperuricemia is a detrimental condition leading to gout. [6]. Hyperuricemia in turn causes deposition of uric acid crystals in joints, nephrolithiasis and chronic nephropathy. Hyperuricemia has recently been associated with diseases like hypertension, metabolic syndrome and cardiovascular diseases [6, 7].

### **Pathophysiology of gout and hyperuricemia**

One of the major condition which leads to gout is hyperuricemia. In majority of people this it develops due to under excretion (excretion <330 mg/d) of urate. However urate overproduction (excretion >600 mg/d) accounts less number of hyperuricemia cases [1]. The inducing factors for acute attack of gout are strenuous exercise, cold, alcoholism and overeating. These conditions promote accelerated degradation of adenosine triphosphate (ATP) into Adenosine monophosphate (AMP), which is a precursor of uric acid [8]. The pathophysiologic events that occur in disease are as follows- Urate crystals are phagocytosed by synoviocytes, subsequently these cells secrete inflammatory mediators such as IL-1, LTB<sub>4</sub>, prostaglandins, TNF $\alpha$ . These engage and stimulate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP). Thus monosodium urate (MSU) crystals are proinflammatory and can initiate, amplify and sustain an intense inflammatory response. The MSU promote the release of Interleukin-1, TNF $\alpha$ . These play a key role in inducing inflammatory symptoms of gout [5, 9]. Recent studies have suggested a major role of interleukin-1 $\beta$  (IL-1 $\beta$ ) in the inflammatory activity linked to deposition of monosodium urate crystals in tissues joints of patients with gout [10]. According to this hypothesis, an attack of acute gout starts when monosodium urate crystals stimulate inflammasome NOD Like

Receptor P-3(NLRP3), which in turn releases IL-1 $\beta$ . This further induces an inflammatory response and leads to vasodilation and mobilization of neutrophils and other immune cells, at the site of the crystal deposit [11]. Based on this hypothesis regarding the role of IL-1 $\beta$  in gout, drug development was focussed on inhibiting IL-1 signal transduction. This led to expansion of therapeutic options available for the management of the Gout.

