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Review

The treatment of hyperuricemia☆

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ABSTRACT

Hyperuricemia has long been established as the major etiologic factor in gout. Alongside with an inflammatory state triggered by urate crystal deposition in the joints, hyperuricemia displayed additional pathophysiological consequences leading to tissue inflammation mainly in the vascular wall. Thus, therapeutic strategies used to treat hyperuricemia in the past decades have often been focused on limiting acute episodes. Recently, evidence has been accumulated suggesting that chronic urate deposition requires a correct treatment not limited to acute episodes based on the modulation of the activity of key enzymes involved in metabolism and excretion of urate including xanthine oxidoreductase (XO) and URAT1. The present review article will try to summarize the most recent evidences on the efficacy of XO inhibitors and uricosuric compounds in lowering uric acid levels in both the bloodstream and peripheral tissues. In particular, we will focus on the effect of novel XO inhibitors in counteracting uric acid overproduction. On the other hand, the effect of lowering uric acid levels via XO inhibition will be correlated with attenuation oxidative stress which leads to endothelial dysfunction thereby contributing to the pathophysiology of diabetes, hypertension, arteriosclerosis, and chronic heart failure. Hence, scavenging and prevention of the XO generated oxygen radical accumulation emerge as an intriguing novel treatment option to counteract uric acid-induced tissue damages.

1. Introduction

Hyperuricemia and gout are pathological conditions characterized by overproduction or under-excretion of uric acid, a product of purine catabolism physiologically excreted in the urine. Both conditions are often associated with chronic diseases such as hypertension, diabetes mellitus, metabolic syndrome, renal and cardiovascular diseases.

As a consequence, uricemia control is fundamental, as well as monitoring of uric acid levels over time. European Guidelines suggest serum uric acid levels ≤6 mg/dL in people having chronic hyperuricemia with urate deposition. In this context, non-pharmacological therapy (diet poor in purine-rich food, sugars, alcohol and rich in vegetables and water intake) is critical; however, if it is not effective in reducing uric acid levels, then pharmacological therapy is required [1].

The most common clinical features of hyperuricemia are accompanied by crystallization and deposition of uric acid in joints and surrounding tissues, however the precise mechanism for uric acid-induced tissue injury remains unclear.

It has been hypothesized that uric acid (UA) overproduction can trigger oxidative stress and that xanthine oxidoreductase (XO), the enzyme responsible for urate formation, may play a critical role in this context. In addition, impaired xanthine oxidase activity appears involved in the onset of cardiovascular diseases associated with hyperuricemia. XO inhibitors are potentially effective drugs to control these uric acid-related dysfunctions. Due to the limitations of currently available XO inhibitory drugs, the development of new ones with more potency, different pharmacological mechanisms, and less toxicity is an active field of research [2].

The aim of this review is to highlight new therapeutic strategies aimed at antagonizing adverse effects of current drugs used for hyperuricemia treatment and to minimize at the same time the risk of cardiovascular diseases.

2. Uric acid: physiology and pharmacology

2.1. Physiology

Uric acid is the final product of purine nucleotide catabolism which can be modulated by different factors such as diet or drugs used for the treatment of multiple cardiovascular risk factors or cardiovascular comorbidities.

Hypoxanthine and xanthine are the intermediate products of this catabolism. Xanthine oxidoreductase catalyzes the final two reactions in the biochemical chain that leads to uric acid formation: the conversion

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of hypoxanthine to xanthine and xanthine to uric acid. Urate is freely filtered at the glomerulus, but up to 90% of filtered urate is reabsorbed. The main transporters responsible for tubular reabsorption are URAT1 and GLUT9 [3].

In most mammals, *uricase* (urate oxidase), an enzyme very effective in lowering uric acid levels, oxidizes uric acid to allantoin which is highly soluble in water and excreted unchanged in the urine. Unfortunately, urate oxidase is not a functional human enzyme and, as a result, humans can develop hyperuricemia. Consequently, uric acid crystals can accumulate in human tissues and in the urinary tract, causing chronic hyperuricemia-related diseases [1].

