

Managing Gout in Women: Current Perspectives

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Abstract: Gout is a common inflammatory arthritis that tends to affect significantly more men than women. However, female gout patients are more likely to have comorbidities such as hypertension, diabetes mellitus, and renal dysfunction. Furthermore, they experience a greater disease burden due to gout than males. While nonbiological causes may possibly contribute to this sex discrepancy in burden, this raises questions regarding whether current gout pharmacotherapies are as efficacious in females as they are in males. In this review, we examine how the clinical profile of female gout patients differs from male patients; we then survey the literature for data on outcomes for female gout patients treated with urate-lowering therapies for chronic management of gout as well as commonly used agents for acute flares. We also discuss considerations for managing gout in women during pregnancy and lactation.

Keywords: gout, women, treatment, flare, prophylaxis, pregnancy

Introduction

Gout is the most common inflammatory arthritis with an overall prevalence of 1–4% worldwide;¹ it is caused by monosodium urate crystal deposition in synovial fluid and other tissues as a result of elevated serum urate levels.² The subsequent inflammatory response to the monosodium urate crystals leads to synovitis and severe arthralgias, and complications can include tophus deposition and chronic arthritis. Serum urate-lowering therapies serve as the mainstay of treatment.^{3,4}

In some populations, gout has been shown to affect up to ten times more males than females.^{1,5} Gout in women typically occurs in post-menopause, with an average age of diagnosis at 65–71 years vs 61–62 years in males,^{6,7} consistent with the known serum urate lowering properties of both estrogen and progesterone.⁸ Gout in pregnancy is also markedly uncommon; there were no cases of gout in a study of 190 pregnant females, of whom 46% had the *ABCG2* allele, which is known to be associated with hyperuricemia.⁹ However, the incidence of gout in elderly males and females approximate each other more closely. For example, in one study, the male-to-female ratio of the incidence of gout in individuals over the age of 70 was noted to be just 2.3.¹⁰

Gout has a strong genetic basis that drives disease activity. In particular, there are polymorphisms in two genes, *PDZK1* and *ABCG2*, that are associated with hyperuricemia, although the functional manifestations of these polymorphisms differ between males and females.¹¹ Specifically, the polymorphisms in *ABCG2* and *PDZK1* confer a disproportionately increased rate of hyperuricemia when present in males compared to females.

Female gout patients are generally afflicted by multiple other comorbidities. Although there is a higher prevalence of the metabolic syndrome in both male and female gout patients,¹² affected females are more likely than males to have concomitant hypertension (77–78% vs 56–57%), diabetes mellitus (28–39% vs 17%), renal dysfunction (24–64% vs 13–31%), and increased BMI (average BMI 33.5 vs 31.9).^{6,7} The increased presence of these and other comorbidities, including stroke, heart failure, coronary heart disease, and sleep apnea, as determined by higher odds ratios, have been recently corroborated in a large United Kingdom Biobank cohort.¹³

Most importantly, while serum urate levels and the rates of podagra, tophi, monoarthritis, polyarthritis, and flares have been shown to be comparable between males and females with gout,⁷ women report greater disability, when assessed with Health Assessment Questionnaire scores, as a sequelae of their gout;⁷ a significantly greater proportion of affected females than males require treatment with analgesics, including opioid-type pain relievers, during flares. This discrepancy in burden experienced by female gout patients could possibly be due to how they are less likely to be prescribed allopurinol and receive a definitive diagnosis of gout through synovial fluid crystal analysis compared to their male counterparts; they also have higher rates of concurrent thiazide diuretic use.⁷ Nonetheless, the discrepancy in gout burden among females raises the obvious question regarding whether current gout pharmacotherapies are as efficacious in females as they are in males. Herein, we review the literature for outcomes data for gout pharmacotherapies in women.

