Review Article

An Overview on the Role of Xanthine Oxidase Inhibitors in Gout Management

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Abstract

Gout is a kind of inflammatory arthropathy that affects a large number of people. Gout and hyperuricemia are becoming more common in developed countries. Xanthine Oxidase (XO) appears to play a key part in excessive uric acid (UA) production. XO inhibitors medications, which reduce serum UA levels by competitive inhibition of XO, are now the medications of choice for the long-term treatment of hyperuricemia. To discuss the role of XO inhibitors in treating gout disease and provide a review of the different available XO inhibitors medications. For articles selection, PubMed database was utilized, and the following keys were used in the Mesh ((“Xanthine Oxidase Inhibitors”[Mesh]) AND (“Gout” [Mesh]) OR (“Hyperuricemia”[Mesh])). The cornerstone of gout treatment is urea-lowering therapy, which aims to control acute flares, avoid recurring episodes, and prevent or reverse consequences. XO inhibitors such as allopurinol and febuxostat lower urate synthesis and can achieve control of the disease. Allopurinol has been the cornerstone of gout and hyperuricemia clinical therapy, and despite significant tolerability concerns and allegedly low patient compliance, it continues to be the current standard of care. Febuxostat is a safe and effective alternative to allopurinol for people who are allergic to it. However, clinical acceptance of febuxostat has been low, but updated care recommendations recommend febuxostat as an alternative to allopurinol.

Keywords: Xanthine Oxidase inhibitors, Gout, Diagnosis, Management

Introduction

Gout is a kind of inflammatory arthropathy that affects a large number of people. According to studies, the prevalence rates in Australia and New Zealand are 1.7% and 2.7%, respectively, with greater percentages in Maori and Islander communities. Gout and hyperuricemia are becoming more prevalent in the US, New Zealand, UK, and Australia [1-4]. According to a study, gout was not discovered in Aboriginal Australians in 1965, but by 2002, the frequency had grown to 9.7% in men and 2.9% in women. In the United States in 2007–08, the prevalence of gout was 6%, whereas the prevalence of hyperuricemia was 21% [3, 5, 6].

XO appears to play a key part in excessive UA production [7]. XO inhibitors medications with uricostatic properties (e.g., allopurinol, febuxostat), which reduce serum UA levels by competitive inhibition of XO, are now the medications of choice for long-term treatment of hyperuricemia [8]. In this paper, we aimed to review the role of XO inhibitors in treating gout disease.

Materials and Methods

For articles selection, PubMed database was utilized, and the following keys were used in the Mesh ((“Xanthine Oxidase Inhibitors”[Mesh]) AND (“Gout” [Mesh]) OR (“Hyperuricemia”[Mesh])).

Regarding the inclusion criteria, the papers were chosen according to the inclusion of one of these topics: Xanthine Oxidase Inhibitors, Gout, and Hyperuricemia.

Exclusion criteria were all other articles, which did not have one of these topics as their primary endpoint.

Results and Discussion

Hyperuricemia is defined as a blood uric acid level of more than 6 mg/dL in females and more than 6.8 mg/dL in males

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[9]. Gout occurs in only 10% of people with hyperuricemia, although 80–90% of gout patients are hyperuricemic [10]. The chance of having gout increases when UA levels in the blood rise. Why a tiny number of patients with hyperuricemia develop clinical gouty arthritis remains a mystery [11]. At this time, there is insufficient evidence to recommend treating asymptomatic hyperuricemia to avoid gouty arthritis, chronic kidney disease, or cardiovascular events [10].

UA has protective characteristics, which include vascular and antinatriuretic impact mediating blood pressure homeostasis in low salt circumstances, antioxidant function, neuroprotection, particularly on dopaminergic neurons, the modulator of the intestinal bacteria, whose composition is thus different in humans and other animals, and an indicator of impaired kidney function [9].

Garrod's finding of the relationship between gout and UA in the early 1900s resulted in the theory that UA is a poison that causes arthritis. UA was first postulated as a toxin for the kidney (thus the term "gouty nephropathy") and the cardiovascular system in 1960. The idea of UA as a nephrotoxic substance was widely accepted, maybe as a result of a continuous study into uremic toxins [9, 12].

