

Clinical Effects of Xanthine Oxidase Inhibitors in Hyperuricemic Patients

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Highlights

- Hyperuricemia is a well-recognized risk factor for gout and has been shown to contribute to vascular damage.
- Large long-term clinical trials have demonstrated xanthine oxidase inhibitors to be generally effective, safe, and relatively well-tolerated.
- New urate-lowering drugs seem to be particularly efficacious for acute treatment of refractory hyperuricemia, though their use is supported by relatively small clinical evidence.

Keywords

Uric acid · Hyperuricemia · Uric acid-lowering drugs · Xanthine oxidase inhibitors

Abstract

This review aims to critically present the available clinical evidence supporting the treatment of chronic hyperuricemia with xanthine oxidase inhibitors. For this reason, the studies published on uric acid (UA)-lowering drugs in the English language from 2000 to August 2019 have been carefully reviewed. The terms “serum uric acid,” “xanthine oxidase,” “allopurinol,” “febuxostat,” and “topiroxostat” were incorporated into an electronic search strategy, alone and in combinations, in both MEDLINE (National Library of Medicine, Bethesda, MD) and the Cochrane Register of Controlled Tri-

als (The Cochrane Collaboration, Oxford, UK). Even if new urate-lowering drugs seem of particular efficacy for acute treatment of refractory hyperuricemia, their use is supported by relatively small clinical evidence. On the contrary, large long-term clinical trials have demonstrated that xanthine oxidase inhibitors (XOIs, namely, allopurinol and febuxostat) are effective, safe, and relatively well-tolerated in most of the patients. They have mainly been tested in the elderly, in patients affected by chronic diseases such as heart failure and cancer, and in patients taking a large number of drugs, confirming their safety profile. Recent data also show that they could exert some positive effects on vascular health, renal function, and glucose metabolism. Their cost is also low. In conclusion, XOIs remain the first choice of UA-lowering drug for chronic treatment.

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Introduction

Uric acid (UA) is the end product of exogenous and endogenous pools of purine metabolism. The exogenous pool includes dietetic factors, such as fructose, animal proteins, purine, and alcohol intake, and physiological conditions such as sex, age, renal function, and cell turnover rate [1], whereas the endogenous pool is mainly from the liver, intestines, and other tissues like muscles, kidneys, and the vascular endothelium. UA production and metabolism are processes involving hepatic production as well as renal and gut excretion of this compound. Xanthine oxidase (XO) catalyzes the 2 terminal reactions of purine catabolism in humans. In particular, XO catalyzes the oxidation from hypoxanthine to xanthine and from xanthine to UA, with the simultaneous reduction of NAD^+ or O_2 . Therefore, XO is the housekeeping and the rate-limiting enzyme in purine catabolism. The serum levels of UA (SUA) are kept at a healthy level [2], mainly thanks to the homeostatic regulation involving the renal transport systems. The proximal tubule is the site of reabsorption and secretion of UA, and almost all of it is reabsorbed into the blood. This is primarily accomplished at the proximal tubular level by transporters that exchange intracellular anions for UA. Almost all reabsorption of UA occurs at the S1 segment of the proximal tubule. In the S2 segment of the proximal tubule, UA is secreted to a greater extent than that which undergoes reabsorption. Post-secretory reabsorption occurs at a more distal site of the proximal tubule, and approximately 10% of the filtered UA appears in the urine. UA is mainly produced in the liver and intestine, being generated from xanthine and hypoxanthine and finally resulting from the purine catabolism. In most living species, such as primates, this metabolic pathway has been highly conserved during the evolutionary process, while some birds and Dalmatian dogs have experienced an increase in circulating levels of UA after losing the functionality of the final step in the degradation of UA [3].

Hyperuricemia may result from the overproduction of urate and mostly from underexcretion of UA, and often from a combination of the both [4, 5]. Lately, attention has been focused on gut microbiota and ABCG2 expression in the intestine as pathogenic mechanisms [6].