Treatment of Gout in Women

Given the central role of hyperuricemia in the pathophysiology of gout, urate lowering therapies, including xanthine oxidase inhibitors, uricosuric agents, and uricases, are employed with the goal of preventing flares, which in turn are most commonly managed with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, glucocorticoids, or anti-IL-1 β agents.¹⁴ The evidence for the above therapies in treating female gout will be reviewed here.

Urate Lowering Therapy for Chronic Gout

In gout, hyperuricemia is generally secondary to decreased renal or gastrointestinal clearance, rather than primary overproduction, of uric acid. The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) both support a urate-lowering approach for patients with gout who have had greater than one flare in a year.^{4,15} The ACR recommends treating to a goal serum urate level of less than 6.0 mg/dl. No professional guidelines or other evidence suggest any benefit in treating female gout patients to a different goal serum urate level.

Xanthine Oxidase Inhibitors

By definition, xanthine oxidase inhibitors prevent production of urate, which leads to a reduction in serum urate levels; as such, they are capable of facilitating crystal dissolution while also preventing further crystal deposition, proportional to the amount of urate lowering achieved.¹⁶ Allopurinol, a competitive inhibitor, and febuxostat, a noncompetitive inhibitor, are the two most commonly used xanthine oxidase inhibitors and serve as first-line therapies for the treatment of gout in all populations.⁴ Due to uncertainty regarding associated increased cardiac risks with febuxostat use and cost considerations, the ACR currently recommends initiating therapy first with allopurinol in all populations and reserving febuxostat for patients who experience adverse events, such as allopurinol hypersensitivity syndrome, or are recalcitrant to allopurinol.⁴ A retrospective analysis compiled data from three different Phase III clinical trials {Febuxostat versus Allopurinol Controlled Trial (FACT),¹⁷ Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat (APEX),¹⁸ and CONFIRMS¹⁹}, which collectively contained 226 female gout patients with serum urate levels greater than or equal to 8.0 mg/dl, to examine the efficacy of varying doses of allopurinol and febuxostat for the treatment of female gout patients.²⁰ Study participants in the three trials had been randomized to receive either allopurinol (at doses of 100mg, 200mg, or 300mg daily based on renal function), febuxostat (40mg, 80mg, 120mg, or 240mg daily), or placebo. Participants were treated for a duration of 24 to 52 weeks following randomization. The primary endpoint utilized by the retrospective study was the proportion of patients with a serum urate level less than 6.0 mg/dl at the final visit. The proportion of females who achieved this was statistically greater among those who were treated with febuxostat 80mg (85.1%) or 120mg (81.0%), compared to febuxostat 40mg (54.3%) or any dose of allopurinol (45.9%), even when the female patients were stratified by renal function (Figure 1). In regard to safety profile, three out of 139 female patients on febuxostat, and three out of 76 patients on allopurinol, experienced a cardiac serious adverse event.

To our knowledge, the above represents the only publicly available data that can be used specifically to evaluate treatment outcomes in female gout patients with xanthine oxidase inhibitors. The retrospective study performed post-hoc analyses on the three individual phase III clinical trials, none of which were inherently powered to evaluate response or adverse effects to treatment with allopurinol or febuxostat among females. In addition, these studies did not utilize doses of allopurinol greater than 300 mg daily. Patients commonly need doses greater than 300 mg per day, up to the maximum

