Seminars in Arthritis and Rheumatism 47 (2017) 115–120

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Colchicine resistance and intolerance in familial mediterranean fever: Definition, causes, and alternative treatments

Seza Ozen, MD[a,*], Isabelle Kone-Paut, MD[b], Ahmet Gül, MD[c]

[a] Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara 06100, Turkey
[b] Paediatric Rheumatology Department, CEREMAI, Université Paris SUD, Hôpital de Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin Bicêtre, Paris, France
[c] Department of Internal Medicine, Division of Rheumatology, Istanbul University Faculty of Medicine, Istanbul, Turkey

ARTICLE INFO

Keywords:
Colchicine resistance
Familial Mediterranean fever
Interleukin-1
Second-line therapy

ABSTRACT

Background: Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory syndrome characterized by recurrent serositis or arthritis attacks and, in some patients, chronic subclinical inflammation that predisposes to secondary amyloidosis. Colchicine is the gold standard of treatment, which reduces attack frequency and amyloidosis risk. However, up to 5% of patients are considered resistant or inadequately respond to colchicine, and some others cannot tolerate the side effects of effective doses of colchicine (colchicine intolerant).
Methods: We examine how the definition of colchicine resistance has evolved along with various characteristics of colchicine that may help explain unresponsiveness to the drug.
Results: Key factors in assessing colchicine resistance include attack frequency and severity, levels of acute phase reactants, colchicine dosage and composition, and treatment compliance. Promising clinical results have been obtained with biologics targeting interleukin-1 in colchicine-resistant or -intolerant patients with FMF.
Conclusions: These results underscore the need to identify patients who are not optimally managed with colchicine and who might therefore benefit from additional biologic therapies.

Introduction

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory hereditary disease characterized by recurrent episodes of fever with sterile peritonitis, pleural inflammation, arthritis, and/or erysipelas-like rash [1,2]. Although these clinical episodes are self-limited, typically lasting 1–3 days, patients are at risk of poor quality of life, sequelae of chronic inflammation, and developing secondary amyloidosis, which can lead to renal failure and early death [3]. In managing FMF, the goals are to prevent clinical attacks and to suppress chronic subclinical inflammation and its sequelae, most importantly secondary amyloidosis [3]. Colchicine is the mainstay of treatment, which has been shown to be effective in preventing clinical attacks of FMF and secondary amyloidosis in studies dating back over 40 years [4–7]. When used at appropriate doses, colchicine is safe and effective in the treatment of FMF. However, some patients do not tolerate colchicine at therapeutic doses or may be intolerant to colchicine because of interactions with other drugs [8]. In addition, up to 5% do not respond adequately to the highest tolerable doses [2].

Over the years, *colchicine resistance* has been defined in different ways. Herein, we examine how the definition of colchicine resistance has evolved along with various characteristics of colchicine that may help explain unresponsiveness to the drug. It is hoped that by improving our understanding of the multiple factors that can influence patient response to colchicine—including colchicine mechanisms of action, metabolism, potential drug–drug interactions, and patient compliance with treatment—it may be possible to better identify those patients who are truly resistant to colchicine and would benefit from alternative therapies such as biologics earlier in the FMF disease process.

Efficacy and safety of colchicine in FMF

Three seminal studies in 1974 established the efficacy of colchicine for the treatment of FMF [4–6]. Zemer et al. [4] identified the

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; CYP, cytochrome P450; ER, extended release; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FAVOR, FMF Arthritis Vasculitis and Orphan Disease Research in Pediatric Rheumatology; FDA, Food and Drug Administration; FMF, familial Mediterranean fever; HRQOL, health-related quality of life; IL-1, interleukin-1; NF-κB, nuclear factor-kappa B; P-gp, P-glycoprotein; SAA, serum amyloid A; VAS, visual analog scale.

The development of this manuscript was sponsored and funded by Novartis Pharma AG.

* Corresponding author.
E-mail address: sezaozen@hacettepe.edu.tr (S. Ozen).

http://dx.doi.org/10.1016/j.semarthrit.2017.03.006

ability of colchicine to prevent clinical attacks of FMF in a 4-month, double-blind, crossover study of 22 patients. At a dose of 0.5 mg twice daily, colchicine significantly reduced the frequency of clinical attacks compared with placebo (5.25 vs. 1.15 attacks per patient over 2 months; $P < 0.01$). In the study by Dinarello et al. [5], 11 patients with long-standing FMF received randomized courses of 0.6 mg of colchicine or placebo three times daily over 28 days; if no attacks occurred, another 28-day course was initiated. Over a study period of 11 months, 60 courses of placebo treatment were associated with 38 FMF attacks, compared with only 7 attacks per 60 courses of colchicine treatment ($P < 0.001$). Goldstein and Schwabe [6] also showed that prophylactic colchicine therapy administered over a period of 3 months was associated with significantly fewer attacks compared with placebo ($P < 0.002$).

