Safety of Urate-Lowering Therapies

Managing the Risks to Gain the Benefits

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KEYWORDS

• Gout • Allopurinol • Febuxostat • Pelgoticase • Safety

KEY POINTS

- Safe use of urate-lowering therapy in patients with gout with multiple comorbidities can be a challenge for the clinician.
- Potential drug-drug interactions between traditional urate-lowering therapies and frequently prescribed medications are more common than usually appreciated, but can be appropriately managed in most patients.
- Allopurinol and other urate-lowering therapies can be safely used in patients with renal disease and other comorbidities.
- New therapies have provided additional options for patients with gout that may allow for safer and better management of their disease.

INTRODUCTION

Gout is the most common inflammatory arthropathy affecting more than 8 million adults in the United States alone.[1] The prevalence of gout continues to increase in the United States as well as abroad.[2,3] Gout affects more than 6 million men and more than 2 million women, and the rising incidence parallels with conditions such as cardiovascular (CV) disease, metabolic syndrome, chronic kidney disease (CKD), and an aging population.[4–6] This association is unlikely coincidental, as there is accumulating evidence suggestive of gout potentially contributing to a number of the aforementioned comorbidities.[7,8] Regardless of whether or not gout plays a causative role, the fact patients with gout frequently have multiple comorbidities is undisputable.[9–12]

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With the increase in the incidence and prevalence of gout, new urate-lowering therapies (ULT) have become available and a renaissance of interest in gout has occurred. Forty years after the introduction of allopurinol (Aloprim; Zyloprim) and 50 years after probenecid (Benemid),[13,14] febuxostat (Uloric) and pegloticase (Krystexxa) have been added to the arsenal against gout. Yet despite the surge in gout interest and new therapies, there is substantial evidence that quality of gout care continues to be inadequate. Patients with gout have been repeatedly shown to have greater morbidity compared with their counterparts without gout.[9,15–18] In some patients, hyperuricemia and gout may be simply a prelude for impending illnesses; but often, by the time a patient is diagnosed with gout, comorbidities are well established and are being treated with multiple medications.

Managing gout is intrinsically straightforward. The goal is to reduce and maintain serum urate (SU) levels well below that of physiologic supersaturation (6.8 mg/dL). Maintaining SU levels below this level allows for the mobilization of monosodium urate crystals out of joints and soft tissue, eventually eliminating the nidus of acute and chronic inflammation. As lower SU levels directly correlate with an increased rate by which tophi resolve,[19] using a target goal of less than 6 mg/dL as a starting point can decrease and ideally eliminate the crystal burden, thereby eradicating tophi and future flares. With appropriate therapy and compliance, most patients with gout should be able to achieve full remission. Challenges arise when clinicians and patients are faced with potential adverse drug reactions (ADRs) owing to decreased renal clearance, hepatic impairment, drug-drug interactions, or simply, intolerance.[9]

All Food and Drug Administration (FDA)-approved medications have risks and benefits. It is paramount to consider potential pitfalls and benedictions of a therapy before its use. Both the provider and the patient must balance a medication's risks and benefits to determine if it is the safest and most efficacious option. It is also important to understand the risk of any therapy for an individual patient is not static; rather it is a dynamic process that involves pharmacokinetics, pharmacodynamics (PD), and drug-drug interactions.[20] This article reviews the safety of current ULT indicated for the use of chronic gout, including allopurinol, febuxostat, pegloticase, and probenecid. Monitoring practices and strategies to decrease the risk of potential adverse effects in clinical practice are also reviewed.

BURDEN OF GOUT AND ADVERSE DRUG REACTIONS

The cost of ADRs caused by all medications is estimated to account for 5% to 9% of all inpatient costs.[21] There is little data regarding the impact of gout therapy–specific ADRs on patient disability and health care costs. Conversely, it has been shown that inadequately treated patients with gout have a poorer quality of life versus their age-matched and comorbidity-matched peers. Also, the annual direct and indirect costs of having gout are estimated to range from $800 to $10,000.[22–24] The impact of gout on the quality of life and potential economic burden emphasizes the importance of treating these patients appropriately and safely.

XANTHINE OXIDASE INHIBITORS

Allopurinol

There has been a renewed surge in the medical management of chronic gout with the development of several new therapies. Even in this light, allopurinol has seemed to have a rebirth of its own. Initially developed as an antineoplastic agent in the mid-1950s, allopurinol is a purine analog, an isomer of hypoxanthine, which inhibits xanthine oxidase. Allopurinol is the most commonly prescribed ULT, and continues to be the foundation