Clinical Communications

Persistence of disease flares is associated with an inadequate colchicine dose in familial Mediterranean fever: a national multi center longitudinal study

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Clinical Implications

- In real life, almost 30% of patients with familial Mediterranean fever display a persistent disease activity not fulfilling the definition of colchicine resistance, but impacting their quality of life. In most of them, colchicine is underdosed and maximum recommended dose is rarely used.

Familial Mediterranean fever (FMF) is characterized by self-limited episodes of fever and polyserositis.[1] *MEFV* gene encodes for a protein named Pyrin, which plays a pivotal role in the activation and secretion of IL-1.[2] Daily colchicine is highly effective in preventing attacks in this disorder in a dose-related fashion.[3] Many definitions of colchicine resistance are available in the literature. The European League Against Rheumatism (EULAR) guidelines defined resistance as one or more attacks per month in compliant patients who had been receiving the maximally tolerated dose for at least 6 months.[4] A similar definition was confirmed by a recent consensus among experts.[5] In the present national multicentric longitudinal study, we analyze the impact of colchicine treatment on disease activity and quality of life in real life in pediatric and adult patients with FMF.

Twenty centers enrolled their patients in the longitudinal version of the Eurofever registry.[6] Response to treatment was defined as *complete* (absence of clinical manifestations and normal laboratory parameters), or *incomplete* (persistence of fever episodes and/or some elevation of acute phase reactants). *Incomplete responders* were further classified as: (1) *resistant* (≥1 episode/month),[4,5] (2) *partial responders* (<1 episode/month), and (3) *partial responders with unknown frequency* (ie, patients presenting episodes without information on their frequency). Starting and maximum doses of colchicine were considered according to EULAR recommendations.[4,5] A specific questionnaire on compliance (adapted from Ben-Chetrit and Aamar[7]) and some aspects of the quality of life (limitations in daily activity, chronic fatigue or pain, and loss of school/workdays) were also collected (see this article's Online Repository at www.jaci-inpractice.org), as recently indicated as basic information for the evaluation of the response to colchicine in FMF.[5] In January 2020, complete baseline information was available for 341 Italian patients with FMF in the registry: 262 patients had at least 1 longitudinal follow-up visit and were eligible for the study; 221 (125 children, 91.2%; 96 adults, 96.9%) were treated exclusively with colchicine, with a median follow-up of 3.7 years (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). At the last follow-up visit, 122 (55.2%) displayed a *complete response*, 17 (7.7%) were classified as *resistant* (≥1 episode/month), 65 (29.4%) as *incomplete responders* (<1 episode/month), and 17 (7.7%) as *incomplete responders with unknown frequency*. The pattern of response to colchicine according to the different age groups is reported in Figure 1. Among patients (65) with an *incomplete response* (<1 episode/month), 37 (59%) displayed 1 to 3 episodes/year (26.2%, 1 episode/year; 20%, 2 episodes; 15.4%, 3 episodes), 15 (21%) displayed 4 to 5 episodes/year (10.7%, 4 episodes; 7.7%, 5 episodes), and 13 (20%) displayed ≥6 episodes/year (13.9%, 6 episodes; 1.5%, 7 episodes; 4.6%, 8 episodes). Overall, patients with *incomplete response* displayed a mean reduction of 10 fever episodes/year (range, 0-18) in respect to the precolchicine observation.

In Table I, median colchicine dose in different age groups, expressed as daily dosage and mg/kg/day, is reported in accordance with response to treatment. Overall, 54 patients with residual disease activity (24.4% of the whole population) were still on their colchicine starting dose, especially in the pediatric subgroup (19 of 48 children with residual disease activity, 39.5%). Among these patients, the presence of side effects possibly related to colchicine was reported in 4 patients only (diarrhea 2 patients, vomiting 1 patient, myalgia 1 patient). None of the patients treated with colchicine reached the maximal recommended colchicine dose (1-3 mg/day according to the age group)[5,6] (Table I). Data on compliance and quality of life were available for 174 patients. One hundred forty-five (83.3%) declared an optimal compliance (compliant to >90% of prescriptions), 20 (11.5%) a good compliance (between 50% and 90% of prescriptions), 3 (1.7%) a poor compliance (<50% of prescriptions), and 6 (3.5%) patients were noncompliant at all. An optimal compliance was observed in 88% of patients with complete response, 76% of incomplete responders, and 73% of resistant patients. Overall, 58 (33.3%) patients reported a limitation in at least 1 item related to the quality of life (limitation of daily activity, presence of chronic pain or fatigue, loss of days of

