Colchicine and Leukopenia: Clinical Implications

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Colchicine is the mainstay of treatment for familial Mediterranean fever. We investigated the frequency of leukopenia in 213 patients with familial Mediterranean fever treated with standard doses of colchicine (0.5-2.0 mg/day). We found that 23 patients (10.8%) had reversible leukopenia, 3 moderate, and none severe and that their rate of infections was not increased. *(J Pediatr 2020;224:166-70).*

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease and is caused by mutations in the *MEFV* gene encoding the pyrin protein.[1] Clinically, the disease is characterized by recurrent fever, accompanied by abdominal pain, chest pain, and/or arthritis with elevated acute phase reactants.[2] Colchicine has been the mainstay of treatment since 1972.[3] Colchicine decreases the frequency of attacks and prevents the most important complication of secondary amyloidosis.[4] The recommended starting dose is ≤0.5 mg/day for children <5 years of age, 0.5-1.0 mg/day for children between 5 and 10 years of age, and 1.0-1.5 mg/day for children >10 years of age and for adults.[5] Colchicine is a safe drug; however, it is associated with several adverse effects. Gastrointestinal adverse effects are more prominent in lower doses; in contrast, serious life-threatening adverse effects, such as bone marrow suppression, can be seen with toxic doses. Colchicine doses should be adjusted if there is renal dysfunction to avoid adverse effects and toxicity.

Colchicine has been also associated with leukopenia, even with lower doses. In this study, we aimed to investigate the frequency of leukopenia and its possible complications in patients with FMF treated with standard doses of colchicine.

Methods

We included 213 consecutive patients with FMF treated with colchicine for ≥6 months who were followed at the Hacettepe University Department of Pediatric Rheumatology between July 2018 and October 2018. Patients were diagnosed as FMF according to the Yalcinkaya-Ozen criteria,[6] and colchicine treatment was started with doses of 0.5 mg/day for children <5 years of age, 1 mg/day between 5 and 10 years, and 1.5mg /day for those >10 years. The maximal dose of colchicine was 2 mg/day. Patients were followed after 2 weeks of treatment for acute adverse effects of colchicine, at 3 months, and then every 6 months with laboratory workup including complete blood count, acute phase reactants, kidney and liver function tests, and urinalysis. If leukopenia was found, a complete blood count was repeated 1 week later. Colchicine doses were decreased in patients who had persistent leukopenia without another possible explanation (including infections, use of additional medications) and were referred to the pediatric hematology department for evaluation if leukopenia was still present after 1 week. Clinical characteristics (demographics, fever, abdominal pain, serositis, and erysipelas-like erythema at the time of diagnosis, attack frequency) and laboratory findings (hemoglobin, white blood cell count with differential, platelet count, serum vitamin B_{12} levels at the time of the lowest white blood cell count) during the course of the treatment were reviewed retrospectively from medical charts and electronic records of the patients. In patients with leukopenia, the time from treatment onset and time to full recovery were also recorded.

Systematic Review

We performed a review of the literature using PubMed, combining the main keywords "Colchicine AND leukopenia"; OR "Colchicine AND leucopenia". The searches were limited to articles in English. Randomized and nonrandomized controlled trials, observational studies (case-control, cohort studies, and case series), and single case reports involving the colchicine induced leukopenia cases were included. One author searched the literature and manually evaluated the titles and abstracts for relevance. Inconsistencies were resolved by discussion with 2 additional authors (**Figure 1**; available at www.jpeds.com).

Statistical Analyses

GraphPad 6.0 (Prism, San Diego, California) and SPSS 21.0 (SPSS Inc, Chicago, Illinois) were used for the statistical analysis. Proportions, medians, minimum, and maximum values were used where appropriate to present the descriptive analyses. For the multivariate analysis, relevant variables were entered into the logistic regression analysis to determine independent predictors of leukopenia.

FMF	Familial Mediterranean fever

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Results

Demographic, clinical, and laboratory features of the patients are summarized in Table I.

