Approach To the Treatment of Hyperuricemia

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Despite a sound understanding of the synthetic and metabolic pathways that control serum uric acid levels, clinicians have been limited to a few urate lowering agents and one urate synthesis inhibitor since the development of allopurinol in 1956.[1] Febuxostat (Uloric) became the second urate synthesis inhibitor when the **Food and Drug Administration (FDA)** approved it in early 2009. The role of febuxostat in the management of hyperuricemia and gout remains to be fully determined. This review will discuss the traditional agents used for the lowering of serum uric acid and address the potential benefits febuxostat may offer in clinical practice.

Sources of Serum Urate

Serum uric acid accumulates from the metabolism of purine nucleic acids which are derived either from cellular breakdown or directly from foods rich in purines such as red meats, beer, shellfish, and yeast extracts.[2] Catabolism of purines is mediated through a cascade of well regulated enzymes that includes **phosphoribosyl pyrophosphate synthetase (PRPS), hypoxanthine-guanine phosphoribosyltransferase (HRPT),** and **xanthine oxidase (XO).**[3] (Figure 1) A deficiency in HRPT or PRPS over-activity results in hyperuricemic syndromes like Lesch-Nyhan and Kelley-Seegmiller, with resultant gouty arthropathy in some patients. Unlike other animal species, humans and other primates do not express uricase, the enzyme which converts uric acid into the more soluble allantoin for excretion. Uric acid is therefore the end product in human purine catabolism and is ultimately excreted in urine and also, to a lesser proportion, in the stool. Drugs that inhibit xanthine oxidase and uricosuric agents that increase renal uric acid excretion are the cornerstone of therapy for hyperuricemia.

Asymptomatic Hyperuricemia

Uric acid exceeds its solubility in extracellular spaces such as the joint or soft tissue at a concentration of 6.8 mg/dL. Uric acid precipitates as **monosodium urate** (MSU) crystals in these compartments but for varying reasons, does not always cause an inflammatory response. The risk of having symptomatic hyperuricemia is related to the degree of serum urate elevation. In an early study, Campion *et al.* demonstrated that in patients with serum urate levels less than 7.0mg/dL, the annual incidence of gouty arthritis was only 0.1% as compared to 4.9% in patients with serum rate greater than 9.0 mg/dL.[4] However, after five years of follow-up even patients with serum urate greater than 9.0mg/dL only had a cumulative incidence of gouty arthritis of 22%, demonstrating that a large proportion of patients with increased serum uric acid remain unaffected by gout. While the extent of hyperuricemia is correlated with a higher risk for gouty arthritis, hyperuricemia for any individual can persists for years without symptoms. Therefore, empiric treatment of asymptomatic hyperuricemia is not advised.

Indications for Treatment of Hyperuricemia

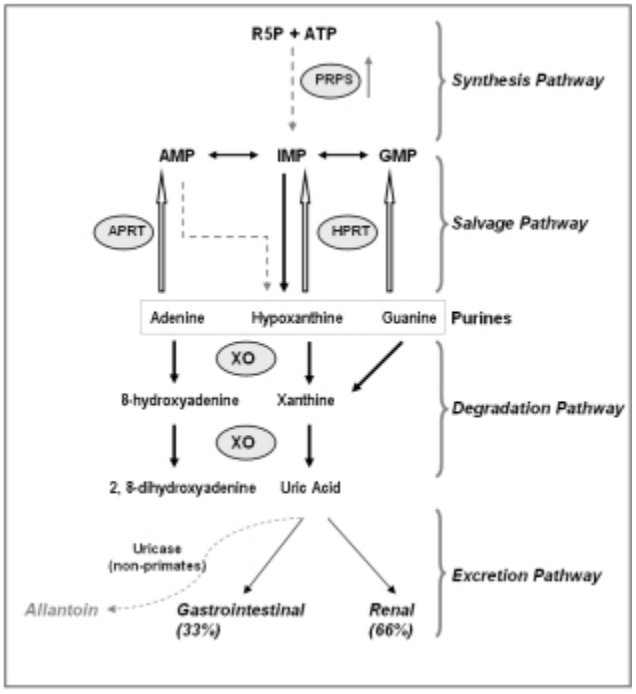
Pharmacologic reduction of hyperuricemia is generally required in patients with symptomatic disease. Most commonly, urate lowering agents are indicated for patients with more than one episode of acute gouty arthritis, all patients with tophaceous gout and chronic gouty arthritis, and patients with uric acid renal stones. Other situations that require the use of allopurinol include hyperuricemia associated with known inherited disorders like the Lesch-Nyhan and Kelley-Seegmiller syndromes, or more frequently as prophylaxis before cytolytic therapy for cancer.

