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Familial Mediterranean fever in children and adolescents: factors for colchicine dosage and predicting parameters for dose increase

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Abstract

Objectives. The aim was to analyse factors influencing the individual colchicine dose in children with FMF, to evaluate the impact of dose adjustment on the clinical course and inflammation and to identify clinical parameters and biomarkers that predict dose increase in the near future.

Methods. Data from 409 paediatric FMF patients (4566 visits) derived from the national auto-inflammatory diseases registry were analysed. Serum concentrations of S100 molecules were determined by ELISA.

Results. The age-dependent colchicine dose is influenced by the present genotype. The body surface area is the anthropometric parameter that correlates best with the applied dosages. Colchicine introduction and dose increase lead to significant reduction of clinical symptoms and inflammation. During established colchicine therapy, an increase of one single biomarker increases the likelihood of a dose increment in the next 12 months with a factor of 1.62–1.94. A combination of biomarkers including S100 molecules increases this odds ratio up to 4.66 when analysing all patients and up to 7.27 when analysing patients with a high risk of severe disease.

Conclusion. Colchicine therapy is currently guided mainly by the occurrence of clinical symptoms and serological inflammation. Other factors, such as the genotype, the body surface area and biomarkers, will help to manage colchicine therapy in a more individualized fashion. The additional analysis of S100 molecules as sensitive biomarkers will help to identify patients at risk for dose increases in the near future.

Key words: Familial Mediterranean fever, colchicine, inflammation, S100 molecules, biomarker, children

CLINICAL SCIENCE

Rheumatology key messages

- In FMF, patients' body surface area is a good estimate to predict the needed colchicine dosages.
- In patients with FMF and a severe genotype, higher colchicine doses should be introduced initially.
- Analysis of S100 molecules identifies FMF patients at risk for colchicine dose increases in the near future.

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Introduction

FMF is the most prevalent hereditary periodic fever syndrome, clinically characterized by highly inflammatory febrile attacks, which are associated with signs of serositis, for example, peritonitis, pleuritis and arthritis [1]. Colchicine is the gold standard for prophylaxis of attacks and amyloid deposition [2–5]. Evidence-based treatment recommendations suggest starting dosages of colchicine according to patient age and subsequent dose escalation in order to control symptoms, (sub)clinical inflammation, or both [6–8]. This approach implies that in most cases the growing child or the adult in certain cirmcumstances of life, for example, during emotional or physical stress or pregnancy, will experience painful attacks before colchicine dosages will be adjusted. Of note, in the very young child febrile attacks can occur without any other symptoms and thus might be difficult to differentiate from infections [9]. When the individually adequate colchicine dose is found (again), most patients experience a complete control or clear improvement of symptoms and are protected from amyloid deposition.

The quality of life of FMF patients is impaired by the uncertainty of experiencing attacks in the future. This is of special interest in patients with a high disease activity, as reflected by frequent and severe attacks and persistent inflammation, who possibly carry a higher risk of developing amyloidosis in the course of the disease, especially if disease activity is related to high-risk genotypes [10, 11]. Therefore, one target in FMF therapy is the prevention of symptoms by an increase of colchicine dosage, before a series of attacks occurs. Some factors that influence the time of colchicine introduction and dosage in individual patients, for example, the occurrence of the M694V mutation, have been described previously [10, 12, 13], but no data on risk factors for the development of symptoms during an ongoing colchicine treatment have been described.

In order to identify such potential parameters, we took advantage of the German auto-inflammatory diseases registry, which provides prospective follow-up data from a large number of children and adolescents with FMF as well as serum samples for further analysis of biomarkers. The objective of the study was the identification of factors (e.g. the genotype, different biometrical parameters, different clinical presentations and the degree of inflammation) that might help in adjusting colchicine dosages in an individualized fashion.

Methods

Auto-inflammatory diseases registry

The national auto-inflammatory diseases registry collects clinical data, demographic information and blood samples of children with auto-inflammatory diseases. Details on the registry have previously been published [14, 15]. In January 2016, 1052 patients were registered from 43 participating hospitals.

Inclusion criteria, disease assessment and definitions

For this study, inclusion criteria were an age $\leqslant$ 18 years, the clinical diagnosis of FMF according to the Tel-Hashomer criteria, colchicine treatment and at least two documented visits in the registry. Patients in whom another additional auto-inflammatory disease was diagnosed or in whom the documentation of the genotype was unclear were excluded. The national auto-inflammatory disease registry was approved by the institutional ethics committee, and informed consent was obtained from patients and their legal guardians. According to national regulatory bodies, no additional approval or consent was required for this study.

