Treatment of Chronic Hyperuricemia

Subjects: Pathology
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1. Introduction

Uric acid [UA] is mostly produced in the intestine and liver, as the final product of purine catabolism. This metabolic pathway has been highly conserved during the evolutionary process in most living species, with some exceptions such as Dalmatian dogs and some birds[1]. During normal homeostasis, serum levels of UA [SUA] are kept lower than 7 mg/dL in men and 6 mg/dL in women[2], mainly thanks to a complex regulation process involving the renal transport systems. However, chronic hyperuricemia might depend on the overproduction of UA and/or a reduced UA renal excretion[3], even though new pathogenic mechanisms also focus on ABCG2 expression in the intestine and the gut microbiota[4]. A number of factors are involved in determining SUA levels, including age (i.e., the prevalence of hyperuricemia increased from the age of 60 years, reaching a plateau after the age of 70 years), sex, cell renewal factor, renal function, and exogenous factors (i.e., dietetic factors, e.g., fructose, purine, and alcohol intake)[5].

Even though very high SUA is a well-known risk factor for gout, SUA levels at the upper limits of normal were shown to increase the chance of developing cardiovascular disease, type 2 diabetes, and chronic kidney disease [CKD] in the general population[6], and the risk of developing metabolic syndrome in elderly[7]. Recent evidence coming from the large epidemiological URRAH study shows that SUA is associated with a significantly increased risk of heart failure (hazard ratio, 1.65 [95% confidence interval—CI, 1.28–2.11]), fatal heart failure (hazard ratio, 1.65 [95% CI, 1.28–2.11]), total mortality (hazard ratio, 1.53 [95% CI, 1.21–1.93]), and cardiovascular death (hazard ratio, 2.08 [95% CI, 1.15–2.97]; $p < 0.001$)[8][9]. The risk seems to increase with SUA levels lower than the ones associated with an increased risk of gout and even lower to the currently considered normal values[10].

Elevated serum UA levels has been associated with greater inflammatory status and greater risk of mortality also in patients with a history of cardiovascular disease and in particular after myocardial infarction[11][12].

Worldwide the percentage of adults with hyperuricemia has been increasing over the past decades and, lately, novel insights into the pathophysiology of this disorder has led to significant advancement in its management which uses traditional agents for mild-to-moderate disease and cutting-edge drugs for individuals with severe or refractory hyperuricemia[13]. Therefore, to recognize which patients mainly overproduce UA, which ones mainly under excrete it, and which ones suffer from both of these conditions is of fundamental importance in clinical practice. This initial differentiation could lead to a more appropriate use of the available UA lowering drugs based on their pharmacodynamics[14].

2. Drugs Reducing the Generation of Uric Acid: The Xanthine Oxidase Inhibitors

Xanthine oxidase [XO] is the form of enzyme xanthine dehydrogenase responsible for converting hypoxanthine to UA in the purine metabolism pathway. During this process, there is the production of reactive oxygen species [ROS][15]. When produced in excess, ROS reduces the synthesis of nitric oxide and lead to endothelial dysfunction[15]. A meta-analysis pooling data from 81 randomized clinical trials (RCTs) (N. 10684 included patients) showed that the xanthine oxidase inhibitors [XOIs] decreases the risk of total and serious cardiovascular events [Odds Ratio—OR = 0.60, $p = 0.001$ and OR = 0.64, $p < 0.01$ respectively] and onset/worsening hypertension [OR = 0.54, $p = 0.002$] in comparison with placebo. Moreover, a sub-analysis pooling data from 9 trials and 616 hyperuricemic subjects found that XOIs are more effective in

secondary prevention, reducing the occurrence of major cardiovascular adverse events in those high-risk patients [Relative Risk—RR = 0.42, $p < 0.01$][16]. Certainly, the potential benefits attributed to XOIs may rely on their antioxidant properties other than SUA reduction, by the inhibition of ROS production[17].

These agents are the first line in urate-lowering therapy for gout, being effective in most hyperuricemic patients with an acceptable tolerability profile [18].