Treating Hyperuricemia: Dietary Approach and Adjunctive Therapy

Approximately 60% of patients who have experienced acute gout arthritis experience a repeat attack within one year, based on historical data.[5] Prospective data to guide physicians are lacking, but it may be beneficial to attempt lifestyle and dietary modification rather than to commit to lifelong therapy in patients with a single attack of gout. If this fails, antihyperuricemic therapy will be necessary.

Patients should be educated on dietary and lifestyle modifications that can reduce serum urate levels. These patients should attempt to reduce purine-rich foods such as red or organ meats and shellfish, and they should avoid alcohol intake, especially beer. Weight loss and

Figure 1. Purine Metabolism Pathway.



XO: xanthine oxidase; HPRT: hypoxanthine-guanine phosphoribosyltransferase; APRT: adenine phosphoribosyltransferase; PRPS: phosphoribosyl pyrophosphate synthetase. AMP: adenosine monophosphate; GMP: guanosine monophosphate; IMP: inosine monophosphate; ATP: adenosine triphosphate; R5P: ribose-5-phosphate.

Adapted from Kassimatis et al, J Nephrol 2005; 18: 447-451. (3)

exercise have been also been shown to have a positive impact on urate reduction.[6] From the clinician's standpoint, loop diuretics or thiazide diuretics should be avoided when possible. Agents with mild uricosuric effects like losartan may be considered instead for patients with hypertension. Likewise, fenofibrate may be preferred for select patients with hypercholesterolemia and gout.

Weighing the Decision to Treat Hyperuricemia

The decision to initiate and commit to treatment with a long term serum urate lowering agent is not an easy one for patients. In a retrospective study of 9,482 patients prescribed allopurinol for gout, only 65.9% filled their initial prescription; of these, 18% were fully compliant with the treatment regimen recommended by their primary providers.[7] It is often difficult for clinicians to convince patients of the need to continue these medications during clinically quiescent periods, especially given the high medical costs incurred by patients with multiple medical conditions.[8]

Measurements of urine uric acid levels are no longer routinely performed during the workup of gout. Twenty-four hour urine uric acid and creatinine measurements continue to be useful in patients who are younger than 25 years old, those with strong family history of early onset gout, or patients with nephrolithiasis.[9] If urine uric acid is greater than 800mg per day, the patient is likely an over-producer of purines where hemolytic syndrome or lymphoproliferative disorders might be considered. If the patient has a uric acid clearance of less than 6ml per minute, then renal excretory defects such as Barter's or Gitelman's disease or lead nephropathy may be possible.[9] The urinary excretion of uric acid should be measured if uricosuric therapy is being considered, as these drugs will increase the possibility of renal stone formation in patients with high uric acid excretion.

The treatment of acute gout is discussed elsewhere in this journal. It is important to note that during the "intercritical" period, when the patient is tapering off higher doses of non-steroidal anti-inflammatory drugs (NSAIDs) or oral prednisone, colchicine at 0.6 mg twice daily has been shown to be useful for preventing recurrent flares. Colchicine or NSAID prophylaxis should be given during the initiation of anti-hyperuricemic therapy and continued until the patient has been free of acute attacks for a prolonged period of time.

Uricosuric Agents

Uricosuric agents are employed less frequently than allopurinol primarily because of the need for three times daily dosing and the requirement for measuring 24-hour urinary uric acid before beginning therapy. Uricosurics continue to be useful in patients with allopurinol intolerance or hypersensitivity or in patients with known defects in renal excretion of uric acid.