Etiology and Pathogenesis

The ionized form of UA found in the body is known as urea. With a pH of 5.8, UA is a weak acid. When serum UA levels climb beyond the usual threshold, urea crystals form in tissues [13, 14]. The solubility of UA in the joint can be affected by a variety of circumstances. Synovial fluid pH, electrolytes level, water concentration, and other synovial components, including collagen and proteoglycans, are among them. The balance between UA production from purine intake in the food or endogenous synthesis through cellular turnover and its elimination by the kidneys and gastrointestinal tract determines the serum UA level in the body. Only 10% of gout cases are caused by increased UA production, whereas the other 90% are caused by renal under-excretion of the substance [15].

Age and gender are two factors that influence serum UA levels. Children have a low level of serum UA, and its levels begin to rise after puberty, eventually reaching normal levels. Levels are greater in males than in females. Serum UA contents in postmenopausal women, on the other hand, rise to men's contents. This justifies why gout affects mostly postmenopausal women, as well as older and middle-aged men. It can occur in children and young adults with some uncommon congenital purine metabolism abnormalities. These enzymatic abnormalities cause a rise in serum UA, leading to UA crystals in the joints and kidneys [16].

UA Overproduction

Overproduction of UA is caused by a lack of enzymes involved in purine metabolism. For instance, Lesch-Nyhan syndrome is an inborn metabolic mistake caused by a lack of hypoxanthine-guanine phosphoribosyltransferase, an enzyme included in UA metabolism. It is an X-linked recessive genetic disease with different grades of intensity based on the mutation type. In addition to renal stones, the clinical picture of this illness includes dystonia, chorea, cognitive impairment, self-mutilation, obsessive harmful behavior, and articular symptoms (early-onset gout). It can lead to tophi development and renal failure if left untreated [17].

The abundance of UA is well recognized to be linked to increased oxidative stress, and XO appears to play a key part in this process. The primary enzyme complex responsible for the production of UA is XO. It stimulates the final two transformations of xanthine to UA and hypoxanthine to xanthine in the biochemical pathway of UA production [8].

Diet

Consumption of purine-rich meals, including processed or cooked foods, particularly those derived from animals and shellfish, is significant in raising UA precursors. While purine-rich foods from plants, like lentils, peas, mushrooms, legumes, beans, and dairy products, pose no danger of hyperuricemia or gout, gout patients can consume them. Furthermore, vitamin C-rich meals, plant oils including sunflower, soy, and olive, and low-fat dairy products were linked to a lower incidence of hyperuricemia and gout. Vitamin C has been shown to enhance UA excretion in the kidneys, making it useful as a gout supplement.

A well-known gout risk factor is alcohol. The alcohol use effect is linked to the consumed amount. Furthermore, the danger of gout and hyperuricemia differs depending on the type of alcoholic beverage consumed. Beer, for example, raises the risk of gout the highest when compared to other alcoholic drinks; meanwhile, wine had the lowest risk of all the alcoholic beverages [18].

Production of Endogenous Urate

Accelerated cellular turnover, like in cancers, hematological, and inflammatory disorders, causes enhanced endogenous UA production. Chemotherapy and tissue injury can also cause an increase in purine production. Furthermore, obesity and increased body weight cause increased UA production, increasing the risk of hyperuricemia. The hormone leptin has been discovered to raise urate levels in the blood. As a result, weight loss and exercise are highly influential in decreasing serum UA contents and lowering the gout risk [19].

Impaired UA Excretion

The kidneys excrete two-thirds of urate, and the remainder is eliminated via the gastrointestinal tract. UA excretion through the gastrointestinal tract is decreased by the secretory activity of the transporter ABCG2, that leads to higher blood UA levels and increased renal excretion. Because UA crystals are not soluble, they must be transported across cell membranes by specialized membrane transporters. The

channel (URAT)/urate transporter, primarily URAT1, and the organic anion transporters (OAT1 and OAT3) are among these transporters [15, 20].

The final consequence of the four stages is UA excretion by the kidneys. The passage of UA over the glomerular filtration (Bowman's capsule) is the initial step, followed by the reabsorption of nearly all urates passing through the proximal tubules. Part of the reabsorbed UA is secreted in the third phase, followed by another reabsorption phase in the proximal tubules. The ejected UA accounts for nearly 10% of the urate filtered by Bowman's capsule, and the remainder is reabsorbed by the body [21].

Urate excretion in the kidney is impaired in several autosomal dominant diseases. Uromodulin is a gene found in the thick ascending limb of the loop of Henle. It is in charge of controlling water permeability. When the uromodulin gene is mutated, the fractional excretion of UA is reduced, resulting in a rise in serum UA [22].