Two hundred thirteen pediatric patients with FMF were included in the study group; 52.3% female. The mean age at disease onset and starting colchicine was 5.7 ± 4.1 years. The median follow-up duration was 70 months and ranged from 8 months to 16.9 years. At the time of diagnosis 175 patients (82.2%) had recurrent fever, 165 (77.5%) had abdominal pain, 89 (42%) had arthritis, and 17 (8%) had chest pain. Homozygote exon 10 mutations were the most common (Table II; available at www.jpeds.com). At the time of the presentation of FMF and start of colchicine, none of the patients had leukopenia.

Twenty-three patients (10.8%) had leukopenia during colchicine treatment. Other causes of leukopenia (including viral infections and other medications) were excluded. Among these 23 patients, 1 had moderate lymphopenia (500-1000/mm^3), 2 had moderate neutropenia (500-1000/mm^3), 7 had mild neutropenia (1000-1500/mm^3), 2 patients had both mild lymphopenia and neutropenia, and 11 had mild leukopenia. All of the patients with leukopenia were attack free and none had an elevation of inflammatory markers. The median interval between the onset of the treatment and the onset of leukopenia was 63 months (range, 3-179 months). At the time of the onset of leukopenia the median colchicine doses per weight were comparable in patients with and without leukopenia (0.026 vs 0.027 mg/kg/day $P = .96$) (Figure 2; available at www.jpeds.com). There were no other significant differences in terms of demographics, clinical features, mutation types, or colchicine formulations. There was no significant difference in the occurrence of gastrointestinal adverse effects and elevation of liver enzymes. Lymphocyte, neutrophil, and platelet counts were also lower in this group (Table I). The diagnostic workup for leukopenia examined the vitamin B_{12} level in 12 patients, and in 2 of them it was found to be low. Leukopenia did not improve after B_{12} replacement in these 2 patients; however, after adjustment of the colchicine dose, the lymphocyte counts normalized. In the multivariate analysis, we did not find any predictor significantly associated with leukopenia, including sex, age at the start of colchicine, daily colchicine dose per weight, clinical features at the time of diagnosis, or other complete blood count measures (Table III; available at www.jpeds.com).

Colchicine doses were decreased in patients with leukopenia (Figure 2). In all patients, leukopenia was transient and completely resolved in a median of 146.0 days (IQR, 70.5-192.0 days). Although there were no increase in the frequency of FMF attacks, the dosages of colchicine were slowly increased and all patients returned to their previous dose. Eleven patients (47.8%) with leukopenia had recurrent, transient episodes The rate of infections was not increased among the patients with leukopenia compared with the other patients.

Discussion

Leukopenia has previously been reported as a rare adverse effect of colchicine in case reports; however, the presented data assesses the frequency, severity, and outcome of leukopenia in a large cohort. Our results justify recommending checking

Table I. Clinical features of the patients with FMF

Features	Without leukopenia (n = 190)	With leukopenia (n = 23)	*P* value
Female sex	52%	52.2%	.99
Age at treatment onset (y)	5.63 ± 4.30	5.69 ± 3.75	.13
Colchicine dose (mg/kg/d)	0.027 (0.019-0.037)	0.026 (0.02-0.038)	.33
Clinical features at the time of diagnosis			
Fever	84%	70%	.14
Abdominal pain	77%	78%	.92
Chest pain	8%	4%	.5
Arthritis	40%	56%	.14
Mutations			
Exon 10/Exon 10	101 (53.1%)	15 (65.2%)	
Exon 10/Exon 2	10 (5.3%)	1 (4.3%)	
Exon 10/-	48 (25.2%)	6 (26.1%)	
Exon 2/Exon 2	4 (2.1%)	–	
Exon 2/-	10 (5.3%)	1 (4.3%)	
-/-	17 (8.9%)	–	
Laboratory findings			
Hemoglobin (g/dL)	12.6 ± 1.7	12.7 ± 1.4	.57
White blood cells* (× $10^3/mm^3$)	7167.7 ± 3093.7	3939.1 ± 625.0	<.0001
Lymphocytes* (× $10^3/mm^3$)	2264.9 ± 924.0	1760.9 ± 512.3	<.0001
Neutrophils* (× $10^3/mm^3$)	4172.3 ± 3074.8	1673.9 ± 574.6	<.0001
Platelets† (× $10^3/mm^3$)	282 399 ± 77 571	249 304 ± 42 568	.003

Values are mean ± SD, median (IQR), percent, or number (%).
Exon 10: M694V, M680I, V726A, A744S, K695R, and R761H.
Exon2: E148Q.
Colchicine doses were comparable in patients with or without leukopenia at the time of leukopenia onset. Adjusted doses were significantly lower.
*$P < .05$.
†$P < .01$.

