Arthritis Research & Therapy

CORRESPONDENCE

Open Access

The needed daily dose of colchicine in patients with Familial Mediterranean Fever may be higher in women: a study on behalf of the JIR cohort

Ilenia Di Cola[1,2], Alessandra Bartoli[1], Léa Savey[1,3,12], Fatima Bensalek[1], Marion Delplanque[1,3,4,12], Rim Bourguiba[1], Zohra Aknouche[1,12], Isabelle Kone-Paut[3,5,12], Linda Rossi-Semerano[3,5,12], Isabelle Melki[6,7], Brigitte Bader-Meunier[3,7,8], Bénédicte Neven[3,7,8], Pierre Quartier[3,7,8], Guilaine Boursier[9,12], Laurence Cuisset[10], Gilles Grateau[1], Véronique Hentgen[11,12] and Sophie Georgin-Lavialle[1,3,4,12*]

Abstract

Background At present, there are no data on the relationship between colchicine dose and weight in patients with Familial Mediterranean Fever (FMF). We aimed at describing the daily colchicine dose in a cohort of FMF patients.

Methods From 2016 to 2023, a retrospective evaluation of prospectively followed homozygous FMF patients at the French National Reference Centre was performed.

Results and conclusions Out of 272 patients, 149 were women (57.8%), with a mean age of 43 years old. The mean weight was 67.8 kg and body mass index 24,2 kg/m^2. Colchicine was taken by 96% of patients. A subgroup of 30 patients received 2.5 mg/day: they were mostly women ($n=23$; 76.7%; $p=0.018$), with a lower mean weight ($p=0.019$); indeed, 26/30 (87%) weighed < 50 kg. Female sex correlated with higher values of daily colchicine dose ($p=0.0208$); weight was not associated with colchicine dose ($p=0.4073$). No toxicity has been noted in patients treated with 2.5 mg/day, including patients weighing < 50 kg, and most of these patients were women. We may speculate that the clinical picture of female patients requiring an increased dose of colchicine may be related to the hormonal background, with a possible exaggeration of pyrin activation. This is the first study to examine the question of colchicine dosage in relation to weight of FMF adult patients and to highlight a possible link with female gender. We advise clinicians to explain that colchicine treatment may be used daily up to 2.5 mg without toxicity.

Keywords Familial Mediterranean Fever, Colchicine, Posology, Weight, Female sex

*Correspondence:
Sophie Georgin-Lavialle
sophie.georgin-lavialle@aphp.fr

Full list of author information is available at the end of the article

Dear Editor,

Familial Mediterranean Fever (FMF) is the most common autoinflammatory monogenic disease worldwide; it is associated with mutations in *MEFV* (MEditerranean FeVer) gene [1]. Colchicine is the gold standard treatment to prevent attacks of the disease and inflammatory amyloidosis (AA) that is its most severe complication [2–6]. There are no available data on the relationship between colchicine dose and weight in patients with FMF, although it is a frequently asked question by patients. Thus, we aimed to describe the daily colchicine dose in a cohort of patients with FMF confirmed by two pathogenic *MEFV* mutations. In addition, we described the clinical features of patients who take the maximum daily colchicine dose (2.5 mg/day) in order to determine their weight and body mass index (BMI). In fact, patients under 50 kg are often reluctant to take such a daily dose of colchicine in clinical practice, and pharmacists may be scared to dispense it. From January 2016 to June 2023, we performed a retrospective evaluation of FMF patients followed at the French national FMF reference centre to analyse their prescribed daily colchicine dose and its association with clinical and laboratory features. Only patients with a confirmatory genotype (presence of 2 pathogenic or likely pathogenic variants in *MEFV* exon 10) and fulfilling Livneh's criteria for FMF [7] were included in the study. All patients consented to anonymous collection of their medical data via the JIR cohort.

Out of 272 patients, 149 were women (57.8%); the median age at inclusion was 39.0 years [min17.0- max 84.0]. The median age at onset of symptoms was 4 years old and at diagnosis 9 [min 1-max 56] years. The homozygous M694V (p.(Met694Val)) pathogenic variant was present in 82.70% of patients. Colchicine was taken by almost all patients (96.0%): patients not treated with colchicine were either those receiving biotherapies because they did not tolerate colchicine or those included at the time of diagnosis. Fifty patients (18.40%) were receiving biological disease-modifying antirheumatic drugs, mainly interleukin-1 inhibitors: anakinra (50%), canakinumab (35.7%) or anti-TNF (11.9%). AA amyloidosis complicated FMF in 4.2% of cases.

