Effects of febuxostat versus allopurinol in patients with elevated serum uric acid levels, chronic gout: A literature review

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Gout is one of the most common etiologies of inflammatory monoarticular arthritis. Recent literature is reviewed to compare a novel advancement in chronic gout medication, febuxostat, to its counterpart allopurinol, through the identification of significant findings and improvements. Literature review concluded that febuxostat serves as a viable alternative when compared to allopurinol.

Keywords: gout, febuxostat, allopurinol, serum uric acid, chronic inflammatory, monoarticular arthritis

Gout, one of the most common and oldest etiologies of chronic inflammatory monoarticular arthritis, is characterized by an increase in uric acid levels due to defective excretion or metabolism (i.e. overproduction) [1]. Uric acid, an inert, insoluble, non-physiologic end-product of purine catabolism, is a weak acid that is subsequently excreted rectally and gastrointestinaly. Under normal physiologic conditions, uric acid is deprotonated to urate, but in excess, uric acid combines with sodium resulting in monosodium urate (MSU) crystals activation and formation. This can ultimately precipitate and form intra-articular deposits. With the increase in diabetes mellitus, dietary changes, life expectancy, and obesity, the prevalence of gout has been on a steady rise [2]. Clinically, gout commonly presents with a painful joint that is tender and warm to-the-touch. This is combined with an erythematous and edematous appearance and associated extra-articular joint destruction (i.e. Martel’s sign) visible on radiographs.

To date, there are a variety of treatments for chronic gout. Novel medications are being altered biochemically to address key comorbidities while reducing serum uric acid (sUC) levels to a therapeutic target of less than 6mg/dL. With these pharmacological advancements, it is essential to understand the signs, symptoms, and treatments of gout in order to avoid further disabilities and increase the overall improvement of the patient’s lifestyle. Our goal is to review the recent literature to compare a novel advancement in chronic gout medication, febuxostat, to its counterpart allopurinol, through the identification of significant findings and improvements.

Methodology

An in-depth literature review was conducted utilizing the online databases PubMed and NIH with pertinent searched keywords including “chronic,” “gout,” “inflammation,” “febuxostat,” and “allopurinol”. These keywords collectively describe (i) the etiology and presentation of chronic gout (ii) mechanism of actions between febuxostat and allopurinol (iii) efficacy of medications (iv) comparative cost-effectiveness through various clinical trials (v) any bias.
Results

Many studies to date have focused on comparing and contrasting the efficacy of febuxostat oral medication to allopurinol oral medication primarily due to the difference in biochemical mechanism of action between the two drugs. To preface, xanthine oxidase (XO), an essential enzyme that is over-expressed in inflamed and ischemic tissues, is responsible for the conversion of xanthine, a purine catabolism by-product, to uric acid. While allopurinol is a designated purine analog XO inhibitor, febuxostat, on the other hand, is a non-purine XO inhibitor [3]. Meaning, allopurinol is subject to metabolism by various purine and pyrimidine synthesis pathways, while febuxostat remains completely unaffected. Moreover, allopurinol inhibits purine nucleoside phosphorylase (PNP) and orotidine-5'-monophosphate decarboxylase (OMPDC), which are two biochemical structures involved in the synthesis of DNA and RNA.

When assessing which treatment modalities are appropriate for gout patients, it is important to evaluate the strength of the medication, as well as minimizing potential side effects. In a randomized trial of 1746 patients, 58.5% of the patient’s taking febuxostat (40mg/day) showed sUC levels below 6.0 mg/dL while only 47.1% of allopurinol (300mg/day) users achieved that same sUC target level [4]. In long-term studies, febuxostat was found to have a shorter and more favorable adverse effect profile compared to allopurinol, as well as achieved the therapeutic target sUC levels more quickly (at 348 days), which, on average, was 62 days shorter compared to allopurinol’s 410 days.

With a hypothetical cohort of 1000 adult gout patients with sUC greater than 8mg/dL, the total cost of febuxostat treatment over a 5-year period was approximately $2,000 greater than allopurinol [5]. However, over the same 5-year period, they reported 72% of the febuxostat patients showed greater treatment success versus the 42% allopurinol patients.

Discussion

Gouty arthritis is an innate inflammatory response due to an overall increase in plasma monosodium urate (MSU) crystals. Naturally, MSU crystals are soluble at plasma concentration levels of 7 mg/dL. Once plasma concentrations increase to 8mg/dL or greater, MSU crystals begin to precipitate in the tissue. Physiologically these crystals promote a pathological inflammatory and degenerative tissue reaction by stimulating cells via toll-like receptor signaling. Subsequently this provides an area to cleave C5, a complement component, while simultaneously promoting the formation of a C5b-9, a complement membrane attack complex also known as terminal complement complex. Eventually, this results in an increase in chemokines, cytokines and inflammatory mediators leading to the influx of neutrophils inundating the afflicted joint [1]. Clinically, the patient will present with a red, hot, swollen, painful joint with limited range of motion. While gout is monoarticular and can occur in any joint of the body, it most commonly affects the first toe and is often associated with diabetes mellitus and increased alcohol consumption [4].

Gout patients are physiologically hyperuricemic, which can be further classified into three categories: overproduction, underexcretion and the combined mechanism of the two. The etiologies of the aforementioned classifications can commonly include, but are not limited to a spectrum of genetic disorders, decreased renal function, and environmental factors (i.e. diet and medication). In addition to understanding the contributing factors that lead to hyperuricemia, it is important to note the strong association of an increased risk to cardiovascular disease secondary to the deleterious effects uric acid has on the vascular endothelium [2].

Conclusion

With the information gathered, these articles have concluded that febuxostat serves as a viable alternative when compared to allopurinol [3]. When factoring in underlying comorbidities, febuxostat, in many cases, had shown significant improvements by reducing sUC levels to less than 6mg/dL and in a shorter period of time [3]. However, one downside to utilizing febuxostat over other gout medications is the increased cardiovascular risk to people taking this drug when compared to other gout medications. There is currently a black box FDA warning, after the
clinical trials revealed 15 heart-related deaths were observed out of 1,000 febuxostat users, compared to 11 heart-related deaths out of 1,000 allopurinol users [6]. Also, despite the fact that febuxostat is provided at a greater expense, it has been shown to have a better cost effectiveness ratio than allopurinol [5]. Ultimately, as medications constantly improve, it is important to consider that the outcomes are highly individualized, as well as the management of systemic hyperuricemia will continually need long-term studies for further evaluation and to eliminate any potential bias.

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**References:**