2.2. Pharmacology

2.2.1. Treatment of acute gout

Therapeutic strategies used to treat hyperuricemia are often focused on limiting acute episodes characterized by an inflammatory response of cells triggered by urate crystal deposition. These events are counteracted using nonsteroidal antinflammatory drugs (NSAIDs), colchicine or glucocorticoids which act through different mechanisms.

In particular, NSAIDs' effect is due to the inhibition of prostaglandin generation by up-regulated COX-2, recognized as the most important event in the stimulation of inflammatory responses which characterize gouty arthritis attacks [4].

In vitro studies have shown that high concentrations of colchicine suppress inflammation by blocking IL-1beta processing in monocytes stimulated by monosodium urate (MSU). Moreover, it down-regulates tyrosine kinases and phospholipases in neutrophils, inhibiting chemotaxis, superoxide anion production, adhesion to cellular substrata, and mobilization and release of lysosomal enzymes during phagocytosis. Further evidence shows that fewer doses of colchicine are also able to alter the expression of endothelial adhesion molecules (E-selectin) on cells required for the recruitment of neutrophils [5]. Other actions are probably due to the capacity of colchicine to disrupt microtubules. However, its interaction with microtubules can cause accumulation of lysosomes and autophagic vacuoles in the cytoskeleton, resulting in pathologic alterations in skeletal muscle and induction of significant axonal neuropathy. These adverse consequences may manifest as myopathy (e.g. rhabdomyolysis), neuropathy, or bone marrow suppression [6].

Glucocorticoids have many well-described anti-inflammatory effects mediated by binding with glucocorticoid receptors, which are localized in the cytoplasm of target cells found in almost all tissues in the human body.

In acute gouty arthritis, the most notable anti-inflammatory action of glucocorticoids depends on the capacity for preventing activation of pro-inflammatory transcription factors such as NFκB and activating protein-1 (AP-1). In particular, glucocorticoids increase the expression of the inhibitor of κB (IκB), the cytoplasmic chaperone that prevents translocation of NFκB to the nucleus, inhibiting IL-1beta production. In addition to NFκB and AP-1, other transcription factors are negatively regulated by the glucocorticoid receptors and target genes include those encoding for a broad range of inflammatory cytokines, enzymes, receptors, and adhesion molecules such as IL-1beta, COX-2, E-selectin, and TNF-alpha [4].

Despite the multiple mechanisms of action of NSAIDs, colchicine and glucocorticoids, none of these options are universally effective in counteracting gout-induced inflammation or completely safe. Indeed, NSAIDs are chosen for patients without comorbid illnesses, but they are inappropriate for patients with renal impairment, congestive cardiac failure and peptic ulcer disease and in those treated with anticoagulants. Moreover, the use of very high doses of NSAIDs for patients with acute gout can induce gastric toxicity, and a reduced creatinine clearance, more relevant in patients affected by renal impairment [7].

Corticosteroids are also effective but they may interfere with blood pressure or glucose control.

Colchicine is used for patients who cannot be treated with NSAIDs or corticosteroids. However, it has a narrow therapeutic index.

As consequence, new therapies have been developed to better manage acute gout. Among them, a growing interest is focused on biological therapies aimed at counteracting the inflammatory effect of IL-1beta, considered a key mediator in the pathogenesis of gout, and triggered by MSU crystals. In particular, an open-labeled study showed that anakinra, an IL-1 receptor antagonist, resulted in rapid and complete pain relief without causing any side-effects in patients who failed conventional treatments such as NSAIDs, colchicine or corticosteroids. Rilonacept (a soluble IL-1 receptor that binds to IL-1 to prevent the binding with its original receptor) and canakinumab (a monoclonal antibody against IL-1beta) also resulted as more effective than allopurinol and corticosteroids [8].

