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Pursuit of a Dual-Benefit Antigout Drug: A First Look at Arhalofenate

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Disease burden of gout

Gout is the most common form of inflammatory arthritis in the US, with an estimated 8.3 million adults affected (1). Despite its well-understood pathophysiology and available treatments (2), its management remains remarkably suboptimal, leading to frequent recurrent flares, a doubling of hospitalization rates in the US, and a worsening economic burden (3,4). Patients with gout have a high level of comorbid cardiovascular (CV)–metabolic–renal conditions (e.g., hypertension in 74%, obesity in 53%) and their sequelae (e.g., myocardial infarction and premature death) (5). The prevalence of the metabolic syndrome is particularly high among patients with gout, with an estimated two-thirds of gout patients and >80% of those with treated gout meeting the revised National Cholesterol Education Program/Adult Treatment Panel III criteria (6). Ideally, comprehensive gout management would tackle both the morbidity associated with gout flares and tophi as well as these CV–metabolic–renal conditions.

Uricosuric agents in the current urate-lowering therapy landscape

Urate-lowering therapy is the mainstay of treatment for long-term management of gout, with a “treat-to-target” paradigm of <6 mg/dl advocated in treatment guidelines as being appropriate for most patients (7–9). Of the 2 available xanthine oxidase inhibitors (allopurinol and febuxostat), allopurinol remains the dominant first-line therapy for gout (7–9), although patients are typically prescribed allopurinol at 300 mg daily, resulting in <50% achieving the serum urate target (7). Probenecid, the only uricosuric agent available in the US until recently, has constituted only 2–3% of urate-lowering therapy use, despite renal underexcretion being the most common reason for hyperuricemia among gout patients. A number of factors may have contributed to this, including dosing inconvenience, concerns about nephrolithiasis, contraindication among urate overexcretors, multiple potential drug interactions, and inefficacy in renal insufficiency.

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In December 2015, lesinurad received Food and Drug Administration approval for the management of hyperuricemia in gout, to be used only in combination with a xanthine oxidase inhibitor. Two other uricosuric agents are available elsewhere in the world: benzbromarone, which is not licensed in the US due to concerns about hepatotoxicity, and sulfinpyrazone, which is no longer marketed in the US. Thus, an efficacious monotherapy uricosuric agent with minimal side effects and drug interactions, along with a relatively easy dosing regimen and that can also be used in the setting of renal insufficiency, has yet to be available in the US. It is in this context of limited uricosuric management options for gout that the study of a new uricosuric agent as reported by Pooley et al in this issue of *Arthritis & Rheumatology* (10) needs to be considered.

Serendipitous discovery of arhalofenate's potential uricosuric property

Arhalofenate was first developed as an insulin sensitizer for type 2 diabetes mellitus. A meta-analysis of 4 blinded phase II trials in type 2 diabetes, reported in an abstract, showed significant reductions in fasting blood glucose, hemoglobin A1c, triglycerides, and interestingly also serum urate, with a 13–29% reduction occurring in a dose-dependent manner (11). Arhalofenate was subsequently demonstrated to inhibit URAT1 (in addition to organic anion transporter 4 [OAT4] and OAT10, 2 other organic anion transporters/exchangers also involved in renal urate reabsorption) without any effect on xanthine oxidase; this uricosuric activity was demonstrated to be more potent than that of probenecid (12). A uricosuric agent that potentially addresses the metabolic syndrome could be an attractive novel approach to gout care by “killing two birds with one stone” if it is indeed demonstrated to have such properties.

Arhalofenate's potential antiinflammatory property

Arhalofenate is also purported to have antiinflammatory activity through inhibition of interleukin-1 β (IL-1 β), as demonstrated in a monosodium urate murine air pouch model (13). Of note, the degree of IL-1 β inhibition in this model was similar to that elicited by dexamethasone (13). A dual mechanism of urate-lowering activity plus antiinflammatory activity would have a distinct advantage over other urate-lowering therapies by mitigating the increased risk of gout flares in the initial phases of urate-lowering therapy, which is related to mobilization of bodily urate stores and dissolution of intraarticular urate crystals that may make them more amenable to phagocytosis (14). The flare prophylaxis regimens currently available and recommended in the US include colchicine and non-steroidal antiinflammatory drugs (NSAIDs), both of which have suboptimal tolerability and contraindications for a sizable proportion of patients with gout. As such, many patients are often started on urate-lowering therapy without flare prophylaxis, including starting target dose urate-lowering therapy without dose up-titration, which increases flare risk further and contributes to nonadherence to urate-lowering therapy. A single agent that can lower both serum urate and the risk of gout flares (in addition to potentially addressing insulin resistance traits, as discussed above) could provide a desirable multifaceted antigout option to address these major unmet needs.

Antiflare effect

In the phase II randomized trial reported in this issue of *Arthritis & Rheumatology* (10), the higher dose of arhalofenate studied (800 mg daily) yielded a significantly lower rate of gout flares (0.66) over 12 weeks compared with 300 mg allopurinol daily without flare prophylaxis (1.24) and compared with placebo (no urate-lowering therapy) (1.13). In contrast, 600 mg arhalofenate daily did not differ significantly from 300 mg allopurinol daily without flare prophylaxis (gout flare rate 1.04 versus 1.24, respectively). Further, the flare rate in subjects receiving 800 mg arhalofenate daily did not differ significantly from that in subjects receiving 300 mg allopurinol plus 0.6 mg colchicine (0.40); however, the study was not powered to detect a difference between those 2 groups. Thus, only the higher dose of arhalofenate demonstrated significantly greater efficacy than 300 mg allopurinol daily without flare prophylaxis. Nonetheless, since many patients cannot use flare prophylaxis with either colchicine or NSAIDs, a 46% lower risk of gout flare compared with allopurinol alone without flare prophylaxis (and a 41% lower risk compared with no treatment at all [placebo]) during the initial phases of urate-lowering therapy appears to be a clinically meaningful reduction in the risk of a gout flare, particularly for the subset of patients with no other alternatives for prophylaxis.

