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REVIEW

New and emerging therapies in gout

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Abstract

Gout is a disease that has been pestering humankind for centuries. Hence, gout therapeutics has always been a field of ongoing research. Beginning from colchicine, which was the first drug to come into use, to the latest inflammasome inhibitors and monoclonal antibodies, therapies for gout have evolved remarkably over the years. Although gout-related research came to a standstill in the late 20th century, the 21st century witnessed a renaissance in gout therapeutics with the advent of new xanthine oxidase inhibitors. Our present armamentarium against gout includes drugs that exploit the newfound knowledge about the various mechanisms involved in the pathogenesis of gout as well as drugs used in other conditions, which are effective in gout as well. Many more drugs that promise better management of gout in the future are in the pipeline.

KEYWORDS

caspase inhibitor, gout, inflammasome inhibitor, urate transporter-1 inhibition

Key points

- Extensive research is happening in the field of gout therapy resulting in the arrival of newer, more effective drugs.
- Interleukin-1 (IL-1) inhibitors, inflammasome inhibitors, and caspase inhibitors have upsurged as effective anti-inflammatory agents in gout.
- Urate transporter-1 (URAT-1) inhibitors, adenosine triphosphate-binding cassette transporter G 2 (ABCG2) activators, and newer Xanthine oxidase inhibitors have been added to our armamentarium against gout.
- Discovery of the hypouricemic potential of common drugs such as atorvastatin, amlodipine, losartan, and fenofibrate has led to more options for the control of gout in people with comorbidities.

1 | INTRODUCTION

Gout is one of the oldest known arthritis dating back to 2640 BC when it was first identified by Egyptians.[1] It belongs to the group of crystalline arthropathies. Hippocrates, the Father of Medicine, rightly called it "The unwalkable disease," the treatment of which remains a challenge even today.

From the use of heat, cold, and counterirritants, and the unscientific use of purgatives and diuretics, the treatment of gout has come a long way. Colchicine, an alkaloid derived from the autumn crocus (also known as "meadow saffron"), was one of the first pharmacological agents to be used. It was first used in the treatment of gout in 6th century AD,[1] but went out of use for fear of gastrointestinal side effects after which it resurged as a therapeutic option in the 18th century. Other drugs with troublesome side effects such as quinine, lithium salts, and salicylates were tried but were soon replaced by safer drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). Presently, NSAIDs are the drugs of choice in acute gout and steroids are used when there are contraindications to the use of NSAIDs.

The use of uricosuric agents for the long-term control of gout started in late 19th century. The commonly used ones were probenecid, sulfinpyrazone, and benzbromarone. However, a major milestone in the therapy of hyperuricemia was the development of xanthine oxidase (XO) inhibitors. The first drug that came into use was allopurinol in 1966. Unfortunately, in the last quarter of

the 20th century, advances in gout therapeutics came to a virtual standstill. During this period, there was not much fruitful research in the field of hyperuricemia and no new drugs were approved for gout management. However, the incidence and prevalence of gout kept increasing in these years. The 21st century has witnessed remarkable advances in gout therapy. This renaissance started with the development of new XO inhibitors (XOIs) such as febuxostat and topiroxostat followed by pegylated uricase and newer uricosuric agents (Figure 1).

In spite of the improved physician understanding and refined management guidelines, many patients are still not meeting the therapeutic goal resulting in considerable morbidity. The prevalence of gout is also steadily increasing across the globe, owing to increase in protein-rich diet, alcoholism, use of drugs causing hyperuricemia, and, more importantly, lifestyle changes that have resulted in reduced physical activity and increasing obesity.

Our understanding of the pathogenesis of hyperuricemia and gout has drastically improved in the recent years, which has resulted in the development of newer, more effective drugs. Gout is now considered to be more of a transportopathy. Various urate transporters are involved in the renal and intestinal excretion as well as renal reabsorption. Urate transporter-1 (URAT-1) is involved in renal reabsorption at the proximal convoluted tubule, while organic anion transporter 1 (OAT1) and OAT3 are involved in urate secretion. Adenosine triphosphate-binding cassette transporter G 2 (ABCG2) is involved in renal urate secretion and in gastrointestinal urate excretion.