Clinical Features and Diagnosis

Monosodium urate crystals are most commonly seen in the metatarsophalangeal joint of the big toe and the joints of the foot, knees, elbows, and hands. The crystals can also accumulate in the soft tissues around joints, forming tophi, which can also develop on the ear cartilage. Gout generally starts as a painful monoarthritis that goes away on its own within a few days to a week. Males after puberty and females after menopause are more likely to develop it. Recurrent episodes of severe joint inflammation mark gout, yet most patients are asymptomatic between attacks [23].

Urate crystals in synovial fluid or the tophus are required for a conclusive diagnosis of gout. A polarized light microscopic examination should be used to analyze the synovial fluid. Recurrent episodes do not require diagnostic aspiration once the final diagnosis has been determined unless joint sepsis is suspected. Because the concentration may not be increased during an acute attack, a normal or low serum urate does not rule out the diagnosis of acute gout. Gouty arthritis is indicated by first metatarsophalangeal joint involvement, local erythema, severe inflammation within 24 hours, and hyperuricemia. However, a response to colchicine and the appearance of tophi are more diagnostically helpful. If the diagnosis is unclear, imaging techniques such as ultrasonography and dual-energy CT scan may be useful [3, 23].

Numerous medicines that are consumed to treat comorbid illnesses have the potential to change serum urate levels. The urate-lowering properties of losartan, atorvastatin, fenofibrate, and calcium channel blockers are all modest [24]. Low-dose aspirin and diuretics, especially thiazide diuretics, raise urate levels in the blood. Thiazide diuretics should not be used to treat hypertension in patients with gout if at all feasible. Other causes of hyperuricemia should not be overlooked. Renal illnesses and myeloproliferative disorders are two examples.

Management

The cornerstone of gout treatment is urea-lowering therapy, which aims to control acute flares, avoid recurring episodes, and prevent or reverse consequences [25, 26]. According to the American College of Rheumatology, all patients suffering from gout should aim for a goal serum of SU less than 6 mg/dl in the lack of tophi and SU less than 5 mg/dl when tophi are present, according to the American College of Rheumatology [27]. Urate-lowering drugs should only be begun after a gout episode has completely resolved because a fast drop in serum urate contents might aggravate a subsequent attack [26]. Existing urea-lowering therapy medicines can be classified based on their mode of action: Allopurinol and febuxostat are XO inhibitors that lower urate synthesis; uricosurics like benzbromarone, sulfinpyrazone, lesinurad, and probenecid enhance renal SU excretion by blocking its reabsorption; and injectable uricases breakdown SU to hydrogen peroxide and more soluble allantoin [28]. Our focus in the present study is on the main XO inhibitors, whereas the rest are out of the scope of this study.

Allopurinol

Allopurinol, a structural isomer of hypoxanthine, has been the cornerstone of gout and hyperuricemia clinical therapy since its debut in 1966. Despite significant tolerability concerns and allegedly low patient compliance, it continues to be the current standard of care. Allopurinol is a hypoxanthine analog that inhibits XO, preventing the production of SU. In the event of chronic hyperuricemia, the usual daily dose ranges from 100 mg to 600 mg [29, 30]. Patients must begin with a low dosage and gradually enhance it. This method reduces the danger of Allopurinol Hypersensitivity Syndrome (AHS), which can be deadly and helps prevent acute gout episodes, that usually happen shortly after the medication [31].

Gastrointestinal discomfort and skin rash are the two most common side effects linked with allopurinol usage. Eosinophilia, hepatitis, interstitial nephritis, and AHS are some of the other side effects. Allopurinol can induce Severe Cutaneous Adverse Reactions (SCARs), such as toxic epidermal necrolysis, Stevens-Johnson syndrome, systemic symptoms, and eosinophilia [32]. Despite certain distinctions, AHS can be categorized as a SCAR or even be used interchangeably [33]. Fever, hepatic dysfunction, and renal failure are also possible symptoms of AHS. Older age and renal impairment are two major risk factors for AHS. AHS has a mortality rate of 20–30%, and it is more likely to be deadly in patients with renal insufficiency and those on thiazide diuretics. A proposal to determine the first daily dosage of allopurinol as 1.5 mg/unit of estimated glomerular filtration rate was made to reduce AHS risk [33]. In around 2% of allopurinol users, hypersensitivity appears as a minor skin rash. Furthermore, approximately 0.4% of people acquire SCARs, which have a mortality rate of up to 32%. [34].