Urate-lowering effect

Serum urate reduction with arhalofenate was modest. Those receiving 800 mg arhalofenate daily experienced a mean 16.5% reduction in serum urate, which roughly translates into a change from a mean serum urate level of 9.3 mg/dl to 7.8 mg/dl. In contrast, those receiving 300 mg allopurinol daily with and without flare prophylaxis experienced 24.9% and 28.8% reductions, respectively, in serum urate (i.e., from 9.2 mg/dl to 6.9 mg/dl and from 9.0 mg/dl to 6.4 mg/dl, respectively). These findings were also reflected in substantially higher proportions of allopurinol-treated subjects than arhalofenate-treated subjects achieving serum urate levels of <6 mg/dl (34.0% and 48.1% of subjects receiving allopurinol with and without prophylaxis, respectively, versus 13.2% and 11.8% of subjects receiving 600 mg and 800 mg arhalofenate, respectively). This modest urate-lowering effect was accompanied by an ~1% absolute increase (an ~25% relative increase) in fractional excretion of urate in the arhalofenate-treated groups. Arhalofenate's effect on fractional excretion of urate is reported to be sustained over a 24-hour period, with limited differences between peak and trough, conferring the ability to provide once-daily dosing (15).

It should be noted that the allopurinol treatment arms likely underperformed in terms of urate-lowering effects, since the median dose required to achieve the target serum urate level is ~400 mg daily (16). Thus, if the allopurinol treatment arms were further up-titrated, one would expect that an even greater proportion of subjects would reach the serum urate target of <6 mg/dl. Whether arhalofenate can be titrated higher than 800 mg daily remains unclear. Nonetheless, the issue of suboptimal allopurinol dosing in trials is not just limited to this one trial. The majority of gout trials to date have been conducted with a single-dose allopurinol comparative arm (mainly due to trial logistic simplicity and practicality), leaving the rheumatology community uncertain as to the practically relevant effectiveness in comparison with an optimized allopurinol dosing strategy. By the same token, high-quality randomized

trial data are needed to definitively demonstrate that uptitration of allopurinol truly results in the anticipated benefits (based on observational data and clinical experience) without undue adverse events.

Arhalofenate's safety profile signal

Another aspect of the reported trial (10) that merits attention is the absence of any potentially concerning safety signal. Of particular interest for a uricosuric agent is renal safety. There were no renal calculi in the arhalofenate treatment arms; 1 instance occurred in an allopurinol-treated subject. Additionally, there were no significant changes in creatinine clearance. However, subjects with a creatinine clearance of <60 ml/minute were excluded; thus, this is a population of patients for whom the safety and efficacy of this uricosuric agent require further clarification.

Remaining unanswered questions

Unfortunately, this report did not present the effects of arhalofenate on metabolic syndrome parameters; such information is needed to fully appreciate arhalofenate's potential unique multifaceted role in the management of gout and associated comorbidities. While the metabolic effects were originally noted in patients with type 2 diabetes mellitus, without those data reported in patients with gout, one cannot speculate about whether these effects are relevant in this patient population. It would also be important to understand this drug's effects on insulin resistance in this patient population as another potential mechanism by which urate-lowering effects may be conferred.

Another caveat of the trial is that the comparison drug, allopurinol, was initiated at 300 mg daily, which is counter to the current recommendation to start at 100 mg daily (or 50 mg among those with renal insufficiency) with subsequent up-titration to achieve the serum urate target (7). The rationale behind this recommendation is 2-fold: to minimize the risk of allopurinol hypersensitivity syndrome and to decrease the risk of triggering a flare during this early phase of urate mobilization. By starting at a higher-than-recommended dose of allopurinol, the 300 mg allopurinol daily treatment arm without flare prophylaxis would have exhibited a higher flare rate than if started at the recommended dose of allopurinol (4,16). To that end, flare data compared with the recommended allopurinol initiation dosing would also be valuable. Further, the relatively modest serum urate reductions also suggest that this therapy should be tested in combination with a xanthine oxidase inhibitor in a phase III program; as of this date, phase II trials of arhalofenate in combination with allopurinol and febuxostat have been completed, with results yet to be published.

Thus, is it not clear whether arhalofenate will meet the need for an efficacious, safe uricosuric monotherapeutic agent. Its safety and efficacy in stage 3 or 4 chronic kidney disease also require clarification. Nonetheless, this phase II randomized trial of arhalofenate provides promising results of a novel agent for gout that appears to tackle at least 2 key aspects of gout management in a single drug—lowering serum urate and providing flare prophylaxis, with the potential for a new class of drug that could be coined “ULAFT”—

urate-lowering, antiinflammatory therapy. Results from well-conducted phase III trials are awaited to see how this drug will fit into the relatively small existing gout care armamentarium.

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