At the time of inclusion, patients had a mean weight of 67.78 (± 14.78) kg [min 37–max 109], and a BMI of 24.17 (± 4.63). Median serum creatinine was 64 mmol/L [min 34.0-max 721.0]. Median C-reactive protein (CRP) was 6.4 mg/L [min 0.25-max 250], and median serum amyloid A (SAA) was 7 mg/L [min 3–max 388].

Thirty patients (11.0%) were treated with a daily colchicine dose of 2.5 mg; 90% of them displayed a homozygous M694V (p.(Met694Val)) pathogenic *MEFV* variant. These patients treated with higher daily doses of colchicine are either those who had disease flare-ups with lower dosages or those who have high levels of inflammatory markers between flare-ups of the disease. Of these, 23 (76.67%) were women with a mean age of 36.57 [19–67] years. The mean weight was 61.74 [41–89], with a BMI of 22.83 (± 4.12) kg/m^2. By comparing these patients with others, we found that patients treated with 2.5 mg/day were mostly women ($p = 0.018$), with a lower mean weight ($p = 0.019$). In this context, 26 patients (86.67% of that subgroup) weighed less than 50 kg. We did not find any differences in the dose of colchicine between patients treated with or without biologics therapies ($p = 0.804$) (Table 1). However, only 6 patients in the colchicine 2.5 mg/day group received biotherapy (anti-IL1; $n = 5$ and anti-TNF; $n = 1$ for spondyloarthritis), and none of them had renal insufficiency. Treatment with IL-1 inhibitors had just started when we collected data, and patients were reluctant to reduce colchicine until they were sure that the biotherapy was working, reason why the daily posology was not reduced at that time.

In addition, female sex correlated with higher values of daily colchicine dose (β = 0.18, [0.03; 0.33], $p = 0.0208$). Amyloidosis (β=-0.74, [-1.09; -0.38], $p < 0.0001$) and age (β=-0.01, [-0.01; -0.0], $p = 0.0009$) were associated with lower values of daily colchicine dose. Weight (β = 0.0, [-0.01; 0.0], $p = 0.4073$) was not associated with colchicine dose. Furthermore, we built four multivariate regression models to evaluate the clinical risk profile of patients treated with a daily colchicine dose of 2.5 mg. In three of these models, female sex was significantly and independently associated with a daily colchicine dose of 2.5 mg (Supplementary Table 1).

No toxicity, in particular gastrointestinal symptoms or hematological abnormalities, has been noted in patients treated with 2.5 mg of colchicine, including patients weighing less than 50 kg. Most of these patients treated with high daily colchicine dose were women. This sex difference may be because women require a higher dose of colchicine due to a more severe phenotype. Indeed, a recent study described an unconventional activation of pyrin, caused by endogenous steroid catabolites (pregnanolone and etiocholanolone) [8]. In this context, it is possible to suggest that disease flare-ups occurring during menstrual cycle may be associated with the peak of progesterone catabolism. For this reason, FMF attacks can worsen during menstrual cycle in women.

Overall, we may speculate that in our cohort the clinical picture of female patients who require an increased daily dose of colchicine may be related to the hormonal background of these women, with a possible exaggeration of pyrin activation. It is noteworthy that treatment adherence is unknown and there may be a disparity between the dosage advised and that taken by the patient, as it often happens in chronic conditions.

In conclusion, to the best of our knowledge, this is the first study to examine the question of colchicine dosage

Table 1 Comparison between patients treated with a daily colchicine dose of 2.5 mg and others

Variable	Daily colchicine dose < 2.5	Daily colchicine dose = 2.5	p-Value
	***N* = 242**	***N* = 30**	
Sex			**0.018**
M	116 (47.93%)	7 (23.33%)	
W	126 (52.07%)	23 (76.67%)	
	N = 242%	*N* = 30	
M694V/M694V pathogenic variant	198 (81.82%) *N* = 242	27 (90.00%) *N* = 30	0.735
Age, years	41.96 (± 16.75)	36.57 (± 12.84)	0.139
	Range: (17.0; 84.0)	Range: (19.0; 67.0)	
	N = 242	*N* = 30	
BMI, kg/m2	24.34 (± 4.67)	22.83 (± 4.12)	0.076
	Range: (15.2; 44.9)	Range: (16.4; 31.4)	
	N = 234	*N* = 29	
Age at diagnosis, years	13.92 (± 12.46)	10.67 (± 10.56)	0.084
	Range: (1.0; 56.0)	Range: (1.0; 40.0)	
	N = 230	*N* = 29	
Biotherapy			0.804
Yes	44 (18.18%)	6 (20.0%)	
No	198 (81.82%)	24 (80.0%)	
	N = 242	*N* = 30	
Weight, kg	68.52 (± 14.92)	61.74 (± 12.27)	**0.019**
	Range: (37.0; 109.0)	Range: (41.0; 89.0)	
	N = 238	*N* = 29	
Creatinine, µmol/L	73.06 (± 52.82)	54.21 (± 11.28)	**<0.001**
	Range: (35.0; 721.0)	Range: (34.0; 82.0)	
	N = 227	*N* = 28	
Amyloidosis			0.614
Yes	11 (4.72%)	0 (0.0%)	
No	222 (95.28%)	28 (100.0%)	
	N = 233	*N* = 28	