Table IV. Systematic review of the literature on leukopenia related to colchicine therapy

Authors	Year	Age/sex	Diagnosis	Colchicine dose (mg/d)	Time between treatment onset and leukopenia	Time to recovery from leukopenia	Hematologic complications	Other medications	Concomitant diseases
Beggs et al[16]	2013	85, male	Pseudogout	0.6	2 mo	NA, continued colchicine with G-CSF and close follow-up	Leukopenia/ neutropenia	Acetaminophen 1000 mg Doxazosin 2 mg/d Polysaccharide–iron complex 150 mg/d Omeprazole 20 mg/d Testosterone enanthate 200 mg/month	Chronic lymphocytic leukemia Pseudogout Osteoarthritis Hypertension
Lee et al[12]	2008	58, female	Behcet disease	1.2	2 wk	35 d	Leukopenia, thrombocytopenia	Prednisolone Azathioprine	–
Lee et al[12]	2008	71, female	Behcet disease	1.2	3 d	18 d	Leukopenia, thrombocytopenia	Methotrexate	–
Dixon and Wall[15]	2001	68, male	Gout	1.2	7 d	3 d with G-CSF supplement	Leukopenia/ neutropenia	Metformin 2000 mg/d Glyburide 20 mg/d Verapamil 480 mg/d Warfarin 5 mg/d Theophylline 900 mg/d Potassium chloride 40 mEq/d Lisinopril 80 mg/d Digoxin 0.125 mg/d Metolazone 2.5 mg/d for 3 d/wk Aspirin 325 mg/d Lansoprazole 30 mg/d Ipratropium bromide oral inhaler 3 × 36 μg daily Triamcinolone oral inhaler 3 × 200 μg/d Fluticasone nasal spray 100 μg/d	Non-insulin-dependent diabetes mellitus Chronic obstructive pulmonary disease Supraventricular tachycardia Sleep apnea Peptic ulcer disease Anemia of chronic disease Cardiomyopathy
Finklestein et al[13]	1987	76, female	Primary biliary cirrhosis	1.2	2 mo	4 d	Leukopenia/ neutropenia	Hydrochlorothiazide/ amiloride	–
Ferrannini and Pentimone[14]	1984	69, male	Gout	8 mg intravenous followed by 2	3 mo	NA	Pancytopenia	–	–

G-CSF, granulocyte-colony stimulating factor *NA*, not available.

white blood cell counts periodically[7] and suggest that leukopenia is not associated with severe adverse effects. In our cohort, 10.8% of patients had leukopenia (87% mild, none severe) and there was not an increased rate of infections these patients.

Patients who developed leukopenia were treated with standard colchicine doses (median of 0.026 mg/kg/day). There were no significant differences between the patients who developed leukopenia and the rest of the cohort in terms of demographics, clinical features, type of mutations, or colchicine formulations. Similar to previous studies in the literature, homozygote exon 10 mutations were the most common in both groups (**Table II**).[7] The clinical features were also comparable between the 2 groups.[7] Although a recent report revealed an increased risk of pneumonia in adult patients treated with colchicine, there was no increased infection rate in our patients even in those with leukopenia.[8]

Colchicine interacts with tubulin monomers, induces a conformational change, and inhibits tubulin assembly which causes destabilization of the microtubules.[9] Neutrophils are the major cells in the pathogenesis of FMF and their effect on inflammation is based on their ability to migrate toward to the site of inflammation. Because this migration is sustained via microtubules, the interaction between colchicine and tubulin monomers blocks microtubule stabilization and prevents neutrophil migration and suppresses the inflammation.[10] Colchicine is usually a safe drug with few adverse effects such as gastrointestinal involvement (especially diarrhea); however, it has a very narrow therapeutic window.[11] Colchicine doses of >0.5 mg/kg/day are highly toxic and even lethal at >0.8 mg/kg/day. Overdose usually manifests with multiorgan failure, including bone marrow suppression and aplasia.[11] In contrast, there are a few case reports showing bone marrow suppression even with treatment with standard doses.[12-16]

