Which definition should be used to determine colchicine resistance among patients with familial Mediterranean fever?

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ABSTRACT

Objective. *Colchicine is the main therapy for familial Mediterranean fever (FMF); however, 5-10% of patients are colchicine-resistant. There is no standard and validated definition for colchicine resistance. We aimed to compare the existing definitions for colchicine resistance in both adult and paediatric FMF patients to find out the best definition to determine colchicine-resistant patients.*

Methods. *385 FMF patients were evaluated and patients receiving anti-interleukin-1 treatment were included. The anti-IL-1 therapy had been initiated by the experts in the past based on their experience. Eleven different definitions (found out after PubMed search for colchicine resistance in FMF) were applied to all patients. Results were re-analysed after excluding the patients who had no clinical attacks but persistently high acute phase reactants (APRs) and/or amyloidosis.*

Results. *Sixty patients (40 adults/20 children) who had been using anti-IL-1 therapy were included into this study as colchicine-resistant patients. The highest percentage of patients fulfilled definition 5 (93.3%). Definition 9 had the poorest performance (26%). Significantly, a higher percentage of adult patients met definitions 4 and 6 than paediatric patients (87.5% vs. 50%, p=0.002; 75% vs. 40%, p=0.008, respectively). After excluding patients without clinical attacks, the highest percentage of patients fulfilled definition 2 (94.4%). We combined the attack frequency (>1 typical episode/3 months) in definition 2 and presence of amyloidosis/APR increase (increase in ≥2/3 APRs) in definition 5 to create a new definition which was met by 59 (98.3%) colchicine-resistant FMF patients.*

Conclusion. *Definition of colchicine resistance is still controversial. Definitions with both clinical and laboratory criteria were met by a higher percentage of resistant patients than those without laboratory criteria. However, the proper definitions for the attack-free period and persistence of APRs are still lacking.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterised by unprovoked and recurrent febrile attacks with serositis (1). Although the attacks are self-limited and last for 1-3 days, patients are at risk of chronic inflammation and developing secondary amyloidosis which is the most serious complication of FMF (1). Colchicine is the main therapy for FMF which effectively prevents clinical attacks, chronic inflammation, as well as secondary amyloidosis (2). However, in approximately 5-10% of FMF patients, full disease control cannot be accomplished despite adequate colchicine dose and these patients are called non-responders or colchicine resistant (3).

Lack of compliance, genetic factors, environment factors, and interaction with other drugs may play a role in the response to colchicine (3).

In initial studies, 'colchicine resistance' was defined based on only the frequency of attacks (4). Over the past years, with the improvement of the knowledge about subclinical inflammation and disease pathogenesis, this definition has evolved. Until today several definitions have been used for colchicine resistance most of which were based on attack frequency and serum levels of APRs (4-11). None of these definitions are accepted universally;

moreover, they all lack the assessment of quality of life and performance in work/school. La Regina *et al*. (12) have conducted a questionnaire study on colchicine resistance and responsiveness. According to this study 93% of physicians prefer attack frequency, 60.7% persistent high APRs, 28.5% organ involvement, 25% colchicine dose, 3.5% work limitations to define colchicine resistance (12).

Currently a standard and validated definition is not available for colchicine resistance. Establishing a standard, universal, comprehensive definition will avoid both misdiagnosis and overdiagnosis. Ozen *et al*. (13) have recently reviewed the existing data on defining colchicine resistance. They also underscored the need to identify patients who are not optimally managed with colchicine and who might benefit from additional biologic treatments.

In this study, we aimed to compare the performance of existing definitions for colchicine resistance in both adult and paediatric FMF patients and try to find out the best definition among them.

Patients and methods

Literature search

To identify published definitions for colchicine resistance in FMF patients, we searched PubMed (from database inception to 1 December 2017) using the following search terms: resistant FMF, colchicine resistant FMF, colchicine unresponsive FMF, and colchicine non-responder FMF patients. The articles including definition for colchicine resistance in FMF were included. The search was restricted to English articles.