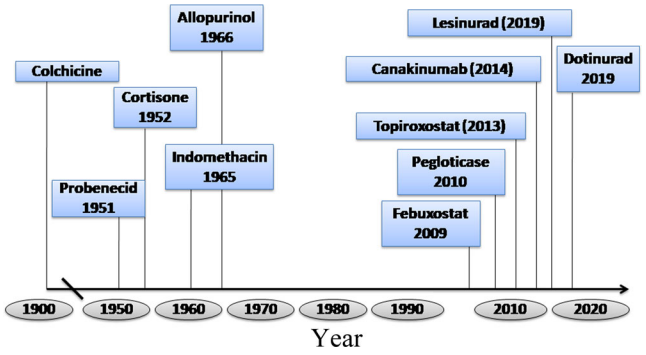

FIGURE 1 History of gout therapy.

2 | NEWER ANTI-INFLAMMATORY THERAPIES

The pathogenesis of gout involves the phagocytosis of monosodium urate crystals by macrophages resulting in the formation of NOD-like receptor protein 3 (NLRP3) inflammasomes, which activate the caspases. The resultant inflammatory cascade leads to release of cytokines, especially interleukin (IL)-1β and IL-18. The binding of active IL-1 to the endothelial IL-1 receptor causes signal transduction, inflammatory mediator release, and neutrophil recruitment, which are responsible for the symptoms and progression of gout. Thus, drugs that inhibit any of the steps in this inflammatory pathway are beneficial in the treatment of gout.

2.1 | IL-1 inhibitors

Anakinra is an IL-1 receptor antagonist with a half life of 4–6 h. It is administered subcutaneously[2] and inhibits the binding of IL-1α and IL-1β to IL receptor. Canakinumab is a human anti-IL-1β monoclonal antibody administered subcutaneously, which has a half life of 26 days.[2] Gevokizumab is a humanized anti-IL-1β monoclonal antibody, which can be administered intravenously. It has a half life of 23 days.[3] Rilonacept is a fusion protein acting as a soluble receptor binding IL-1α and IL-1β with a half life of 7–9 days. It is administered subcutaneously[2] (Table 1).

2.2 | Bucillamine

Bucillamine is a derivative of D-pencillamine with anti-inflammatory and antioxidant actions. It was actually approved for the treatment of rheumatoid arthritis in Japan. Studies in United States have found that at a dose of 900 or 1800 mg/day, bucillamine is equally or more effective than 1.8 mg of colchicine.

TABLE 1 IL-1 inhibitors used in gout

Name	Anakinra	Canakinumab	Rilonacept	Gevokizumab
Structure	IL-1 receptor antagonist	Human monoclonal antibody against IL-1β	Dimeric fusion protein (IL-1 receptor combined with Fc portion of IgG)	Humanized anti-IL-1β monoclonal antibody
Dose and route of administration	100 mg Subcutaneously daily for 3 days	150 mg Subcutaneously	80–120 mg Subcutaneously weekly	60 mg Intravenously monthly
Indications	Refractory gout	Refractory gout	Refractory gout	Refractory gout
Approval and usage	Approved for JIA, Periodic fevers. Off-label use in refractory gout	Approved by European Medical Agency for refractory gout	Not freely available commercially	Approved for pyoderma gangrenosum. Ongoing clinical trials in refractory gout

Abbreviation: IL-1, interleukin-1; JIA, juvenile idiopathic arthritis.

2.3 | Caspase inhibitors

Pralnacasan is a reversible caspase-1 inhibitor, whereas Emricasan is an irreversible orally active pan-caspase inhibitor. They act through blockade of IL-1β secretion as caspases, especially caspase 1, are involved in the intracellular processing of pro-IL-1β.[4]

2.4 | NLRP3 inflammasome inhibitors

NLRP3 (also known as cryopyrin) inflammasome activation results in secretion of IL-1β and IL-18 via caspase-1. This is the vital step in the pathogenesis of gout. Dapansutrile is an oral β-sulfonyl nitrile molecule that selectively inhibits NLRP3 inflammasome, thereby reversing the inflammatory changes.[5] Studies demonstrate a reduction in activated caspase-1 levels by about 35%, with no effects on levels of tumor necrosis factor-α or IL-1β and IL-18 precursors. It reduces joint pain and inflammation and hence has a potential in the treatment of gout flares as well as other NLRP3-mediated diseases. Although the optimal dose of dapansutrile is yet to be determined, dose upto 2000 mg/day has an acceptable safety profile comparable to IL-1 inhibitors.[6]

