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USE COLCHICINE IN TREATING GOUT AND HYPERURICEMIA AS ASELECTION DRUG

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Abstract
Therapeutic strategies for gout and hyperuricemia have been subjected to systematic and formal consensus review processes and disseminated in various Rheumatology Society guidelines and in clinical quality measures. The principal immediate goal of therapy in patients with acute gout is rapid, safe improvement in pain and inflammation. Long-term objectives include limiting recurrences of acute gouty arthritis and inhibiting chronic gouty synovitis and progression to erosion and other manifestations of permanent joint damage. Treatment of both the pain and inflammation associated with acute gout is achieved with anti-inflammatory agents. Other modalities (e.g., topical ice packs, acetaminophen) are adjunctive measures.

Keywords: gout, gouty arthritis, uric acid, flare, interleukin, NSAIDs, systemic corticosteroids, colchicine, European League Against Rheumatism (EULAR).

Introduction

Acute gouty arthritis is triggered by initial activation of resident cells, such as synovial lining cells, mast cells, and synovial fluid mononuclear phagocytes associated with tissue deposits of monosodium urate crystals. The process is driven forward by multiple mechanisms involving phagocytes. These include monocyte ingress and activation (with associated NLRP3 inflammasome activation), monocyte maturation to activated inflammatory macrophages, and by a continuing cycle of neutrophil ingress and intraarticular neutrophil activation. Processes involved, and therapy targets, include generation, release, and signaling of multiple mediators, including interleukin-1β (IL-1β), IL-8, and other inflammatory cytokines; C5 cleavage on the urate crystal surface and generation of C5a and C6b C9; generation of leukotriene B4; phagocyte ingestion of urate crystals in the joint space; and adhesion of circulating phagocytes to endothelium. Epigenetic factors, as part of innate immune memory and training, appear to play a role regulating inflammation associated with urate crystal deposition and primed by hyperuricemia. Current evidence-based treatment strategies rely on broad inhibition (by nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and colchicine) of different combinations of inflammation mechanisms.

Multiple effective drug options and dosing regimens for antiinflammatory treatment can be used for acute gout. Selection of the appropriate option is influenced by the patient's comorbid conditions (e.g., renal, cardiac, hepatic, or gastrointestinal [GI] disease), drug interactions, acute gout flare duration, and number and accessibility to injection of the joints involved. The typical response of acute gout to first-line options (NSAIDs, systemic corticosteroids, colchicine) is rapid

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but incomplete such that only approximately 50% pain reduction is achieved by 2 to 3 days in most patients.

Nonsteroidal antiinflammatory drugs. Multiple NSAIDs are effective for acute gout. NSAIDs are typically given in full doses for at least 3 days and then tapered until the acute gouty arthritis subsides. GI and central nervous system (CNS) side effects often limit the use of indomethacin. The author prefers naproxen to treat acute gout, but numerous other NSAIDs are effective alternatives. The selective cyclooxygenase-2 selective inhibitor celecoxib requires a high dose to be comparable to indomethacin for acute gout flare treatment.

Corticosteroids and adrenocorticotropic hormone (Acth). Prednisolone (30–35 mg/day for 5 days) appears to be at least comparable in efficacy and tolerance to NSAIDs in the first days of acute gout treatment. High starting doses of systemic corticosteroids are needed for acute gout (e.g., ≥0.5 mg/kg daily for oral prednisolone), especially with severe polyarticular flares. Triamcinolone (60 mg intramuscularly once) or a methylprednisolone dose pack can be used as starting therapy for acute gout. Effectiveness of intraarticular injection of a depot corticosteroid for gout involving one or two large joints has been supported by small, open studies. Initiation of adjunctive, daily low-dose prophylactic colchicine with systemic corticosteroids should be added to attempt to inhibit the occurrence of rebound gout flares after stopping corticosteroid therapy that may be driven by corticosteroid induction of the inflammasome constituent nucleotide oligomerization domain (NOD)-like receptor protein 3 (NLRP3). Adrenocorticotropic hormone (ACTH) not only induces adrenal corticosteroid production but also has a distinct peripheral antiinflammatory effect via melanocortin receptor signaling. ACTH, though not practical to employ, remains an effective option for acute gout in patients without preexisting adrenal suppression, particularly for those unable to ingest anything orally.

Colchicine, Clinical pharmacology of colchicine and drug–drug interactions. Colchicine is readily bioavailable after oral administration. The lipophilic nature of colchicine facilitates cell uptake by allowing colchicine to bind tubulin, its primary target. Colchicine is predominantly eliminated by biliary and fecal excretion. Extrusion of colchicine from cells (including gut-lining cells), enterohepatic recirculation, and marked drug enrichment in bile are critical for drug elimination, with ABCB1 (P-glycoprotein multidrug resistance transporter) playing a central role. Plasma membrane ABCB1 pumps multiple classes of substrates out of cells, thereby mediating multiple drug–drug interactions that can develop even with low colchicine doses. Clarithromycin, cyclosporine, and tacrolimus are prime examples of potent ABCB1 inhibitors. Most ABCB1 inhibitors also inhibit cytochrome P450 3E4 (CYP3A4), which carries out hepatic demethylation of colchicine to inactive metabolites before hepatobiliary excretion of the colchicine. Colchicine neuromyopathy can develop weeks after the initiation of cyclosporine. Two macrolide antibiotics, clarithromycin and erythromycin, are known to promote serious colchicine toxicity, including death. In contrast, another macrolide, azithromycin, inhibits ABCB1 only weakly, does not significantly increase plasma concentrations of colchicine in healthy volunteers, and appears to be safe to use with colchicine. Both renal disposition of colchicine and CYP3A4 metabolism are more import ant in patients with hepatobiliary dysfunction. Finally, colchicine and multiple statins have the potential to synergistically potentiate myopathy (including rhabdomyolysis).