The response to colchicine treatment was calculated by analysing the mean change of CRP concentrations in the 12 months before and after dose increase as well as the change in attack frequency during the same time period. For the analysis of colchicine response, only patients compliant to the medication, with no change of colchicine dosage 12 months before and after the increase and with a follow-up of at least 12 months, were included (therefore, 40 patients were excluded).

Disease severity was assessed by mean of the F-SS-2 (Mor-Score) using the number of attack sites in a single attack and during the disease course, the colchicine dose to achieve remission, the number of pleuritic and erysipelas-like erythema attacks and the age of onset [16]. In the registry, persistent proteinuria and occurrence of amyloidosis were retrieved. In the event of positive answers, centres were asked whether suspected amyloidosis was confirmed or symptoms resolved.

Colchicine resistance was defined as proposed (patient suffers from either more than six typical FMF attacks per year or more than three typical FMF attacks within 4–6 months despite reaching the maximal tolerable dose according to the EULAR recommendations [7, 8]).

Laboratory parameters

ESR (in millimetres per hour), serum amyloid-A protein (SAA; in nanograms per millilitre) and CRP (in milligrams per litre) were determined by the local institutions. Serum samples were centrifuged within 2 h after acquisition, frozen at $-20\,^{\circ}$C and shipped to Münster for analysis of S100 molecules [17].

Statistical analysis

The cut-off date for this study of the Auto-Inflammatory Diseases-Net registry was in January 2015. Statistical analyses were conducted with the programs IBM SPSS Statistics 22 (IBM Corp, Armonk, NY) and STATA 12.1 (StataCorp LP, College Station, TX).

Data were presented with standard descriptive statistics, including the absolute and relative frequencies for categorical variables and the mean and S.D. for continuously distributed variables. The mean unadjusted and adjusted colchicine doses for a given age were estimated by non-parametric local polynomial regression models for graphical visualization of the data. To assess the impact of colchicine dose increase on CRP concentration and

attack frequency, the Wilcoxon signed-rank test was used. In order to identify possible predictors of dose increases, generalized linear mixed models were applied to account for the longitudinal study design. The dependent variables thereby related to the presence or absence of a dose increase in the upcoming months, and the independent variables were the potential predictors. Initially, the potential factors were analysed separately by univariate regression analysis, followed by a multiple regression analysis including all combinations of the factors of interest. The statistical significance level for all tests was $P \leqslant 0.05$.

Results

Patients

The data of 409 [n = 228 (55.7%) male and n = 181 (44.3%) female] children or adolescents with FMF and colchicine treatment from the auto-inflammatory diseases registry were analysed (Table 1). There were 4566 visits documented, with an average of 11 visits per patient (mean of 3.2 visits/year per patient) and a mean period of follow-up of 63 months. Three thousand six hundred CRP values, 2993 ESR values, 1884 SAA values, 612 S100A12 values and 495 S100A8/9 values were available for analysis. Molecular genetic analysis was available in all patients.

Colchicine was, in general, well tolerated; only 5.4% of the patients showed mild and 0.8% moderate mostly gastrointestinal side-effects according to the World Health Organization toxicity scale (grades 1 and 2, respectively).

Besides colchicine, which was an inclusion criterion for our study, the following concomitant medications were documented: mostly on demand, 81 patients (19.8%) took non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, diclofenac, acetaminophen, aspirin, cyclooxygenase-2 inhibitors) and 19 patients (4.6%) took steroids, whereas continuously, 15 patients (3.7%) took anakinra, 8 patients (2.0%) etanercept, 5 patients (1.2%) methotrexate, 2 patients (0.5%) adalimumab and 1 patient (0.2%) infliximab.

None of the analysed patients demonstrated a positive amyloidosis screening.

Applied colchicine dose according to patient age

Previously, it has been recommended that colchicine should be started with an age-adjusted dosage and stepwise increase in the amount of colchicine in order to control symptoms and inflammation [6]. When analysing the whole study population, 0.89 mg colchicine/day was prescribed irrespective of the patients' age and underlying genotype. Figure 1A shows in more detail the colchicine dosages according to age. From the 5th year of life, most patients received 1.0 mg colchicine/day and from the 12th year of life most received 1.5 mg colchicine/day. At the age of 18 years, 32.3% received 2.0 mg colchicine/day and 11.9% >2 mg/day.