Very high SUA is a well-recognized risk factor for gout, but it should be recognized that SUA levels even below the upper limits of normal seem to increase the chance of developing cardiovascular disease (CVD), type 2 diabetes mellitus, and CKD [7, 8]. So, the recognition of a possible independent causal role of hyperuricaemia in

the pathogenesis of vascular damage could be of considerable clinical importance, given that the hypouricemic drugs currently available in clinical practice are very effective in reducing levels of circulating UA. The main biological mechanisms by which elevated plasma levels of UA can contribute to vascular damage are the following: prooxidant actions, inducing an increased production of oxygen free radicals and a series of other alterations that are potentially damaging to the vascular wall and other tissues [9]; endothelial dysfunction mediated by the increase in UA through the reduction of endothelial release of nitric oxide and the activation of the renin-angiotensin system with consequent damage at the vascular and renal levels [10, 11], endothelial and vascular smooth muscle cells proliferation through the induction of multiple kinases and intracellular growth factors [12, 13]; increased synthesis and release of endothelin-1; and pro-inflammatory action through activating the transcription of the nuclear factor- κB to induce the synthesis of tumor necrosis factor- α and interleukin-1 and expression of various other chemokines including the monocyte chemoattractant factor-1 (a chemokine directly involved in the processes of atherogenesis) and through the activation of cyclooxygenase-2 of protein kinase C and other protein kinases [14, 15]. Further experimental evidence suggests that hyperuricaemia may also play a causal role in the etiopathogenesis of insulin resistance (a known cardiovascular risk factor) through the induction of systemic endothelial dysfunction and pro-inflammatory and oxidative alterations, especially at the level of adipocytes [16].

Xanthine oxidase inhibitors (XOIs) are UA-lowering drugs with perhaps the most positive effects on cardiovascular outcomes beyond their consolidated positive action on gout risk [11]. This narrative review aims to shortly summarize the pharmacological profile (Table 1) and the main clinical indications (Table 2) of the clinically tested XOIs in hyperuricemic patients.

A recent meta-analysis of 16 randomized clinical trials including 1,211 patients with CKD has shown that SUA-lowering therapy halves the relative risk (RR) for kidney failure events; they reduce by more than half the RR for cardiovascular events, though not having a statistically significant impact on the risk of all-cause death [17]. Of note is a recently published case-matched cohort study evaluating the risk of death from CVD and all causes in patients with gout who received or did not receive urate-lowering therapy (ULT); this study showed that patients with gout treated with ULT had a lower risk of CVD and all-cause mortality relative to patients with gout not treated with ULT [18].

Table 1. Main pharmacological characteristics of the available xanthine oxidase inhibitors

Drug	Oral bioavailability, %	Protein binding, %	Metabolism	Biological half-life, h	Hypouricemic action, %
Allopurinol (C ₅ H ₄ N ₄ O)	78±20	Negligible	Liver (80% oxipurinol, 10% allopurinol ribosides)	2–3 (oxipurinol 14–30)	–24±2
Febuxostat (C ₁₆ H ₁₆ N ₂ O ₃ S)	>80	99	Liver (25–45% unchanged, 22–44% febuxostat acyl glucuronide)	5–8	–27±3
Topiroxostat (C ₁₃ H ₈ N ₆)	80	>92	Liver	4.5–7.5	–44±5

Table 2. Main clinical indications of xanthine oxidase inhibitors

Drug	Data available in humans	Main therapy	Add-on therapy	Suitable for use in gout	Suitable for use in asymptomatic hyperuricemic subjects	Safely administered in renal failure
Allopurinol	Yes	Yes	No	No	Yes	No
Febuxostat	Yes	Yes	No	Yes	No	Yes
Topiroxostat	Yes	Yes	No	Yes	Yes	Yes