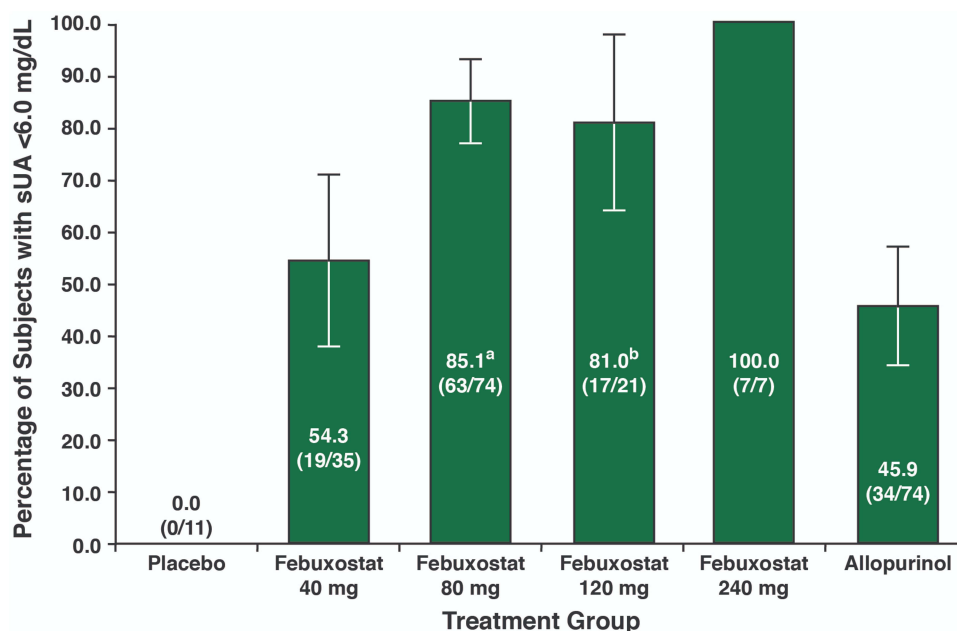


Figure 1 Percentage of female gout patients with a serum urate level less than 6.0 mg/dl after treatment with febuxostat and allopurinol. Two subjects with a creatinine clearance of less than 60 mL/minute received allopurinol 100 mg and 32 received allopurinol 200 mg, while the remaining subjects received allopurinol 300 mg. The 95% confidence intervals are indicated by the error bars. Reproduced from Chohan S, Becker MA, MacDonald PA, Chefo S, Jackson RL. *Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol. Arthritis Care Res (Hoboken)*. 2012;64(2):256–261. Copyright © 2012 by the American College of Rheumatology.²⁰ ^aWhen using Fisher's exact test to compare to the allopurinol group, $P < 0.001$. ^bWhen using Fisher's exact test to compare to the allopurinol group, $P = 0.006$.

dose of 800 mg per day, to achieve goal serum urate concentrations,⁴ and this could also be true for female gout patients in particular.

Of note, a separate study investigated the pharmacokinetics, pharmacodynamics, and safety of febuxostat 80mg once daily between healthy males and females.²¹ There were no differences in any of the parameters. However, the major limitation of this analysis was that all study participants were healthy; as such, conclusions cannot be extrapolated to the female gout population.

From a safety perspective, the occurrence of adverse events in female febuxostat and allopurinol users was comparable to those among participants in the overall FACT, CONFIRMS, and APEX trial populations. Additionally, a separate study specifically comparing the rate of adverse events between male and female gout patients using febuxostat did not reveal any significant differences.²² In terms of cardiovascular safety, various studies, none of which are stratified by sex, have demonstrated mixed findings with regard to whether febuxostat carries greater cardiovascular risks compared to allopurinol.^{23–25} Fortunately, data from the recent Febuxostat versus Allopurinol Streamlined Trial (FAST) has been more reassuring about the cardiovascular safety of febuxostat.²⁶ This was a randomized, blinded-endpoint noninferiority trial containing 6128 male and female gout patients, with at least one additional cardiovascular risk factor, from Denmark, United Kingdom, and Sweden who received either allopurinol or febuxostat. The primary endpoint was hospitalization for non-fatal myocardial infarction, biomarker positive acute coronary syndrome, nonfatal stroke, and cardiovascular death. Findings demonstrated that febuxostat was noninferior to allopurinol, with 1.72 compared to 2.05 events per 100 patient years among febuxostat and allopurinol users, respectively. As described above, female gout patients have a higher rate of comorbid cardiovascular risk factors compared to their male counterparts and thus, additional studies specifically assessing the cardiovascular safety of xanthine oxidase inhibitors in female gout patients will be crucial in guiding further clinical decision-making for this demographic. Ultimately, shared decision-making between female gout patients and physicians will be crucial when initiating urate lowering therapy with a xanthine oxidase inhibitor, particularly for those who have cardiovascular comorbidities.