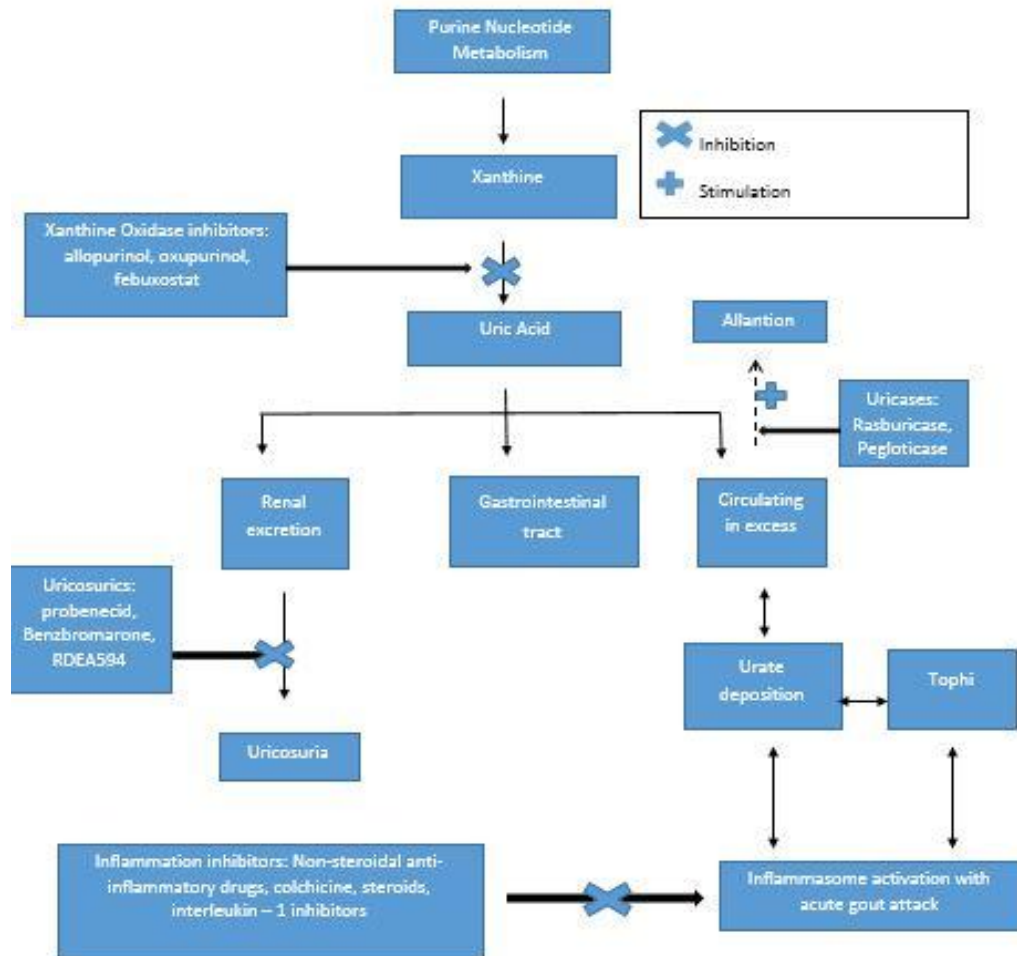


Figure 1 Flow chart for drug acting at various levels in pathophysiology of Gout and Hyperuricemia (Adopted from Principles of Pharmacology by Golon 4 th edition)

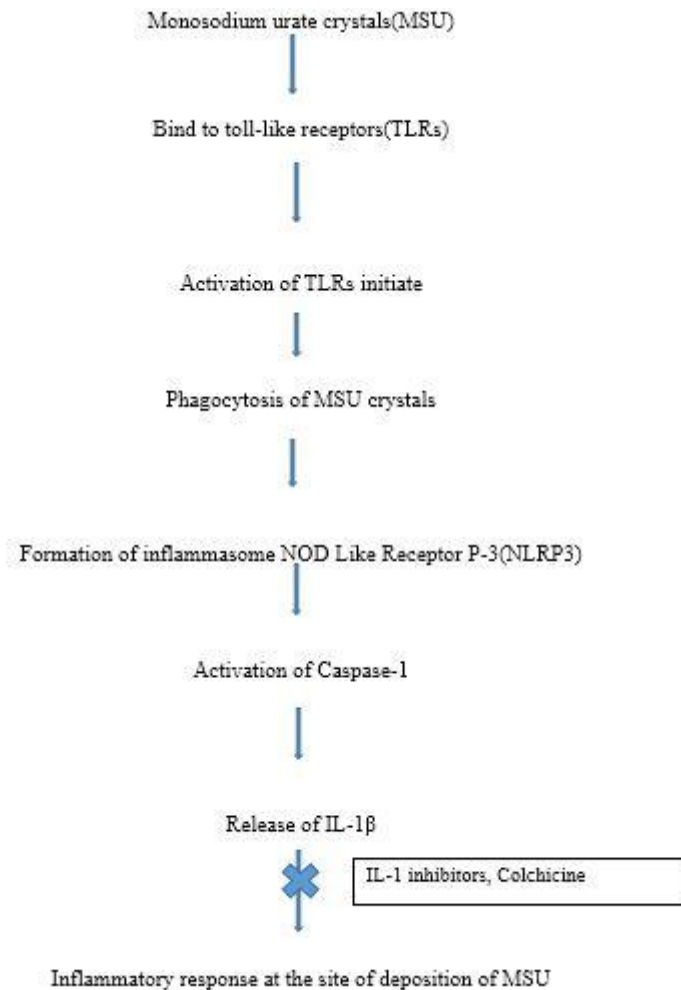


Figure-2 Mechanism of inflammatory response to urate crystals (Adopted from Principles of Pharmacology by Golon 4th edition)

### Pharmacotherapy of Gout and Hyperuricemia

At present the therapeutic strategies applied for treatment of gout and hyperuricemia are mostly directed towards controlling the acute episodes which are triggered by urate crystal deposition leading to inflammation of soft tissues and joints. Hyperuricemia is treated by either reducing the production of uric acid or by increasing the excretion of uric acid.

Acute Gout- The drugs used in treatment of acute gout are NSAIDs, Colchicine and Corticosteroids [9].

#### NSAIDs in Gout

In gout, there occurs an upregulation of the cyclooxygenases-2 (COX-2). This step is important in the inflammatory response of gouty arthritis. NSAID'S inhibit the prostaglandin generation, which occurs due to upregulation of COX-2. In

addition, NSAIDs are known to inhibit the urate crystal phagocytosis. Among the NSAIDs Aspirin is known to cause renal retention of uric acid at low doses hence not used in treatment of gout. Indomethacin is commonly used in initial treatment of Gout. Naproxen, piroxicam, diclofenac and etoricoxib are widely used in gout. They are quite effectively in terminating the attack but may take 12-24hrs, while complete resolution takes 5-10 hrs. The response is slower than with colchicine. Oxaprozin which is known to lower the serum uric acid levels, theoretically should also be a good choice [9].

