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Discontinuation of Colchicine Therapy in Children With Familial Mediterranean Fever

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ABSTRACT. ***Objective.*** Colchicine has been considered a lifelong therapy for familial Mediterranean fever (FMF). Recent studies describe patients who discontinued colchicine, but there is a lack of data pertaining to predictors of success. The aims of our study were to describe a cohort of pediatric patients with FMF who discontinued colchicine therapy, and to identify factors predicting successful termination of colchicine.

Methods. This study describes a cohort of pediatric patients with FMF who discontinued colchicine therapy following a relatively prolonged attack-free period (> 6 months), and identifies factors predicting successful termination. Data collected included demographic, clinical, and laboratory characteristics of children diagnosed with FMF aged < 16 years who underwent a trial of colchicine discontinuation. Data from patients who successfully ceased colchicine therapy were compared to those of patients who relapsed.

Results. Of 571 patients with FMF, 59 (10.3%) discontinued colchicine therapy. The average attack-free period before enrollment was 0.97 ± 1.4 years. Follow-up after ceasing colchicine was 5.0 ± 3.05 years, during which time 11 (20%) patients had an attack. The most common symptoms were fever (100%) and abdominal pain (80%). For those failing discontinuation, colchicine was restarted within 1.3 years (range 0.3–5.0, median 0.7 yrs). A longer attack-free period prior to colchicine discontinuation predicted success. Myalgia and arthritis prior to colchicine cessation were more common among children who required renewal of colchicine.

Conclusion. Cessation of colchicine therapy should be considered following prolonged remission in a select group of patients. Patients with arthritis or myalgia are more likely to have an attack after ceasing colchicine therapy.

Key Indexing Terms: FMF, colchicine, *MEFV* gene, treatment

Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease globally and frequently occurs among persons of Mediterranean origin, including Sephardic Jews, Turks, Armenians, and Arabs. FMF is characterized by recurrent self-limited attacks of fever and painful polyserositis such as peritonitis, pleuritis, and arthritis, as well as myalgia- and erysipelas-like episodes.[1,2] Mutations in the *MEFV* (Mediterranean fever) gene encoding for pyrin or marenostrin were shown to be the genetic cause of this disease.[3] Despite progress in understanding the pathophysiology and treatment of FMF, the diagnosis is still based on clinical criteria. In endemic areas, it is often difficult to diagnose in children due to the prevalence of recurrent infections or atypical FMF attacks.[4]

Colchicine is the main form of treatment for patients with FMF.[5] Response to colchicine is considered one of the diagnostic criteria of FMF. Colchicine decreases attack frequency and severity while preventing the development of amyloidosis.[6] Although colchicine is a relatively safe drug, there are specific side effects as well as a risk of overdose.[7] Further, lifelong daily use of colchicine is a social and economic burden for patients and their families.

It has been reported that some patients with FMF were able to stop colchicine without subsequent FMF attacks. However, there are no data regarding predictors of success associated with discontinuation of colchicine.[8] The aims of our study were to describe a cohort of pediatric patients with FMF who discontinued colchicine therapy following a relatively prolonged attack-free period, and to identify factors predicting successful termination.

METHODS

Study population. The pediatric rheumatology and FMF clinics at Hadassah-Hebrew University and Rambam Health Care Campus serve as tertiary

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The authors declare no conflicts of interest relevant to this article.

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referral centers for the diagnosis and treatment of children suspected of having FMF. During the study period (2008–2018), 571 patients diagnosed with FMF prior to the age of 16 years and followed in our clinics were included. The study was approved by each hospital's local institutional review board (Rambam Helsinki committee approval [0164-18 RMB] and Hadassah Medical Organization Helsinki committee approval [0193-18 HMO]).

