Treatment of Familial Mediterranean Fever: Colchicine and Beyond

Ahmet Gül MD

Department of Internal Medicine, Division of Rheumatology, Istanbul University Faculty of Medicine, Istanbul, Turkey

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"The right dose differentiates a poison from a remedy"

Paracelsus

Familial Mediterranean fever, the most common form of hereditary autoinflammatory disorders, is characterized by recurrent episodes of fever and sterile inflammation resulting in peritonitis, pleuritis, arthritis, and/or erysipelas-like erythema. In addition to these self-limited inflammatory episodes that last 1–3 days and mainly affect serosal membranes, FMF has also been associated with an increased risk for reactive (AA type) amyloidosis [1].

FMF is considerably common in eastern Mediterranean countries and exerts a significant disease burden. Colchicine has been accepted as the standard of care for prophylactic treatment of inflammatory episodes and prevention of reactive amyloidosis in FMF patients long before the elucidation of the genetic basis of FMF [2-5]. Identification of the pathogenic mechanisms of FMF, after the *MEFV* gene variations were found to be the cause of the autosomal recessively inherited disease, enables the optimum use of colchicine as well as the development of more targeted therapies for patients with inadequate response to colchicine.

This review updates the treatment options for patients with FMF by summarizing the available data on colchicine and its current alternatives.

Colchicine provides an effective and safe treatment option in FMF patients, but it has a narrow therapeutic margin

COLCHICINE

Colchicine is an alkaloid extracted from *Colchicum autumnale* (also known as autumn crocus or meadow saffron). Colchicum extracts have been used successfully for ages as an anti-inflammatory medication primarily in the treatment of gout but for other inflammatory and non-inflammatory conditions as well [6,7].

FMF = familial Mediterranean fever

After the initial favorable observations [2,3], the important role of colchicine in the treatment of FMF was documented by clinical trials showing its efficacy in the prevention of recurrent inflammatory episodes and development of secondary amyloidosis [4,5,8]. Since then, colchicine has been accepted as the standard treatment for both pediatric and adult FMF. Following its success as a prophylactic therapy, mounting information has been collected through clinical practice, which provided reliable safety data for continuous daily use of colchicine in patients with FMF, including pediatric, pregnant and nursing patients [9-12].

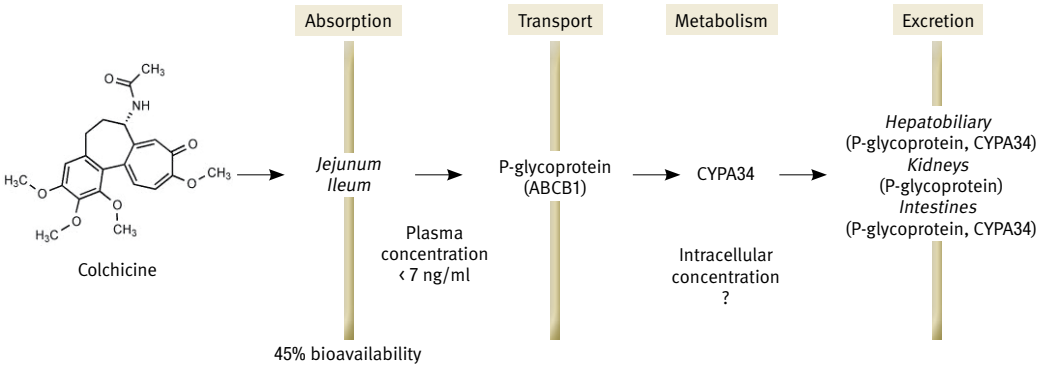
CLINICAL PHARMACOLOGY

Despite its established success, colchicine has limitations, mainly the result of its narrow therapeutic index due to its pharmacokinetic and pharmacodynamics properties. The historical legacy of colchicine as a natural and safe remedy for inflammation lies in its dose-dependent adverse effects, especially those on the gastrointestinal system (i.e., increased motility, diarrhea, abdominal pain, vomiting), which limit its oral use at toxic doses. However, in view of its widespread use in patients from all age groups with possible risks associated with co-morbidities and concomitant medications, it has become necessary to reevaluate all available safety data.