Patients

This is a single-centre, retrospective study. 385 FMF patients consecutively referred to the Adult and Paediatric Rheumatology outpatient clinics of Hacettepe University between January and December 2016 were enrolled. Among these (n=385), 60 patients who were on anti-IL-1 treatment were included into the study group and the rest of the FMF patients (n=325) were included into the control group. The anti-IL-1 therapy had been initiated by the experts in the past based on their experience (the experts were SO, SK, AIE, AA, UK, and OK). The main indications for anti-IL1 therapy (retrieved from the medical files of the patients) are mentioned in Table I.

Table I. The main indications for anti-interleukin 1 therapy in familial Mediterranean fever (FMF) patients (n=60).

Recurrent FMF attacks, n (%)	28 (46.7)
Recurrent FMF attacks and persistently elevated AFR, n (%)	12 (20)
Recurrent FMF attacks and amyloidosis, n (%)	12 (20)
Amyloidosis, n (%)	3 (5)
Only persistently elevated APR, n (%)	3 (5)
Recurrent articular attacks and persistently elevated APR, n (%)	1 (1.66)
Recurrent articular attacks, n (%)	1 (1.66)

APR: acute phase reactants.

All patients fulfilled both the Tel Hashomer and/or the Turkish paediatric FMF criteria (14, 15). The patients were classified as adults and children (<18 years of age) according to their current age. Demographic data, clinical manifestations, C-reactive protein (CRP; mg/dl, normal value ≤0.5), erythrocyte sedimentation rate (ESR; mm/h, normal range 0-20), number of attacks per year, anti-IL-1 drug usage and *MEFV* variant analysis were recorded by medical file screening and face-to-face interview. All FMF patients were controlled regularly every 3-6 months, and APRs were checked in each visit in our centre. Number of the attacks was determined according to patients' history (the patients brought attack diary at each visit). Amyloidosis was diagnosed by renal biopsy in all patients. Subclinical inflammation was defined as presence of persistently elevated APRs in attack-free periods without evidence of infection.

The colchicine resistant FMF (CRFMF) definitions in the literature were applied to the study group patients (n=60) according to the features these patients had at the moment of the visit when anti-IL-1 therapy was commenced. For the control group (n=325), the definitions were applied at the time of the last visit available in the follow-up period.

Data were re-analysed after excluding the study group patients with persistently high APRs only and/or amyloidosis but who were clinically asymptomatic and/or had low attack frequency (≤2/year) in order to find out the best clinical definition for colchicine resistance.

This study was approved by the ethics committee of Hacettepe University (October 25, 2016; GO 16/500-13).

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 21.0; IBM Corporation, Armonk, NY, USA). Continuous data were described as median and minimum-maximum values and categorical variables as percentages. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov) to determine whether or not they were normally distributed. Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. The Mann-Whitney U test was used to compare the non-normally distributed continuous data between two groups. A p value <0.05 was considered significant.

Results

Eleven different definitions for colchicine resistance in FMF were found out after MEDLINE/PubMed search (4, 6-12, 16-21). These definitions were presented in Table II. It is noteworthy that the definitions in the literature were mainly non-validated proposals. The statement "despite taking 2 mg/day of colchicine" in definitions 2, 3, 7, 8, and 9 was modified as "maximum tolerated dose of colchicine" during analysis.

A total of 60 FMF patients: 40 (67%) adults and 20 (33%) children, were included in the study group. The demographic and clinical characteristics of these patients are presented in Table III and the *MEFV* variants of the FMF patients in the study and control group are presented in Supplementary

Table II. The definitions for colchicine resistance in familial Mediterranean fever (FMF) in the literature.