We conducted a retrospective study using chart review to collect data from clinical visits. Children included in this study were those with a diagnosis based on the clinical Tel Hashomer criteria.[9] Clinical manifestations, demographic data, family history, laboratory studies, and genetic analysis of *MEFV* mutations were obtained during the first visit. As part of standard history taking, the families were queried regarding a family history of amyloidosis. At subsequent visits, clinical and laboratory variables were evaluated. Follow-up visits were scheduled at 3- to 12-month intervals, depending on clinical status. During each visit, the patient's response to colchicine therapy was assessed by self-reporting of typical FMF attacks since the last visit; reports of primary physicians and hospitals emergency departments; and laboratory signs of inflammation, if relevant, such as elevated erythrocyte sedimentation rate and C-reactive protein. Adherence to medication schedules was assessed by reviewing the charts, checking prescription refills, and checking primary physician correspondence. Genetic data for many of the patients were obtained by Sanger sequencing for the 9 most common *MEFV* variants (M694V, M694I, M680I, K695R, R761H, A744S, P369S, V726A, and E148Q).

In our clinics, colchicine therapy is started in all children who have a diagnosis of FMF according to the Tel Hashomer criteria.[9] Whether colchicine discontinuation was physician- or patient-initiated with subsequent physician approval, it was based on a combination of factors including no family history of amyloidosis, absence of FMF attacks for ≥ 6 months, absence of 2 mutations in the *MEFV* gene associated with severe phenotype, normal levels of acute-phase reactants in between attacks, and absence of proteinuria. Colchicine was restarted if an attack occurred as diagnosed by 1 of 2 experienced rheumatologists (YB or YBA). Because of the retrospective nature of the study, exertional and resting myalgia were considered in the same category. Patients noncompliant with follow-up were excluded from the study. The outcomes of children diagnosed with FMF who successfully ceased colchicine therapy were analyzed and compared to those of patients who relapsed, as determined by recurrence of FMF attacks.

Statistical analysis. All statistical analyses were performed using SPSS statistical package software (SPSS Inc.). Data are expressed as median, mean ± SD, or percentages. To measure differences between groups, chi-square test, Mann-Whitney *U* test, and *t* test were used. A P value < 0.05 was accepted as statistically significant.

Multivariate logistic regression model was conducted to find the dependent variables associated with successful termination of colchicine. Variable selection was based on (1) the level of significance in the univariate analysis, and (2) the number of observed variables for which there were data on > 5 patients. Myalgia or arthritis were not included in the multivariate analysis due to the small number of cases.

RESULTS

Of the 571 patients with FMF, 59 (10.3%) discontinued colchicine therapy. Four children were excluded from the study due to poor follow-up. The demographic and clinical data of 55 patients (mean age 12.9 ± 3.8 yrs, M:F 1.04) in the study cohort are listed in Table 1. The most common clinical features at the time of FMF diagnosis were attacks of fever and abdominal pain. All patients fulfilled the Tel Hashomer criteria for FMF[9] and 85.4% of them fulfilled the new Eurofever classification criteria for FMF.[10] The mean time from diagnosis of FMF to colchicine discontinuation was 3.5 ± 2.5 years.

Table 1. Demographic data and course of 55 patients with FMF who ceased colchicine therapy.

	Mean ± SD or n
Age at last visit, yrs	14.2 ± 3.9
Age at diagnosis, yrs	6.5 ± 3.4
Sex ratio, M:F	28:27
Sephardic Jewish:Arab	42:13
Attack rate per month	1.2 ± 0.68
Duration of colchicine therapy prior to cessation, yrs	3.4 ± 2.65
Time from last attack to colchicine discontinuation, yrs (range)	1.38 ± 0.98 (0.5–4)

FMF: familial Mediterranean fever.

The majority of patients (n = 36, 65.5%) presented with a single mutation in the *MEFV* gene (Table 2). Five (9.1%) children had 2 mutations, and in 14 (25.4%) no mutations were detected. For those with mutations in the *MEFV* gene, M694V was found in 23 patients, E148Q in 12, and V726A in 8. Of patients with 2 mutations, 3 had E148Q on 1 allele (2 patients with E148Q/V726A and 1 with E148Q/M694V), and 2 patients were homozygote for V726A.

Characteristics of patients who successfully discontinued colchicine therapy, as compared to those who failed, are shown in Table 2. Of the 55 patients who stopped colchicine therapy after an average follow-up of 5 ± 3.05 years, 11 (20%) needed to renew colchicine due to recurrence of symptoms (1 patient with E148Q/M694V variants, 4 patients with M694V, 3 with V726A, and 2 with no mutations). The average time to renewal of colchicine therapy was 1.3 (range 0.32–5; median 0.74) years. There were no differences in either sex or age between the 2 groups.