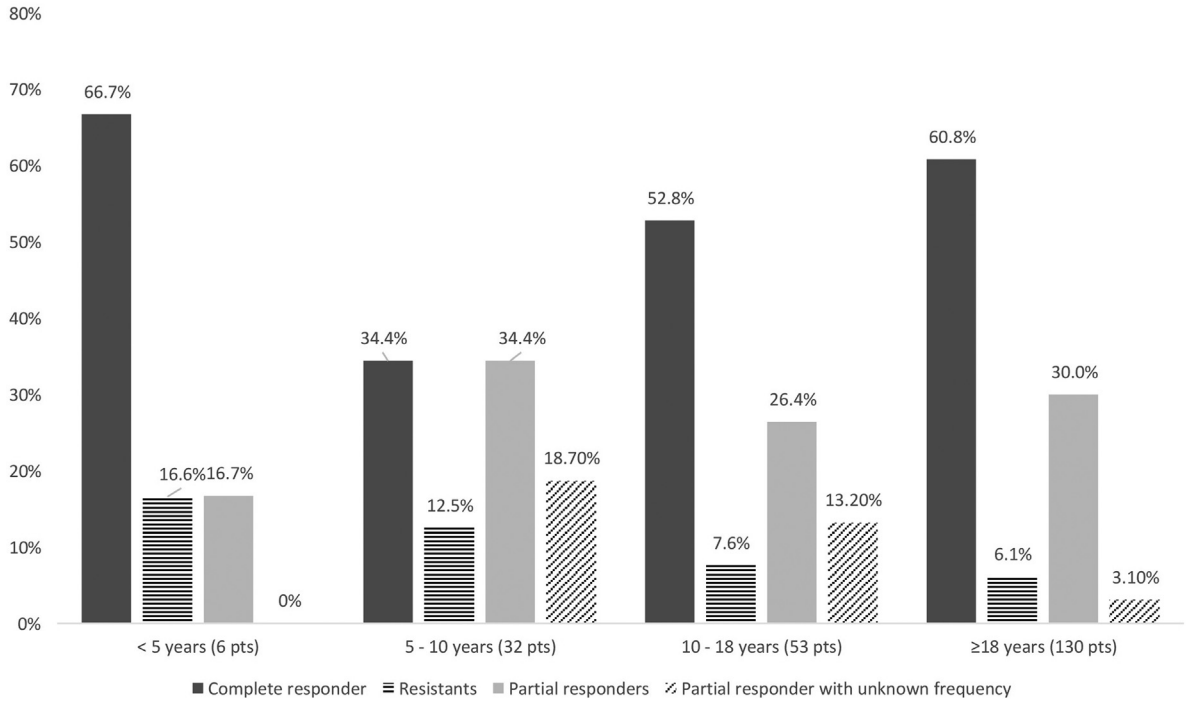

FIGURE 1. Response to colchicine in Italian patients with FMF according to age groups. *FMF,* Familial Mediterranean fever.

school/work) (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), with a limitation of daily activities/presence at school or work or the presence of chronic pain or fatigue involved one-third of partial responders. This multicenter nationwide study provides the first longitudinal data on the actual impact of colchicine in the management of pediatric and adult patients with FMF in a western European country. Even if the percentage of patients fulfilling the EULAR definition for colchicine resistance (≥1 episode/month) is around 7%, a relevant percentage of patients display some degree of disease activity. Almost 30% of the population has a relevant impact on some aspects of the quality of life. In general, the vast majority of patients with ongoing disease activity resulted to be undertreated, with few of them reaching the maximum recommended dose. Overall, the dose of colchicine was overall relatively low, with a median dose-age specific of 0.5 mg/day (patients aged <5 years), 0.75 mg/day (5-10 years old), and 1 mg/day in adolescents and adults who are certainly far below the suggested doses indicated by EULAR recommendations.[4] The reason for the general tendency for the underdosage of colchicine in the present study is not univocal. The overall compliance to the drug was generally optimal or good. Few patients displayed colchicine-related side effects at the moment of the follow-up visit. One limitation of this longitudinal study was the lack of information on the possible occurrence of colchicine-related side effects in the previous history of each patient. This could be a possible cause for the tendency not to increase the dose despite a partial control of the disease, especially in children. Moreover, most of them displayed a clear reduction of fever episodes in respect to the pretreatment period, thus suggesting us to maintain the ongoing dosage. In any case, the present study shows that at least 30% of patients classified as partial responders declared an overall impact of disease activity on their quality of life, suggesting us to reconsider the number of episodes indicative for a resistance to colchicine.[4,5,8,9] A careful evaluation of the number of fever episodes and quality of life should guide the treating physicians to optimize the colchicine dose in nonresponder patients with FMF and, in case of poor tolerability, to consider an additional treatment with IL-1 blockers.

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TABLE I. Colchicine dosage according age groups

