Mechanism of Action of Colchicine in the Treatment of Gout

Nicola Dalbeth, MD[1]; Thomas J. Lauterio, PhD, MBA[2]; and Henry R. Wolfe, PhD[3]

[1]Department of Medicine, University of Auckland, Auckland, New Zealand; [2]Medical Affairs, URL Pharma Inc, Philadelphia, Pennsylvania; and [3]Kyowa Kirin Pharma, Inc, New Jersey

ABSTRACT

Purpose: The aims of this article were to systematically review the literature about the mechanism of action of colchicine in the multimodal pathology of acute inflammation associated with gout and to consider the clinical utility of colchicine in other chronic inflammatory diseases.

Methods: The English-language literature on PubMed was searched for articles published between 1990 and October 2013, with a cross-reference to citations across all years. Relevant articles pertaining to the mechanism of action of colchicine and the clinical applications of colchicine in gout and other inflammatory conditions were identified and reviewed.

Findings: The molecular pathology of acute inflammation associated with gouty arthritis involves several concurrent pathways triggered by a variety of interactions between monosodium urate crystals and the surface of cells. Colchicine modulates multiple pro- and antiinflammatory pathways associated with gouty arthritis. Colchicine prevents microtubule assembly and thereby disrupts inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes and cytokines, and phagocytosis. Many of these cellular processes can be found in other diseases involving chronic inflammation. The multimodal mechanism of action of colchicine suggests potential efficacy of colchicine in other comorbid conditions associated with gout, such as osteoarthritis and cardiovascular disease.

Implications: Colchicine has multiple mechanisms of action that affect inflammatory processes and result in its utility for treating and preventing acute gout flare. Other chronic inflammatory diseases that invoke these molecular pathways may represent new therapeutic applications for colchicine. (*Clin Ther.* 2014;36:1465–1479) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: colchicine, gout, inflammatory arthritis, mechanism of action.

INTRODUCTION

Gout is an inflammatory arthritis that is the result of the precipitation of serum urate into crystallized deposits of monosodium urate (MSU) in and around the joint. These crystals cause recurrent episodes of severe inflammatory arthritis that present as swelling, redness, heat, pain, and stiffness in the joints, most often seen in the first metatarsophalangeal joint. Colchicine is a natural product originally extracted from plants of the genus *Colchicum* (*autumn crocus*) and has been used to treat gouty arthritis for centuries.[1] Clinical trial results have demonstrated that low-dose colchicine is effective for the management of acute gout flares as well as for long-term prophylactic maintenance.[2–4]

Current treatment guidelines recognize the efficacy of colchicine in the treatment of acute gouty arthritis and for the prevention of gout flares. The American College of Rheumatology Guidelines for Management of Gout recommend the pharmacologic treatment of acute gout flares within 24 hours of onset and recommend colchicine, NSAIDs, selective cyclooxygenase-2 inhibitors, and corticosteroids as first-line therapies for treating the pain of acute flares.[5] A recent update of the European League Against Rheumatism (EULAR) guidelines for the management of gout, carried out by a multidisciplinary panel of experts from the United States, also recommends that the initial treatment of acute gout flares begin with low-dose colchicine, NSAIDs, and glucocorticoids.[6] The EULAR guidelines indicate that prophylaxis for acute gout attacks during the first 6 to 12 months of therapy with urate-lowering agents can be achieved with colchicine.[6]

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These changes in treatment guidance have been the result of an increased understanding of the molecular pathology underlying the acute inflammation associated with gout and the potential benefits of early and aggressive treatment. In light of this new information, there is growing evidence that the therapeutic response of colchicine is multifaceted and intervenes at several different pathways involved in inflammation. The objectives of this review were to determine the current views regarding the mechanism of action of colchicine and to consider the potential clinical utility of colchicine in other chronic inflammatory diseases.

MATERIALS AND METHODS

The PubMed database was searched for relevant studies published between 1990 and October 2013 and restricted to the English language. All medical-subject heading searches were explored using Boolean-based key word search criteria and included the terms *gout, inflammation, colchicine, osteoarthritis,* and *cardiovascular disease*. The focus was on the following questions: (1) What is the process of inflammation in gout?; (2) What is the mechanism of action of colchicine?; and (3) What are the clinical applications of colchicine in gout and other medical conditions? Additionally, references noted in relevant articles were also accessed and reviewed. Studies that included original research and explored recent advances in the understanding of the molecular pathology of inflammation associated with gout, the multimodal mechanism of action of colchicine in response to inflammation, and the potential use of colchicine in other chronic inflammatory diseases were critically discussed.

RESULTS

A total of 756 scientific and clinical articles published in English were identified through a cross-comparative search. After medical review, 693 were evaluated as outside the scope of the focus of this review. The remaining 63 publications were carefully reviewed to identify potentially relevant articles for retrieval.

Inflammation and Gout

Awareness of the multiple actions of colchicine in gout requires an understanding of the inflammatory cascade underlying the symptoms of this debilitating disease. Gout is a disease process triggered by interactions between MSU microcrystals and the local tissue environment. The affected synovium of patients with acute gouty arthritis is infiltrated with neutrophils, mononuclear phagocytes, and lymphocytes, resulting in marked swelling of the tissues and vascular injury.[7] The biochemical mechanisms that link MSU crystal precipitation with joint inflammation have not been definitively elucidated and likely involve a variety of leukocytes, cytokines, and chemokines that participate in the innate immune system response (**Figure**).

MSU Crystal Formation

Precipitation of urate into MSU crystals is central in acute gouty arthritis. However, the mechanism by which MSU crystals form directly at the site of joint inflammation is not well understood. Monosodium urate crystallizes when the plasma concentration of urate exceeds its solubility (~7 mg/dL).[9] Factors in addition to plasma concentration that have been shown to affect urate solubility in vitro include pH, temperature, ionic strength, and the binding of urate to plasma macromolecules.[9–13] However, environmental conditions and/or mechanisms favoring/limiting crystal formation in vivo are likely different from in vitro models. The de novo formation of MSU crystals within the joint may be triggered by excessive alcohol or red meat intake and large-scale cell death from trauma, surgery, or anticancer therapies. Plasma macromolecules such as albumin have been suggested as possible MSU crystal–nucleating agents.[11,14] Circulating antibodies, including immunoglobulin (Ig) G and IgM, recognize MSU crystal surfaces, stabilize them, and promote further crystallization.[15–17]

MSU Crystal Stimulation of Pro-Inflammatory Cells

Endogenous MSU crystals act as danger-associated molecular patterns (DAMPs) that are recognized by the innate immune system, notably neutrophils and macrophages/monocytes, as well as mast cells and dendritic cells.[8,18–21] Uric acid DAMP signaling activates dendritic cells and macrophages to secrete pro-inflammatory cytokines, including interleukin (IL)-1β.[22,23] The mechanism by which pro-inflammatory cells interact with MSU crystals is a major area of research focus and likely involves different pathways operating simultaneously to initiate the inflammatory cascade as described subsequently.