Table 1 Patient characteristics

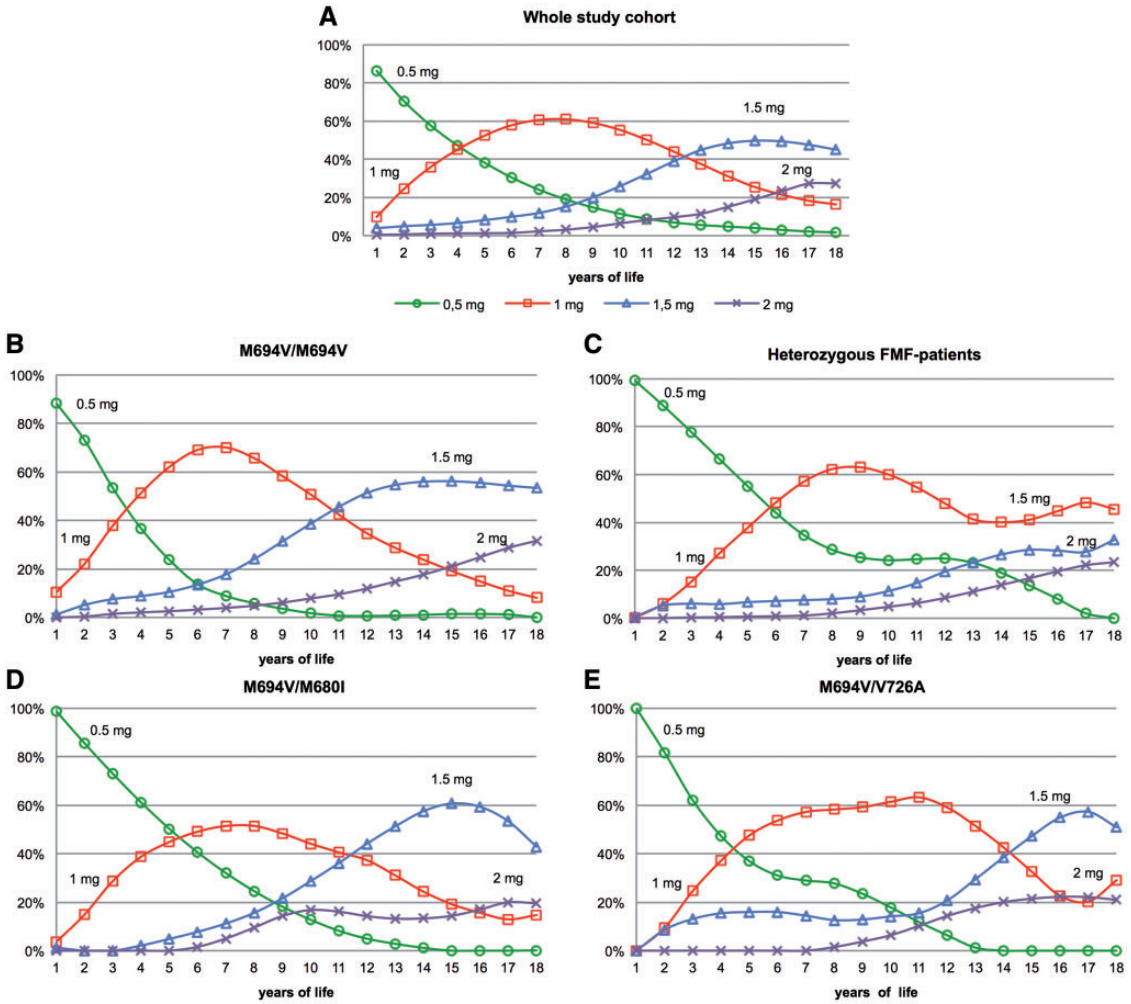
Observation period, mean (S.D.), months	62.5 (43.6)
Number of visits, mean (S.D.)	11 (8.3)
Sex, n (%)	
Female	181 (44.3)
Male	228 (55.7)
Positive family history, n (%)	248 (67.6)
Appendectomy, n (%)	29 (8.7)
Consanguineous parents, n (%)	93 (30.1)
Age at diagnosis, mean (S.D.), years	6.04 (3.8)
Age at onset of symptoms, mean (S.D.), years	3.95 (3.36)
Onset of symptoms <10 years, n (%)	347 (93.8)
Onset of symptoms >10 years, n (%)	23 (6.2)
Mean diagnostic delay, mean (S.D.), months	62.5 (43.6)
Ethnic background, n (%)	
Turkish	310 (82.7)
Arabic	42 (11.2)
Armenian	5 (1.3)
German	9 (2.4)
Italian	2 (0.5)
Greek	1 (0.3)
Others	6 (1.6)
Missing	34 (8.2)
Genotype, n (%)	
M694V/M694V	111 (27.1)
Heterozygous	116 (28.4)
M694V/M680I	35 (8.6)
M694V/V726A	27 (6.6)
M694V/E148Q	10 (2.4)
V726A/M680I	9 (2.2)
M680I/M680I	8 (2.0)
V726A/V726A	7 (1.7)
E148Q/E148Q	6 (1.5)
E148Q/P369S	4 (1.0)
M694V/R761H	5 (1.2)
Other rare variants	65 (15.8)
No mutation found	6 (1.5)