For those who failed colchicine cessation, there was a significantly higher rate of musculoskeletal (MSK) manifestations (myalgia and arthritis) at the initial visit and during follow-up. The duration between the last attack and cessation of colchicine was shorter in children who had to resume colchicine therapy. The most common symptoms on renewal of therapy were fever, followed by abdominal pain, arthritis, and pleuritic pain (Table 2).

A stepwise, multiple regression analysis was performed using age, sex, and the duration between the last attack and cessation of colchicine. The only factor found to be significant was the duration between last attack and time of cessation of colchicine therapy ($P = 0.04$; OR 4.97, 95% CI 1.10–22.35). There were no differences in response whether a pediatric rheumatologist or a community pediatrician initiated colchicine therapy (Table 2).

DISCUSSION

In the past, colchicine treatment after a diagnosis of FMF was considered lifelong. It was reported previously that some adult FMF patients with lower disease severity and mostly abdominal manifestations had prolonged (> 3 yrs) remission after colchicine discontinuation.[11] In the last few years, there have been reports of successful discontinuation of colchicine in children

Table 2. Characteristics of patients with failed and successful colchicine discontinuation.

	Patients, n (%)	Colchicine Discontinuation		*P**
		Failed, n = 11	Successful, n = 44	
Age at discontinuation, yrs		12.6 ± 3.7	13.3 ± 3.9	0.59
Sex, M:F		5:6	23:21	
Fever	55 (100)	11 (100)	44 (100)	> 0.99
Abdominal pain	44 (80)	9 (82)	35 (79.5)	> 0.99
Myalgia	7 (12.7)	4 (36)	3 (7)	**0.02**
Pleuritis	3 (5.4)	1 (9)	2 (4.5)	
Arthralgia	9 (16.4)	2 (18)	7 (16)	> 0.99
Arthritis	5 (11)	4 (36)	1 (2)	**0.004**
Time from last attack to discontinuation, yrs, median (range)		0.77 (0.5–2.6)	1.5 (0.5–4.00)	**0.03**
Rheumatologist-initiated therapy, n/N (%)		10/13 (77)	27/36 (75)	> 0.99
M694v/-		4 (36)[a]	18 (41)[a]	> 0.99
E148Q		3 (27)[a]	6 (14)[a]	> 0.99
Mutations				
None		2 (18)	12 (27)	0.26
1		8 (73)	28 (64)	
2		1 (9)[b]	4 (9)[c]	

Values in bold are statistically significant. * *P* value was only reported when n ≥ 5. [a] Percentage of children with genetic diagnosis. [b] E148Q + M694V variants. [c] 2 patients with V726A + E148, and 2 with homozygote for V726A.

with FMF who were heterozygous for mutations in the *MEFV* gene.[8] In our study, colchicine was discontinued in a significant number of patients (10.3%) following a prolonged attack-free period.

The distribution of mutations in our patients who qualified for discontinuation of colchicine was different than that of mutations in the overall population of patients with FMF (approximately 60–70% with 2 *MEFV* gene mutations, 25–35% with 1 mutation, and 5% without an identified mutation).[8] In our cohort, 90.9% of patients who discontinued colchicine had either 1 or no identified mutations in the *MEFV* gene.

The study results are encouraging as they indicate that colchicine discontinuation was successful in a majority of targeted low-risk patients with prolonged attack-free periods. As colchicine is the sole drug capable of preventing secondary amyloidosis and late-onset amyloidosis may occur at any time, it is important to maintain close follow-up of all patients who had colchicine discontinuation. Candidates for discontinuation should be patients who are at very low risk for developing amyloidosis and have an attack-free period of at least 6 months, absence of 2 mutations in the *MEFV* gene associated with severe phenotype, normal levels of acute-phase reactants, no family history of amyloidosis, and no proteinuria. Our finding that a longer attack-free period was associated with greater success of ceasing colchicine therapy suggests that longer observation periods may be warranted in specific patients.