2.5 | Recombinant AAT-Fc

Targeting the proteases involved in the extracellular processing of IL-1β maybe a promising strategy for the control of acute gout. Subcutaneous injection of recombinant human alpha-1 anti-trypsin (AAT)-Immunoglobulin G1 Fc fusion protein (AAT-Fc) was found to increase circulating endogenous IL-1 receptor antagonist levels in mouse models.[7] A single dose was found to be effective for a drastic reduction of joint inflammation, cellular infiltration, and synovial IL-1β production.

3 | NEWER URATE-LOWERING THERAPIES

3.1 | XOIs

XOIs are equally effective in overproducers and underexcretors. They have good efficacy and safety, as well as excellent risk benefit ratio in both overproducers and underexcretors, compared with uricosurics, and are hence considered as the drugs of choice for urate-lowering therapy.

Topiroxostat is a nonpurine selective XOI, which acts by structure and mechanism-based inhibition.[8] It has also been shown to inhibit ABCG2 *in vitro*. It is mainly inactivated by hepatic metabolism and eliminated via urine and feces. As topiroxostat and its metabolites are unaffected by renal conditions, it is an effective option in patients with chronic kidney disease. Additionally, it decreases albuminuria in these patients. It has been approved for use in Japan in 2013 at doses ranging from 20 to 80 mg twice a day. A dose of 120 mg/day is as effective as 200 mg allopurinol in achieving target uric acid levels. Adverse effects include nasopharyngitis, elevated transaminases, leucopenia, and eczema.

LC350189 is a novel selective XOI presently in Phase II trials.[9] Its urate-lowering properties are found to be comparable to febuxostat.

3.2 | Uricolytics

Uricase is an enzyme that converts uric acid to water-soluble allantoin, thereby facilitating its excretion via urine. It is present in lower animals but absent in humans. Recombinant uricase, although effective in gout, is highly immunogenic. Pegylation serves to lower the immunogenicity but even Pegloticase (pegylated uricase) use results in formation of antipegloticase antibodies. SEL212 is pegylated uricase co-administered with ImmTOR[10] to reduce the formation of antidrug antibodies (which are the product of immune response to biologics). It is a uricase replacement therapy with improved immune reaction designed for use in refractory gout. Presently, it is undergoing Phase 3 clinical trials.

3.3 | Uricosurics

These drugs are preferred in "underexcretion" type of hyperuricemia. Lesinurad is a selective urate reabsorption inhibitor (SURI).[9] Besides URAT-1, it also inhibits OAT 4, which is involved in diuretic-induced hyperuricemia. It is devoid of major drug interactions, as it does not interfere with OAT-1 and OAT-3. It is actually the metabolite of a non-nucleoside reverse-transcriptase inhibitor that was developed for the treatment of human immunodeficiency virus infection.[8] It is used at a dose of 200 mg daily, combined with a XOI, and causes a sustained decrease in serum urate levels. Combination of lesinurad and febuxostat has been demonstrated to be superior to febuxostat alone.[11] Common side effects are renal dysfunction and nephrolithiasis. It is contraindicated in tumor lysis syndrome, Lesch–Nyhan syndrome, renal transplant recipients, low creatinine clearance (<30 ml/min), unstable angina, uncontrolled hypertension, decompensated heart failure, and recent myocardial infarction.[12]

Verinurad is another SURI, which is currently in Phase II trials. It is 3 times more potent than benzbromarone and 100 times more potent than probenecid.[8] Dotinurad is a novel SURI, which was developed in Japan as a safer alternative to benzbromarone.[13] It was structurally designed to avoid the hepatotoxicity seen with benzbromarone. It effects excellent uric acid excretion without inhibiting gastrointestinal excretion and renal urate secretion.[13] The urate-lowering effect of dotinurad is not affected by renal dysfunction and hence thought to be beneficial in hyperuricemic patients with moderate renal impairment. No serious adverse effects have been observed with Dotinurad use.