Definitions (reference number)	Explanation for the definition
Definition 1 (16)	Despite taking adequate colchicine treatment, at least 1 episode per month (≥6 years, ≥1.5 mg/day for at least 3 months or <6 years, ≥1.2 mg/day)
Definition 2 (4, 11, 17)	Despite taking ≥2 mg/day* colchicine, more than 1 typical episode per 3 months
Definition 3 (10)	Despite ≥receiving 2 mg/day* colchicine, 3 or more attacks within the last 6 months
Definition 4 (18)	i) Despite the fact that adequate doses of colchicine (maximum dose of colchicine is 2 mg/day for adolescents and for younger children as the maximum tolerated dose), at least one episode per month during the following 3 months and increased ESR or increased CRP or increased SAA between attacks ii) Presence of amyloidosis iii) Protracted febrile myalgia and frequent need of steroid treatment iiii) Presence of persistent arthritis
Definition 5 (8)	i) More than 3 episodes in 4-6 months, or more than 6 typical episodes per year, despite full compliance to treatment ii) In case of incomplete attacks, an increase in at least two out of three APRs (CRP, ESR, and SAA) between attacks
Definition 6 (19)	i) One or more episodes per month despite the use of maximum tolerated dose of colchicine for at least 6 months ii) and/or presence of amyloidosis
Definition 7 (12)	i) At least 1 episode per month despite taking 2 mg/day* colchicine ii) Persistently elevated APR iii) Organ involvement (especially renal) iiii) Losing job or not continuing to school
Definition 8 (6) *(NIAMS:Clinicaltrials.gov., NCT00094900, Interleukin-1 trap in the treatment of autoinflammatory diseases)*	i) Despite taking ≥2 mg/day* of colchicine, at least 1 episode per month ii) Symptoms continue despite ≥2 mg/day* colchicine intake iii) ESR, CRP or SAA elevation ≥1.5 times higher than the normal limit between attacks despite treatment with maximally tolerated dose of colchicine.
Definition 9 (9)	Despite 2 mg* of colchicine, at least 2 episodes per month and elevation of CRP and SAA between attacks
Definition 10 (7, 20)	In presence of at least two *MEFV* mutations, and at least one attack per month in any of the FMF sites despite maximum tolerated dose of colchicine
Definition 11 (21)	≥3 episodes during 3 months despite treatment with colchicine at ≥1-2 mg/day (based on age) for at least 3 months

APR: acute phase reactants; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FMF: familial Mediterranean fever; MEFV: Mediterranean fever; SAA: serum amyloid A.
*The statement "despite taking 2 mg/day of colchicine" in definitions 2, 3, 7, 8, and 9 was modified as "maximum tolerated dose of colchicine" during analysis.

Table I. The three highest allele frequencies were for M694V (77.5%), M680I (9.2%), and V726A (2%). Forty-one patients (68.3%) were homozygous for M694V mutation. The median (minimum-maximum) age of patients at symptom onset was 3 (0.2-9) and 10 (1-37) years for children and adults, respectively. The median age at diagnosis was 4.5 (1-14) years for children and 19.5 (2-47) years for adults. Arthritis and pleuritic chest pain were significantly more frequent in adults than in children (p=0.001 and p=0.037, respectively).

Thirty-four (85%) adult patients were using anakinra and 6 (15%) canakinumab, while 12 (60%) paediatric patients were using canakinumab and 8 (40%) anakinra as anti-IL-1 treatment. There was a significant difference in the drug used between adults and children (p<0.001). The mean (±SD) age at anti-IL-1 initiation was 11.8 (5.1) years for children and 33.2 (10.6) years for adults. Time from diagnosis to initiation of anti-IL-1 drugs were significantly longer in adults than in children (p=0.001). All patients but one continued colchicine treatment while taking biological agents. In one patient colchicine was discontinued due to persistently high transaminase levels.

Comorbidities in the study group (n=60) were as follows: In adult group; 10 patients had chronic kidney disease, 8 hypertension, 3 hypothyroidism, 8 ankylosing spondylitis, 2 inflammatory bowel disease (IBD), and 1 patient each had polyarteritis nodosa, Behçet's disease, sarcoidosis, multiple sclerosis, epilepsy, and juvenile idiopathic arthritis. Two adult patients had renal transplantation because of amyloidosis. From paediatric patients, two had IBD, 1 patient had diabetes, 1 had IgA vasculitis/Henoch-Schönlein purpura, and 1 had restrictive cardiomyopathy. Of note, the presence of amyloidosis had been evaluated as an indication for anti-IL1 therapy by experts; however, other comorbidities did not seem to affect the decision directly.