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Colchicine binds tightly to unpolymerized tubulin and forms a tubulin–colchicine complex that regulates microtubule and cytoskeleton function. Binding of the tubulin–colchicine complex at the ends of microtubules physically acts on elongation of the microtubule polymer. Colchicine thereby regulates cell proliferation, signal transduction, gene expression, chemotaxis, and neutrophil secretion of granule contents. Colchicine acts disproportionately on highly proliferating cells (e.g., bone marrow, GI tract lining). It also concentrates in neutrophils, possibly related to low ABCB1 expression. Nanomolar colchicine concentrations, achievable in plasma with low daily prophylactic doses of colchicine, suppresses E-selectin redistribution in the endothelial cell plasma membrane, thereby inhibiting neutrophil adhesion, and in macrophages, activates the nutritional biosensor AMP activated protein kinase, which transduces multiple antiinflammatory effects of colchicine in macrophages.

Oral colchicine is believed but not unequivocally proven to be most effective when given in the first 36 hours of gout flares. A large, randomized, controlled multicenter trial found that a low-dose colchicine regimen of 1.2 mg followed by 0.6 mg in 1 hour (1.8 mg total, patient administered within 12 hours of onset of the acute gout flare) was equally effective and much better tolerated than higher dose colchicine. Based on pharmacokinetics, this regimen can be followed 12 hours later by prophylactic dosing of colchicine, until the acute gout flare resolves. Alternative European League Against Rheumatism (EULAR) guidance for treatment of acute gout with colchicine recommends a maximum of three colchicine 0.5 mg tablets per 24-hour period.

Side effects. Gastrointestinal toxicity (diarrhea; sometimes severe nausea; and to a lesser degree, vomiting) is the most frequent adverse event with oral colchicine. Bone marrow depression is common with colchicine overdose, with the nadir occurring 1 week after drug initiation. Cardiac toxicity with more severe overdosing can include arrhythmia. Colchicine overdose is also hepatotoxic and can cause alopecia. Colchicine myopathy, which affects proximal more than distal muscles and is accompanied by elevated creatine kinase in the early phase and by varying neuropathy, can mimic inflammatory muscle disease. Colchicine is, at most, weakly dialyzable. Severe cases of colchicine intoxication and can be lethal.

Limitation of the subclinical joint inflammation in gout underpins the prophylactic effect of colchicine. The most common adverse event on initiation of urate-lowering therapy (ULT) is acute gout flare. More intense ULT regimens precipitate more acute flares early in therapy, probably mediated by local inflammatory effects of urate crystal deposit remodeling. For prophylaxis of acute gout, low-dose colchicine therapy is the first choice. Ideally, colchicine flare prophylaxis is commenced 1 to 2 weeks before initiation of ULT and typically continued for 3 months after the serum urate has returned to normal (<6mg/dL). This generally works out to a minimum of a 6 month time window in all after colchicine initiation. In cases of palpable tophaceous disease, or particularly severe gout flare activity, colchicine flare prophylaxis is generally continued longer, until severe gout flares and palpable tophi subside. Low-dose NSAID therapy is an alternative choice if NSAID risk management is appropriate, although the evidence is limited. Low-dose prednisone therapy should be avoided but is sometimes necessary as a last resort. The recommended dosage of colchicine for gout flare prophylaxis is 0.6 mg once or twice daily in the United States, or 0.5 mg once or twice daily outside the United States, in an average-sized patient with preserved renal and hepatobiliary function and no-medications that interfere with colchicine

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metabolism. Specific severe drug interactions (e.g., with clarithromycin, erythromycin, tacrolimus or cyclosporine) should be avoided by not using colchicine. Low-dose prophylactic colchicine dosing should be reduced by 50% in patients with an estimated glomerular filtration rate (GFR) lower than 45 mL/min and even more so (to 0.5 or 0.6 mg once or twice per week) in those with end-stage kidney disease.

All in all, Colchicine is readily bioavailable after oral administration via uptake in the jejunum and ileum, and the lipophilic nature of colchicine allows ready absorption by multiple cell types and binding to its primary target tubulin, which serves as a drug reservoir. Colchicine is predominantly eliminated by biliary and fecal excretion, with a major role played by extrusion of colchicine from cells mediated by the multidrug resistance transporter molecule ABCB1 (P-glycoprotein [P-gp]). Catalysis of demethylation of colchicine to inactive metabolites by enteric and hepatic cytochrome P450 3E4 (CYP3A4) and renal elimination normally play lesser but significant roles (<10% and 10%–20%, respectively) in colchicine metabolism.

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