Tranilast is a molecule that was originally developed as an anti-inflammatory agent for allergic conditions, but was found to have urate-lowering properties owing to the inhibitory action on URAT-1 and glucose transporter-9.[9] It has an additional benefit of reducing urate crystal associated inflammation.[8] The main side effect is headache.

Levotofisopam is the S-enantiomer of the benzodiazepine derivative, Tofisopam, used in anxiety and autonomic instability. It increases the fractional excretion of uric acid,[9] although its mechanism of action is uncertain.

Canaglifozin is a sodium glucose cotransporter 2 inhibitor, which acts by increasing urinary glucose excretion. It has been reported to lower serum uric acid levels.[14] At doses of 100–300 mg, there is 13% reduction in serum uric acid.

UR-1102 is a potent inhibitor of URAT-1, OAT1, and OAT3,[8] still in preclinical phase.

4 | DRUGS WITH DUAL MECHANISMS

Arhalofenate is an emerging drug with dual action and long half-life of about 50 h, which was originally developed as a drug for Type 2 diabetes mellitus.[8] Owing to the slow equilibration of serum levels, arhalofenate slowly reduces serum uric acid levels by increasing urinary uric acid and the fractional excretion of uric acid[2] by selective inhibition of URAT-1 and OAT 4,[8] thereby inhibiting tubular reabsorption of uric acid. Besides the uricosuric action, it exerts anti-inflammatory effect and reduces gout flares by inhibiting the urate crystal-induced production of IL-1β through action on peroxisome proliferator-activated receptor (PPAR)-γ.[9] This drug is thought to be an effective alternative to colchicine. Combination of arhalofenate with febuxostat was found to be synergistic, being more effective than febuxostat monotherapy, while combination with allopurinol did not have any additional benefit over allopurinol monotherapy. Arhalofenate has some additional beneficial actions in patients with multiple comorbidities. It retains its urate-lowering property even in the presence of renal insufficiency.[9] Also, by its action on OAT 4, it is effective in patients on diuretic therapy, including thiazides, similar to Lesinurad. It also has a lipid and glucose-lowering action, which is advantageous in patients with co-existing diabetes and dyslipidemia.

Merbarone (RLBN1001) is a Type-II DNA Topoisomerase inhibitor, originally developed for the treatment of solid tumors. It was found to cause profound hypouricemia by bifunctional inhibition[15] of XO and URAT-1, and hence is of use in severe tophaceous gout.

AC 201 is an IL-1β modulator that was originally developed for the treatment of osteoarthritis. It not only reduces gout flares by its IL-1β inhibition but also exerts a uricosuric action by increasing the fractional excretion of uric acid.[9]

KUX-1151 is a Japanese molecule that inhibits both XO and URAT1.[9]

5 | DRUGS INCREASING GASTROINTESTINAL EXCRETION

Intestinal tract, owing to expression of high levels of XO and exposure to large amounts of nucleic acid, is a significant site of uric acid production from exogenous purines, whereas the liver produces uric acid from endogenous purines. ABCG2 contributes to about 40% of the total elimination of uric acid. In the gut, small intestine is the major producer of uric acid and ABCG2 is expressed most abundantly in jejunum and ileum.[16] The role of ABCG2 transporter is hence relevant. Promotion of uric acid excretion can be achieved by activation of ABCG2. This may be of benefit to those with normal ABCG2 and those with mutant ABCG2 with partial loss of function. ABCG2 activation maybe achieved through transcription factors such as PPARα, PPARγ, NRF2, and AhR. PPAR-α selective agonists such as fibrates, originally used for dyslipidemia in diabetics, induce ABCG2 in the intestine and liver.[17] PPAR-γ agonists such as pioglitazone, used as oral hypoglycemics, also induce ABCG2 in certain cell types.[18] Fumarate esters, sulphoraphane, and astemizole activate NRF2, which targets ABCG2 in liver through its action on antioxidant machinery.[19] Drugs such as Omeprazole,[20] a proton pump inhibitor, and Carbidopa,[21] used in Parkinson's disease, are potent activators of AhR, which works through xenobiotic response element. As epigenetic mechanisms such as promoter hypermethylation cause suppression of ABCG2, drugs preventing DNA methylation maybe beneficial in that aspect. Two such drugs are Decitabine and Azacitidine, which are actually anticancer drugs. Laccaic acid, a natural food additive, and Epigallocatechin-3-gallate, found in green tea, are also inhibitors of DNA methylation.[22,23]