There are several possible explanations of the mechanism of colchicine-induced leukopenia. It was suggested that colchicine may induce the destruction of circulating leukocytes and at the same time an inhibition of leukocyte production by a direct toxic effect. One other mechanism was attributed to decreased clearance with underlying hepatic or renal dysfunction, along with other drug interactions. In contrast, some reports emphasized that leukopenia may be associated with concomitant viral infections and may not be due to just colchicine treatment. Vitamin B_{12} malabsorption should also be considered, in cases of leukopenia.[17] However, Gemici et al did not observe significant decrease in the levels of vitamin B_{12} among adult patients with FMF treated with colchicine for ≥2 years.[18] In fact, in our study, vitamin B_{12} was low in only 2 of the 12 patients in whom vitamin B_{12} was checked. Leukopenia was reported as an accompanying finding during attacks of fever and abdominal pain, which resolved after colchicine treatment. The authors suggested that leukopenia may be due to continued inflammation resulting in removal of unwanted inflammatory cells as a result of increased apoptosis.[19] However, these explanations fail to explain fully the mechanism of leukopenia. Ozen et al showed that apoptosis of neutrophils is indeed increased during attacks of FMF, compared with both attack-free and control groups.[20] Thus, patients with FMF may present with leukopenia and/or neutropenia, either initially or during the follow-up of attacks. One other potential mechanism was explained by autophagia. In FMF, alterations in the inflammatory response and metabolic stress of the cells may induce inhibition of the mammalian target of rapamycin signaling pathway (this pathway was shown to protect cellular response under danger signals), which leads to activation of the autophagic process.[21] Autophagy in myeloid precursor cells has been shown to lead to neutropenia. In some cases, persistent leukopenia may be attributed to subclinical inflammation, which might be at a sufficient level to initiate leukocyte damage but not to induce symptoms. However, our patient cohort did not confirm this hypothesis because they were not experiencing attacks when they had leukopenia.

It is also noteworthy that nearly one-half of the patients with leukopenia had transient and intermittent episodes.

A limitation of the presented study is the lack of data for serum colchicine levels, because we lack reliable methods to measure colchicine levels. We cannot comment on whether dose lowering is indicated in all of these patients. Further studies may shed light on whether leukopenia is related directly to the disease, the treatment, or other pharmacogenomic factors.

In the systematic literature review, there were only 6 adult patients who had leukopenia while treated with standard doses of colchicine (**Table IV**). Three of these 6 patients had neutropenia, 2 had thrombocytopenia, and 1 had pancytopenia. All of them were transient values; however, granulocyte-colony stimulating factor supplementation was needed in 2 patients.[12-16] There are no data in the literature on children.

Colchicine caused leukopenia in 10.8% of the pediatric patients with FMF in our cohort. Only 3 patients had moderate cytopenia and none had severe leukopenia. All of the cases were fully reversible after dose adjustment and there were no clinical consequences. ■

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Table II. Mutation distribution of the patients with FMF

Mutations	Without leukopenia (n = 190)	With leukopenia (n = 23)
Exon10/Exon10	101 (53.1%)	15 (65.2%)
M694V/M694V	58	9
M680I/M680I	3	–
V726A/V726A	–	1
M694V/M680I	22	2
M694V/V726A	8	1
M680I/V726A	10	–
M694V/A744S	–	1
M694V/R761H	–	1
Exon 10/Exon 2	10 (5.3%)	1 (4.3%)
M694V/E148Q	8	1
M680I/E148Q	1	–
R761H/E148Q	1	–
Exon 10/-	48 (25.2%)	6 (26.1%)
M694V/-	33	2
V726A/-	10	2
M680I/-	4	1
R761H/-	1	–
K695R/-	–	1
Exon 2/Exon2	4 (2.1%)	–
E148Q/E148Q	4	–
Exon 2/-	10 (5.3%)	1 (4.3%)
E148Q/-	10	1
-/-	17 (8.9%)	–

Exon 10: M694V, M680I, V726A, A744S, K695R, R761H.
Exon 2: E148Q.