All these drugs can represent valid alternative treatments for those patients in whom cardiovascular, renal and gastrointestinal comorbidity would preclude the use of NSAIDs, corticosteroids and colchicine.

Another recent advance in the management of acute gout regards the use of lower doses of colchicine. Indeed, it has been observed that lower doses of colchicine were as effective as higher doses in relieving pain showing a reduction of side-effects [9].

2.2.2. Long-term management of hyperuricemia

Despite of the progresses in acute gout therapy, it is also evident that urate deposition is a chronic disease requiring a correct treatment not limited to acute episodes.

In the development of gout, the first step is characterized by urate saturation in serum. Over the saturation level, formation of MSU crystals occurs with a consequent interaction with the inflammatory system. Drugs given for long-term prophylaxis act at the first step for reducing serum urate levels.

Currently, the long-term management of hyperuricemia is aimed at modulating the activity of key enzymes involved in the metabolism and excretion of urate as XO and URAT1. They are divided in two main classes: uricostatic drugs (e.g. allopurinol), which reduce uric acid production through competitive inhibition of xanthine oxidase and uricosuric drugs (e.g. sulphinpyrazone, probeneceid and benzbromarone), which increase urinary uric acid excretion by blocking renal tubular reabsorption of urate [8].

Primary urate-lowering therapy is often initiated with a XO inhibitor such as allopurinol or febuxostat. Allopurinol is generally a safe drug, but ~2% of patients develop hypersensitivity reactions, which can sometimes be severe and fatal with a mortality rate of ~20%. Moreover, allopurinol can have both dose-related (e.g., gastrointestinal intolerance and rashes) and idiosyncratic side effects. This occurs especially among patients with renal impairment, in whom the dose of allopurinol has not been appropriately reduced. On the other hand, lower doses of allopurinol used in these patients do not adequately control gout [10,11].

Febuxostat is a non-purine, xanthine oxidase inhibitor with a chemical structure different from allopurinol. It was recently approved by the National Institute for Health and Care Excellence (NICE) for use in patients intolerant to allopurinol and its antihyperuricemic efficacy has been shown at 80 to 120 mg/day. This lower dosage in comparison with the "standard dosage" of allopurinol (300 mg/day) might be due to its selectivity toward xanthine oxidase in the purine/pyrirmidine metabolic pathway. The most commonly reported adverse drug reactions are liver function abnormalities, diarrhea, headache, nausea, and rash. Febuxostat appears less toxic than allopurinol and in patients with mild to moderate renal impairment, dose adjustments are not needed, as it is mainly metabolized in the liver. Moreover, its pharmacokinetics and pharmacodynamics are not significantly altered in patients with moderate hepatic impairment [8].

Despite the beneficial effects of allopurinol and febuxostat in gout therapy, the number of patients achieving serum urate levels <6 mg/dL (<0.35 mmol/L) is in the range of 20–40% for allopurinol and 45–67%

for febuxostat (Phase III data), indicating the need for additional therapies [3,8].

A potential drug under preclinical study for the treatment of hyperuricemia by inhibiting XO activity is 3,4-dihydroxy-5-nitrobenzaldehyde (DHNB), a derivative of natural protocatechuic aldehyde. DHNB inhibits XO in a time-dependent manner similarly to allopurinol. In particular, DHNB displays potent mixed-type inhibition of the activity of XO, and shows an additive effect with allopurinol at low concentrations. DHNB interacts with the molybdenum center of XO and is able to directly scavenge free radicals [12].

Uricosuric drugs are an option in patients who are intolerant to allopurinol. Among them, probenecid, the older URAT1 inhibitor, is still available in some countries, but is contraindicated and ineffective in patients with renal calculi and renal impairment respectively, whereas benzbromarone has largely been withdrawn because of liver toxicity [3].

Other uricosuric drugs in clinical development are mainly URAT1 inhibitors such as lesinurad, arhalofenate, levotofisopam and RDEA3170. Lesinurad can achieve target serum urate levels when given with allopurinol or febuxostat in 60–100% of the patients [13–15].