Uricosuric Agents

Probenecid and lesinurad are two agents that both inhibit the renal transporter URAT-1, which leads to urate lowering via uricosuria. Lesinurad is no longer commercially available in the United States, leaving probenecid as the only readily available pharmacologic agent in this class. Probenecid can be used alone or in combination with a xanthine oxidase inhibitor, depending on the severity of disease. It should be noted that renal disease precludes the use of uricosuric agents. A retrospective observational study assessing the efficacy of probenecid included 13 females and 17 males, all of whom were treated with probenecid monotherapy.²⁷ Collectively, ten out of 30 patients achieved target serum urate levels, the primary endpoint of the study. It is unclear how many of the non-responders were males compared to females, as the data were not stratified by sex. Probenecid is not as widely used as xanthine oxidase inhibitors, and as expected, there is only minimal data on the efficacy in females.

Uricases

Rasburicase and pegloticase are both uricases, which degrade uric acid. There are multiple individual case reports documenting the marked urate lowering efficacy of rasburicase in female patients who were intolerant or unresponsive to allopurinol.^{28–30} However, rasburicase's immunogenicity prevents it from serving as a sustainable treatment option, as host antibodies directed against the agent increase with usage. Pegloticase is less immunogenic due to the polyethylene glycol component, although patients can still develop antibodies to polyethylene glycol, leading to infusion reactions. These can be mitigated with concomitant immunosuppressive therapy. Two replicate, randomized, placebo-controlled six-month trials and an open-label treatment extension study that led to the approval of pegloticase contained a total of 38 females and 172 males, but the results were not stratified by sex;^{31,32} as such, conclusions regarding the efficacy of pegloticase in females involved in this study cannot be made. However, a descriptive study consisting of three females with refractory gout assessed baseline and post-pegloticase therapy serum urate levels and tophus volumes, as measured by dual-energy CT scans.³³ Two of the female participants were considered responders, defined by those who maintained a serum urate level less than 6.0 mg/dl for at least 80% of the study duration; these two patients further exhibited 96.96–100% of tophus volume reduction. The third female patient was considered a partial-responder with a 73.10% reduction in tophus volume. Owing to the relative recency of pegloticase's approval for gout, there is minimal data on the effectiveness of pegloticase in females in particular.

Management of Acute Flares

The 2020 ACR guidelines recommend treating acute gout flares with NSAIDs, colchicine, and glucocorticoids (systemic or intraarticular), in addition to supportive care with topical ice.⁴ For cases refractory to the above therapies, treatment with anti-IL1B therapy, namely anakinra, is indicated.⁴ Similar to the chronic therapies above, there is only limited female-specific data for the acute therapies. Published gout medication usage data demonstrate that comparable proportions of males and females utilize colchicine, oral steroids, and NSAIDs.

Indomethacin is the preferred NSAID for acute gout management.³⁴ A pooled-subgroup analysis in which patients experiencing an acute gout flare were randomized to receive indomethacin 50mg three times a day compared to etoricoxib 120mg daily (now discontinued in the United States) contains the only known female-specific data for NSAID use in acute gout.³⁵ In total, 147 males and 14 females received indomethacin 50mg three times a day, and the subgroup analysis did not reveal any difference in primary endpoint efficacy, defined by self-reported pain ratings, between male and female patients.³⁵ Importantly, there are cardiovascular risks associated with NSAID use; up-regulation of the COX1 pathway following the use of selective and even non-selective cyclooxygenase inhibitors, such as indomethacin, leads to vasoconstriction and platelet aggregation, ultimately facilitating intravascular thrombosis. Therefore, among female gout patients who are vulnerable to cardiovascular disease due to their higher rates of predisposing comorbidities, NSAID use should be employed cautiously even if only used during acute flares.⁷ Similarly, utilization in patients with renal disease, which is more prevalent in female gout patients, should be avoided.⁷