6 | OTHER NEW APPROACHES

6.1 | Purine nucleoside phosphorylase (PNP) inhibitors

PNP is the enzyme that converts purines into hypoxanthine. Ulodesine is a well-tolerated PNP inhibitor without much drug interactions. It has synergistic action when combined with allopurinol. It causes dose-dependent reduction in xanthine and hypoxanthine.[8]

6.2 | Marine active 10

Commercial tuna extract produced by ion-exchange purification and spray drying from a hotwater extract of skipjack and yellowfin tuna, without enzymatic hydrolysis.[24] Originally developed as an antifatigue drug, it was found to have marked urate-lowering property[9] owing to the presence of imidazole compounds. Studies show

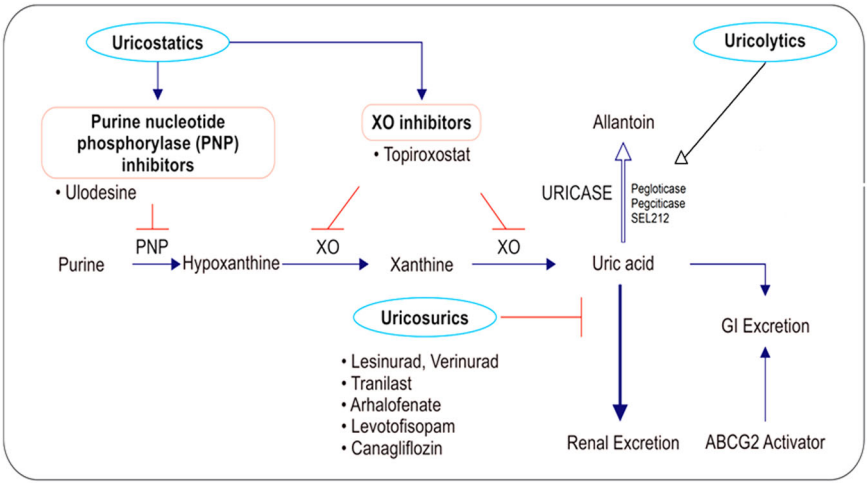

FIGURE 2 Mechanism of action of the new drugs. Abbreviations: ABCG2, adenosine triphosphate-binding cassette transporter G 2; GI, gastrointestinal; XO. xanthine oxidase.

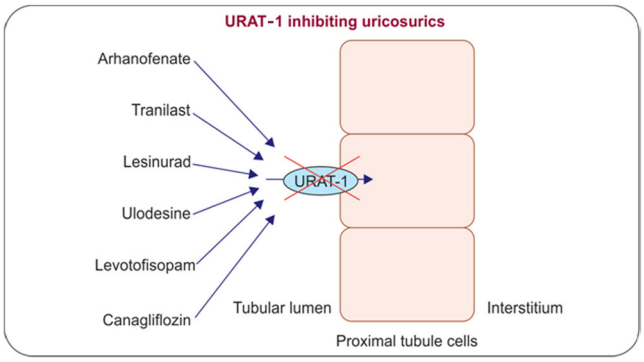

FIGURE 3 Urate transporter-1 (URAT-1) inhibitors.

significant increase in hypoxanthine phosphoribosyl transferase levels in the liver of those treated with tuna extract. Hypoxanthine phosphoribosyl transferase utilizes hypoxanthine and guanine for purine synthesis, thereby inhibiting uric acid synthesis.[24] Tuna extract metabolites excreted in urine stabilize urinary pH, which improves solubility of uric acid and accelerates its excretion.[24] Mechanism of action of the new drugs and URAT-1 inhibitors are shown in Figures 2 and 3.

7 | NEW ROLE FOR OLD DRUGS

7.1 | Adrenocorticotropic hormone (ACTH)

The mechanism of action of ACTH in gout is not entirely understood. ACTH triggers the release of endogenous steroids and also downregulates inflammatory responses by activating melanocortin 3 receptors (MC3R) on innate immune cells such as macrophages.[25] Stimulation of MC3R was found to significantly reduce inflammatory response to MSU crystals by reducing activities of nuclear factor-κB and heme oxygenase. ACTH is also thought to exert an anti-IL-1 effect. Studies have shown that ACTH is an effective option for treatment of gout in patients with multiple comorbidities, especially postoperative patients and those on steroids for other conditions such as post-renal transplant.[26] A single injection of 60 IU IM is more effective than corticosteroids.