Further drugs acting through different mechanisms are the non-absorbable phosphate binder sevelamer that increases gastrointestinal elimination, BCX4208, an inhibitor of purine nucleotide phosphorylase and the pegylated uricases (pegloticase and pegadricase) that reduce urate levels by increasing its metabolism [13].

Pegloticase is approved for patients refractory to conventional treatments (mainly used in severe tophaceous gout) and pegadricase has been in Phase I trial. Pegloticase has been shown to rapidly reduce serum urate levels so the majority of patients experience acute gout flares, and hence, pegloticase is co-prescribed with colchicine, NSAIDs or corticosteroids [3,8].

Pegloticase can only be used over a short period (~3–6 months) because many patients often develop anti-pegloticase antibodies that can reduce its efficacy. Consequently, pegloticase may be used for a short time in patients refractory to current prophylactic treatments, before the administration of other drugs as allopurinol or febuxostat. This would allow the management of hyperuricemia for a longer time [8]. Therefore, all these last emerging treatments are aimed at improving efficacy and reducing the side effects of traditional therapies (Table 1).

Table 1
Pharmacology of hyperuricemia.

	Mechanism
Treatment of acute gout	
Drugs	
NSAIDs	COX-2 inhibitors
Colchicine	Inhibition of IL-1beta processing Down-regulation of tyrosine kinases and phospholipases in neutrophils Inhibition of chemotaxis, superoxide anion production, adhesion to cellular substrata, mobilization and release of lysosomal enzymes Disruption of microtubules
Corticosteroids	Prevention of pro-inflammatory transcription factor activation with inhibition of inflammatory cytokines, enzymes, receptors, and adhesion molecules
Drugs in development	
Anakinra	IL-1 receptor antagonist
Rilonacept	Soluble IL-1 receptor
Canakinumab	Monoclonal anti-IL-1beta antibody
Long-term management of hyperuricemia	
Drugs	
Allopurinol	XO inhibitor
Febuxostat	XO inhibitor
Sulphinpyrazone	URAT1 inhibitor
Probenecid	URAT1 inhibitor
Benzbromarone	URAT1 inhibitor
Drugs in development	
Lesinurad	URAT1 inhibitor
Arhalofenate	URAT1 inhibitor
Levotofisopam	URAT1 inhibitor
RDEA3170	URAT1 inhibitor
BCX4208	Purine nucleoside phosphorylase inhibitor
Pegloticase	Pegylated uricase
Pegadricase	Pegylated uricase
DHNB	XO inhibitor

3. Chronic hyperuricemia and cardiovascular disease

In recent years, a large body of evidence suggests that hyperuricemia may play a role in the development and pathogenesis of a number of metabolic, hemodynamic, and systemic pathologic diseases, including metabolic syndrome, hypertension, stroke, and atherosclerosis.

The mechanisms underlying the role of uric acid in disorders other than gout are not well established but recent investigations point toward oxidative stress as the major pathophysiological event common to systemic diseases mentioned above. Uric acid has both pro-oxidant and antioxidant activity. As an antioxidant, it chelates metals and scavenges oxygen radicals. As a pro-oxidant, it oxidizes lipids, reduces nitric oxide availability in endothelial cells, and increases reactive oxygen species. As a result high levels of serum uric acid cause inflammation which would be expected to disrupt reverse cholesterol transport causing an increase of cardiovascular risk [16].

Reactive oxygen species (ROS) overproduction may be also caused by the enhancement of XO expression and activity. This hypothesis is supported by clear evidence showing that XO is involved in various forms of ischemic and vascular injuries, inflammatory diseases, and chronic heart failure [17–19].