Colchicine is mainly absorbed from jejunal and ileal mucosa, and its oral bioavailability may show individual differences ranging from 24% to 88% (mean 45%) in healthy volunteers [6]. Mucosal injury, associated with long-term colchicine use, was reported in the jejunum of patients, possibly related to high drug concentrations in the main absorption site [13]. P-glycoprotein multidrug transporter (ABCB1) and cytochrome P450 (CYP3A4) proteins are important in its transport and metabolism, respectively [Figure 1]. Colchicine reaches the peak plasma concentration about 1 hour after administration of a single oral dose, while its accumulation within the cells, such as granulocytes or mononuclear leukocytes, may take 2 days [14].

Colchicine is mainly eliminated by biliary excretion, along with 10%–20% contribution by the kidneys [7], and both CYP3A4 and ABCB1 proteins play an important role. Plasma drug levels may reach toxic levels in patients with liver or

Figure 1. Proteins involved in the transport and metabolism of colchicine



renal dysfunction. Similarly, drugs interacting with ABCB1 or CYP3A4 proteins may also affect its elimination and result in toxicity [7,15]. Fatalities were reported due to concomitant use of macrolide antibiotics, such as clarithromycin, a frequently used strong CYP3A4 inhibitor in pediatric and adult patients [16]. Also, in FMF patients with renal transplantation, administration of cyclosporine may cause severe toxicity. Since cyclosporine and other ABCB1 transporter inhibitors may interfere with intestinal excretion of the drug, there may be an increased toxicity risk due to masking of gastrointestinal adverse effects and delay of colchicine-induced diarrhea, a manifestation that usually serves as a warning sign for impending colchicine toxicity [7].

Inadequate response to colchicine could be observed in FMF patients due to an imbalance resulting from a higher inflammatory activity, which exceeds the anti-inflammatory capacity of colchicine

Colchicine has a stable pharmacokinetic pattern in children and adults [17]; at the suggested daily oral doses of not more than 2 mg in children and 3 mg in adults, serious or fatal adverse events are rare [18]. On the other hand, toxic serum levels can easily be reached before appearance of gastrointestinal toxicity signs, when colchicine is used intravenously [19].

MECHANISM OF ACTION

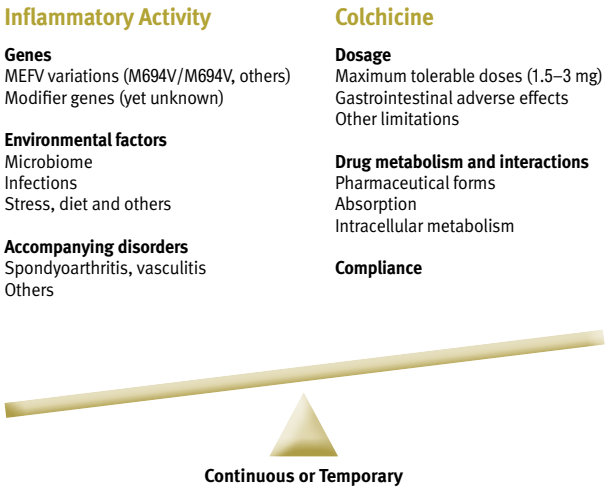
Colchicine is known to prevent microtubule elongation by binding to tubulin monomers and inhibiting polymer formation [20]. Colchicine and derivatives are used in the laboratory to arrest mitosis at metaphase due to their effects on cytoskeletal microtubules. Its efficacy has traditionally been associated with disruption of microtubule structure, affecting migration, signal transduction, or secretory functions of inflammatory cells [7]. However, within the narrow therapeutic window of colchicine, a clinical response is already observed with a blood level of less than 7 ng/ml. Usually, much higher serum levels of colchicine are required for the disruption of microtubules, and these levels are achieved only in toxic conditions. Serious toxicities and fatal outcomes due to multi-organ failure and cardiovascular collapse are associated with high serum levels of colchicine, usually > 10 ng/ml [6]. Recent studies show that colchicine concentration > 7.5 ng/ml in medium is required to disrupt microtubules in different cell lines, and changes in the actin cytoskeleton are observed at concentrations of 250 ng/ml [21]. Although there may be a difference between effective serum and intracellular colchicine concentrations, the dissociation between clinically effective and microtubular disruptive serum levels suggests that colchicine's effects on microtubules may not be the sole explanation for its mode of action. Peak serum concentration becomes particularly important if colchicine's relatively specific efficacy in inflammasome-related inflammatory conditions, such as FMF and gout, is taken into account. Further studies are therefore required to identify other possible targets of colchicine, which may have a putative role in the inflammasome complex.