Influence of genotype on colchicine dosage

The average colchicine dosages according to the genotype and regardless of the patients' age and anthropometric parameters were calculated. In homozygous M694V mutation carriers, a mean colchicine dose of 1.19 mg/day was applied. There was no significant difference in comparison to patients carrying compound heterozygous M694V/M680I (1.11 mg) and M694V/V726A (1.16 mg) or homozygous M680I mutations (1.09 mg/day). In contrast, the average colchicine dose was significantly lower in patients with the M694V/E148Q genotype (0.84 mg/day, $P < 0.05$) or any heterozygous mutation (0.81 mg/day, $P < 0.05$).

Colchicine dosages were most rapidly increased in patients with homozygous M694V mutations. Within this group, most patients receive at least 1.5 mg/day after 11 years of age (Fig. 1B). In the compound heterozygous V726A/M694V and M680I/M694V carriers (Fig. 1D and E), colchicine dose increase was slightly delayed compared with patients with the homozygous M694V mutation. In

Fig. 1 Colchicine dose according to age (in years of life) and to genotype



Shown are the percentages of patients who received particular colchicine doses [0.5 mg (green circle); 1 mg (red square); 1.5 mg (blue triangle); 2 mg (violet cross); *y*-axis] according to years of life (yol; *x*-axis). For every patient, the mean colchicine dose taken during the single year of life was calculated. Owing to the low numbers of patients >16 years, in (**D**) and (**E**) the values might not be representative. (**A**) Whole study cohort [number of patients (n) = 409; total numbers of registered yol with colchicine intake = 1971]. (**B**) M694V/M694V (n = 111, yol = 680). (**C**) Heterozygous patients (n = 116, yol = 366). (**D**) M694V/M680I (n = 35, yol = 237). (**E**) M694V/V726A (n = 27, yol = 157).

contrast to the other genotypes, 1 mg/day was the most frequently prescribed colchicine dose in adolescents carrying a heterozygous *MEFV* mutation (Fig. 1C).

Influence of anthropometric parameters on colchicine dosage

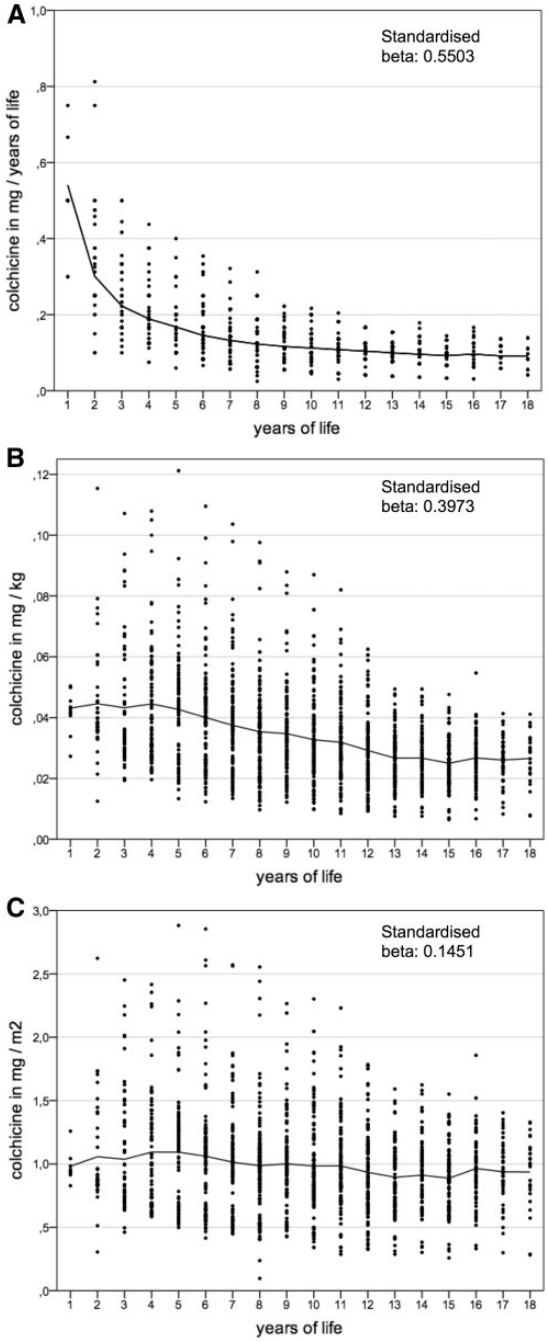
The analysis of the whole study cohort revealed that the average doses were 0.14 mg colchicine/year of life (median 0.125 mg), 0.036 mg colchicine/kg body weight (median 0.032 mg) and 1.03 mg/m^2 body surface area (median 1.00 mg).