Literature Search

The literature search strategy was based on the availability of clinical pharmacology data and preliminary or advanced clinical data on the efficacy and safety of UA-lowering drugs. We searched MEDLINE, Embase, and the Cochrane Database of Systematic Reviews to identify randomized clinical trials, meta-analysis, and systematic reviews published from inception to August 1, 2019 and related to the keywords: “serum uric acid,” “xanthine oxidase,” “allopurinol,” “febuxostat,” and “topiroxostat,” and only human data were considered and nonhuman experimental data were excluded from the review, as regards the clinical effects of XOIs in hyperuricemic patients. Two authors independently subsequently reviewed all of the citations retrieved from the electronic search in order to identify potentially relevant articles for the present review and determine their eligibility. Quality assessment of each article was performed evaluating the study’s aim, case and control definitions, inclusion and exclusion criteria, sample selection and analysis, and statistical definition of significant differential expression. Bibliographies of all identified studies and review articles were reviewed looking for additional papers of interest; no language restriction was used in the literature search. This review represents a careful and updated revision of the most significant literature in the field.

XO Inhibitors

In the purine metabolism pathway, XO in the form of xanthine oxidoreductase converts hypoxanthine into UA. This process brings about the production of reactive oxygen species, which in excess reduces nitric oxide synthesis, finally leading to endothelial dysfunction. A recent meta-analysis of 81 randomized clinical trials overall involving 10,684 patients showed that XOIs significantly reduce the risk of total and serious cardiovascular events (OR = 0.60, 95% CI [0.44, 0.82] and OR = 0.64, 95% CI [0.46, 0.89], respectively) and onset hypertension (OR = 0.54, 95% CI [0.37, 0.80]) when compared to placebo. Furthermore, a sub-analysis carried out on 9 studies and 616 hyperuricemic subjects showed that XOIs are more effective in secondary prevention, significantly reducing the occurrence of major adverse cardiovascular events in individuals with previous transient ischemic attacks, stroke, unstable angina, or myocardial infarction (RR = 0.42, 95% CI [0.23, 0.76]; $p < 0.01$; $I^2 = 0\%$) [19]. These potential benefits attributed to the XOIs may rely on their antioxidant properties other than SUA reduction as they inhibit the production of reactive oxygen species by the XO [20]. Also, these agents are the first-line drugs in ULT for gout, being effective in overproducers as well as in under-excretors of UA [21].

Allopurinol

Allopurinol and its metabolite oxypurinol are analogs of hypoxanthine and xanthine, respectively, and prevent the formation of UA by binding to XO and inhibiting it [22]. Allopurinol is an orally and parenterally administrable drug for the treatment of gout and preventing the recurrence of kidney stones. Treatment with allopurinol has been associated with an improvement in the flow-mediated dilation [23] and a slowdown in the progression of CKD [24, 25]. Moreover, it is the mainstay of prophylactic treatment for hyperuricemia in patients undergoing chemotherapy [26].

Immediately after oral administration, allopurinol is quickly absorbed in the upper digestive tract. It reaches peak plasma concentrations in about 30 min after ingestion and has a plasma half-life of about 2–3 h. The primary active metabolite of allopurinol is oxypurinol, which is filtered and partially reabsorbed in the kidneys. Oxypurinol has the same mechanism of action of allopurinol, but a longer plasma half-life of 14–30 h and lower oral bioavailability than its precursor [27].

Allopurinol has a dose-dependent effect of lowering serum urate levels, and the usual daily dosages given for the treatment of chronic hyperuricemia range from 100 to 600 mg [28]. The maximal daily allopurinol dose may, however, be as much as 800–900 mg based on the country and product label [29]. A well-designed meta-analysis has shown that only lower doses of allopurinol (≤ 300 mg/day) can reduce the risk of total cardiovascular events, while subjects treated with allopurinol at higher doses do not seem to have any significant reduction in risk [11]. The explanation for this could be that higher doses of allopurinol may lead to loss of cardiovascular protection, considering that higher levels of oxypurinol may promote oxidative stress, as suggested by the study of Stamp et al. [30]. They observed that higher concentrations of oxypurinol promote a switch from an antioxidant to a prooxidant state, given that oxypurinol is a suitable substrate for myeloperoxidase (released by neutrophils in inflammatory states such as gout and hyperuricemia), generating radicals capable of oxidizing urate and promoting deleterious effects.