The comorbidities in the control group (n=325) were as follows: Four patients had IgA vasculitis/Henoch-Schönlein purpura, four had ankylosing spondylitis, four had juvenile idiopathic arthritis, two had psoriatic arthritis, and two had IBD.

The number of FMF patients in the study and control group defined as being colchicine resistant according to

Table III. Demographic, clinical and laboratory characteristics of 40 adults and 20 paediatric familial Mediterranean fever (FMF) patients with colchicine resistance (study group).

Characteristics	Adult patients (n=40)	Paediatric patients (n=20)	*p*-value
Age, years, median (min-max)	35 (22-70)	14 (2-18)	<0.0001
Gender, % (F/M)	60/40	70/30	0.44
Time from diagnosis to the initiation of IL-1 blockage, years, median (min-max)	13 (0-33)	6 (0-13)	0.001
Number of attacks per year prior to anti-IL-1, median (min-max)	12 (0-96)	8.5 (0-24)	0.29
Abdominal pain, n (%)	38 (95)	19 (95)	1
Fever, n (%)	38 (95)	20 (100)	0.54
Arthralgia, n (%)	38 (95)	16 (80)	0.08
Arthritis, n (%)	37 (92.5)	11 (55)	0.001
Pleuritic chest pain, n (%)	29 (72.5)	9 (45)	0.037
History of appendectomy, n (%)	14 (35)	2 (10)	0.039
Amyloidosis, n (%)	15 (37.5)	0 (0)	0.002
Family history of FMF, n (%)	26 (65)	7 (35)	0.02
Parental consanguinity, n (%)	11 (27.5)	4 (20)	0.52
Family history of hemodialysis associated with FMF, n (%)	2 (5)	0 (0)	0.54
Family history of amyloidosis associated with FMF, n (%)	2 (5)	2 (10)	0.58
CRP just before initiation of IL-1 blockage, mg/dl, median (min-max) (normal value ≤0.5)	2.5 (0.14-20.1)	2.75 (1.06-14.4)	0.38
ESR just before initiation of IL-1 blockage, mm/h, median (min-max) (normal value 0-20)	35 (2-94)	40 (3-78)	0.24

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FMF: familial Mediterranean fever.

Table IV. Number of familial Mediterranean fever (FMF) patients defined as being colchicine resistant according to different definitions.

Definitions	All study group patients (n=60)	Adult study group patients (n=40)	Paediatric study group patients (n=20)	*p*-value*
Definition 1, n (%)	29 (48.3)	21 (52.5)	8 (40)	0.36
Definition 2, n (%)	51 (85)	33 (82.5)	18 (90)	0.44
Definition 3, n (%)	50 (83.3)	32 (80)	18 (90)	0.32
Definition 4, n (%)	45 (75)	35 (87.5)	10 (50)	0.002
Definition 5, n (%)	56 (93.3)	36 (90)	20 (100)	0.29
Definition 6, n (%)	38 (63.3)	30 (75)	8 (40)	0.008
Definition 7, n (%)	52 (86.7)	37 (92.5)	15 (75)	0.10
Definition 8, n (%)	54 (90)	34 (85)	20 (100)	0.06
Definition 9, n (%)	16 (26.6)	14 (35)	2 (10)	0.06
Definition 10, n (%)	27 (45)	19 (47.5)	8 (40)	0.58
Definition 11, n (%)	32 (53.3)	25 (62.5)	7 (35)	0.058

*p values are for the comparison between paediatric and adult patients in the study group.

different definitions are shown in Table IV. In the study group, the highest percentage of FMF patients fulfilled the definition 5 (93.3%). It is noteworthy that significantly higher percentage of adult patients were meeting definitions 4 and 6 than paediatric patients (87.5% *vs*. 50%, p=0.002; 75% *vs*. 40%, p=0.008; respectively). None of the patients in the control group met any definitions.