Probenecid is the primary uricosuric agent available in the United States. It blocks the renal proximal tubule exchanger URAT1, which reabsorbs uric acid. A study of forty patients with uncomplicated chronic gout receiving probenecid, or sulfinpyrazone versus allopurinol found the similar recurrence rates of acute gouty attacks, although serum urate level was lower in the allopurinol group. Other smaller trials suggest that uricosuric agents are just as efficacious as allopurinol in chronic gout patients without renal impairment.[8]

Initial dosing of probenecid is recommended to start at 0.5 grams per day to minimize flares, and then titrated to a typical dose of 0.5 grams twice a day to three times a day to a maximum dose of 3 grams per day. The contraindications for uricosurics are patients who have any history of nephrolithiasis, patients with low urine output, or patients with reduced renal excretion (GFR less than 60ml per minute). Significant drug interactions include the elevation of penicillin, salicylate, dapsone, heparin or zidovudine serum concentration by inhibition of renal tubular excretion.[2]

Xanthine Oxidase Inhibitors

Allopurinol

Allopurinol and its metabolite, oxypurinol, competitively block xanthine oxidase conversion of hypoxanthine to xanthine and xanthine to uric acid. It is very effective in lowering serum urate levels and reducing tophus size as shown in a study of sixty-three patients who received allopurinol with or without concurrent bezbromarone, a uricosuric used in Europe and Asia.[10]

Allopurinol is generally well tolerated, with mild gastrointestinal intolerance being the most common side effect experienced. **Allopurinol hypersensitiv-**

Table 1. Suggested Dosing of Allopurinol . Treatment should be initiated on a dose of allopurinol adjusted according to renal function. Then the dose of allopurinol should be titrated until serum uric acid is less than 6.0 mg/dL.

CrCl (ml/min)	Initial Dose
HD	50mg QDay (Administer after HD)
0	50mg Q 3 Days
1-10	50mg Q 2 Days
11-20	50mg Q Day
21-40	50mg Q Day
41-60	100mg Q Day
61-80	100mg Q Day
81-100	100mg Q Day
101-120	100mg Q Day
120-140	100mg Q Day
> 140	300mg Q Day

CrCl: creatinine clearance; HD: hemodialysis.

ity syndrome (AHS) may occur during the first three months of therapy. It is estimated to occur in 0.1% of patients and has a mortality rate of as high as 26%.[11,12] Signs and symptoms of AHS include severe exfoliative dermatitis progressing to toxic epidermal necrolysis, stomatitis, peripheral eosinophilia, leukocytosis, fever, hepatitis, and acute renal insufficiency. There exists no specific treatment for AHS other than discontinuation of allopurinol and supportive care, with the role of systemic steroids unsubstantiated.[13]

Patients who develop an allergic reaction to allopurinol can be treated using an allopurinol desensitization protocol. Desensitization, however, should be attempted only in patients with mild to moderate reactions to allopurinol ranging from maculopapular rash, mild fever to peripheral eosinophilia without any liver or renal impairment.[11,14]

Initial allopurinol dose should be based on the patient's GFR. A suggested starting dose according to creatinine clearance is provided in Table 1.[15] The starting dose, however, is often inadequate to reduce serum urate to target levels. In a study of 250 patients in New Zealand who were prescribed a fixed allopurinol dose based on renal dosing calculator, only 19% of the study cohort reached a target serum urate level of less than 6.0 mg/dL.[16] Uric acid levels should be monitored at six to eight week intervals, and allopurinol increased until the serum uric acid is less than 6.0 mg/dL.