In an observational study carried out on 6,428 dose escalators and as many non-escalators, dose escalation has been associated with a small increase ($<10\%$) in all-cause mortality, showing that it is unlikely to improve 10-year survival [31]. However, it is generally recommended that patients start with a low dose of allopurinol and increase it gradually. This conservative approach significantly lowers the risk of potentially fatal hypersensitivity syndrome

and helps to prevent acute gout attacks, which tend to occur immediately after starting the treatment; gradual titration of the dosage has been shown to mitigate this effect [32]. However, in order to decrease the risk of acute attacks of gout, the administration of anti-inflammatory drugs or low-dose colchicine can be useful as needed during the initiation of therapy with allopurinol [33].

The most common documented side effects are gastrointestinal distress and skin rash that can range in severity. Apart from potentially severe skin reactions, serious side effects include allopurinol hypersensitivity syndrome, a rare as well as potentially fatal condition consisting of eosinophilia, hepatitis, and interstitial nephritis. In particular, subjects starting on high doses of allopurinol and CKD patients in treatment with thiazide diuretics are at increased risk for developing allopurinol hypersensitivity syndrome; clinicians therefore tend to use lower ranges for maximum dosing in patients with renal impairment. Moreover, pharmacogenomics plays a role in the side effect profile of allopurinol, and the risk of severe side effects increases in patients with the HLA-B*5801 haplotype, commonly found in Han Chinese and Thai ethnicities other than in Korean descents with at least stage 3 CKD [34]. Some of these concerns can lead to allopurinol underdosing, consequently resulting in ineffective control of hyperuricemia [35].

Finally, allopurinol is contraindicated in patients on didanosine [36]. Also, the concomitant use of allopurinol at a dose of 300–600 mg/day with mercaptopurine or azathioprine requires a reduction in dose of these agents to approximately one-third or one-fourth of their usual dose. Therapeutic response and toxicities should be monitored accordingly [37].

Febuxostat

Febuxostat is an oral non-purine selective XO inhibitor that can inhibit both the oxidized and the reduced form of XO by binding them. Unlike allo/oxypurinol, febuxostat prevents enzyme turnover, avoiding the consequent production of ROS by blocking the active pterin-molybdenum center of the enzyme-substrate complex [38]. After oral administration, it is absorbed in the upper digestive tract and achieves its peak plasma concentrations within an hour, having a plasma half-life of around 5–8 h [30]. Febuxostat is metabolized and mainly excreted through the hepatic conjugation processes. In the past, several studies have clarified that it is more powerful and effective than allopurinol in lowering SUA levels and exerting anti-inflammatory effects on the endothelial cells [39, 40]. Its efficacy has been partly related to its ability to

inhibit glycosaminoglycan-bound and endothelial cell-bound XO [41]. However, febuxostat seems to exert a different inhibitory effect on XO in terms of central and peripheral endothelial function. A study comparing the effect of febuxostat and allopurinol in patients with gout has shown that febuxostat is more effective in preventing peripheral arterial stiffening as measured by carotid-femoral pulse wave velocity over 1 year [42]. On the contrary, a recent phase 4 randomized, placebo-controlled, double-blind, crossover trial has found that febuxostat does not significantly improve coronary endothelial dysfunction in patients with known stable cardiovascular artery disease and magnetic resonance evidence, though it lowers SUA levels [43].