INADEQUATE RESPONSE TO COLCHICINE

Colchicine is effective in most patients with FMF. However, about 30% may experience a partial response, and nearly 5% of FMF patients are considered resistant to colchicine despite full compliance [18].

Inadequate response to colchicine may be due to an imbalance between the disease-associated inflammatory activity and anti-inflammatory capacity of colchicine that could be achieved with tolerable doses [Figure 2]. FMF-related *MEFV* variations are responsible for increased activation of interleukin-1β pathway, and a higher inflammatory activity may be associated with particular *MEFV* variations such as homozygous M694V genotype [22]. Also, variations in yet unknown modifier genes, environmental factors (such as infections, stress or diet) or accompanying inflammatory conditions (spondyloarthritis, vasculitis) may also contribute to the development of a stronger inflammatory response, which may exceed colchicine's anti-inflammatory effects [23-25]. On the other hand, colchicine has a daily dose limit of up to 3 mg for an adult patient to achieve

Figure 2. Factors contributing to inadequate response to colchicine



the highest anti-inflammatory capacity without experiencing a serious adverse event [6,7,18,25]. In addition to the colchicine dosage, variability in its metabolism and transport as well as its interactions with other drugs may also affect its concentration in serum and different cells [25,26]. Another important aspect of inadequate response to colchicine is its temporary nature in at least a subgroup of FMF patients. Some FMF patients with a strong genetic impact may consistently show an incomplete response to colchicine. However, a subset of FMF patients experience temporary periods of higher disease activity that cannot be controlled by colchicine, and they may become colchicine-responsive later in their life.

Therefore, an unmet need exists for a subset of FMF patients who continue to experience acute attacks (six or more typical attacks in a year or three in 4–6 months), with an elevated acute-phase response between attacks, despite being fully compliant with colchicine therapy at the highest tolerable doses [18]. Also, FMF patients with secondary amyloidosis, chronic renal failure, systemic vasculitis and chronic arthritis are considered difficult cases for management and may require additional or alternative treatments.

TARGETED THERAPIES

In patients with inadequate response to colchicine, different treatments such as azathioprine, thalidomide or interferon-alpha were tried to control disease activity. Anti-tumor necrosis factor biologic agents were also used in such instances, mainly in patients with chronic arthritis, amyloidosis, or Crohn's disease [27]. However, after identification of *MEFV* variations as the cause of autosomal recessively inherited FMF and its inflammasome-related pathogenesis, IL-1 blockade has become the first choice in FMF patients with inadequate response to colchicine [18]. FMF has been classified among the inflammasomopathies [1]. *MEFV* variations have been associated with increased activation of IL-1β pathway due to either gain-of-function or loss-of-function mutations [28,29]. In parallel with the genetic background, a favorable clinical response was reported in colchicine-resistant FMF patients with IL-1 inhibition by anakinra (a recombinant IL-1 receptor antagonist), canakinumab (a monoclonal anti-IL-1β antibody), or rilonacept (a receptor fusion protein acting as IL-1 decoy receptor), but none of these agents has yet been licensed for FMF patients.

Efficacy of anakinra was observed both in patients with inadequate response to colchicine [30-35] and in patients with reactive amyloidosis, renal failure and transplantation [35-38]. Similarly, a favorable response to canakinumab was reported in a patient with destructive arthritis [39]. The only randomized placebo-controlled trial conducted involved rilonacept given to pediatric FMF patients resistant to or intolerant of colchicine [40]. Rilonacept was shown to reduce the frequency of FMF attacks, and patients experiencing no attacks were more common in the rilonacept group. However, no difference was observed in the duration of inflammatory attacks between patients receiving placebo and rilonacept [40].