In our series, 12 patients carried the E148Q allele, 3 carried the E148Q variants as part of a complex allele, and 9 as a single allele. E148Q variant, one of the 5 most frequent *MEFV* mutations, is recognized to have a mild effect on patients with FMF[12,13] and amyloidosis is rarely reported in those patients. However, when E148Q is part of complex allele, it has been suggested that it may have an aggravating effect. In our series, the diagnosis of FMF was based on established criteria of FMF,[9] suggesting that those patients with the E148Q variant had symptoms consistent with the diagnosis of FMF. Interestingly, these patients had symptoms consistent with the mild phenotype, and 3/12 (25%) patients (1 with complex allele and 2 as a single allele) had recurrence of symptoms after stopping colchicine, which was similar to the rest of the group.

What is notable about the cohort is a paucity of MSK manifestations. For those with MSK manifestations (i.e., arthritis, arthralgia, myalgia) either at the time of diagnosis or during clinical follow-up, the rate of relapse of FMF attacks was greater, suggesting that MSK manifestations are a negative predictor of success. The clinical challenge is deciding whether colchicine discontinuation should be attempted in FMF patients with MSK manifestations, as it is known that patients with arthritis have more severe disease.[14]

Other groups have reported successful discontinuation of colchicine therapy. Hentgen, *et al* followed a small cohort of heterozygous pediatric patients with FMF who had relatively mild disease.[15] At puberty, a significant number of heterozygotes (5/18, 27.8%) had a relative remission, which allowed for successful discontinuation of colchicine during this period.[15]

In a study of Turkish patients with heterozygous FMF, 22/146 children were successfully weaned from colchicine following a prolonged attack- and inflammation-free period (mean 27, range 24–84 months). During follow-up over an average of 22.5 (range 6–102) months, 2/22 (9%) patients had colchicine restarted due

to disease relapse.[12] More recently, a larger study was published that evaluated 64 children with FMF from Turkey who stopped colchicine therapy following an attack-free period of 18.2 (range 6–148) months. In that series, 17 (26.6%) patients needed to renew colchicine therapy, similar to our findings of 20%. Patients who did not need to restart colchicine were older at the time of discontinuation and had received colchicine for a longer duration.[16]

Recently, the European League Against Rheumatism (European Alliance of Associations for Rheumatology) published recommendations for the management of FMF.[17] In their position paper, FMF experts suggested that colchicine dose reduction may be considered for those patients who are attack-free for more than 5 years and do not have elevated acute-phase reactants. For children, it may be possible to stop colchicine therapy at an even earlier stage, as suggested by our study.

There are several limitations to our study. The sample size was not sufficiently large to enable us to better characterize those patients most likely to succeed in a discontinuation trial. The study was retrospective, and for approximately 25% of patients, the primary care physician initiated colchicine treatment before consulting a pediatric rheumatologist (Table 2). Although we were unable to show differences between patients diagnosed by a rheumatologist or a primary care physician, there is a possibility that some of the patients who successfully discontinued colchicine therapy were incorrectly diagnosed.

There is also the challenge in diagnosing young children with FMF, especially in endemic areas. Due to the frequency of viral infections, recurrent fever is not a rare symptom among young children, in addition to periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA), all of which have overlapping symptoms with FMF and have been shown to be more common among the Mediterranean population.[18,19] Moreover, fever may be the only early manifestation of FMF in young children.[19] Typical serositis may not appear for many years after the initial febrile manifestation.[19] These factors can lead to the misdiagnosis or overdiagnosis of FMF and could affect our findings.

In our study, we utilized the Tel Hashomer criteria, which are based on clinical and laboratory factors for the diagnosis of FMF. These criteria serve as the basis for initiating therapy and were utilized at our center prior to the publication of newer Eurofever/Paediatric Rheumatology International Trials Organisation classification criteria in patients with FMF. It is possible that based on the new criteria, which have better sensitivity but lower specificity,[20] some of our patients (heterozygotes) would not have received a diagnosis of FMF. We believe that with regard to initiating and discontinuing colchicine therapy, the Tel Hashomer criteria are more appropriate. In the future, when initiation of colchicine therapy is based solely on Eurofever criteria, then the issue of discontinuation will have to be reevaluated.

In conclusion, cessation of colchicine therapy following prolonged remission in a select group of patients should be considered. An important clinical issue is when to discontinue colchicine and for which patients. Larger prospective studies are needed to confirm our findings and provide more information as to which patients with FMF are likely to successfully discontinue colchicine therapy.

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