### **Colchicine in Gout**

It is an alkaloid from *colchicum autumnale*, being used in treatment of gout since 1763. This drug is neither analgesic nor anti-inflammatory, but suppresses gouty inflammation. It also does not inhibit synthesis or promotes secretion of uric acid. Colchicine suppress inflammation in gout by inhibiting the processing of interleukin-1 in monocytes which gets triggered by monosodium urate [11]. The second messengers like tyrosine kinases and phospholipases in neutrophils are downregulated thus inhibiting chemotaxis. Colchicine alters E-selectin adhesion molecules which are involved in mobilising the neutrophils [12]. Colchicine interferes with microtubules, leading to accumulation of lysosomal and autophagic vacuoles in cytoskeleton leading to pathologic alteration in skeletal muscles and induction of axonal neuropathy. These are evident in form of myopathies, neuropathy and bone marrow suppression. [12] Colchicine is the fastest acting drug to control an acute attack. Control of attack occurs in about 6-12 hrs and resolution takes 3-5 days. The response with colchicine is dramatic but because of higher toxicity it is considered as second line drug for gout [13].

### **Glucocorticoids**

Glucocorticoids are well known for anti-inflammatory effects which occur due to binding with glucocorticoids receptors, in cytoplasm of target cells of all tissues in human body. In acute gouty arthritis, the most important anti-inflammatory action of glucocorticoids is to inhibit the cascade of pro-inflammatory transcription factors such as NFkB and activity protein-1(AP-1) [13] NSAIDs, Colchicine and glucocorticoids inhibit the inflammation via different mechanisms they are not universally effective in counteracting gout induced inflammation and none of them are completely safe. NSAIDs are prescribed for patients without comorbid illness. They are not suitable for patients with renal impairment, congestive cardiac failure and peptic ulcer disease and those who are on anticoagulants. In addition, the use of high dose of NSAIDs for patient with acute gout can induce gastric toxicity, reduce creatinine clearance, especially in patient affected by renal impairment. Corticosteroids are very effective, but they interfere with blood pressure and glucose control. Colchicine is preferred for patients where NSAIDs or corticosteroids cannot be prescribed. But Colchicine has a narrow therapeutic index [13]. Looking at the current therapeutics regarding hyperuricemia and Gout, a growing interest is focused on biological therapies aimed at counteracting the inflammatory effect of IL-1 beta, which is considered as a key mediator in pathogenesis of Gout.

### **Interleukin 1 Inhibitors**

Anakinra is Interleukin 1 beta receptor antagonist. In an open labelled study this drug showed a quick and complete pain relief without any side effect in patients who failed conventional therapy [13]. Randomised control trial has shown a non-inferior efficacy of anakinara for treatment of acute gout flares [14]. A soluble interleukin-1 receptor known as Rilonacept, binds to interleukin thus blocking the interaction with its original receptor. Rilonacept is a soluble decoy receptor. It is fully-human, recombinant, protein engineered from human IL-1 receptors and IgG1Fc which binds to IL-1 $\alpha$  and IL-1 $\beta$ . This binding prevents the activation of cell surface receptors [15]. Rilonacept is also called IL-1 Trap as it was generated using Trap technology. The half-life of rilonacept is approximately 1 week [16]. In clinical trial of Rilonacept versus placebo, for prevention of acute gout flare among patients initiating ULT with allopurinol, Rilonacept has shown significant efficacy [17]. In contrast one study has demonstrated that adding rilonacept to an indomethacin treatment regimen and use of rilonacept alone provided neither significant additional pain relief nor superior pain relief, compared with indomethacin alone over the 72-hour period after treatment initiation in acute gouty arthritis [16]. Canakinumab is a monoclonal antibody against interleukin-1 which is more effective than allopurinol and corticosteroids. Canakinumab is the third IL-1 inhibitor that has been approved for the treatment of inflammatory disorders. Canakinumab has advantage of being highly specific for IL-1 $\beta$  and does not interfere with other IL-1 pathways. Its longer half-life reduces the need of frequent injections. Canakinumab is considered to be safe and effective choice for the treatment of acute gout flares. It significantly reduces the risk of recurrent flares. It is inappropriate to treat all cases of acute gout with this drug, but it is a promising alternative therapy (17). Gout being most common form of inflammatory arthritis in adults, is frequently found with comorbidities, which initiate the use of conventional therapies. With a better understanding of the role of interleukin-1  $\beta$  in inflammatory process of gout, drugs like anakinra, canakinumab have opened up new avenues and therapeutic progress [5]. In patients who are refractory to standard and conventional therapies or in whom standard therapies are contraindicated, this development of drugs have brought a new hope for treatment. All the above drugs represent valid alternatives and new hope for treatment of patients in with cardiovascular, renal and gastrointestinal comorbidity, where the use of NSAIDS, corticosteroids and colchicine is not possible [5].

