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To treat or not to treat (to target) in gout

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Gout, the most common inflammatory arthritis, is a disease whose pathophysiology is well-understood with effective treatments available. Yet the management of gout is poor, with ~70% of patients experiencing recurrent flares.(1) Serum urate elevations >6.8 mg/dL under normal physiologic conditions can lead to monosodium urate crystallization. Hyperuricemia is not a mere “comorbid risk factor”(2) but rather the main pathophysiologic culprit of gout that causes flares, tophi, and joint damage, and therefore rendering the management of hyperuricemia a key tenet of disease control.

It is in this context that we review the ACP’s systematic literature review and guidelines for gout diagnosis and management.(2–5) We agree with the authors’ conclusions and support for the use of colchicine, NSAIDs, and glucocorticoids for gout flare management as having a high strength of evidence despite there being few placebo-controlled trials (none for glucocorticoids) because of “the known physiology of gout,” and “that symptoms arise from an inflammatory reaction to the deposition of urate crystals, which occurs when serum uric acid rises above its saturation point in blood”.(4) The authors also acknowledge evidence that urate-lowering therapy (ULT) reduces serum urate, which is a strong predictor of flares, and data from open-label extension studies of ULT trials support an association between lower serum urate levels and lower risk of gout flares. It is therefore puzzling that the strength of evidence for monitoring serum urate, a prerequisite to ensuring adequate ULT dosing, is judged to be low. Using similar extrapolation as applied to the assessment of gout flare management, we find the strength of evidence supporting the monitoring of serum urate to be at least moderate in strength.

The authors suggest that a reactive “treat-to-symptoms” approach may be a reasonable strategy with ULT instead of proactive “treat-to-target” because the latter has not been adequately tested. However, “treat-to-symptoms” has not been tested either. With “treat-to-symptoms”, providers might consider suppressive anti-inflammatory therapy and/or treating each flare as a sufficient strategy without addressing underlying hyperuricemia. When patients are never on ULT or on inappropriately low doses of ULT, there is ongoing urate deposition leading to progression of tophaceous deposits, further joint damage, and

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functional limitations. At that stage, such patients need much more aggressive (and expensive) treatment than they would otherwise have required had their serum urate been appropriately targeted early on. Another concern is the confusion about what “treat-to-symptoms” means, particularly since gout flares during ULT initiation are an expected physiologic outcome. If a patient flares four months into ULT treatment, this might be expected, but without checking serum urate, there is no way to know if this relates to poor ULT adherence or need for higher dosing. Additionally, perpetuating a management strategy of starting allopurinol at an inappropriately high dose (specialty treatment guidelines do not recommend starting patients at 300mg/d)(6) will continue the problem of unnecessarily increasing flare risk since this risk in the early treatment phase is directly proportional to the potency of ULT employed. Moreover, allopurinol doses of 300 mg/d or less leaves more than half of all patients undertreated.

We acknowledge that existing literature only indirectly addresses what serum urate target is most optimal. However, it is a disservice to our patients and primary care colleagues to suggest that “treat-to-symptoms” is acceptable with ULT in the absence of evidence. At the very least, based on urate’s biochemistry, a treatment target below the physiologic threshold of urate crystallization (<6.8 mg/dL) would be appropriate, even if a lower target has not yet been supported by randomized trials. A target of <6.8mg/dL (or <6mg/dL accounting for assay variation) would seem more than reasonable based on the authors’ own admission that serum urate levels exceeding this threshold are the cause of gout. Using the example of diabetes, no one would advocate for a treat-to-symptoms strategy for diabetes. Even though hypoglycemic agents have potential side effects, it is recognized that end-organ micro- and macrovascular damage prevention is important and that therapy isn’t just aimed at preventing symptoms of hyperglycemia. Suggesting that an unfavorable benefit:risk ratio for treat-to-target observed in diabetes should raise similar caution for gout is unnecessarily alarmist. It is clear that low blood glucose can be detrimental, even fatal. There are no such data with serum urate. In pegloticase trials,(7) serum urate values as low as 1–2 mg/dL were well tolerated, for several months without observed adverse effect. In fact, mean serum urate values around the turn of the 20th century in the US averaged 3–4 mg/dL, levels that are rarely achieved with standard ULT using contemporary treatment paradigms. Of course testing of specific targets in a formal trial would provide insight, but whether a funding agency would be willing to support a large trial that would require 2–3 years of follow-up to adequately address the question of “treat-to-target” is doubtful.

The discussion regarding ULT discontinuation is interesting, but based primarily on two reports from a single small observational cohort.(8, 9) In the first report, ~40% of patients had a recurrence of gout flares within 6–60 months (median 2–4 years).(8) In the second, there were only 27 patients with serum urate levels <7mg/dL; it is unclear how long all 27 patients were followed for, including issues of loss-to-follow-up and refusal of joint aspiration to confirm gout recurrence.(9) It is premature to discuss ULT discontinuation based on such sparse data.

As for incremental harms and costs of continuing long-term ULT, particularly for patients who succeed in starting allopurinol without a hypersensitivity reaction in the first ~180 days, the likelihood of developing a reaction later on is exceedingly low.(10) The cost of

allopurinol and of the requisite measurement of serum urate is minimal, particularly compared with the damage that can occur over time with urate deposition and use of more aggressive and expensive therapy for their tophaceous disease down the road.

In summary, while some approaches may not have yet been formally tested in trials, a clear understanding of gout's pathophysiology provides a strong foundation for rational recommendations while awaiting clarity on these important clinical issues.

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