IL-1 blockade may provide an effective and safe alternative for patients with an inadequate response to colchicine, but randomized trials are needed

These observations and the results of two yet unpublished open-label pilot studies with canakinumab* in adult and pediatric patients with colchicine-resistant and/or intolerant FMF warrant further investigations. Randomized controlled trials are needed to document the efficacy and safety of IL-1 inhibitors as well as determine their ideal dose, injection intervals and duration of treatment in FMF patients. IL-1 inhibitors are already licensed for the treatment of CAPS patients. However, there may be differences in the requirement for IL-1 inhibition between FMF and CAPS patients. Gain-of-function mutations in the *NLRP3* gene in CAPS patients are associated with continuous overproduction of IL-1β, and these patients need lifelong use of IL-1 blocking drugs. On the other hand, IL-1 activation dynamics are different in FMF, and colchicine would still be the mainstay treatment for FMF patients, considering the safety and pharmacoeconomic profiles of available treatment options. However, temporary or continuous blockade of IL-1 may also be needed in at least a subset of FMF patients with inadequate response to colchicine.

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IL = interleukin

CAPS = cryopyrin-associated periodic syndrome

Address for correspondence:
Dr. A. Gul
Dept. of Internal Medicine, Division of Rheumatology, Istanbul University Faculty of Medicine, 34093 Fatih, Istanbul, Turkey
Phone/Fax: (90-212) 631-8699
email: dr.agul001@gmail.com; agul@istanbul.edu.tr