Subsequent studies confirmed the efficacy of colchicine in FMF. Notable among these studies was an investigation of 350 children who were treated with colchicine at doses of 1–2 mg/day for 6–13 years [9]. Colchicine provided complete remission of febrile attacks in 64% of the cohort, and partial remission in 31%. In this study, partial remission was defined as either a significant decrease in the frequency and severity of all forms of attacks (abdominal, articular, pleuritic, and fever alone) or remission of one form of attack but not another. Importantly, none of the children developed secondary amyloidosis while receiving colchicine treatment. Growth, development, and subsequent fertility were judged to be normal. The efficacy of colchicine at the recommended dose of 1.0–1.5 mg/day in adults was confirmed in a recent systematic review, although colchicine clinical trials were suggested to have some quality problems in comparison to current trial approaches [10]. Intravenous colchicine has also shown efficacy in some patients who do not respond to oral colchicine [11,12]. In one study of 5 patients who had frequent FMF attacks despite maximal oral colchicine therapy (2–3 mg/day), treatment with adjunctive weekly IV infusions of 1 mg colchicine for 6 months was associated with a 50% reduction in frequency of febrile abdominal and chest attacks [11]. However, early warnings signs of toxic doses in the gastrointestinal system induced by oral administration could not be seen when colchicine is used intravenously. Considering the substantial risk of toxicity associated with overdoses, intravenous colchicine should not be recommended as an alternative treatment for patients not responsive to standard oral use [3].

Oral colchicine appears safe and generally well-tolerated when used at recommended doses. Gastrointestinal side effects including diarrhea, cramps, and abdominal pain are seen in up to 20% of FMF patients at therapeutic doses [13], but are generally mild and transient. To reduce side effects, the daily dose of colchicine can be divided, but it carries the risk of potentially reducing treatment compliance, which in turn can negatively affect the response to the drug [3]. Other options for minimizing the gastrointestinal effects of colchicine include reducing the dose, modifying the patient's diet to reduce dairy intake, and adding antidiarrheal and spasmolytic agents to the treatment regimen [3]. In some cases, it may be beneficial for a patient to switch to another formula of colchicine, which may or may not be combined with an anticholinergic agent to reduce diarrhea (Colchimax).

Of particular note, colchicine has been shown to be a safe medication in children, even during infancy, and in pregnant women. In a study of pediatric FMF patients, colchicine treatment resulted in diarrhea in a small percent of patients (14%), which was controlled by reducing colchicine dose, and only a mild transitory increase in transaminase levels [14]. Several studies have also demonstrated the safety of colchicine treatment during pregnancy [15,16]. In a study of 238 colchicine-exposed pregnancies and 964 pregnancies with non-teratogenic exposure, no significant differences in major congenital anomalies was observed between the 2 groups, nor were any cytogenetic anomalies reported in the colchicine group [16].

Colchicine also has a relatively narrow therapeutic window, and therefore patients should not receive more than the maximum dose they can tolerate, which is less than 3 mg/day in adults and less than 2 mg/day in prepubescent children [2]. One interdisciplinary group has recommended a starting dose of ≤ 0.5 mg/day for children who are younger than 5 years, 1.0 mg/day for children ages 5–10, and 1.5 mg/day for children over 10, which can be increased to no more than 2.0 mg/day if needed [17]. More recently, a study of steady-state pharmacokinetics in pediatric and adult patients with FMF resulted in the following recommendations for starting doses in children: 0.6 mg/day for patients 2–4 years and 4–6 years of age (half the US adult dose), and 0.9 mg/day for patients aged from 6 to less than 12 years (three-quarters of the US adult dose) [18]. However, this dosing regimen is not applicable in the EU, as colchicine is available only in 0.5 and 1 mg tablets.

Moreover, colchicine is a substrate for the cytochrome P450 (CYP) 3A4 isoenzyme and the P-glycoprotein-1 (P-gp) efflux transporter [19–21]. Concomitant administration of CYP3A4 or P-gp inhibitors can limit the safety and tolerability of colchicine, and accordingly require reduction of the maximum colchicine dose [2]. Drug–drug interactions as well as neuromuscular, hepatic, and hematological toxicities, including rhabdomyolysis, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia may also limit colchicine use [13]. It should be emphasized that toxicities associated with colchicine treatment remain relatively rare and preventable following recommendations of use, and colchicine has an excellent long-term safety profile [3].

Definitions of colchicine resistance

As noted above, up to 5% of patients do not respond to colchicine even when used at the highest tolerable dose [2,9,22]. The meaning of "*colchicine resistance*" has evolved over the past decade, although a consensus definition remains elusive (Table). Early definitions were based on the frequency of clinical attacks; for example, non-responders were defined as patients with more than 1 clinical attack every 3 months despite treatment with colchicine 2 mg/day [23]. Unfortunately, this definition cannot be applied universally since some patients cannot be treated with a 2 mg/day dose. Moreover, it does not consider the severity of FMF manifestations, including symptoms occurring outside of febrile attacks, such as myalgia and vasculitis.

