Emerging Therapies for Gout

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KEYWORDS

• Gout • Urate-lowering therapy • Febuxostat • Pegloticase • Lesinurad • Ulodesine • Interleukin-1 inhibitor • Melanocortin

KEY POINTS

- The most commonly used dose of allopurinol achieves urate reduction to the minimal target of less than 6.0 mg/dL in only 35% to 40% of gouty patients.
- The new generation of uricosuric agents, when used in combination with current xanthine oxidase inhibitors, results in synergistic urate lowering not achievable by oral monotherapy.
- Activation of the NLRP3-inflammasome and its promotion of interleukin-1β production are central to the pain and inflammation of gout. Interrupting this pathway is an effective way of treating gout-driven pain.
- Corticotropin and other melanocortin peptides are effective in treating gout inflammation by interacting with the melanocortin receptors on macrophages.

The prevalence of gout worldwide has been steadily increasing over the past several decades. It has been estimated that in the United States 8.3 million people, or almost 3% of the population, suffer from gout, and 12% to 15% have hyperuricemia.[1] Similar statistics are found in most developed countries. This expanding market would be enough to draw the interest of the pharmaceutical industry, but other factors have come into play. Over the past 10 years clinicians have been inundated with studies showing how inadequate the traditional approaches to this destructive arthritis have been. The time-honored therapies for treating the pain and inflammation of gout include nonsteroidal anti-inflammatories (NSAIDs), colchicine, and oral corticosteroids. Yet in the few controlled trials conducted with these agents, one finds that patients can expect to still have 50% of their acute pain after 36 to 48 hours of treatment regardless of which agent is used.[2,3] Given the severity of acute gout symptoms, 50% reduction still leaves patients in considerable pain. Patients, physicians, and the pharmaceutical industry recognize a large unmet need for better and more specific anti-inflammatory approaches to gout.

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Similarly, deficiencies in the use and efficacy of urate-lowering therapies (ULTs) have also been brought to light by recent studies. Allopurinol and probenicid had been the mainstays of gout therapy since the 1960s. Intolerance to these drugs usually meant that the gout patient would go untreated, and over years would slowly advance to a chronic crippling form of arthritis. The concept of treating the serum urate level (sUA) to a target was not widely held by the medical profession until this approach was strongly endorsed by the European League Against Rheumatism, and more recently in the American College of Rheumatology (ACR) guidelines on managing gout.[4,5] Data from the early febuxostat trials by Takeda Pharmaceuticals demonstrated the inadequacy of the most commonly used dose of allopurinol (300 mg/d) in bringing patients' sUA levels down to the target of less than 6.0 mg/dL, with only 35% to 40%, achieving even this minimal target.[6] Again, the need for more aggressive treatment, as well as safer and more effective alternatives to allopurinol, was made apparent by study after study.[7]

This article strives to outline the current therapies under development for the management of gout. In general, these agents build on a wealth of new information about the mechanism of gouty inflammation and urate elimination that was unknown a decade ago.

URATE-LOWERING THERAPIES

Reducing sUA levels to below the solubility limit of urate in body fluids (ie, <6.8 mg/dL) has long been recognized as the definitive treatment for gout. The generally agreed therapeutic target of less than 6.0 mg/dL is safely below the solubility threshold, and will certainly prevent new crystallization of urate and further expansion of the body's urate burden. Many studies support the concept that decreasing the sUA level to less than 6.0 mg/dL will, over time, reduce gout symptoms, shrink tophaceous deposits, and improve the quality of life.[8] It has also been demonstrated that these good outcomes can be achieved more rapidly if the sUA level is pushed even lower than the minimal target of less than 6.0 mg/dL.[9]

Allopurinol was approved by the Food and Drug Administration (FDA) in 1966, and clinicians have a lot of experience with its efficacy and toxicity profiles, although this is only true for daily doses of 300 mg or less. Although it is approved in doses of up to 800 mg/d, little is known about the safety of allopurinol in the higher dose ranges. Two new ULTs were introduced in the past 5 years. The new xanthine oxidase inhibitor, febuxostat, was approved in 2009 as an alternative for patients intolerant to allopurinol or for those who could not be adequately dosed with allopurinol because of chronic kidney disease. Febuxostat has a simpler dose escalation schedule than allopurinol, and was recommended in the recent ACR gout management guidelines as a first-line agent to accompany allopurinol.[5]

Savient's pegylated uricase, pegloticase, was approved by the FDA in 2010 for use in patients with severe, recalcitrant gout. It is the first parenteral therapy for gout, and has shown dramatic ability to lower serum urate and promote tophus resorption in subjects with advanced disease.

ULTs currently in development include lesinurad, arhalofenate, ulodesine, and levotofisopam.

Lesinurad (RDEA594)

Lesinurad is a uricosuric agent in development for the chronic management of gout and hyperuricemia. It was discovered by Ardea Biosciences as a major metabolite of a candidate nonnucleoside reverse transcriptase inhibitor, RDEA809, and was