As mentioned above, xanthine oxidoreductase catalyzes the final two reactions in the biochemical chain that leads to uric acid formation. The second step of this process is responsible for the superoxide anion radical and/or hydrogen peroxide H_2O_2 formation. XO is therefore a critical source of ROS and, in particular, of superoxide which can rapidly react with NO to form cytotoxic oxidant peroxynitrite ($ONOO^-$). $ONOO^-$ production together with the pro-oxidant properties of UA contributes to the decrease of nitric oxide levels leading to endothelial dysfunction and contributing to atherosclerosis and cardiovascular diseases [16,20]. These mechanisms suggest that there is a need for novel, more specific antioxidant and anti-inflammatory approaches aimed at preventing ROS formation by targeting molecular pathways directly involved in ROS generation (e.g. XO) and counteracting overt oxidative stress (Fig. 1).

4. Old and new XO inhibitors in the management of cardiovascular diseases

4.1. Allopurinol and oxypurinol

Recent data indicate that XO plays an important role in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure. It has been demonstrated that XO inhibitors allopurinol and oxypurinol, the active metabolite of allopurinol, have beneficial effects in the treatment of these conditions. Indeed, administration of allopurinol or oxypurinol has positive effects on reperfusion-induced arrhythmias and infarct size in different animal models. The cardioprotective effect of allopurinol or oxypurinol, in response to brief periods of ischemia, is probably due to the inhibition of XO activity but also to non-selective actions of these compounds that are able to act as free radical scavengers, copper chelators and inhibitors of lipid peroxidation [16].

Recent evidence reveals a role for the xanthine oxidase metabolic pathway also in the pathophysiology of chronic heart failure (CHF). In particular, several studies show that xanthine oxidase inhibition increases contractile capacity due to a calcium (Ca^{2+}) sensitizing

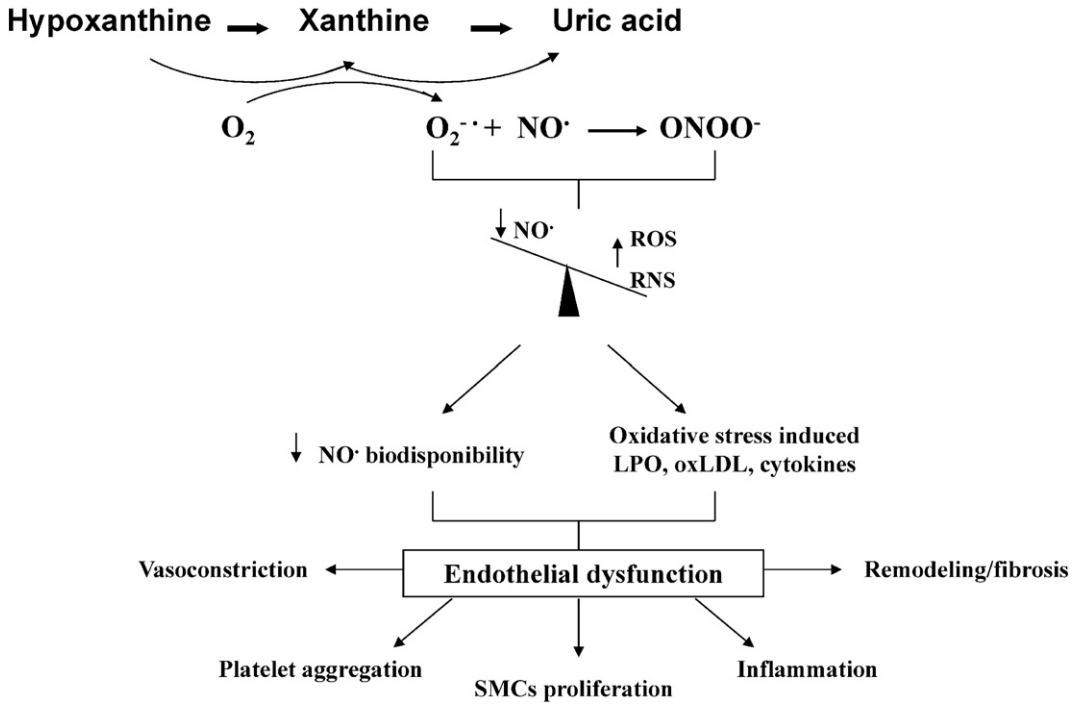

Fig. 1. Uric acid induces endothelial dysfunction enhancing the risk of cardiovascular disease development. ROS: reactive oxygen species; RNS: reactive nitrogen species; LPO: lipid peroxidation; oxLDL: oxidized low density lipoproteins; SMCs: smooth muscle cells.
Modified from [20].