The performance of definition 2 (94.4%) was better than the other definitions in this cohort, after excluding the colchicine resistant patients with persistently high APRs and/or amyloidosis but who were clinically asymptomatic and/or had low attack frequency (≤2/year). The number of patients according to different definitions is shown in Table V. Of note, significantly higher percentage of adult patients were fulfilling definition 4 than paediatric patients (75% *vs*. 44.4%, p=0.02). The best performance was of the definition 5 in the whole group and the definition 2 performed best in the selected group (patients with only frequent attacks making them defined as colchicine resistant). We have combined the clinical definition in definition 2 and APR definition in definition 5 to suggest a new definition as "more than 1 typical episode per 3 months OR an increase in at least two out of three APRs (CRP, ESR, and serum amyloid A [SAA]) between attacks despite taking maximum tolerated dose of colchicine". When we applied this definition to our patients in the study group, 57 (95%) patients met this definition. After adding "the presence of amyloidosis" to this definition, 59 (98.3%) patients fulfilled the definition. Of note, none of the patients in the control group met this new definition, either.

Discussion

In the presented study, we assessed the performances of all existing definitions for colchicine resistance in the literature (4, 6-12, 16-21). Definition 5 (more than three episodes in 4-6 months, or more than six typical episodes per year, despite adequate dosage of colchicine or increase in two out of three APRs in attack-free periods) had the best performance and was fulfilled by 93.3% of the colchicine resistant FMF patients. Definition 9 had the poorest performance, where 26% of the resistant patients met the definition. Significantly higher percentage of adult patients fulfilled definitions 4 and 6 as compared to paediatric patients. In the control group, none of the patients met any of the definitions. When we applied the new combined definition that we have suggested (more than 1 typical episode per 3 months OR an increase in at least two out of three APRs (CRP, ESR, and SAA) between attacks OR the presence of amyloidosis despite taking maximum tolerated dose of colchicine) to the study group patients, 98.3% of the patients fulfilled this new definition. None of the patients in the control group met this new definition, either.

Among the previously suggested definitions the performance of definition 5 was better than the others, probably because it has the advantage of including the criterion of "high APRs between attacks" in contrast with definitions 1, 2, 3, and 6. In addition, to meet the attack criterion in definition 5, the patient should have less frequent attacks than defined in definitions 4, 7, 8, 9, 10 and 11. The definition with the

Table V. Number of familial Mediterranean fever (FMF) patients defined as being colchicine-resistant according to different definitions; only patients of study group with clinical symptoms included (n=54).

Definitions	All patients (n=54)	Adult patients (n=36)	Paediatric patients (n=18)	*p*-value
Definition 1, n (%)	29 (53.7)	21 (58.3)	8 (44.4)	0.33
Definition 2, n (%)	51 (94.4)	33 (91.7)	18 (100)	0.54
Definition 3, n (%)	50 (92.6)	32 (88.9)	18 (100)	0.28
Definition 4, n (%)	35 (64.8)	27 (75)	8 (44.4)	0.02
Definition 5, n (%)	50 (92.6)	32 (88.9)	18 (100)	0.28
Definition 6, n (%)	29 (53.7)	21 (58.3)	8 (44.4)	0.33
Definition 7, n (%)	29 (53.7)	21 (58.3)	8 (44.4)	0.39
Definition 8, n (%)	29 (53.7)	21 (58.3)	8 (44.4)	0.39
Definition 9, n (%)	16 (29.6)	14 (38.9)	2 (11.1)	0.05
Definition 10, n (%)	27 (50)	19 (52.8)	8 (44.4)	0.773
Definition 11, n (%)	32 (59.3)	25 (69.4)	7 (38.9)	0.042

poorest performance was definition 9, which included only attack frequency without mentioning APRs, or amyloidosis, or quality of life. Furthermore, all other definitions required >1 attack whereas definition 9 required at least 2 attacks per month, which was a further cause of its poor performance. Definition 2 covered the highest number of our patients since the required attack frequency was the lowest (more than 1 attack per 3 months). It should be noted that in the recent recommendations endorsed by European League Against Rheumatism (EULAR), the sentence of treatment resistance does not specifically include increased APRs and thus we have written its definition as such (definition 6) (19); however, the whole text implies that subclinical inflammation should be controlled and that it suggests resistance, which would warrant additional biologic therapy (19).