Ben-Chetrit and Ozdogan [24] attempted to create FMF response criteria by using an approach with indexes similar to the American College of Rheumatology (ACR) response criteria in rheumatoid arthritis. They suggested that FMF response can be defined based on the percentage reduction in attack frequency (e.g., FMF-50 would represent a 50% reduction in attack frequency). This paradigm allowed comparisons before and after colchicine treatment; those not reaching an FMF-50 response would be classified as non-responders. However, before the patient could be classified as a non-responder, it would be necessary to ensure that he or she was fully compliant with colchicine therapy, which is hard to estimate by measuring plasma colchicine levels because of lack of reliable detection methods and absence of a correlation between plasma and intracellular concentrations.

An interdisciplinary group of French and Israeli physicians and geneticists recognized that an FMF-50 response does not provide information about remaining symptoms [2]. They considered patients with mild and severe FMF; the former may have few remaining symptoms whereas the latter may still suffer from very frequent attacks that predispose to secondary amyloidosis. To address this issue, the group recognized that both attack frequency and severity should be considered, even though it would complicate the scoring system and make it difficult to use in daily clinical practice. Their consensus recommendation indicated that fully

Table
Different approaches for assessing colchicine response

Reference	Main criteria	Additional considerations
Lidar et al. (2004) [23]	Non-responders defined as patients with >1 clinical attack every 3 months despite treatment with colchicine 2 mg/day	Some patients cannot be treated with a 2-mg/day dose; definition does not account for the severity of symptoms
Ben-Chetrit et al. (2008) [24]	FMF response defined based on the % reduction in attack frequency; patients not reaching an FMF-50 response would be classified as non-responders	FMF-50 response does not provide information about remaining symptoms
Hentgen et al. (2013) [2]	Fully compliant patients considered colchicine resistant if they have >6 typical FMF attacks per year or >3 attacks over 4–6 months	If attacks are incomplete, an increase in at least 2 of 3 acute phase reactants is also necessary to define resistance
Ozen et al. [25]	Beyond attack frequency, FMF-50 now also requires ≥50% improvement in 5 of 6 criteria; patients not achieving FMF-50 response considered to be colchicine resistance	6 criteria include: % change in frequency of attacks, % change in duration of attacks, patient/parent global assessment of disease severity, physician global assessment of disease severity, % change in arthritis attacks, and % change in acute phase reactants
Ozen et al. (2016) [3]	Colchicine resistance defined by ≥1 attacks per month in compliant patients receiving the maximally tolerated dose for ≥6 months	Some patients receiving colchicine may not tolerate infrequent attacks or may have heightened risk of secondary amyloidosis; additional or alternative therapy may be warranted

compliant patients should be considered colchicine-resistant if they have more than 6 typical FMF attacks per year or more than 3 typical attacks over a 4–6-month period. In cases where attacks are incomplete, then increases in at least 2 of 3 acute phase reactants (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and serum amyloid A [SAA]) between attacks would identify the patient as colchicine-resistant.

The FMF Arthritis Vasculitis and Orphan Disease Research in Pediatric Rheumatology (FAVOR) and Turkish FMF study group revisited the concept of an FMF-50 response for assessing outcome in FMF [25]. Instead of looking solely at attack frequency as with the FMF response criteria of Ben-Chetrit and Ozdogan, the revised FMF-50 required at least 50% improvement in 5 of 6 criteria with treatment without worsening in any single criterion: percent change in frequency of attacks, percentage change in duration of attacks, patient/parent global assessment of disease severity (scored on a 10-cm visual analog scale [VAS]), physician global assessment of disease severity (10-cm VAS), percentage change in arthritis attacks, and percentage change in CRP, ESR, or SAA. Compliant patients not achieving a FMF-50 response were considered to be colchicine resistant.

The European League Against Rheumatism (EULAR) recently published recommendations for management of FMF, in which colchicine resistance was defined by 1 or more attacks per month in compliant patients who had been receiving the maximally tolerated dose for at least 6 months [3]. The guidelines also recognize that some patients receiving colchicine may not tolerate even infrequent attacks or may have evidence of significant subclinical inflammation that places them at heightened risk of secondary amyloidosis, and thereby would warrant additional or alternative therapies. We believe that the EULAR definition of a colchicine-resistant patient is inadequate for several reasons, particularly its definition of colchicine resistance as “one or more attacks per month.” This definition implies that a treatment response has been achieved even in a patient, for example, who has had 11 attacks during a year of treatment. We also believe that a more substantial and data-driven definition that can be validated in different ethnic groups is needed.

Colchicine mechanism of action

To better understand why some patients are resistant to or intolerant of colchicine, it is important to consider its mechanisms of action. Colchicine is well recognized to inhibit microtubule assembly in in vitro conditions [26]. Microtubules are filamentous structures that are involved in maintaining the structure of cells and allowing cell movement for functions such as cell and nuclear division, cytokine secretion, and regulation of ion channels [27]. Microtubules are also necessary for activation of the NLRP3 inflammasome, a complex that converts pro-IL-1β to active IL-1β and is associated with inflammatory diseases such as FMF [28,29]. The anti-inflammatory effect of colchicine in FMF has traditionally been thought to result from microtubule disruption in neutrophils, which prevents their migration in response to chemotactic factors [30]. Another line of evidence suggests that colchicine has a beneficial effect in FMF through activation of the GTPase RhoA and subsequent phosphorylation of the 14-3-3 protein and inhibition of pyrin-induced inflammasome formation; recently Park et al. [31] have found that colchicine resistance may also arise when certain mutations in pyrin prevent binding to the 14-3-3 protein.