The dose of colchicine according to age is high in toddlers, declines in childhood and plateaus in adolescence (Fig. 2A). The colchicine dose per kilogram bodyweight continously declines during childhood (Fig. 2B). The colchicine dose according to the body surface is the most stable variable over time, with values of ~1 mg/m^2 throughout childhood and adolescence (Fig. 2C). But for all parameters—the colchicine dose per years of life (median 0.125 ± 0.39 mg/years of life), body weight (median 0.032 ± 0.02 mg/kg) and body surface area (median 1.00 ± 0.39 mg/m^2), respectively—there was a wide range of colchicine doses for all age groups.

Effects of colchicine intake on inflammation and symptoms

Two hundred and thirty-eight of 409 patients had at least one increase of colchicine dosage during follow-up. Compared with the remaining group, more patients carried a homozygous M694V mutation (38.2 *vs* 11.7%) and

FIG. 2 Colchicine dose according to different anthropometric parameters and age (in years of life)



The colchicine doses according to the age [in years of life (yol); **A**], the body weight (in kilograms; **B**) and the body surface area (in metres squared; **C**) are plotted against the age (in yol). The line represents the mean applied dose in the respective age group; the scatterplot shows the applied dose per patient. Standardized β corresponds to the standardized regression coefficient. It allows direct comparison of the magnitude of the relative effect of yol on colchicine doses by body weight, body surface and age.

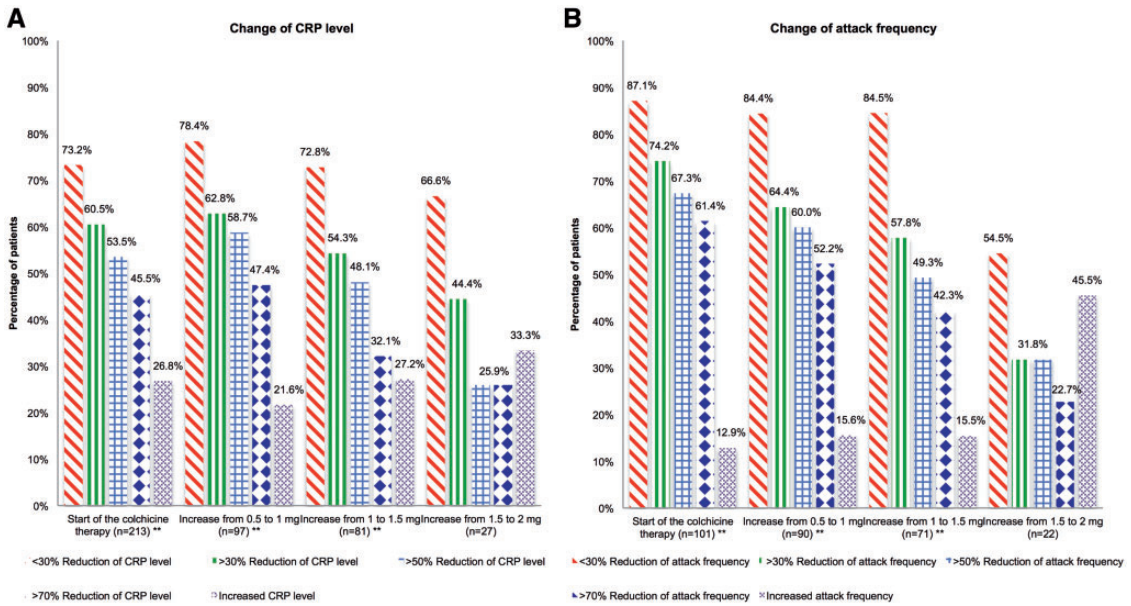
fewer patients a heterozygous mutation (18.1 *vs* 42.7%). Before introduction of therapy, the patients did not show significant differences in disease severity (Mor-Score 1: 27.6 *vs* 26.3%; Mor-Score 2: 42.9 *vs* 42.1%; Mor-Score 3: 29.4 *vs* 31.6%). The introduction of therapy (irrespective of the dosage) led to a CRP reduction of >70% in 45.5% of patients (difference between mean CRP during 12 months before and 12 months after introduction) and to a >70% reduction of attack frequency in 61.4% of patients (Fig. 3A and B and supplementary Table S1, available at *Rheumatology* Online). Within this group, CRP decreased from a mean concentration of 39.3 mg/l to 14.1 mg/l ($P \leqslant 0.001$). Further dosage increases also led to a subsequent improvement of inflammation as determined by the average CRP concentrations (e.g. after dosage increase to 2 mg colchicine/day, mean CRP declined from 19.8 to 12.6 mg/l and attack frequency was reduced >70% in 22.7% of patients). However, after dosage increases from 1.5 to 2.0 mg colchicine/day, in 33.3% of patients an increase of inflammation and in 45.5% an increase of attack frequency was detected. The inclusion of patients with low inflammatory activity might mask the effect of colchicine therapy. When analysing only patients with CRP concentrations $\geqslant$ 5 mg/l before dosage increase, an overall better response rate was observed at least in the group receiving low colchicine dosages (supplementary Fig. S1 and supplementary Table S1, available at *Rheumatology* Online).