### **Long term management of Hyperuricemia**

Although there have been improvements and addition of novel therapies for acute gout, hyperuricemia being a chronic condition, demands correct treatment not limited to acute episodes. At present the long term management of hyperuricemia is based on targeting the enzymes and transporters involved in metabolism and excretion of urate such as xanthine oxidase and uric acid transporters respectively [5]. The two main classes of drugs which are used in current practice are uricostatic drugs such as Allopurinol, which inhibit uric acid production by competitive inhibition of Xanthine oxidase and uricosuric drugs such as sulphapyrazone, probenecid, which enhance urinary uric acid excretion [9]. The first line treatment for hyperuricemia, as recommended by all guidelines are

xanthine oxidase inhibitors. Uricosuric agents are second line for treatment of hyperuricemia. All guidelines recommend combination of agents (XOIs and uricosurics) when monotherapy is ineffective [9].

### **Xanthine Oxidase inhibitors (XOIs)**

XOIs are the first line drugs for treatment of hyperuricemia in gout. Allopurinol and febuxostat are two drugs in this class of drugs, allopurinol being more commonly used for hyperuricemia [5].

### **Allopurinol**

Efficacy and low cost of Allopurinol makes it the first line agent. This drug inhibits XO, being a nonspecific non-competitive inhibitor. It is converted into oxypurinol [9]. Though allopurinol is an established drug, target concentrations of serum urate levels are not always achieved. Multiple factors which includes failure to monitor serum urate levels, low adherence to medication, inadequate dosing and lack of awareness and concerns about the possible side effects such as allopurinol hypersensitivity syndrome (AHS) on the part of physicians [18]. Though AHS is rare, it is associated with significant morbidity and mortality. It is considered as a severe and life-threatening adverse reaction. Preventive measures should be taken into consideration before the initiation of the therapy with allopurinol. Patient education regarding AHS and the need to stop allopurinol may reduce the severity when it occurs [18]. Pre-testing for HLA-B\*5801 should be done in subgroups of Asian and African ethnicity. [19]. Low starting dose of allopurinol, 100mg daily or 50mg in cases of CKD will reduce the risk of AHS. Alternative therapies should be considered in patients of severe CKD or patients with comorbid conditions who are on treatment with diuretics. Allopurinol is generally a safe drug, but ~2% of patients develop hypersensitivity reactions, which at times may be fatal with mortality up to 20% [20, 21, 22]. Allopurinol is also known to cause idiosyncratic reactions especially in patients with renal impairment, where dose has not been reduced. But then the other side of story is that dose reduction in such patients does not control gout. Hence it is important that physicians acquire good therapeutic knowledge and skills for administration of allopurinol and prevent and minimise the development of AHS and other adverse effects associated with allopurinol [20].

### **Febuxostat**

Febuxostat is a novel, orally administered antihyperuricemic drug. It is a non-purine potent and selective inhibitor of xanthine oxidase approved by FDA in 2009. Various clinical trials it has shown been that febuxostat at daily dosing of 80mg or 120 mg was more effective than allopurinol at a standard 300mg daily dose in reducing serum urate levels. Febuxostat is approved at doses of 40 or 80 mg for treatment of chronic hyperuricemia in gout patients [22]. Although it appeared to be more effective than allopurinol as urate lowering therapy, the allopurinol dosing was limited to 300mg/d, thus not reflecting the actual dosing regimens which are widely used in clinical practice. At present, dosing equivalence of allopurinol and febuxostat is not known [21]. Prophylactic treatment with NSAIDs or Colchicine should be initiated at the beginning of

Febuxostat therapy to prevent gout flares. Hypersensitivity reactions are rare with febuxostat [21]. It is well tolerated even in patients with history of allopurinol intolerance. Abnormalities in liver function tests are the most frequent adverse effects with this drug. Thus it requires monitoring of liver functions at regular intervals. This drug is metabolised in liver to active metabolite and require no dose adjustment even in patients of with renal disease [22, 23]. After the review of CARES trial, US FDA has issued a boxed warning for febuxostat, advising to avoid treatment with febuxostat in patients who have pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate [22, 23]. According to various clinical guidelines febuxostat is recommended for treatment only when allopurinol is not tolerated or contraindicated. Patients should be counselled about cardiovascular risk with febuxostat and advise them to seek medical attention immediately if they experience any cardiovascular event. Febuxostat is relatively new drug which requires to be used with caution and active reporting of adverse drug reactions [23, 24].