The recommended dosage of febuxostat is 80–120 mg/day, even though remarkable decreases in SUA levels have also been observed at the lower dose of 40 mg/day. In particular, the number of subjects who can reach target SUA values (<6 mg/dL) with 40 mg febuxostat seems to be more than the number of subjects in treatment with allopurinol 300 mg [44]. Febuxostat is indicated for the treatment of hyperuricemia in gout patients, being a valid alternative therapy for individuals in whom allopurinol is contraindicated due to a previous allergic reaction [45]. On the contrary, it is not indicated in asymptomatic hyperuricemic patients since evidence is lacking [46].

Recent findings have shown that no dosage adjustments are necessary in patients with mild-to-moderate or severe hepatic and renal impairment (with CrCl <30 mL/min), even if this drug has not just been studied in patients on dialysis. In general, side effects associated with febuxostat include muscle pain, stomach pain, diarrhea, and a slight elevation in liver enzymes [47]. A meta-analysis of available comparative clinical trials showed that febuxostat tolerability is overall significantly higher than that of allopurinol in patients with hyperuricemia or gout [48] and especially in the ones with renal failure, having a lower incidence of adverse events (OR 0.85, 95% CI [0.75, 0.97]) [49]. Febuxostat is also supposed to have nephroprotective activity compared to allopurinol [50] and has recently been demonstrated to effectively and safely reduce SUA levels also in kidney transplant patients [51, 52]. For these reasons, even if 2016 updated European League Against Rheumatism (EULAR) guidelines suggest the use of febuxostat as second-line SUA-lowering agent for the patient either not responding or intolerant to allopurinol [53], the latest guidelines – such as the guidelines of the American College of Physicians (ACP 2017) – consider febuxostat as a first-line agent in hyperuricemia treatment [54].

According to a lately published meta-analysis carried out on 10 trials, including 14,402 patients, febuxostat is neutral toward cardiovascular events [55]. However, based on the largely criticized results of the more recent “Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)” trial [56], the Food and Drug Administration to limit the approved use of febuxostat to patients who are not treated effectively or experience severe side effects with allopurinol, suggesting special attention to patients at high risk for cardiovascular events, already assuming the drug [57]. Besides, in the recent “Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy – FREED,” no negative impact of febuxostat on cardiovascular events has been observed [58], while in a recent observational study carried out on mild-to-moderate heart failure patients, febuxostat seems to have a positive impact on cardiovascular mortality compared with allopurinol [59]. Finally, a recent meta-analysis of randomized clinical trials showed no difference between allopurinol and febuxostat in terms of association with major cardiovascular events [60].

Topiroxostat

Approved for therapeutic use in Japan since 2013, topiroxostat is another selective XO inhibitor with good oral bioavailability in humans. Its pharmacologically active metabolite (1,000 times less than the parent drug) is the *N*-glucuronidated topiroxostat (F11741), which is produced in the liver [61]. In db/db mice, this drug has been shown to cause a dose-dependent reduction in both urinary albumin excretion and plasma XO activity [62]. Similar findings have been safely confirmed in hyperuricemic patients with CKD stage III, in whom topiroxostat 160 mg was reported to effectively decrease SUA and urinary albumin excretion [63].

The “Effects of Topiroxostat for hyperUricemic patients with overt Diabetic nephropathy (ETUDE)” study [64] and the “Uric acid-lowering and renoProtective effects of topiroxostat in patients With diAbetic nephropathy and hyperURicemia (UPWARD)” study [65] have confirmed the positive impact of topiroxostat on renal function in patients with overt diabetic nephropathy. Overall, these results suggest topiroxostat may have a renal protective effect over and above its UA-lowering action [66].

The long-term (58 weeks) efficacy and tolerability have been further confirmed in a hyperuricemic patient with or without gout [67]. The results of a new trial (Effect of Xanthine Oxidase Inhibitor in Chronic Heart Fail-

ure Patients Complicated with Hyperuricemia study – Excited-UA) study carried out on heart failure patients are soon expected [68]. Topiroxostat has also been demonstrated to significantly and safely decrease SUA levels in hyperuricemic patients receiving hemodialysis at the minimum dose compared to allopurinol ones [69]. Moreover, since topiroxostat is not dialyzable, unlike the other XOIs, the dose reduction is not required even in patients with lowered renal function [70]. While the preliminary clinical data are promising, larger long-term studies are required to better characterize the efficacy and safety profile of topiroxostat [71].