Next, the response rates after introduction of colchicine according to the genotype were analysed. Patients with two mutations did not differ significantly in their responses compared with heterozygous patients (Fig. 4A and B, χ^2 test for group difference in response (Fig. 4A): compound heterozygous *vs* homozygous P = 0.361, compound heterozygous *vs* heterozygous P = 0.233, homozygous *vs* heterozygous P = 0.695; and (Fig. 4B): compound heterozygous *vs* homozygous P = 0.318, compound heterozygous *vs* heterozygous P = 0.891 and homozygous *vs* heterozygous P = 0.951).

The three groups were comparable with respect to age and colchicine dosages (supplementary Tables S2 and S3, available at *Rheumatology* Online), but compared with patients who had compound heterozygous or homozygous mutations the heterozygous patients had lower systemic inflammation and attack frequency before colchicine therapy was introduced [mean CRP (in milligrams per litre)/mean attack frequency (in 12 months before start of colchicine therapy): heterozygous 21.8/5.1; compound heterozygous 45.6/19.3; homozygous 46.4/13.3; supplementary Table S4, available at *Rheumatology* Online].

By applying the recently proposed criteria for colchicine resistance, 15 patients (3.7%) were identified who did not show adequate response to maximally tolerable doses of the drug. Of these 15 patients, 5 were homozygous for M694V, 4 compound heterozygous for M694V/M680I, 3 heterozygous for M694V, 1 compound heterozygous for M694V/V726A, 1 compound heterozygous for V726A/M680I and 1 homozygous for M680I. The maximal tolerable dosage ranged between 2 and 3 mg colchicine/day.

Fig. 3 Effect of colchicine dose increase on inflammation and attack frequency



Change between mean CRP 12 months before and 12 months after introduction of colchicine or dose increase (**A**) and corresponding change of attack frequency (**B**). Only patients with at least 12 months observation before and after dose increases were analysed. Patients who experienced two dose increases within the observation period were excluded. Numbers of patients in (**A**)/(**B**) are as follows: start of colchicine therapy: 213/101; increase from 0.5 to 1.0 mg colchicine/day: 97/90; increase from 1.0 to 1.5 mg colchicine/day: 81/71; increase from 1.5 to 2.0 mg colchicine/day: 27/22. */**Change of mean CRP concentration/attack frequency before and after introduction of colchicine or dose increase is significant at a level of $\leqslant 0.05/\leqslant 0.01$ (both sides).