Additionally, colchicine has been shown to alter the distribution of cell adhesion molecules on neutrophils and endothelial cells, thereby reducing neutrophil transmigration [32]. Interestingly, low concentrations of colchicine altered the distribution of E-selectin molecules on the endothelium, whereas higher therapeutic concentrations reduced the number of L-selectin molecules on neutrophils. Recently, colchicine was found to alter the deformability of neutrophils, with the reduction in cytoplasmatic elasticity correlated with a decreased number of cytoplasmatic microtubules [33]. This resulted in a decrease in neutrophil migration through small pores, which is considered critical for neutrophil extravasation to inflammatory sites. Despite the known effects of colchicine on microtubules and benefits in FMF and gout, it has not shown efficacy in other inflammasome-associated hereditary fever disorders such as mevalonate kinase deficiency, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and severe neonatal onset multisystem inflammatory disorder (NOMID).

Increasing evidence suggests that the effects of colchicine in FMF may be due to additional mechanisms beyond those affecting microtubules in neutrophils. For example, Ben-Chetrit et al. [30] found that incubation of human vascular endothelial cells with colchicine for short periods (30 or 120 minutes) affected expression of genes involved in the cell cycle and its regulation, whereas longer incubation periods (12–24 hours) were needed before colchicine regulated the expression of genes involved in neutrophil migration or other inflammatory processes. These temporal differences may possibly help explain why colchicine is not effective when administered at the time of an acute attack in FMF patients.

The underlying genetic defect in FMF is a mutation in *MEFV*, the gene that encodes pyrin, a protein expressed in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts and thought to be an important regulator of inflammation and innate immunity [34]. Pyrin is found predominantly in the nucleus, but also in association with the cytoskeleton in the cytoplasm. The N-terminal of pyrin contains a domain found in several regulators of apoptosis

and inflammation. Pyrin interacts with the adapter protein ASC, which promotes formation of large perinuclear structures (known as specks) and modulates inflammasome activity including activation of caspase-1 and IL-1β, and nuclear factor-kappa B (NF-κB) [34]. Colchicine has been shown to down-regulate pyrin expression, reduce ASC speck formation in cells expressing mutant pyrin, and induce reorganization of the actin cytoskeleton in the human monocytic cell line THP-1 at high doses [35].

Multiple mutations have been identified in *MEFV*, the most severe ones being those in exon 10, mainly M694V, M694I, and M680I. It appears that the penetrance of the mutations may influence response to colchicine. For example, Lidar et al. [36] found that patients homozygous for the most penetrant M694V exhibited more severe disease and required higher doses of colchicine compared with M694V/V726A compound heterozygotes and V726A homozygotes (average dose/day: 1.98, 1.47, and 1.13 mg, respectively) Clinical attack rates were higher among the M694V homozygotes compared with the other 2 groups. Another genetic factor that may underlie colchicine resistance is drug transporter gene ABCB1 (MDR1) 3435 C to T polymorphism [37]. This drug transporter extrudes colchicine out of cells, and patients with the C genotype have been shown to be more resistant to colchicine that patients with the TT allele.

Taken together, available evidence suggests that colchicine has multiple mechanisms of action in FMF [38]. Importantly, variations in any of these pathways may influence the efficacy of colchicine, and thereby contribute to colchicine resistance, at least in some patients.

Colchicine metabolism and potential drug–drug interactions

As noted previously, colchicine is a substrate for CYP3A4 and P-gp, and therefore concomitant administration of drugs that inhibit these enzymes may increase plasma colchicine concentrations. In 2009, when a single-ingredient oral dose of colchicine (Colcrys) was first approved by the US Food and Drug Administration (FDA) for the treatment of FMF and acute gout flares, 117 deaths had been reported at therapeutic doses (i.e., not counting potential overdoses), and of these, about half occurred in patients who were also taking clarithromycin [39,40]. Terkeltaub et al. [41] looked specifically at colchicine interactions with seven known inhibitors of CYP3A4 and P-gp [cyclosporine, ketoconazole, ritonavir, clarithromycin, azithromycin, verapamil extended release (ER), and diltiazem ER], and concluded that the colchicine dose needs to be reduced when used concomitantly with each of these agents except for azithromycin. Other drug–drug interactions and adverse outcomes have been observed with colchicine, including myopathy or rhabdomyolysis with digoxin, statins, and gemfibrozil [13,42,43], and thrombocytopenia with the anti-PD-1 inhibitor nivolumab [44].

