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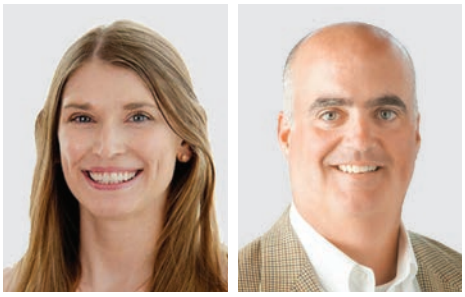
Editorial

Long-Term Adherence to Urate-Lowering Therapy in Gout: A Glass Half Empty or a Glass Half Full?



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Characterized by flares of intensely painful arthritis, gout is the most common type of inflammatory arthritis worldwide. National prevalence estimates approaching 4% translate to more than 9 million persons living with gout in the United States alone, with worldwide estimates reaching as high as 10% in some regions.[1,2] The painful nature of gout flare often leads patients to seek acute care, which, in turn, results in increased healthcare costs in addition to decreased work attendance and productivity.[3,4] Central to disease pathogenesis, hyperuricemia is a necessary (albeit insufficient) risk factor in gout development. Several highly effective and well-tolerated urate-lowering therapies (ULTs; eg, allopurinol, febuxostat, probenecid) are available for use and collectively provide the real potential of reducing or even preventing flares. Allopurinol, the most commonly used ULTs, is relatively inexpensive, retailing at approximately $20 to $30 per month in the US without insurance or even as little as $5 per month with select prescription programs.[5] Although widely accessible and well tolerated by most, fewer than 50% of patients with a gout diagnosis are started on urate-lowering medications.[6] Perhaps even more disheartening is the dismal number of patients who adhere to ULT once initiated. A retrospective cohort study of over 13,000 patients with gout recently initiated on allopurinol demonstrated that 57% of patients took their medication less than 80% of the time over the course of a year, and 68% of subjects did not reach a goal serum urate (SU) of < 6 mg/dL.[7] A metaanalysis pooling data from 22 studies found that adherence (defined by a variety of methods including prescription claims, pill counts, self-report, and interview) was 47%.[8] Collectively, results from available studies beg important questions that need to be addressed: Why is ULT adherence low in gout, and what can we do to make it better?

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American College of Rheumatology and European Alliance of Associations for Rheumatology guidelines separately recommend a treat-to-target strategy for gout consisting of systematic SU lowering to achieve and maintain a goal of < 6.0 mg/dL through serial SU testing and ULT titration. Most adherence studies to date have examined ULT adherence or persistence outside the treat-to-target paradigm and therefore even less is known about treatment adherence in patients with gout managed according to a guideline-concordant approach.

Coleman and colleagues have helped to address this prevailing knowledge gap in their report that appears in this issue of *The Journal of Rheumatology*.[9] This study is a post hoc analysis of a 24-month study (12-month trial, followed by a 12-month open-label extension) conducted in Aotearoa New Zealand, in which patients with gout were randomized to different allopurinol dose escalation schemes, with the primary endpoint of reaching an SU < 0.36 mmol/L (< 6.0 mg/dL) for at least 3 consecutive months.[10,11] Individuals included in the post hoc analysis included surviving trial participants who had consented to additional follow-up. The primary outcome of interest was the proportion of surviving subjects who remained on ULT since trial cessation and the number of subjects at target SU. Secondary outcomes included survival, change in allopurinol dosing, renal function, reasons for allopurinol discontinuation, adherence, and number of flares. Herein, the authors report that 82% of participants were still receiving allopurinol, with approximately 50% being on stable dosing after a mean follow-up of 6.5 years after trial enrollment. A small subset (4.2%) of patients were switched to febuxostat during follow-up. Of patients with SU available, 58% remained at SU target of < 0.36 mmol/L compared with 74% at last study visit at 24 months. Notably, one-third of study participants with follow-up data available were on a lower dose of allopurinol, although the authors were unable to identify the precise reasons for this decrease with the limited data available. The authors reported, however, that 77 subjects had posttrial assessments of renal function and of these, 69% demonstrated decreased renal function. These observations suggest, but do not prove, that at least some of the de-escalation in allopurinol dosing post trial may have related to decreases in

See Allopurinol dose escalation follow-up, *page xxx*

renal function. The most common reason for patient nonadherence to ULT was inconvenience of drug schedule and not fitting with participant lifestyle, though 5 participants reported discontinuation because they "no longer needed" ULT as they stopped experiencing flares. Approximately 1 of 5 patients remaining on any ULT reported a flare within the last 12 months. The authors concluded that this dose escalation study led to good real-world persistence based on the number of participants remaining on long-term ULT and at SU goal.

Indeed, 82% of patients remaining on allopurinol represents higher adherence than observed in most observational studies to date that have been primarily based on real-world data. The higher ULT persistence observed in the present study may simply reflect the effects of exposure to a rigorous treatment protocol, which reinforced to patients the importance of long-term treatment adherence. Though the higher ULT adherence observed is encouraging, the observation that 42% of subjects were above SU goal at follow-up is simultaneously disappointing, particularly when this figure is compared to rates of SU goal achievement that have been reported in recent clinical trials of treat-to-target ULT. Recent randomized controlled trials incorporating treat-to-target ULT have demonstrated rates of target SU achievement between 80% and 95% after 1 to 2 years.[12,13]

The study of Coleman et al[9] and of the others cited above collectively demonstrate that in the setting of a treat-to-target ULT, the initial attainment of target SU goal in gout appears to be readily achievable, but not necessarily durable. With these results, we begin to shift from "how do we treat gout" to "how do we keep patients on their gout medications at optimal doses?" The more evidence we gain from clinical trials, the more we see that ULT works well at lowering SU and reducing gout burden. However, results of this post hoc analysis would suggest that treating patients to target and then discharging them from clinic might not be an effective long-term strategy for the management of this lifelong disease.

Gout is a chronic condition requiring chronic management. Ideally, to ensure its optimal long-term management, gout should be viewed no differently than any other chronic condition. For example, a patient seen for hypertension is not simply given medications for treatment and then sent away. Best practice mandates that hypertensive patients are routinely monitored to ensure that medications are working, antihypertensive dosing is appropriate, and patients are compliant with prescribed therapies. A similar long-term approach needs to be the standard of care in gout management. Recent evidence to support this line of thinking comes from a randomized study in which treat-to-target ULT was administered as part of nurse-led care that included patient education and frequent follow-up specifically for gout.[12] In this study, patients receiving the nurse-led intervention had significantly greater ULT persistence (96%) after 2 years compared to usual care treatment (56%).[12] With an ongoing specialty physician shortage that is projected to worsen in the coming years, these data provide reassurance that nonrheumatologist/nonphysician providers can play a vital role in facilitating highly effective gout management. This is relevant not only to rheumatologists but also to primary care physicians who, on average, are tasked with addressing between 2 to 7 clinical items per 15- to 20-minute clinic visit.[14]

Available evidence suggests that in the coming years, the burden posed by gout will only continue to grow. For the vast majority of persons living with gout, clinicians already have the tools needed to successfully manage this condition with highly effective and accessible ULTs at our disposal. Yet, the problem remains that even with highly effective therapies available, patients with gout too often receive suboptimal care. Specifically, time and again, patients with gout discontinue ULT or maintain ULT at inadequate doses that fail to attain goal SU and to subsequently prevent flares or tophaceous deposits. We desperately need to develop and validate novel, highly scalable efforts to address the problem of ULT durability. If not, this highly treatable condition will continue to plague millions and impose enormous costs to the global economy and healthcare systems.

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