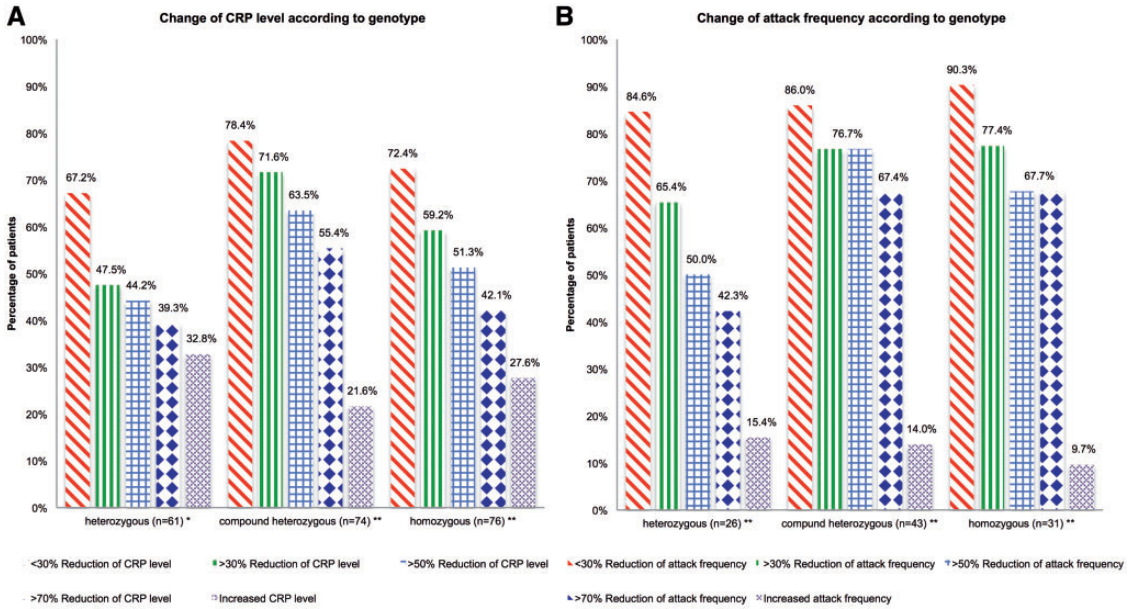
Subsequently, anakinra was started in four patients; in an additional three patients anakinra was introduced temporarily. Furthermore, 11 patients were registered who were already being treated with anakinra before entering the auto-inflammatory diseases registry. In these patients, data on clinical presentation before introduction of anakinra therapy were not available.

Predictors of colchicine dosage increase

In newly treated patients, the severity of disease at diagnosis, assessed by the Mor-Score, decreased the probability of a dosage increase in the first 12 [odds ratio (OR) = 1.60; P = 0.017)] and 24 months (OR = 1.47; P = 0.038). The amount of colchicine initially applied rises with the disease severity [mean colchicine dosage (in milligrams per day)/mean age at start of therapy (in years): mild disease: 0.6/7; moderate: 0.7/5; severe: 0.9/6]. In contrast, other factors, such as sex, age at diagnosis and onset of first symptoms, Pras Score, ethnic origin, skin involvement, genotype (heterozygous, homozygous M694V, M694V/M680I, M694V/V726A, M694V/E148Q, homozygous M680I, V726A/M680I, homozygous E148Q, homozygous V726A, P369S/R408Q, E148Q/P369S), pleural involvement, joint involvement, attack frequency before diagnosis and inflammation parameters, did not show any significant correlation with the probability of a dosage increase in the months after diagnosis (supplementary Table S5, available at *Rheumatology* Online).

Next, we analysed whether a single parameter (attack frequency and/or various biomarkers) or combinations of them predicted an upcoming dose increment in patients who were already being treated (Table 2). Persistent attacks, as well as elevated CRP, SAA, S100A12 or S100A8/9 concentrations, increased (as the sole parameter analysed) the likelihood for a dose increase with a factor of 1.62–1.94 (Kaplan–Meier analysis over 24 months; see supplementary Fig. S2, available at *Rheumatology* Online). Combining two parameters led to a better predictive value, especially when attack frequency and S100A12 or S100A8/9 were analysed (OR of 3.38 and 3.29). When analysing combinations of three parameters, it became obvious that combining SAA and CRP did not lead to a significant increase in the predictive value. This is also in line with the observation that these markers of inflammation are very well correlated with each other (0.852 and 0.668, respectively; supplementary Table S6, available at *Rheumatology* Online). When four or five parameters were increased, the OR for a dosage increase ranged between 4.26 and 4.66. The only exceptions were patients with an increase in four biomarkers but no clinical symptoms (OR = 3.11). When analysing only patients with homozygous M694V mutations even higher associations were observed. In particular, the inclusion of the biomarker S100A12 increased the OR for a dosage increase in the next 12 months up to 7.27 (supplementary Table S7, available at *Rheumatology* Online).