In our study, there was a significant difference between adult and paediatric patients in questionnaires 4 and 6. The major difference of definitions 4 and 6 as compared to the others, was the presence of amyloidosis. Among 40 colchicine-resistant adult patients, 15 (37.5%) had amyloidosis while no children with FMF had amyloidosis; this explains the different performance among adults and children. Corsia *et al*. (22) investigated the main differences among physicians assessing colchicine resistance in adult and paediatric care settings, and demonstrated that the frequency of attacks was the main concern in paediatric clinics while in adult clinics, the presence of amyloidosis became important to define colchicine resistance (22).

Our new suggested definition which was formed by combining definitions 2 and 5, has the advantages of including attack frequency, APRs in the attack-free period, and the presence of amyloidosis. The attack frequency was defined as in definition 2 (>1 attack/3 months) to cover more patients. However, there are still points to consider for this new combined definition. First of all, attack-free period was not defined clearly in the presented definitions. And secondly, the attack frequency may decrease with older age which may cause a necessity to define this parameter differently in children and adults. In addition, new definitions were still not covering drug compliance and quality of life. Recently, JAIMAR (Juvenile AutoInflammatory disease Multidimensional Assessment Report) was developed to assess functional status, pain, therapeutic compliance and health-related quality of life with disease outcome in autoinflammatory diseases (23). It may be useful to include some parameters of this report to the definitions for colchicine resistance in FMF. The FMF Arthritis Vasculitis and Orphan Disease Research in Pediatric Rheumatology (FAVOR) and Turkish FMF study group previously proposed an FMF50 score to assess outcome in FMF (24). Compliant patients not achieving this, were considered to be colchicine resistant. This score requires at least 50% improvement in 5 of 6 criteria without worsening in any single criterion: change in frequency of attacks, in duration of attacks, patient/parent global assessment of disease severity, physician global assessment of disease severity, change in arthritis attacks and in CRP, ESR, or SAA. However, Hashkes *et al*. (25) showed that FMF50 score did not differentiate well between responders and non-responders in the controlled trial of rilonacept for colchicine resistant FMF patients (25).

Most recently, Ozen *et al*. (13) revisited the different definitions for colchicine resistance in FMF. They have concluded that it was not appropriate to mention the maximum dose of colchicine as 2 mg/day since some patients cannot be treated with this dose. We have modified the dose of colchicine in our definition as "maximum tolerated dose". They have also drawn attention to the deficiency of symptoms (as myalgia, vasculitis, etc.) other than clinical attacks in the existing definitions (13). Furthermore, they mentioned the difficulty of determining incompliant patients since there is no reliable and practical detection methods to estimate active colchicine levels (13).

Ours is the first study in the literature comparing the different definitions for colchicine resistance in FMF. The major limitation of our study was its retrospective characteristics. In addition, there were patients in the adult group who had symptom onset in childhood who might have different characteristics when compared to the patients with disease onset at adulthood. We also lack measurements of colchicine levels in these patients. Another limitation was that the patients were classified as being resistant to colchicine by the judgement of different experts. They did this evaluation in the context of daily clinical practice, did not depend on structured criteria. Thus, the strategy was not homogeneous. Moreover, the expert opinion at the time of anti-IL-1 initiation had probably been affected by the available criteria in the literature anyway. However, it is difficult to dissect those since the experts besides evaluating lots of FMF patients, are reading the literature to improve their knowledge. Another point is that the new criteria would not cover

colchicine-resistant patients who have persistent FMF-related articular complaints. It is crucial to validate this definition in new, larger cohorts of patients with diverse characteristics.

In conclusion, we suggest that combining definitions 2 and 5 as: "more than 1 typical episode per 3 months OR an increase in at least two out of three APRs (CRP, ESR, and SAA) between attacks OR the presence of amyloidosis despite taking maximum tolerated dose of colchicine" provides the best definition for colchicine resistance in FMF. However, further prospective, multicentre studies and consensus of an international panel of experts are required to find and validate the best definition for colchicine resistance in FMF.

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