Colchicine inhibits tubulin aggregation, thereby downregulating inflammatory pathways. A multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study assessed the efficacy of low-dose vs high-dose

colchicine, compared to placebo, for the treatment of 185 patients, including nine females, experiencing a gout flare.³⁶ The primary endpoint was defined as a greater than or equal to 50% reduction of pain without the use of rescue medications. Approximately 38% of patients in the low-dose colchicine group, compared to 33% in the high-dose and 16% in the placebo group, were considered responders. Although there is no sex-specific stratified data available, a computation of the odds ratio for confounding bias suggested that demographic parameters, such as age, sex, and race, were not confounders.

Colchicine may also serve a secondary purpose in female gout patients. A meta-analysis of five studies containing 11,816 coronary artery disease patients who were randomly assigned to a low-dose colchicine or placebo treatment group demonstrated that low-dose colchicine led to a reduction in major adverse cardiac events, specifically myocardial infarction, stroke, and the need for coronary revascularization.³⁷ In addition, a randomized-controlled trial assessing the efficacy of colchicine in chronic coronary disease did not reveal difference in efficacy between males and females.³⁸ Therefore, female gout patients, who have higher rates of predisposing comorbidities such as hypertension and diabetes mellitus than male patients, may further benefit from colchicine therapy, although studies regarding the cardioprotective properties of colchicine remain ongoing.⁷

Intraarticular and systemic steroids serve as additional treatment options for patients with acute gout flares, particularly those with renal disease. In one prospective trial, 12 patients with acute gout flares were treated with oral prednisone or methylprednisolone.³⁹ Four of these were female patients treated with an oral prednisone taper starting anywhere between 20 and 40mg daily, with complete resolution of symptoms occurring between four and nine days. One additional female patient was treated with an initial dose of methylprednisolone 50mg and had complete resolution of symptoms after six days. Unfortunately, to our knowledge, there is no available data on the efficacy of intraarticular steroids for treatment of acute gout flares specifically in female patients.

Anakinra, the newest therapeutic for acute gout and an anti-IL1 β agent, serves as a second-line treatment option for those unresponsive to the above therapies. In the initial pilot, open-label study, ten patients, including two females, were treated with anakinra 100mg daily for three days for acute gout after failing the above therapies.⁴⁰ The two female patients reported a 70–80% reduction in pain after treatment with anakinra. Furthermore, a retrospective chart review of ten patients treated with anakinra for acute gout contained two females, both of whom had a “good” response, defined as complete or near complete resolution of joint symptoms.⁴¹ A double-blind, placebo-controlled, active-comparator, non-inferiority trial consisted of 88 patients, including five females, but did not stratify findings by sex.⁴² Anakinra has recently been increasingly utilized in hospitalized patients with numerous comorbidities that preclude the use of the above therapies. A retrospective chart review of 13 ICU patients being treated with anakinra for acute gout included one female patient, who reportedly had “a significant response”.⁴³ The largest known observational study assessing the efficacy of anakinra for the treatment of acute gout in hospitalized patients did not stratify by sex.⁴⁴