### **Uricosuric drugs**

Glomerulus freely filters urate but up to 90% of the filtered urate is reabsorbed. Tubular reabsorption of uric acid involves URAT 1 and GLUT9 as main transporters [25, 26]. Probenecid and Sulfinpyrazone is a uricosuric drug which inhibits URAT1, thus reducing the reabsorption of uric acid. This leads to increase in urinary excretion of uric acid. In patients who respond favourably, tophaceous deposits of urate are reabsorbed, with relief of arthritis and remineralisation of bone. Due to increase in uric acid excretion, there is increased propensity of nephrolithiasis. Thus the urine volume at a high level and urinary pH should be maintained above 6.0 by administration of alkali. Uricosuric therapy should be given to patients with under excretion of uric acid when allopurinol and febuxostat is contraindicated or when tophi are present. Therapy should only be started after 2-3 weeks of acute attack. This class of drugs are second line drugs for treatment of hyperuricemia. They are preferred in hyperuricemia which occurs due to under excretion of urate. These drugs should not be used in cases of renal insufficiency. They should be used only when creatinine clearance is greater than 50ml/min [25, 26].

### **Lesinurad (RDEA594)**

This is a novel uricosuric drug, increases renal urate excretion by selective inhibition of renal uric acid transporter 1 (URAT 1). It is rapidly absorbed after oral administration. It should be preferably administered, after food and fluid intake. Lesinurad has been approved by FDA and EMA for combined therapy with XOI. Few Pivotal phase III studies of lesinurad were CLEAR 1, CLEAR 2 and CRYSTAL which led to approval of lesinurad. This drug along with XOI, is indicated for adjunctive treatment of hyperuricemia in gout patients where XOI monotherapy is ineffective. The recommended dose of lesinurad is 200mg once daily. It should be prescribed in morning with food and water and patient should be instructed to stay well hydrated as these factors influence the pharmacokinetics of the drug. Lesinurad must be co-administered at the same time as morning dose of a XOI.

The combination of lesinurad with XO1 inhibits both renal uric acid resorption as well as urate production. [25-28].

### **Tranilast**

Tranilast is an anti-inflammatory agent developed for allergic conditions such as asthma, allergic Rhinitis as well as atopic dermatitis. It is also indicated for keloid and hyperkeloid scar. This drug has shown to have urate-lowering actions through inhibition of renal transporters URAT1 and Glucose Transporter 9(GLUT9). In a study of single dose and seven-day treatment tranilast has shown to reduce the serum level of uric acid along with decrease in urate associated inflammation.[29] Tranilast single dose in healthy volunteers decreased mean SUA by 0.17 mg/dl at 4h and 0.24mg/dl at 24 hr. Seven-day treatment with tranilast in doses of 300, 600 or 900mg reduced the mean SUA by 1.1, 3.2 and 3.3 mg/dl, respectively. One of the prominent side effect of tranilast was headache. Presently phase II clinical trials are underway for tranilast for treatment of hyperuricemia in patients of moderate to severe gouty arthritis and results are awaited.[30]