	<5 y		5-10 y		10-18 y		>18 y	
Response to colchicine	**mg/d***	**mg/kg/d***	**mg/d***	**mg/kg/d***	**mg/d***	**mg/kg/d***	**mg/d***	**mg/kg/d***
Complete response	0.5 (0.5-0.5)	0.026 (0.024-0.028)	0.75 (0.5-1)	0.028 (0.016-0.053)	1.0 (0.5-1.5)	0.026 (0.010-0.044)	1 (0.5-2)	0.016 (0.006-0.033)
Partial response (<1 episode/mo)	0.5 (0.5-0.5)	0.041 (0.041-0.041)	0.5 (0.25-1)	0.026 (0.011-0.056)	1.25 (0.5-2)	0.026 (0.015-0.033)	1 (1-2.5)	0.017 (0.010-0.031)
Partial response with unknown frequency	–	–	0.8 (0.5-1.25)	0.033 (0.020-0.036)	1.5 (1-2)	0.028 (0.014-0.043)	1 (1-1)	0.014 (0.013-0.015)
Resistant (≥1 episode/mo)	0.75 (0.075-0.075)	0.042 (0.042-0.042)	0.75 (0.075-1)	0.035 (0.033-0.050)	1.50 (1-2)	0.029 (0.028-0.051)	1 (0.5-1)	0.015 (0.007-0.019)
Total	0.5 (0.5-0.75)	0.028 (0.024-0.042)	0.75 (0.25-1.25)	0.029 (0.010-0.056)	1 (0.5-2)	0.028 (0.010-0.051)	1 (0.5-2.5)	0.016 (0.006-0.033)

*Median (range).

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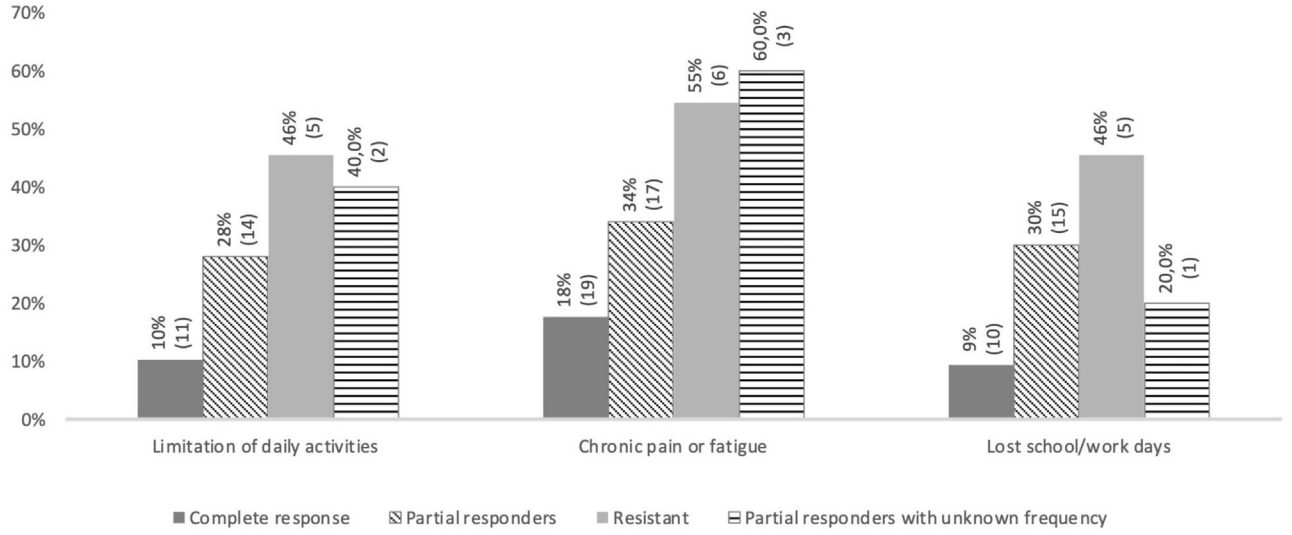

FIGURE E1. Impact on quality of life, according to the different responses to colchicine treatment.

TABLE E1. Demographic data and genotype of patients on exclusive colchicine treatment

Response to colchicine	Whole population	Pediatric population	Adult population
Total	221	125	96
Male:Female	119:102	68:57	51:45
Median age of onset (range)	6.2 (0.2-57)	3.3 (0.2-16.3)	14.9 (0.5-57)
Median age at enrolment (range)	14.8 (0.9-73.3)	7.6 (0.9-18.5)	36.1 (18.2-73.3)
Median age at diagnosis (range)	14.2 (0.7-64.3)	7.4 (0.7-18.5)	30.3 (9.8-64.3)
Median diagnostic delay (range)	4.2 (0-61)	2.3 (0.1-14.9)	14 (0-61)
Disease onset $\leq$18 y, N (%)	186 (84.2)	125 (100)	61 (63.5)
Median follow-up duration	3.7 (0.1-15.7)	5.4 (0.3-15.3)	2.5 (0.1-15.7)
Median disease duration	12.5 (1.8-71.7)	8.2 (1.9-22.7)	24.1 (1.8-71.7)
Mutations of *MEFV*, N (%)			
2 pathogenic mutations	75 (33.9)	43 (34.4)	32 (33.3)
1 pathogenic mutation in heterozygosis	44 (19.9)	19 (15.2)	25 (26.1)
1 pathogenic mutation and 1 VOUS/benign mutation	64 (28.9)	38 (30.4)	26 (27.1)
2 VOUS/benign mutations	12 (5.4)	9 (7.2)	3 (3.1)
1 VOUS/benign mutation in heterozygosis	14 (6.4)	11 (8.8)	3 (3.1)
Wild type	12 (5.5)	5 (4.0)	7 (7.3)

VOUS, variant of unknown significance.