Colchicine is clinically effective in most FMF patients at blood concentrations < 7 ng/mL, but can cause serious toxicities, multiple organ failure, and death at concentrations > 10 ng/mL [45,46]. Accordingly, care is needed to ensure that patients are not exposed to excessive colchicine concentrations, particularly those who are treated with concomitant CYP3A4 or P-gp inhibitors. The maximum dose of colchicine should be reduced to 0.6 mg/day in patients treated with strong CYP3A4 and P-gp inhibitors. Unless blood levels of colchicine are verified, these reductions, in theory, may result in subtherapeutic exposure in some patients and possibly contribute to apparent colchicine resistance.

Colchicine compliance

Several studies have shown that full compliance with colchicine treatment may not be particularly common in FMF patients. In a cohort of 38 FMF patients (aged 7–57 years) seen at a Jerusalem clinic, only 5 (13%) filled all colchicine prescriptions that they received from their physician [22]. In total, 13 patients (34%) filled less than 50% of their prescriptions and 3 (8%) did not fill any of the prescriptions, suggesting that approximately 40% had poor compliance with colchicine. Similar results were reported in a cohort of 96 consecutive FMF patients seen at a Turkish clinic: 35.5% of the patients did not use colchicine regularly [47]. Poor compliance with colchicine therapy may contribute to inadequate responses, thereby hindering the assessment of true “colchicine resistance.” Accordingly, expert opinion and management guidelines recognize that patients can be classified as colchicine-resistant only if they have been shown to be fully compliant with the treatment regimen and are still not responding to therapy [2,3,25]. Patients cite a range of reasons for poor compliance, including side effects such as diarrhea, worries about using a drug for a lifetime, and concerns about sexual fertility or effects on the fetus [3]. Because there are no accessible assays for measuring colchicine in the blood and definitively establishing compliance, EULAR guidelines note that lack of compliance should be considered in all patients who do not respond adequately to colchicine [3].

Looking forward

Overall, we see that many factors can contribute to inadequate response to colchicine, including lack of compliance, adverse events, potential drug interactions, and genetic background (Fig.). Clinicians are thus confronted with multiple pathways that complicate an assessment of true colchicine resistance in their patients. The situation is further complicated by two issues: first, a consensus definition of colchicine resistance has not yet been reached, and second, our definition of patient response must also include an assessment of compliance, which is often problematic. Having rigorous criteria for defining patient response to treatment and potential colchicine resistance is particularly important now that new biologics are available for patients who do not respond to or are intolerant of colchicine. These biologics target IL-1, and include the recombinant IL-1 receptor antagonist, anakinra; the IL-1 fusion decoy receptor, rilonacept; and the anti-IL-1β monoclonal antibody, canakinumab.

Several case studies suggest that anakinra may be effective in patients with colchicine-resistant FMF [48–54]. In one report, anakinra successfully reduced attack frequency and levels of acute phase reactants in 6 patients who had experienced at least 2 attacks per month and had elevated CRP despite regular colchicine therapy [51]. Notably, the TNF inhibitor etanercept was ineffective in these patients, leading the investigators to speculate that the relative superiority of blocking IL-1β over TNFα may reflect effects on pyrin and the IL-1β inflammatory pathway. In other case reports, anakinra reduced attack frequency and normalized acute phase reactants in patients with colchicine-resistant FMF with secondary amyloidosis; however, follow-up was not sufficient to evaluate the impact of anakinra on amyloidosis [53,54]. In a 4-month double-blind, randomized, placebo-controlled trial in 25 colchicine-resistant FMF patients, 12 patients receiving anakinra had an attack rate of 1.7/month, compared with 3.5/month for the 13 patients receiving placebo ($P = 0.037$) [55]. Quality of life was also found to be better in the anakinra group ($P = 0.045$). The rate of adverse events was comparable between the two groups, and the only patients who prematurely discontinued the study were in the placebo group.

Rilonacept reduced the frequency of FMF attacks in a randomized, double-blind, alternating-treatment study of 14 patients with colchicine-resistant or -intolerant FMF [56]. In the study, patients were randomized to treatment sequence, consisting of two

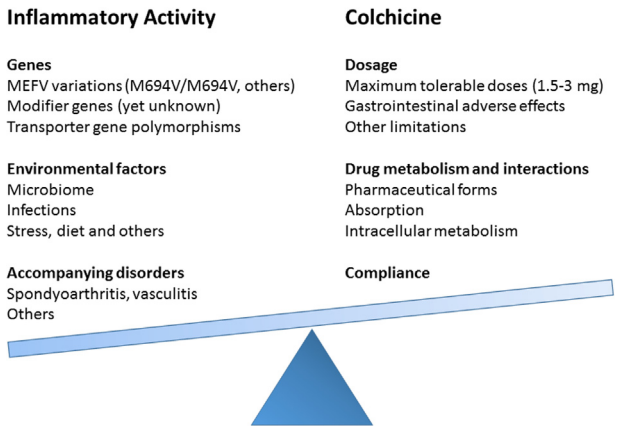

Fig. Factors contributing to inadequate response to colchicine. Multiple factors are associated with inadequate response to colchicine, including lack of compliance, genetic factors (e.g., FMF-related *MEFV* variations), environmental factors (e.g., diet and stress), colchicine dosage and interaction with other drugs. The imbalances may be due either to temporary factors such as diet, stress, infections, or other accompanying inflammatory conditions that can be controlled by a short-term intervention with biologic agents, or due to permanent factors such as genetics requiring a continuous need for additional treatment [45]. (Adapted with permission from Gül [45]).