3,4-Dihydroxy-5-Nitrobenzaldehyde

3,4-Dihydroxy-5-nitrobenzaldehyde (DHNB) is a new and powerful time-dependent XOI with a mechanism of action still under investigation, but that seems to be similar to allopurinol. Some studies have suggested that DHNB has low toxicity and enhances therapeutic efficacy, even at low doses, in co-administration with allopurinol. Moreover, DHNB has a direct antioxidant capacity and reduces the production of free radicals and ROS at source, in order to limit cell damage. However, while it appears to be extremely safe and effective in mice, no human data are available yet [72].

Concluding Remarks

A clear role for SUA level has been shown convincingly only for gout and nephrolithiasis, but the possible role of hyperuricaemia in the pathogenesis of CVD continues to be a subject of intense scientific debate, as it is not completely clear whether the increase in uremia is simply a marker or a true cardiovascular risk factor [1, 5, 6]. However, hyperuricemia also seems to be an independent risk factor for developing type 2 diabetes, CKD, hypertension, atrial fibrillation, coronary artery disease, and heart failure; it also predisposes to gout, so optimizing SUA levels is increasing as a public health priority [73, 74]. Currently, there is no general agreement on lifestyle modification, which might be more effective in reducing SUA levels, insofar as a low-energy Mediterranean diet aimed at achieving optimal body weight seems reasonably the best approach [75].

The available urate-lowering drugs can be grouped by their mechanism of SUA reduction; XOIs reduce urate production, while the uricosuric agents probenecid, benzbromarone, sulfapyrazone, and lesinurad increase renal excretion of SUA by inhibiting its reabsorption. Fi-

nally, the injectable uricase enzymatically degrades UA to allantoin [76].

The XOIs are undoubtedly the most studied both for their ability to reduce SUA and for their extra-UA effects [77]. A meta-analysis of 24 studies has shown that adherence to ULT among gout patients is poor, suggesting the need for more attention by clinicians [78]. Furthermore, considering the amount of cardiovascular risk associated with hyperuricemia, the use of lipid-lowering and antihypertensive drugs (such as fenofibrate and losartan), which are able to improve SUA levels, is recommendable, insofar as the use of these drugs has not just been clearly demonstrated to reduce the SUA-related risk for human health beyond their effects on lipids and blood pressure [13]. Certainly, this approach should be even more rigorous in diabetic patients because the use of SGLT2 inhibitors rather than other antidiabetic drugs has been shown to reduce SUA by up to -0.63 mg/dL (95% CI $[-0.98, -0.59]$) [79]. At the same time, medications increasing SUA levels, such as old-generation β -blockers [80] and high-dose thiazides [81], should be substituted with other metabolically neutral antihypertensive drugs. Finally, considering the need for chronic treatment, the choice of an SUA-lowering drug should be oriented both by the knowledge of the pathophysiological mechanism of the disease and by consideration about product safety and tolerability [82], other than its positive effect on the cardiometabolic and renal outcome measures [83].

Even if new urate-lowering drugs seem of particular efficacy for acute treatment of refractory hyperuricemia, their use is supported by relatively small clinical evidence [84]. On the contrary, large long-term clinical trials have clearly demonstrated that XOIs (namely, allopurinol and febuxostat) are effective, safe, and relatively well-tolerated in the most patients [55]. They have been largely tested in the elderly, in patients affected by chronic diseases such as heart failure and cancer, and in patients taking a large number of drugs, confirming their safety profile. In conclusion, XO remains the first choice of UA-lowering drug for chronic treatment.

Conflict of Interest Statement

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