References

1. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Ann Rev Immunol* 2009; 27: 621-68.
2. Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med* 1972; 287 (25): 1302.
3. Aral O, Ozdogan H, Yazici H. The other physician behind the use of colchicine for the treatment of familial Mediterranean fever. *Clin Exp Rheumatol* 2001; 19 (5 Suppl 24): S13-14.
4. Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attacks of familial mediterranean fever. *N Engl J Med* 1974; 291 (18): 932-4.
5. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW. Colchicine therapy for familial mediterranean fever. A double-blind trial. *N Engl J Med* 1974; 291 (18): 934-7.
6. Niel E, Scherrmann JM. Colchicine today. *Joint Bone Spine* 2006; 73 (6): 672-8.
7. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009; 38 (6): 411-19.
8. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986; 314 (16): 1001-5.
9. Padeh S, Gerstein M, Berkun Y. Colchicine is a safe drug in children with familial Mediterranean fever. *J Pediatr* 2012; 161 (6): 1142-6.
10. Ben-Chetrit E, Berkun Y, Ben-Chetrit E, Ben-Chetrit A. The outcome of pregnancy in the wives of men with familial mediterranean fever treated with colchicine. *Semin Arthritis Rheum* 2004; 34 (2): 549-52.
11. Ben-Chetrit E, Ben-Chetrit A, Berkun Y, Ben-Chetrit E. Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified? *Arthritis Care Res* 2010; 62 (2): 143-8.
12. Ben-Chetrit E, Scherrmann JM, Levy M. Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; 39 (7): 1213-17.
13. Hart J, Lewin KJ, Peters RS, Schwabe AD. Effect of long-term colchicine therapy on jejunal mucosa. *Dig Dis Sci* 1993; 38 (11): 2017-21.
14. Chappey ON, Niel E, Wautier JL, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. *Clin Pharmacol Ther* 1993; 54 (4): 360-7.
15. Todd BA, Billups SJ, Delate T, et al. Assessment of the association between colchicine therapy and serious adverse events. *Pharmacotherapy* 2012; 32 (11): 974-80.
16. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005; 41 (3): 291-300.
17. Berkun Y, Wason S, Brik R, et al. Pharmacokinetics of colchicine in pediatric and adult patients with familial Mediterranean fever. *Int J Immunopathol Pharmacol* 2012; 25 (4): 1121-30.
18. Hentgen V, Grateau G, Kone-Paut I, et al. Evidence-based recommendations for the practical management of familial Mediterranean fever. *Semin Arthritis Rheum* 2013; 43 (3): 387-91.
19. Bonnel RA, Villalba ML, Karwoski CB, Beitz J. Deaths associated with inappropriate intravenous colchicine administration. *J Emerg Med* 2002; 22 (4): 385-7.
20. Ravelli RB, Gigant B, Curmi PA, et al. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature* 2004; 428 (6979): 198-202.
21. Taskiran EZ, Cetinkaya A, Balci-Peynircioglu B, Akkaya YZ, Yilmaz E. The effect of colchicine on pyrin and pyrin interacting proteins. *J Cell Biochem* 2012; 113 (11): 3536-46.
22. Lidar M, Yonath H, Shechter N, et al. Incomplete response to colchicine in M694V homozygote FMF patients. *Autoimmun Rev* 2012; 12 (1): 72-6.
23. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum* 2007; 56 (5): 1706-12.
24. Ben-Zvi I, Brandt B, Berkun Y, Lidar M, Livneh A. The relative contribution of environmental and genetic factors to phenotypic variation in familial Mediterranean fever (FMF). *Gene* 2012; 491 (2): 260-3.
25. Lidar M, Scherrmann JM, Shinar Y, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. *Semin Arthritis Rheum* 2004; 33 (4): 273-82.
26. Tufan A, Babaoglu MO, Akdogan A, et al. Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever. *J Rheumatol* 2007; 34 (7): 1540-4.
27. Akgul O, Kilic E, Kilic G, Ozgocmen S. Efficacy and safety of biologic treatments in familial Mediterranean fever. *Am J Med Sci* 2013; 346 (2): 137-41.
28. Chae JJ, Cho YH, Lee GS, et al. Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1beta activation and severe autoinflammation in mice. *Immunity* 2011; 34 (5): 755-68.
29. Hesker PR, Nguyen M, Kovarova M, Ting JP, Koller BH. Genetic loss of murine pyrin, the Familial Mediterranean Fever protein, increases interleukin-1beta levels. *PLoS One* 2012; 7 (11): e51105.
30. Belkhir R, Moulonguet-Doleris L, Hachulla E, Prinseau J, Baglin A, Hanslik T. Treatment of familial Mediterranean fever with anakinra. *Ann Intern Med* 2007; 146 (11): 825-6.
31. Kuijk LM, Govers AM, Frenkel J, Hofhuis WJ. Effective treatment of a colchicine-resistant familial Mediterranean fever patient with anakinra. *Ann Rheum Dis* 2007; 66 (11): 1545-6.
32. Gattringer R, Lagler H, Gattringer KB, et al. Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky. *Eur J Clin Invest* 2007; 37 (11): 912-14.
33. Roldan R, Ruiz AM, Miranda MD, Collantes E. Anakinra: new therapeutic approach in children with Familial Mediterranean fever resistant to colchicine. *Joint Bone Spine* 2008; 75 (4): 504-5.
34. Ozen S, Bilginer Y, Aktay Ayaz N, Calguneri M. Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. *J Rheumatol* 2011; 38 (3): 516-18.
35. Meinzer U, Quartier P, Alexandra JF, Hentgen V, Retornaz F, Kone-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. *Semin Arthritis Rheum* 2011; 41 (2): 265-71.
36. Moser C, Pohl G, Haslinger I, et al. Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation. *Nephrol Dial Transplant* 2009; 24 (2): 676-8.
37. Alpay N, Sumnu A, Caliskan Y, Yazici H, Turkmen A, Gul A. Efficacy of anakinra treatment in a patient with colchicine-resistant familial Mediterranean fever. *Rheum Int* 2012; 32 (10): 3277-9.
38. Stankovic Stojanovic K, Delmas Y, Torres PU, et al. Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure. *Nephrol Dial Transplant* 2012; 27 (5): 1898-901.
39. Mitroulis I, Skendros P, Oikonomou A, Tzioufas AG, Ritis K. The efficacy of canakinumab in the treatment of a patient with familial Mediterranean fever and longstanding destructive arthritis. *Ann Rheum Dis* 2011; 70 (7): 1347-8.
40. Hashkes PJ, Spalding SJ, Giannini EH, et al. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med* 2012; 157 (8): 533-41.

"Three grand essentials to happiness in this life are something to do, something to love, and something to hope for"

Joseph Addison (1672-1719), English essayist, poet, playwright and politician