3-month courses of rilonacept 2.2 mg/kg SC weekly and two 3-month courses of placebo. Rilonacept significantly reduced the median number of attacks per month compared with placebo (0.77 vs. 2.00; $P = 0.027$), and produced more treatment courses without attacks (29% vs. 0%; $P = 0.004$) and with 50% or greater reductions in attack frequency (75% vs. 35%; $P = 0.006$). However, rilonacept did not alter the duration of attacks. Health-related quality of life (HRQOL) was assessed as part of this study; rilonacept significantly improved the physical summary score ($P = 0.025$), but not the psychosocial summary score ($P = 0.55$), compared with placebo in these patients [57].

Canakinumab has been assessed in retrospective reviews and two open-label phase II studies of colchicine-resistant patients [52,58–61], and it is the only biologic agent approved by the U.S. FDA for the treatment of FMF based on data from a pivotal phase III clinical trial [62,63]. Both phase II studies, 1 in 9 patients aged 12–34 years and 1 in 7 children aged 7–15 years with colchicine-resistant FMF, established the efficacy of canakinumab in reducing the frequency of FMF attacks and maintaining low levels of acute phase reactants, with no unexpected adverse events [59,61]. In the ongoing phase III study, 63 patients with colchicine-resistant or -intolerant FMF were randomized to receive canakinumab 150 mg SC or placebo every 4 weeks [62]. At week 16, canakinumab compared with placebo produced a significantly higher responder rate (i.e., resolution of the index attack by day 15 and no new disease attacks: 61.3% vs 6.3%), and higher rates of physician global assessment of disease activity <2 (i.e., minimal/none: 64.5% vs. 9.4%), CRP $\leq$ 10 mg/L (67.7% vs. 6.3%), and SAA ($\leq$10 mg/L (64.5 vs. 9.4%) at week 16 (all $P < 0.001$). Adverse event rates with canakinumab were generally comparable to placebo and consistent with previous clinical experience with the drug.

Recent guidelines from EULAR and a French/Israeli consortium recognize that IL-1 blockade may be a promising second-line approach for colchicine-resistant or -intolerant patients [2,3]. These guidelines recommend that colchicine should be co-administered with the IL-1 inhibitor, as it may reduce the risk of amyloidosis when the inflammation cannot be controlled with colchicine alone. For patients with amyloidosis, FMF treatment needs to be intensified using the maximum tolerated dose of colchicine and supplemented with the biologic as needed. The optimal use of these agents in colchicine-resistant FMF, whether temporarily, periodically, or continuously, requires further clinical investigation.

In addition, clinicians will need to consider other factors influencing the optimal use of biologics, particularly their cost and the need, in some cases, of daily injections. Biologic agents are derived from manipulation of living organisms and cells, and are typically more expensive than conventional drugs [64]. Moreover, not only can the frequency of injection can be inconvenient for many patients, but the cost of these drugs may influence the injection schedule, as clinicians attempt to tailor therapies for their patients that balance safety, efficacy, quality of life, and cost [65].

Conclusion

Life-long daily colchicine is the gold standard of treatment for FMF, but a significant proportion of patients may not respond adequately or may be resistant, placing them at heightened risk of complications, most importantly secondary amyloidosis. Multiple definitions of colchicine resistance have been suggested, although a consensus definition has not been reached. Identifying which patients cannot be adequately treated with colchicine and which may have inadequate response due to factors other than compliance (e.g., genetics, intolerance, and drug interactions) is of increasing importance, as new biologic therapies that could potentially improve the care of colchicine-resistant patients continue to become available.

Acknowledgments

We would like to thank Joe Hirsch from BioScience Communications for editorial assistance with this manuscript, supported by Novartis Pharma AG.

Appendix

Novartis Pharma AG provided financial support for editorial development of this manuscript.

- With author guidance, Joe Hirsch from BioScience Communications developed a draft manuscript, incorporated author revisions, and oversaw the submission/resubmission process.
- The authors directed editorial development of the manuscript throughout the process, and all authors had equal input on the final content of the article.

References

[1] Masters SL, Simon A, Aksentijevich I, Kastner DL. *Horror autoinflammaticus*: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621–68.
[2] Hentgen V, Grateau G, Kone-Paut I, Livneh A, Padeh S, Rozenbaum M, et al. Evidence-based recommendations for the practical management of familial Mediterranean fever. Semin Arthritis Rheum 2013;43:387–91.
[3] Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G,, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 2016;75:644–51.
[4] Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 1974;291:932–4.
[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;291:934–7.
[6] Goldstein RC, Schwabe AD. Prophylactic colchicine therapy for familial Mediterranean fever. A controlled-double blind study. Ann Intern Med 1974;81:792–4.
[7] Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J, et al. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med 1986;314:1001–5.
[8] Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. Am J Med 2015;128:461–70.
[9] Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long-term colchicine treatment in children with familial Mediterranean fever. Arthritis Rheum 1991;34:973–7.