2.1. Allopurinol

Allopurinol and its metabolite oxypurinol are respectively analogs of hypoxanthine and xanthine, and decrease UA formation by binding and inhibiting XO[19]. This drug can be administered orally or parenterally, to treat gout and prevent the recurrence of kidney stones.

Allopurinol treatment is the mainstay in the prophylaxis of hyperuricemia in patients receiving chemotherapy[20]. Moreover, it was associated with an improvement in flow-mediated dilation[21] and a slowdown in CKD evolution [22][23]. An ongoing clinical trial (ClinicalTrial.gov ID: NCT03865407) will clarify the effect of allopurinol treatment on renal function in pediatric CKD patients with high UA levels and establish whether it alters renal injury biomarkers.

After oral administration, allopurinol is quickly absorbed in the upper gastrointestinal tract. The peak plasma concentration is reached in ~30 min after ingestion, and the plasma half-life is 2–3 h[24].

The main active metabolite of allopurinol is oxypurinol, which is filtered and partially reabsorbed in the kidneys, having the same mechanism of action as allopurinol but a plasma half-life of the order of 14–30 h[24] .

Allopurinol has a dose-dependent SUA-lowering effect and is usually administered at a daily dose of 100 mg to 600 mg/day for the treatment of chronic hyperuricemia[25]—the maximum daily dose can however reach 800–900 mg/day, by country and product-label[21]. Notwithstanding that a meta-analysis has lately showed that only lower doses of allopurinol (≤300 mg/day) can reduce the risk of cardiovascular events ($p < 0.001$)[26].

In general, patients are recommended to start on a low dose of allopurinol and then gradually increase it. This expedient allows to contain the risk of hypersensitivity syndrome [AHS] and provides a chance to prevent acute gout attacks immediately after starting the treatment[17]. Moreover, the risk of acute attacks of gout can be further prevented by the co-administration of an anti-inflammatory drug or low-dose colchicine[27].

The most common reported side effects related to allopurinol use include gastrointestinal distress and skin rash ranging in severity. In addition to adverse skin reactions, treatment-emergent adverse events include AHS (which is rare but also potentially fatal), hepatitis, interstitial nephritis, and eosinophilia. CKD patients treated with thiazides have an increased risk for developing AHS so that patients with renal impairment are recommended to use lower allopurinol doses. Furthermore, pharmacogenomics plays a role in the safety of allopurinol use and the risk of serious adverse events augments in patients with the HLA-B*5801 haplotype, highly prevalent in Thai and Han Chinese ethnicities with at least stage 3 CKD [28].

Finally, allopurinol is contraindicated in patients on didanosine[29], while the concomitant administration of 300–600 mg/day allopurinol and azathioprine or mercaptopurine requires a reduction in dosage of the immunosuppressants to approximately one-third or one-fourth of the usual dose. In these cases, the therapeutic response and toxicity need to be monitored[30].

However, it must be acknowledged that these concerns can lead to allopurinol underdosing, and determining inadequate management of hyperuricemia of consequence[31].

2.2. Febuxostat

Febuxostat is an oral non-purine selective XO inhibitor able to blind and inhibit both the reduced and the oxidized form of XO. Febuxostat prevents enzyme turnover and blocks the active pterin–containing molybdenum center in enzyme-substrate complex, reducing the consequent ROS production[32]. Following oral administration, it is absorbed in the upper gastrointestinal tract and reaches the peak plasma concentration within 1 h. Its plasma half-life is of the order of 5–8 h.

Febuxostat is metabolized and excreted mainly through hepatic conjugation. It is more effective than allopurinol in reducing SUA concentrations and exerts also anti-inflammatory properties on the endothelium[33][34].

Febuxostat efficacy has been partly related to the inhibition of glycosaminoglycan-bound and endothelial XO cell-bound[35]. By comparing the effect of febuxostat and allopurinol in gouty patients, febuxostat is more effective in preventing arterial stiffening over 1 year[36]. Contrarily, a recent phase 4 randomized, double-blind, crossover designed, a placebo-controlled clinical trial showed that febuxostat does not significantly improve coronary endothelial dysfunction in patients with known stable cardiovascular artery disease, even though it lowers SUA[37].