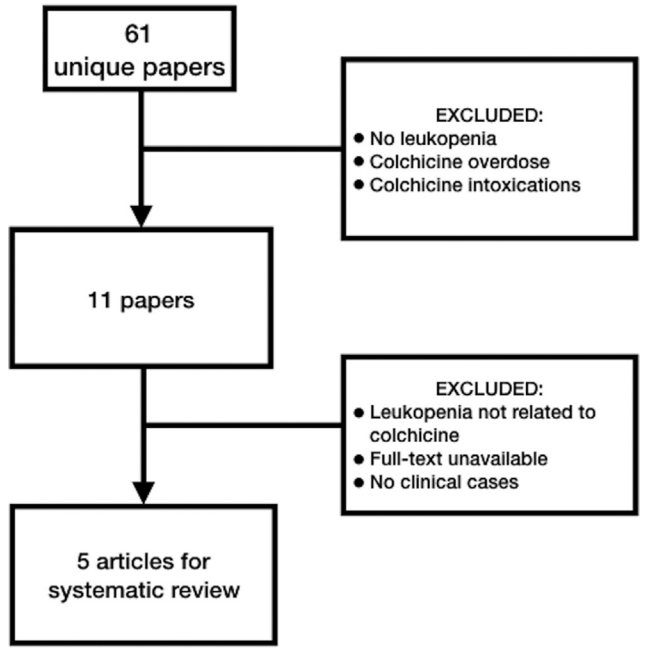

Figure 1. Flowchart of the systematic review.

Table III. Multivariate analysis to investigate the cause of leukopenia

Variables	Rate ratio (95% CI)	*P* value
Sex	0.81 (0.32-2.10)	.66
Age at colchicine onset	0.97 (0.85-1.08)	.53
Colchicine dose (mg/kg/d)	6.9 (0.00-104.2)	.92
Clinical features at the time of diagnosis		
Chest pain	3.1 (0.35-27.60)	.31
Abdominal pain	0.91 (0.29-2.89)	.87
Arthritis	0.61 (0.24-1.54)	.3
Fever	2.99 (0.98-8.91)	.05
Hemoglobin g/dL	0.95 (0.66-1.39)	.82
Platelets $\times 10^3/mm^3$	1.00 (1.00-1.00)	.05

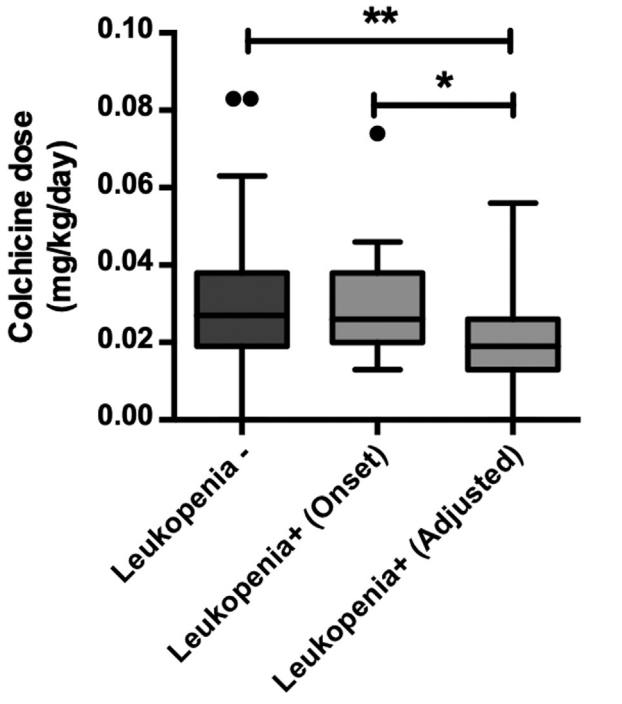

Figure 2. Colchicine doses in patients with FMF.