Febuxostat

Febuxostat is a non-purine inhibitor of xanthine oxidase. Because it is dissimilar from the structure of purines, it does not interfere with purine and pyrimidine metabolism. Furthermore, it is degraded by glucuronide formation and oxidation in the liver, with half of all febuxostat and its active metabolites excreted in the stool, with the other half in the urine.[17] Unlike allopurinol, febuxostat does not require renal dose adjustment.[18,19] The major reservation is its use in patients with underlying liver disease, current alcohol use, or history of alcohol abuse, but short term use of febuxostat 80mg daily for seven days was demonstrated to be safe in 8 patients with Child-Pugh A liver disease and 8 patients with Child-Pugh B disease.[17]

In the first phase III randomized-double-blind 52-week multicenter trial of 762 patients with gout with serum urate levels greater than 8.0 mg/dL (FACT trial), febuxostat 80mg daily or febuxostat 120mg daily was compared with allopurinol 300mg daily.[18] The study population was composed primarily of Caucasian men with a mean age of 51 years. Patients with a creatinine greater than 1.5mg/dL, any history of alcohol abuse, or current alcohol use of more than fourteen drinks a week were excluded from the study. The authors found that a higher proportion of patients in the two febuxostat groups (53% & 62%) achieved serum urate levels of less than 6.0mg/dL than patients in allopurinol controls (21%). Patients receiving febuxostat also experienced a larger decrease in tophus size compared to patients on allopurinol. An important criticism is that patients given allopurinol were not allowed dose increases during the study. This arbitrary distinction underestimates the true efficacy of allopurinol in clinical practice.

Adverse events were minor across all groups. Self limited reactions like diarrhea, headache, joint discomfort, and mild elevations in transaminase levels occurred in similar frequency in all groups. However, it was noted that significantly more patients in the febuxostat groups dropped out of the study and experienced more acute gout flares. An unexpected finding was four deaths in the febuxostat cohorts, as opposed to none in the allopurinol arm. The cause of death appeared unrelated to febuxostat and ranged from congestive heart failure, metastatic colon cancer complications, cardiac arrest, and anti-coagulation related diathesis.

To address some of the concerns raised in the FACT trial, a 28-week, phase III randomized-double-blind placebo controlled trial was completed in 2008 (APEX trial).[19] The same investigators studied 1,072 gout patients with serum urate greater than 8.0mg/dL. This study included patients with creatinine between 1.5 mg/dL to 2.0mg/dL. The demographics of the study population were similar to the FACT trial, composed predominantly of Caucasian men. The authors looked at five study cohorts: patients either received febuxostat 80mg daily, 120mg daily, 240mg daily, allopurinol dosed according to serum creatinine levels, or placebo. Similar to the FACT trial, the APEX trial found that febuxostat reached the primary endpoint of serum urate less than 6.0 mg/dL in higher proportion by the end of the study: 36% of patients on febuxostat 80mg; 52% of patients on febuxostat 120mg; 66% of patients on febuxostat 240mg; 10% of patients on allopurinol; 0% of patients on placebo. Similar results were seen in patients with renal impairments. They were unable to demonstrate a decrease in tophus size or number due to the short length of the study. The occurrence of minor and serious adverse reactions requiring hospitalization was similar across study group. Liver enzyme dysfunction was higher in patients receiving either febuxostat or allopurinol compared to placebo controls (19%-25% versus 15%). Unlike the FACT trial, no deaths were reported during the study.

Though the authors had intended to study febuxostat in patients with impaired renal function, only 40 patients recruited had creatinine between 1.5mg/dL to 2.0mg/dL. Additionally, patients with more impaired renal functions were excluded from this study, as in the FACT trial. Published data on febuxostat use patients with renal impairment or hepatic impairment continue to be lacking and will require ongoing post-market surveillance.

Conclusion

Management of hyperuricemia in the setting of recurrent or tophaceous gout has traditionally relied on the use of allopurinol. Uricosuric agents have proven utility but are beneficial in a limited number of situations. Febuxostat as described here and synthetic uricase as described elsewhere in this journal are much welcomed additions to the rheumatologist's armamentarium. Experience with these agents is limited and their cost-effectiveness remains unstudied. Therefore, allopurinol will remain the first line agent for uric acid lowering therapy. In patients with clinical factors that preclude the use of probenecid and in those who had experienced allopurinol hypersensitivity, febuxostat may prove to be a valuable alternative.

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