The recommended daily dosage of febuxostat is 80–120 mg/day, even if remarkable reductions in SUA levels can be achieved also with lower dosages (i.e., 40 mg/day). In particular, treatment with 40 mg/day febuxostat seems to be able to reach the target value of SUA (<6 mg/dL) more easily than allopurinol 300 mg.

Febuxostat is indicated in hyperuricemic patients with gout, being a valid alternative treatment for individuals who experienced an allergic reaction with allopurinol[38]. No dosage adjustments are needed in patients with mild-to-moderate or severe hepatic impairment, though the American College of Rheumatology (ACR) recommends using low dose febuxostat (40 mg/die) in patients with severe renal impairment (eGFR < 30 mL/min/m^2) [39]. The ongoing LUMINA trial (ClinicalTrial.gov ID: NCT03200210) is investigating the long-term effect of the drug on cardiovascular outcomes in continuous ambulatory peritoneal dialysis patients with hyperuricemia.

Treatment-emergent adverse events associated with febuxostat include stomach pain, diarrhea, muscle pain, and slight elevations in transaminases[40]. These observations have been corroborated by a recent meta-analysis that, pooling data from 13 RCTs (13,539 patients overall), concluded that febuxostat has a similar cardiovascular safety when compared with allopurinol (side effects OR = 0.72, p = 0.55) and a halved risk of skin reactions (OR = 0.50, p = 0.01)[41].

Recently febuxostat has been shown to be better tolerated than allopurinol in hyperuricemic and gouty patients, especially when renal failure was present [adverse events OR = 0.85][42]. Febuxostat has also been investigated for its nephroprotective activity in comparison with allopurinol and has recently been shown to safely reduce SUA in patients after kidney transplantation[43][44].

For these reasons, even if the 2016 guidelines of the European League Against Rheumatism [EULAR] suggest the use of febuxostat as an alternative SUA lowering agent[45], the latest American College of Physicians' guidelines (ACP 2017) suggest febuxostat as a first-line agent for the management of hyperuricemia[46]. The latest recommendation differs from the most recent one of the ACR placing allopurinol as the preferred first-line urate-lowering therapy, following the potential cardiovascular safety concerns attributed to febuxostat[39].

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial reported a higher risk of cardiovascular mortality with the use of febuxostat versus control[47]. Following these results, the Food and Drug Administration (FDA) added a new boxed warning indicating that there is an increased risk of heart-related death and death from all causes with febuxostat. However, the available evidence regarding the effects of febuxostat on mortality and major cardiovascular adverse events in patients with gout is controversial. Most recently the Febuxostat versus Allopurinol Streamlined Trial (FAST) has yielded findings coming out in the opposite direction of CARES[48].

2.3. Topiroxostat

Topiroxostat is a selective XOI that has good oral bioavailability. Its pharmacologically active metabolite—namely the N-glucuronide topiroxostat (F11741)—is produced by the liver[49].

In vivo, topiroxostat causes a dose-dependent decrease in the excretion of urinary albumin [UAE] and the plasma activity of XO[50]. Then, similar findings were safely confirmed in hyperuricemic patients with stage III CKD, where 160 mg/day topiroxostat has been reported to decrease SUA levels and UAE[51].

Topiroxostat treatment was also shown to safely reach a significant decrease in SUA in hyperuricemic patients undergoing hemodialysis, at a lower dose rather than allopurinol[52]. The ETUDE trial has confirmed the positive impact of topiroxostat on renal function in patients with overt diabetic nephropathy[53]. Recent trials suggest that topiroxostat has a good safety and efficacy profile, however it seems to exert a weaker renoprotective and antioxidant effects than febuxostat in patients with hyperuricemia and CKD [INSERT REFERENCE: Sezai, A., Unosawa, S., Taoka, M., Osaka, S., Sekino, H., & Tanaka, M. (2020). Changeover Trial of Febuxostat and Topiroxostat for Hyperuricemia with Cardiovascular Disease: Sub-Analysis for Chronic Kidney Disease (TROFEO CKD Trial). *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia*, *26*(4), 202–208. https://doi.org/10.5761/atcs.oa.19-00162].

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