Special Considerations: Pregnancy and Lactation

Gout in pre-menopausal women is a rare occurrence and often manifests in patients with inherited conditions such as familial juvenile hyperuricemic nephropathy.^{45,46} Underlying kidney disease and gestational diabetes are other predisposing factors for the onset of gout in pre-menopause.⁴⁷ Pregnant and breastfeeding women with acute gout flares should generally be treated with glucocorticoids; these may be used cautiously or contraindicated in those with gestational hypertension or gestational diabetes, depending on severity. NSAIDs can be utilized for the treatment of acute flares during lactation and the first two trimesters of pregnancy but are strictly contraindicated in the third trimester as they can cause premature closure of the ductus arteriosus. On the contrary, colchicine is generally avoided altogether during both pregnancy and lactation due to reports of colchicine-induced chromosomal damage and secretion into breastmilk.^{48,49} In regard to chronic management, women with recurrent flares during pregnancy and lactation can be treated with low dose-glucocorticoids for prophylaxis. Allopurinol is a category C teratogen since it inhibits purine synthesis and thereby may impair fetal growth and development;⁵⁰ its use is discouraged during pregnancy. On the contrary, allopurinol can be continued in lactating females.⁵¹ However, since it can be excreted in breast milk, breastfed infants of lactating females who require treatment with allopurinol should be closely monitored for adverse processes, including hypersensitivity reactions and cytopenias. Notably, the full range of effects of allopurinol on infants remains unclear.

Table 1 Summarization of Review Highlights and Opportunities for Future Research in Female Gout

Key Highlights
While gout is less common in women, the comorbidity burden among females appears to be greater than in men.
Gout is more common in post-menopausal rather than pre-menopausal women. Development of gout in pregnancy is rare but poses unique management challenges since colchicine and NSAIDs are generally contraindicated for these patients.
Female gout patients report greater disability and are more likely to require treatment with analgesics and opioids.
Women are vastly underrepresented in clinical trials and other gout outcomes-related studies.
There is currently only one large study that has explored outcomes for gout treatment agents in women with gout. It demonstrated that commonly used doses of febuxostat are more effective at reducing serum urate levels than lower doses of allopurinol.
Areas for Further Research
Increase participation of female gout patients in clinical trials and outcomes-related studies.
When available, report outcomes separately for female gout patients involved in randomized-controlled trials.
Study the impact of comorbidities on the efficacy of gout treatments for female gout patients.

Dietary Recommendations

The risk factor profile for the development of gout in both males and females is in part driven by beef, seafood, and alcohol consumption.⁷ While only less than 20% of female gout patients consume beer, wine, or hard liquor, greater than 75% consume beef and dairy products, both of which have a high purine content.⁷ Thus, minimizing consumption of these foods could serve as a nonpharmacologic intervention that would help female gout patients achieve goal serum urate levels and reduce the frequency of flares.

Conclusion

The increased prevalence of gout in males explains the paucity of appropriately well-powered, randomized-controlled trials investigating the efficacy of the above therapies in female gout patients. This poses major challenges for the management of female gout patients since they carry a greater burden of cardiovascular and renal morbidity, which is known to modulate the pathophysiology of gout; as such, conclusions regarding the efficacy of treatments for females cannot be extrapolated from investigative studies that are predominantly male. Data is most abundant for xanthine oxidase inhibitor use in female patients and suggests that commonly prescribed doses of febuxostat appear to be more effective than lower doses of allopurinol, with no clear differences in cardiovascular morbidity or mortality among women treated with these two medications. Aside from this, there is only minimal data, in most cases limited to case reports, case series, or small pilot studies, which demonstrate the responsiveness of small numbers of female gout patients to uricosuric agents and uricases for chronic management and NSAIDs, colchicine, systemic steroids, and anakinra for treatment of acute flares. Lastly, flares during pregnancy and lactation are rare occurrences but pose unique challenges; in these cases, glucocorticoids are favored over other gout pharmacotherapies for safety reasons. Clinical trials and outcomes studies in gout should attempt to include more female patients and report outcomes separately for female study participants. Table 1 summarizes key highlights from this review and outlines areas in need of further research.

Disclosure

Dr Angelo L Gaffo reports personal fees and royalties from UptoDate, outside the submitted work. The authors report no other conflicts of interest in this work.

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