[10] Demirkaya E, Erer B, Ozen S, Ben-Chetrit E. Efficacy and safety of treatments in Familial Mediterranean fever: a systematic review. Rheumatol Int 2016;36:325–31.
[11] Rozenbaum M, Boulman N, Feld J, Avshovich N, Petrovich S, Elias M, et al. Intravenous colchicine treatment for six months: adjunctive therapy in familial Mediterranean fever (FMF) unresponsive to oral colchicine. Clin Exp Rheumatol 2009;27(2 Suppl. 53):S105.
[12] Lidar M, Kedem R, Langevitz P, Pras M, Livneh A. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. J Rheumatol 2003;30:2620–3.
[13] COLCRYSTM (colchicine) Prescribing Information. Rev 01; July 2009.
[14] Padeh S, Gerstein M, Berkun Y. Colchicine is a safe drug in children with familial Mediterranean fever. J Pediatr 2012;161:1142–6.
[15] Rabinovitch O, Zemer D, Kukia E, Sohar E, Mashiach S. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. Am J Reprod Immunol 1992;28:245–6.
[16] Diav-Citrin O, Shechtman S, Schwartz V, Avgil-Tsadok M, Finkel-Pekarsky V, Wajnberg R, et al. Pregnancy outcome after in utero exposure to colchicine. Am J Obstet Gynecol 2010;203:144 e1–e6.
[17] Kallinich T, Haffner D, Niehues T, Huss K, Lainka E, Neudorf U, et al. Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 2007;119:e474–83.
[18] Berkun Y, Wason S, Brik R, Butbul Y, Ben-Chetrit E, Hashkes PJ, et al. Pharmacokinetics of colchicine in pediatric and adult patients with familial Mediterranean fever. Int J Immunopathol Pharmacol 2012;25:1121–30.
[19] Ferron GM, Rochdi M, Jusko WJ, Schermann JM. Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. J Clin Pharmacol 1996;36:874–83.
[20] Tateishi T, Soucek P, Caraco Y, Guengerich FP, Wood AJ. Colchicine biotransformation by human liver microsomes. Identification of CYP3A4 as the major isoform responsible for colchicine demethylation. Biochem Pharmacol 1997;53:111–6.
[21] Dahan A, Sabit H, Amidon GL. Multiple efflux pumps are involved in the transepithelial transport of colchicine: combined effect of p-glycoprotein and multidrug resistance-associated protein 2 leads to decreased intestinal absorption throughout the entire small intestine. Drug Metab Dispos 2009;37:2028–36.
[22] Ben-Chetrit E, Aamar S. About colchicine compliance, resistance and virulence. Clin Exp Rheumatol 2009;27(2 Suppl. 53):S1–3.
[23] Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum 2004;33:273–82.
[24] Ben-Chetrit E, Ozdogan H. Non-response to colchicine in FMF—definition, causes and suggested solutions. Clin Exp Rheumatol 2008;26(4 Suppl. 50):S49–51.
[25] Ozen S, Demirkaya E, Duzova A, Erdogan O, Erken E, Gul A, et al. for the FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR) and Turkish FMF study group. FMF50: a score for assessing outcome in familial Mediterranean fever. FMF50: a score for assessing outcome in familial Mediterranean fever. Ann Rheum Dis 2014;73:897–901.
[26] Andreu JM, Timasheff SN. Interaction of tubulin with single ring analogue of colchicine. Biochemistry 1982;21:534–43.
[27] Caviston JP, Holzbaur EL. Microtubule motors at the intersection of trafficking and transport. Trends Cell Biol 2006;16:530–7.
[28] Misawa T, Takahama M, Kozaki T, lee H, Zou J, Saitoh T, et al. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. Nat Immunol 2013;14:454–60.
[29] Omenetti A, Carta S, Delfino L, Martini A, Gattorno M, Rubartelli A. Increased NLRP3-dependent interleukin 1β secretion in patients with familial Mediterranean fever: correlation with MEFV genotype. Ann Rheum Dis 2014;73:462–9.
[30] Ben-Chetrit E, Bergmannn S, Sood R. Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis. Rheumatology 2006;45:274–82.
[31] Park YH, Wood G, Kastner DL, Chae JJ. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat Immunol 2016;17:914–21.
[32] Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96:994–1002.
[33] Paschke S, Franziska Weidner A, Paust T, Marti O, beil M, Ben-Chetrit E. Technical advance: inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. J Leukoc Biol 2013;94:1091–6.
[34] Chae JJ, Wood G, Richard K, Jaffe H, Colburn NT, Masters SL, et al. The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-κB through its N-terminal fragment. Blood 2008;112:1794–803.
[35] 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;113:3536–46.
[36] Lidar M, Yonath H, Shechter N, Sikron F, Sadetzki S, Langevitz P, et al. Incomplete response to colchicine in M694V homozygote FMF patients. Autoimmun Rev 2012;12:72–6.
[37] Tufan A, Babaoglu MO, Akdogan A, Yasar U, Calguneri M, Kalyoncu U, et al. Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever. J Rheumatol 2007;34:1540–4.