Abbreviations: N: number of patients; W: women; M: men; BMI: body mass index; *P* <0.05 was considered statistically significant

in relation to weight of FMF adult patients and to highlight a possible link with female sex. We wish to highlight the importance of discussion with patients, and their parents, in the case of young patients. We advise clinicians to explain that colchicine treatment may be used daily up to 2.5 mg without toxicity, if renal function is normal and no drug interactions are present. This information should also be shared with pharmacists, who might occasionally advise against a prolonged use of colchicine at high dosage in FMF patients.

Abbreviations

FMF	Familial Mediterranean Fever
MEFV	MEditerranean FeVer
AA	Inflammatory amyloidosis
BMI	Body mass index
SAA	Serum amyloid A
CRP	C-reactive protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-024-03440-4.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
SGL designed the study SGL and IDC wrote the manuscriptIDC performed statistical analysis and collected dataLS, MD, VH, GG included, followed patients and edited the manuscriptLC, GB, sequenced MEFV exon 10AB, ZA, FB, RB: collected dataIKP; LR, IM, BBM, BN, PQ: recruited patientsAll authors approved the manuscript.

Funding
No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethical approval

and patient consent: this study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol and written informed consent has been obtained from the subjects. After collection of patient informed consents, we extracted data from the Juvenile Inflammatory Rheumatism (JIR) cohort, an international multicentric data repository authorized by the National Commission on Informatics and Liberties (CNIL, authorization number 914677).

Consent for publication

not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Internal Medicine Department, Tenon Hospital, AP-HP, Paris, France
[2]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[3]ERN RITA European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network, Utrecht, Netherlands
[4]Sorbonne University, Paris, France
[5]Pediatric Rheumatology Department, Kremlin Bicêtre Hospital, AP-HP, Le Kremlin Bicêtre, France
[6]Pediatric Department, Trousseau Hospital, AP-HP, Paris, France
[7]Centre de référence national maladies rares pour les rhumatismes inflammatoires et les maladies auto-immunes systémiques de l'enfant (RAISE), Paris 75015, France
[8]Pediatric Rheumatology Department, Necker Hospital, AP-HP, Paris, France
[9]Department of Molecular Genetics and Cytogenomics, Rare and Auto Inflammatory Diseases Unit, CHU Montpellier, University of Montpellier, Montpellier, France
[10]Genetic Department, Cochin Hospital, AP-HP, Paris, France
[11]Pediatric Department, Versailles Hospital, Le Chesnay, France
[12]French National Reference Center for Autoinflammatory Diseases (CEREMAIA), Paris, France

Received: 12 September 2024 / Accepted: 22 November 2024
Published online: 19 March 2025

References

1. Savey L, Grateau G, Georgin-Lavialle S. [Familial Mediterranean fever in 2020]. Nephrol Ther. 2021;17S:S119–25. https://doi.org/10.1016/j.nephro.2020.02.013.
2. Lancieri M, Bustaffa M, Palmeri S, Prigione I, Penco F, Papa R, et al. An update on familial Mediterranean Fever. Int J Mol Sci. 2023;24. https://doi.org/10.3390/ijms24119584.
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. https://doi.org/10.1136/annrheumdis-2015-208690.
4. 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;314:1001–5. https://doi.org/10.1056/NEJM198604173141601.
5. Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med. 1972;287:1302. https://doi.org/10.1056/NEJM197212212872514.
6. 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. https://doi.org/10.1056/NEJM197410312911804.
7. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40:1879–85. https://doi.org/10.1002/art.1780401023.
8. Magnotti F, Chirita D, Dalmon S, Martin A, Bronnec P, Sousa J, et al. Steroid hormone catabolites activate the pyrin inflammasome through a non-canonical mechanism. Cell Rep. 2022;41:111472. https://doi.org/10.1016/j.celrep.2022.111472.

Publisher's note