### **Pegloticase**

Pegloticase is a drug which has opened a new class of drug in the urate lowering therapy. Urate oxidase is an enzyme, converts uric acid to allantoin which is soluble in water. This enzyme is found in animals but not humans. Pegloticase is a recombinant mammalian uricase that is covalently attached to methoxy polyethylene glycol (mPEG) to prolong the circulating half-life and diminish the immunogenic response to the recombinant enzyme. [31].Pegloticase maintains low urate levels for up to 21 days after single dose at doses of 4-12mg, allowing IV dosing every 2 weeks [32]. Pegloticase should not be indicated for asymptomatic hyperuricemia. Some patients develop immune response to pegloticase. The presence of antipegloticase antibodies leads to shortened circulating half-life and loss of response leading to a subsequent increase in plasma urate levels. This drug also shows higher rate of infusion reactions and anaphylaxis. Anaphylaxis is known to occur in 6 to 15% of patients receiving pegloticase.[33] Pegloticase was approved by the US Food and Drug Administration (FDA) in 2010 for chronic gout in adult patients who are refractory to conventional therapy. Pegloticase was developed to treat refractory gout and has proved to benefit these patients in clinical trials and open-label extensions. But pegloticase has the potential for inciting immunogenicity, and some patients develop antipegloticase antibodies with accompanying loss of efficacy and potential development of infusion reactions[34]. Discontinuation of pegloticase at the time of treatment failure reduces the potential for infusion reactions and renders the agent roughly as safe as other biologic infusions. The pegloticase is currently a 'last resort' medication, thus consequences for patients who need to discontinue pegloticase therapy can be significant. Immunosuppression has shown potential for decreasing the rate of pegloticase failure, and high-zone tolerance approaches are also under study. If effective, either of these strategies could be easily implemented in clinical practice, and would expand the spectrum of individuals who could benefit from pegloticase treatment (34). Pegloticase, a recombinant uricase is the new drug which is covalently attached to methoxy polyethylene glycol (mPEG), with

prolonged half-life. At present it is indicated for indicated for the treatment of chronic gout in adult patients' refractory to conventional therapy. It is important to keep in mind that it is not indicated for asymptomatic hyperuricemia. Pegloticase being a recombinant drug has risk of anaphylaxis as well as infusion reactions. Thus careful and meticulous administration and monitoring of this drug is important.

## **Discussion**

The prevalence of hyperuricemia and gout has witnessed the rise over past decade [28b]. Chronic hyperuricemia which is associated with gout affects the overall quality of life and burden on healthcare resources. At present the therapeutic strategies applied for treatment of gout and hyperuricemia are mostly directed towards controlling the acute episodes which are triggered by urate crystal deposition leading to inflammation of soft tissues and joints. Hyperuricemia is treated by either reducing the production of uric acid or by increasing the excretion of uric acid. The current pharmacotherapy for gout and hyperuricemia is limited and the urate lowering therapy have unfavourable side effects which also involve drug- drug interactions associated with comorbidities. Thus there is a gap between the requirement of ideal therapy and the growing need. Newer drug such as anakinra, canakinumab have brought hope for patients with refractory gout and have broadened the physicians armamentarium for treatment of gout. The conventional therapy for symptomatic hyperuricemia requires careful titration and monitoring of the therapy to be safe and effective in treating hyperuricemia. With Current advances in the understanding of the pathophysiology of hyperuricemia and Gout, newer drug targets have been explored and at present plenty of investigational drugs are under the process of development and undergoing clinical trials. It would be interesting to see how febuxostat performs as a second-line drug after allopurinol as a urate lowering drug in days to come. Leniurad and tranilast are addition in class of uricosuric drugs which need to be explored further and evaluate how they are used in refractory patients to further develop guidelines and therapy of hyperuricemia. Pegloticase belongs to a new class of drug being a recombinant uricase enzyme. It is currently indicated for refractory patients and is used as last resort in hyperuricemia patients. The disadvantage of this drug is that it is given parenterally and is known for anaphylaxis, infusion reactions. Immunosuppression during the therapy with pegloticase has shown to be effective in exploratory studies but confirmatory studies need to be done to understand the role of immunosuppression with pegloticase therapy.

## **Conclusion**

Gout foists a significant burden on our healthcare system, and the patients it affects. In spite of the fact that we have a number of oral urate-lowering medications to treat these patients, a significant degree of treatment failure and refractory disease persists. As new therapies are evolving we need to focus on improving the use of allopurinol through patient education and training of physicians, understand and monitor the use of febuxostat in conventional therapy. The newly developed drugs like lesinurad needs further evaluation of more wide and wise use. The IL-1 inhibitors are a recent addition to the

armamentarium of drug used in therapy acute attacks of gout for refractory patients and patients with comorbidities, where use of NSAIDs, Colchicine and glucocorticoids is not possible.

### Future Prospects

With continuous technological advancement in field of medicine we should be looking at newer therapeutic targets. Along with this strengthening of protocols for current available treatment should be considered especially with old drugs like Allopurinol. ADR monitoring for newer drugs like Febuxostat, Lesunirad and more randomized control trials should be taken up. Immunosuppression along with use of Pegloticase should be explored to improve efficacy and reduce adverse effects of Pegloticase.

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