[38] Leung YY, Hui LLY, Kraus VB. Colchicine—update on mechanisms of action and therapeutic uses. Sem Arthritis Rheum 2015;45:341–50.
[39] FDA Alert. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys). Available at: ⟨http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174315.htm⟩; 2009.
[40] Hung IFN, Wu AKL, Cheung VCC, Tang BS, To KW, Yeung CK, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clin Infect Dis 2005;41:291–300.
[41] Terkeltaub RA, Furst DE, DiGiacinto JL, Kook KA, Davis MW. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheum 2011;63:2226–37.
[42] Tufan A, Dede DS, Cavus S, Altintas ND, Iskit AB, Topeli A. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. Ann Pharmacother 2006;40:1466–9.
[43] Chattopadhyay I, Shetty HG, Routledge PA, Jeffery J. Colchicine induced rhabdomyolysis. Postgrad Med J 2001;77:191–2.
[44] Solomon LR. Thrombocytopenia due to low-dose colchicine therapy: a possible drug interaction with nivolumab and implications for supportive care. Acta Oncol 2015;54:1235–7.
[45] Gül A. Treatment of familial Mediterranean fever: colchicine and beyond. Isr Med Assoc J. 2014;16:281–4.
[46] Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol 2010;48:407–14.
[47] Karaaslan Y, Dogan J, Omma A, Can Sandika S. Compliance to colchicine treatment and disease activity in familial Mediterranean fever (FMF) patients in Middle/Black Sea Region of Turkey (in Çorum region). Pediatr Rheumatol 2015;13(Suppl. 1):P81.
[48] 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;75:504–5.
[49] Belkhir R, Moulonguet-Doleris L, Hachulla E, Prinseau J, Baglin A, Hanslik T. Treatment of familial Mediterranean fever with anakinra. Ann Intern Med 2007;146:825–6.
[50] Meinzer U, Quartier P, Alexandra JF, Hentgen V, Retornaz F, Koné-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum 2011;41:265–71.
[51] 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;38:516–8.
[52] Cetin P, Sari I, Sozeri B, Cam O, Birlik M, Akkoc N, et al. Efficacy of interleukin-1 targeting treatments in patients with familial Mediterranean fever. Inflammation 2015;38:27–31.
[53] Moser C, Pohl G, Haslinger I, Knapp S, Rowczenio D, Russel T, et al. Successful treatment of familial Mediterranean fever with anakinra and outcome after renal transplantation. Nephrol Dial Transplant 2009;24:676–8.
[54] Stankovic Stojanovic KS, Delmas Y, Torres PU, Peltier J, Pelle G, Jéru I, 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;27:1898–901.
[55] Ben-Zvi I, Kukay O, Giat E, et al. Anakinra for colchicine resistant FMF—a randomized, double blinded, placebo-controlled trial [abstract]. Isr Soc of Rheumatol Annual Meeting Proc 2016;23. [as cited in Haviv R, Hashkes PJ. Canakinumab investigated for treating familial Mediterranean fever. Expert Opin Biol Ther 2016;16:1425-34].
[56] Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, et al. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. Ann Intern Med 2012;157:533–41.
[57] Hashkes PJ, Spalding SJ, Hajj-Ali R, Giannini EH, Johnson A, Barron KS, et al. The effect of rilonacept versus placebo on health-related quality of life in patients with poorly controlled familial Mediterranean fever. . Biomed Res Int 2014:2014–854842.
[58] 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;70:1347–8.
[59] Brik R, Butbul-Aviel Y, Lubin S, Ben Dayan E, Rachmilewitz-Minei T, Tseng L, et al. Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study. Arthritis Rheum 2014;66:3241–3.
[60] Eroglu FK, Besbas N, Topaloglu R, Ozen S. Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents. Rheumatol Int 2015;35:1733–7.
[61] Gül A, Ozdogan H, Erer B, Ugurlu S, Kasapcopur O, Davis N, Sevgi S. Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis Res Ther 2015;17:243.
[62] De Benedetti F, Anton J, Gattorno M, Lachmann H, Kone-Paut I, Ozen S, et al. A phase III pivotal umbrella trial of canakinumab in patients with auto-inflammatory periodic fever syndromes (colchicine resistant FMF, HIDS/MKD, and TRAPS). Ann Rheum Dis 2016;75(Suppl. 2):615.
[63] Ilaris (canakinumab) Prescribing Information. Novartis Pharmaceuticals Corporation. September 2016.
[64] Howe A, Eyck LT, Dufour R, Shah N, Harrison DJ. Treatment patterns and annual drug costs of biologic therapies across indications from the Humana commercial database. J Manag Care Spec Pharm 2014;20:1236–44.
[65] Lipsker D, Lachmann H. IL-1 Inhibition in cryopyrin-associated periodic syndrome and beyond: a million dollar question about the injection schedule of biotherapies. Dermatology 2011;223:119–21.