7.2 | Fenofibrate

Using fenofibrate, a lipid lowering agent, with other urate-lowering agents is beneficial in patients with metabolic syndrome where hypertriglyceridemia may coexist with hyperuricemia. Fenofibrate exerts urate-lowering action by inhibition of URAT-1[27] thereby increasing the fractional excretion of urate.[28] Renal stones may develop as a side effect of this uricosuric action. The drug should also be used with caution in patients with renal insufficiency. Fenofibrate, being a PPAR activator, downregulates COX-2 expression. The resultant anti-inflammatory action maybe helpful in preventing gout flares.[28]

7.3 | Losartan

This orally active Angiotensin II receptor blocker is found to effect dose-dependent increase in the fractional clearance of uric acid,[29] especially in the first 4 h after drug intake. Although angiotensin reduces renal excretion of uric acid, this effect is independent of angiotensin blockade. As the active metabolite of losartan does not modify uric acid excretion,[30] the uricosuric action is probably a property of the parent compound. The target of Losartan is thought to be URAT-1.[31] Losartan also counters thiazide-induced hyperuricemia.[32] By raising the urinary pH, this drug reduces the risk of uric acid stones associated with the uric acid excretion and this property is unique to Losartan among uricosurics.[33]

7.4 | Amlodipine

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial showed that the calcium channel blocker Amlodipine reduced the long-term risk of gout compared with other antihypertensives,[34] thus making it a useful drug in hypertensives with coexisting hyperuricemia. Amlodipine significantly increases the glomerular filtration rate and urate clearance, and is found to be an effective option in renal transplant patients with Cyclosporin-A induced hyperuricemia and hypertension.[35]

TABLE 2 Newer drugs in the treatment of gout

Newer agents for acute gout	Newer urate-lowering drugs
Selective inflammasome inhibitor: ◦ Dapansutrile	Uricostatics: ◦ Ulodesine ◦ Topiroxostat
IL-1 inhibitors: ◦ Anakinra ◦ Rilonacept ◦ Canakinumab	Uricosuric agents: ◦ Lesinurad ◦ Verinurad ◦ Dotinurad ◦ Tranilast ◦ Arhalofenate ◦ Levotofisopam ◦ Canaglifozin
Corticotrophin and melanocortin: ◦ γ-MSH	Uricolytic drugs (Uricases): ◦ Pegloticase ◦ Pegsiticase ◦ SEL-212
Caspase inhibitors ◦ Pralnacasan ◦ Emricasan	Urate transporters to intestinal lumen ◦ ABCG2 activators

Abbreviations: γ-MSH, γ-melanocyte-stimulating hormone; ABCG2, adenosine triphosphate-binding cassette transporter G 2; IL-1, interleukin-1.

7.5 | Atorvastatin

Atorvastatin was found, in various studies, to significantly reduce serum uric acid levels. Although the exact mechanism is unclear, atorvastatin is thought to exert its hypouricemic action by augmenting the fractional excretion of uric acid mainly by reducing the proximal tubule reabsorption.[36] This is considered a pleiotropic effect and not a class effect, as other statins do not have this effect. The atorvastatin-induced decrease in serum uric acid levels was found to be independent of the lipid-lowering effect. Thus, atorvastatin is a preferred option in patients with dyslipidemia and hyperuricemia, besides fenofibrate (Table 2).

AUTHOR CONTRIBUTION

Both authors are equally involved in the research and compilation of the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in this article shall be available with the corresponding author upon reasonable request.

ETHICS STATEMENT

Not applicable, as it is a review article.