It is worth noting that patient adherence difficulties might indicate the increased incidence of allopurinol usage, compared to other urate-lowering treatments, rather than any unique feature of allopurinol. Allopurinol is a mild competitive XO inhibitor quickly converted to the more powerful oxypurinol, an isostere of xanthine, and subsequently eliminated by the kidneys. Clinically, allopurinol is utilized to reduce UA contents, especially in gouty arthritis and kidney stones/lithiasis. Additional indications involve myeloproliferative illness and genetically related enzyme abnormalities associated with UA overproduction, such as tumor lysis syndrome and Lesch-Nyhan syndrome. Allopurinol has been suggested to have other pharmacology, like decreasing creatinine contents and blood pressure, supporting the idea that XO inhibition can have influences other than lowering urate levels [35-37].

Febuxostat

Febuxostat is a non-purine, selective XO inhibitor authorized by the FDA in 2009 to treat hyperuricemia in gout patients but not for asymptomatic hyperuricemia. Febuxostat is approved for usage in the US at dosages of 40 and 80 mg per day and up to 120 mg per day in Europe and 10–60 mg per day in Japan. Febuxostat is a safe and effective alternative to allopurinol for allergic people [38]. A large number of studies comparing the efficiency and safety of different doses of febuxostat (40–240 mg daily) versus allopurinol (100–300 mg daily) revealed that adverse reactions rates (including cardiovascular events) were similar in all treatment groups; deaths that occurred during the studies were unrelated to this agent [39, 40].

The Cardiovascular Safety of Febuxostat and Allopurinol in Participants with Gout and Cardiovascular Comorbidities (CARES) research found that gout patients who took febuxostat had a greater risk of cardiovascular-related death than those who took allopurinol, even though this study had several methodological flaws that were widely discussed [41, 42].

Muscle pain, gastric upset, skin rashes, diarrhea, and a modest increase in liver enzymes levels are the most prevalent adverse effects linked with febuxostat. Skin rashes, in particular, had an incidence equivalent to that seen with allopurinol. The manufacturer advises that liver function be monitored at the start of treatment and again if indications of liver damage appear. Nonetheless, unless the daily dose of febuxostat surpasses 120 mg/day, the risk of adverse effects is limited [43].

Febuxostat elimination is mostly mediated by hepatic metabolism, implying the possibility of broader prescription in patients with compromised renal function, but this has yet to be thoroughly evaluated in the clinic. Furthermore, febuxostat has been shown to have fewer drug-drug interactions and is better tolerated in individuals with AHS than allopurinol. However, clinical acceptance of febuxostat has been low, partly due to the higher expense of febuxostat compared to generic allopurinol ($7 per pill vs. $0.20–0.60 for allopurinol in the United States). Following this, updated care recommendations recommend febuxostat as an alternative to allopurinol [35, 41].

Topiroxostat

Topiroxostat is a selective XO inhibitor with high oral bioavailability in humans. It comes as oral tablets in dosages of 20, 40, and 60 mg, with the usual advice being to start with a 20 mg dose two times a day and work up to an 80 mg dose twice daily, with clinical effectiveness documented at 120 mg/day. Topiroxostat inhibits XO by producing a hydroxylated 2-pyridine metabolite that forms a covalent bond with molybdenum via oxygen and interacts with amino acid residues in the solvent channel [35, 44-46].

Topiroxostat has been shown to reduce serum SU contents in hyperuricemic patients on hemodialysis safely and effectively. Furthermore, unlike the other XO inhibitors, topiroxostat is not dialyzable. Thus dosage decrease is not necessary even in individuals with impaired renal function. The Renoprotective Effects of Topiroxostat for Hyperuricaemic Patients with Overt Diabetic Nephropathy (ETUDE) study has validated topiroxostat's beneficial effect on renal function in these patients. A rise in liver enzymes, polyarthritis, and nasopharyngitis are among the side effects of topiroxostat that have been documented in the literature. Most of these side effects are mild to moderate in severity [47-50].

Conclusion

The cornerstone of gout treatment is urea-lowering therapy, which aims to control acute flares, avoid recurring episodes, and prevent or reverse consequences. XO inhibitors such as allopurinol and febuxostat lower urate synthesis and can achieve control of the disease.

Allopurinol has been the cornerstone of gout and hyperuricemia clinical therapy, and despite significant tolerability concerns and allegedly low patient compliance, it continues to be the current standard of care. Febuxostat is a safe and effective alternative to allopurinol for people who are allergic to it. However, clinical acceptance of febuxostat has been low, but updated care recommendations recommend febuxostat as an alternative to allopurinol.

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