mechanism and improves myocardial efficiency by reducing myocardial oxygen consumption [21].

In addition, it has been demonstrated that the cardioprotective effect of allopurinol and ascorbate in dogs with heart failure can be prevented by nitric-oxide synthase (NOS) inhibition, suggesting that XO-derived superoxide may interfere with NO regulation of myocardial energetics [22]. Interestingly, the deficiency of neuronal NOS but not endothelial NOS was associated with an enhancement in XO mediated superoxide production which induced a contractile depression of cardiomyocytes. Superoxide-mediated cardiomyocyte dysfunction was prevented by allopurinol, suggesting that nNOS, inhibiting XO activity, suppresses XO-dependent superoxide production [16].

XO-derived superoxide production farther contributes to the development of diabetic cardiomyopathy, and XO inhibition with allopurinol improves diabetes-induced cardiac dysfunction by decreasing oxidative/nitrosative stress. As a consequence, allopurinol inhibits activation of downstream effector pathways of oxidative stress and fibrosis, suggesting its multiple possible benefits in the treatment of diabetes [23].

4.2. Febuxostat

Febuxostat is able to inhibit both oxidized and reduced forms of the enzyme, preventing ROS and $ONOO^-$ formation as well as inflammation promoted by oxidative stress.

The marked protection afforded against vascular inflammation might be due to a more potent XO inhibitory effect than allopurinol caused by its binding to both oxidized and reduced forms of XO; moreover, it blocks substrate access to the active site. Indeed, the administration of febuxostat is able to reduce nitro-oxidative stress highlighted by nitrotyrosine formation, lipid peroxidation and over-expression of various inflammation-related molecules promoting the onset and the progression of the inflammatory state [20,24]. In addition, febuxostat inhibits circulating XO, preventing its binding to the surface of endothelial cells by glycosaminoglycans (GAGs), a process involved in the pathogenesis of endothelial injury [25].

This novel drug is also beneficial in the CHF as well as during the initial phase of left ventricular remodeling and cardiac functional deterioration after myocardial infarction. Besides the effect of febuxostat on ventricular dysfunction and myocardial hypertrophy, it also limits ventricular collagen synthesis, preventing fibrosis. The cardiac protective effect may also be associated with a reduced oxidative stress. Despite this evidence, the role of febuxostat in humans requires further investigation [20].

5. Natural antioxidants and prevention of hyperuricemia-induced CVR

It has been demonstrated that plant-derived antioxidants have anti-gout potential. In in vitro studies, flavonoids, alkaloids, essential oils, phenolic compounds, tannins, iridoid glucosides, and coumarins show the potential of anti-gout effects by their XO inhibitory action. Phenolic compounds and flavonoids inhibit UA production, showing uricosuric anti-inflammatory effects. Moreover, recent evidence has demonstrated a therapeutic potential for natural polyphenols such as bergamot derived polyphenols, alone or in combination therapy, to counteract detrimental effects of oxidative stress which characterize pathological states associated with the main cardiovascular risk factors. This dual effect of polyphenols, XO inhibitors and free radical scavengers respectively, suggests new therapeutic perspectives to prevent hyperuricemia, UA-induced oxidative stress, inflammation and tissue injury. Moreover, it will be possible to hypothesize alternative therapeutic strategies based on the use of low doses of XO inhibitors in combination with natural antioxidants to minimize their side effects [26–30].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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