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REFERENCES

1. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther*. 2006;8(Suppl 1):S1. doi:10.1186/ar1906
2. Paul BJ, James R. Gout-an Asia pacific update. *Int J Rheum Dis*. 2017;20:407-416.
3. So A, Dumusc A, Nasi S. The role of IL-1 in gout. *Rheumatology*. 2018;57:i12-i19.
4. Edwards NL, So A. Emerging therapies for gout. *Rheum Dis Clin North America*. 2014;40:375-387.
5. Marchetti C, Swartzwelter B, Gamboni F, et al. OLT1177, a β-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. *Proc Natl Acad Sci U S A*. 2018;115(7):E1530-E1539.
6. Kluck V, Jansen TLTA, Janssen M, et al. Dapansutrile, an oral selective NLRP3 inflammasome inhibitor for treatment of gout flares-an open label, dose adaptive, proof-of-concept, phase 2 trial. *Lancet Rheumatol*. 2020;2:e270-e280.
7. Joosten LAB, Crişan TO, Azam T, et al. Alpha-1-anti-trypsin-Fc fusion protein ameliorates gouty arthritis by reducing release and extracellular processing of IL-1β and by the induction of endogenous IL-1Ra. *Ann Rheum Dis*. 2016;75(6):1219-1227.
8. Sattui SE, Gaffo AL. Treatment of hyperuricemia in gout: current therapeutic options, latest developments and clinical implications. *Ther Adv Musculoskelet Dis*. 2016;8(4):145-159.
9. Shahid H, Singh JA. Investigational drugs for hyperuricemia. *Expert Opin Invest Drugs*. 2015;24(8):1013-1030.
10. Selecta Biosciences Inc. 2022. A randomized Double-blind, Placebo-controlled study of SEL-212 in patients with gout refractory to conventional therapy (DISSOLVE).
11. Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a selective uric acid reabsorption inhibitor, in combination with febuxostat in patients with tophaceous gout: findings of a phase III clinical trial. *Arthritis Rheumatol*. 2017;69(9):1903-1913.
12. Bardin T, Richette P. Novel uricosurics. *Rheumatology*. 2018;57:i42-i46.
13. Hosoya T, Sano T, Sasaki T, et al. Dotinurad vs benzbromarone in Japanese hyperuricemic patient with or without gout: a randomized, double-blind, parallel group, phase 3 study. *Clin Exp Nephrol*. 2020;24(suppl1):562-570.
14. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2015;17:426-429.
15. Pascart T, Richette P. Investigational drugs for hyperuricemia, an update on recent developments. *Expert Opin Invest Drugs*. 2018;27(5):437-444.
16. Ristic B, Sikder MOF, Bhutia YD, Ganapathy V. Pharmacologic inducers of the uric acid exporter ABCG2 as potential drugs for treatment of gouty arthritis. *Asian J Pharm Sci*. 2020;15(2):173-180.
17. Hirai T, Fukui Y, Motojima K. PPARalpha agonists positively and negatively regulate the expression of several nutrient/drug transporters in mouse small intestine. *Biol Pharm Bull*. 2007;30:2185-2190.
18. Szatmari I, Vámosi G, Brazda P, et al. Peroxisome proliferator-activated receptor γ-regulated ABCG2 expression confers cytoprotection to human dendritic cells. *J Biol Chem*. 2006;281:23812-23823.
19. Cuadrado A, Manda G, Hassan A, et al. Transcription factor NRF2 as a therapeutic target for chronic diseases: a systems medicine approach. *Pharmacol Rev*. 2018;70:348-383.
20. Jin UH, Lee S, Safe S. Aryl hydrocarbon receptor (AHR)-active pharmaceuticals are selective AHR modulators in MDA-MB-468 and BT474 breast cancer cells. *J Pharmacol Exp Ther*. 2012;343:333-341.
21. Ogura J, Miyauchi S, Shimono K, et al. Carbidopa is an activator of aryl hydrocarbon receptor with potential for cancer therapy. *Biochem J*. 2017;474:3391-3402.
22. Fagan RL, Cryderman DE, Kopelovich L, Wallrath LL, Brenner C. Laccaic acid A is a direct, DNA-competitive inhibitor of DNA methyltransferase 1. *J Biol Chem*. 2013;288:23858-23867.

23. Zwergel C, Valente S, Mai A. DNA methyltransferases inhibitors from natural sources. *Curr Top Med Chem*. 2015;16:680-696.
24. Kubomura D, Yamada M, Masui A. Tuna extract reduces serum uric acid in gout-free subjects with insignificantly high serum uric acid: a randomized controlled trial. *Biomed Rep*. 2016;5(2):254-258.
25. Daoussis D, Bogdanos DP, Dimitroulas T, Sakkas L, Andonopoulos AP. Adrenocorticotropic hormone: an effective natural biologic therapy for acute gout? *Rheumatol Int*. 2020; 40(12):1941-1947.
26. Daoussis D, Antonopoulos I, Andonopoulos AP. ACTH as a treatment for acute crystal-induced arthritis: update on clinical evidence and mechanisms of action. *Semin Arthritis Rheum*. 2014;43(5):648-653.
27. Jung JY, Choi Y, Suh CH, Yoon D, Kim HA. Effect of fenofibrate on uric acid level in patients with gout. *Sci Rep*. 2018; 8:16767.
28. Lee YH, Lee CH, Lee J. Effect of fenofibrate in combination with urate lowering agents in patients with gout. *Korean J Intern Med*. 2006;21(2):89-93.
29. Nakashima M, Uematsu T, Kosuge K, Kanamaru M. Pilot study of the uricosuric effect of DuP 753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol*. 1992;42: 333-335.
30. Sweet CS, Bradstreet DC, Berman RS, Jallard N, Saenz A, Weidler DJ. Pharmacodynamic activity of intravenous E-3174, an angiotensin II antagonist, in patients with essential hypertension. *Am J Hypertens*. 1994;7:1035-1040.
31. Enomoto A, Kimura H, Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature*. 2002;417:447-452.
32. Soffer BA, Wright JT, Pratt JH, Wiens B, Goldberg AI, Sweet CS. Effects of Losartan on a background of hydrochlorothiazide in patients with hypertension. *Hypertension*. 1995;26:112-117.
33. Shahinfar S, Simpson RL, Carides AD, et al. Safety of losartan in hypertensive patients with thiazide induced hyperuricemia. *Kidney Int*. 1999;56:1879-1885.
34. Juraschek SP, Simpson LM, Davis BR, et al. The effects of antihypertensive class on gout in older adults: secondary analysis of the antihypertensive and lipid lowering treatment to prevent heart attack trial. *J Hypertens*. 2020;38(5):954-960.
35. Chanard J, et al. Amlodipine reduces cyclosporin-induced hyperuricaemia in hypertensive renal transplant recipients. *Nephrol Dial Transplant*. 2003;18(10):2147-2153.
36. Milionis HJ, Kakafika AI, Tsouli SG, et al. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. *Am Heart J*. 2004;148(4):635-640.

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Graphical Abstract

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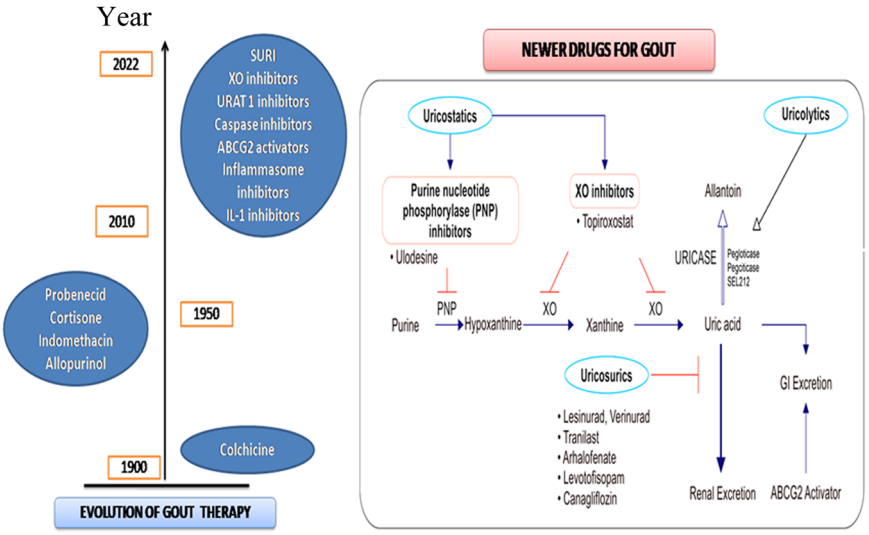

Evolution of gout therapy and newer drugs for gout.