FIG. 4 Effect of colchicine introduction on inflammation and attack frequency



The effect of colchicine introduction on inflammation and attack frequency according to the genotype is shown in (**A**) and (**B**), respectively. In (**A**), the change between mean CRP 12 months before and 12 months after colchicine introduction is shown. (**B**) The change of attack frequency in response to colchicine introduction. Only patients with an observation time of 12 months before and after start of the therapy and registered biomarkers were analysed. Patients who experienced two dose increases within the observation period were excluded. */**Change of mean CRP concentration/attack frequency before and after start of colchicine therapy is significant at a level of $\leqslant 0.05/\leqslant 0.01$ (both sides).

Discussion

The effect of prophylactic colchicine therapy on the prevention of attacks, inflammation and amyloid deposition has been well established in randomized trials [2–4] and subsequent cohort studies [5, 18–22]. Evidence-based guidelines for the use of colchicine in FMF recommend an oral starting dose of 0.5 mg/day or less (<5 years of age), 1.0 mg/day (5–10 years of age) and 1.5 mg/day (>10 years of age), followed by an increase of colchicine dose up to a maximum of 2.0 mg/day in children and adolescents and 3.0 mg/day in adults in order to control disease and inflammation [6, 7]. Although some individual factors influencing the dose of colchicine in FMF have been previously described, these parameters were not sufficient to allow more personalized treatment recommendations. But ideally, treatment strategies should include as many individual parameters as possible in order to develop individual care programmes.

By using a large cohort of children and adolescents with FMF registered within the national Auto-Inflammatory Diseases-Net, we therefore analysed various factors that influence colchicine dosage in a real-life setting.

Previously, it has been shown that the age of introduction of colchicine [10] and requirement for higher colchicine dosages [12, 13] are associated with mutations at position 694. Our analysis confirms the influence of the genotype on the colchicine dosages administered (heterozygous < compound heterozygous M694V/V726A, and M694V/M680I < homozygous M694V). In patients with homozygous M694V mutations, the colchicine dosages are well correlated with the previously recommended age-dependent doses [6–8]. But in other genotypes, lower doses were prescribed, especially in patients with heterozygous mutations. Although a large number of visits were registered, further subanalysis of other genotypes or extra correlations, for example, with the degree of subclinical inflammation or persistent clinical symptoms, or both, were hampered by the low patient numbers.

Ideally, the amount of drug needed to control disease activity can be predicted by an easily accessible anthropometric parameter. In our study, young children received higher doses of colchicine according to their body weight compared with older children. A recent analysis demonstrated that steady-state pharmacokinetic parameters are comparable across age groups despite the higher dosages of colchicine on a milligram per kilogram per day basis in the younger age groups [23]. This pharmacokinetical analysis underlines the rationality of applying relatively higher dosages of colchicine in young children. Furthermore, our analysis revealed the best correlation of colchicine intake with the body surface area ($\sim$1 mg/m^2). This association is remarkably stable, even in a rather high number of very young children. The body surface area is principally recommended to be used as the basis for drug dose calculation in children, because many important physiological factors are correlated with this parameter [24]. But taken together, the wide

Table 2 Logistic regression: predictors for dose increase in the upcoming 12 months

Dose increase in the next 12 months	AUC	OR (95% CI)	P-value
Single			
Attack frequency	0.573	1.80 (1.41, 2.30)	<0.001
SAA	0.537	1.62 (1.25, 2.11)	<0.001
CRP	0.549	1.58 (1.28, 1.94)	<0.001
S100A8/9	0.513	1.93 (1.15, 3.24)	0.013
S100A12	0.523	1.94 (1.30, 2.90)	0.001
Combination of two			
Attack frequency/SAA	0.585	2.55 (1.81, 3.60)	<0.001
Attack frequency/CRP	0.588	2.37 (1.74, 3.23)	<0.001
Attack frequency/S100A12	0.592	3.38 (2.03, 5.62)	<0.001
Attack frequency/S100A8/9	0.580	3.29 (1.80, 6.03)	<0.001
SAA/CRP	0.559	1.94 (1.45, 2.59)	<0.001
SAA/S100A12	0.546	2.61 (1.65, 4.13)	<0.001
SAA/S100A8/9	0.542	2.62 (1.48, 4.63)	0.001
CRP/S100A12	0.560	2.52 (1.63, 3.88)	<0.001
CRP/S100A8/9	0.555	2.52 (1.46, 4.37)	0.001
S100A8/9/S100A12	0.519	2.23 (1.33, 3.73)	0.002
Combination of three			
Attack frequency/SAA/CRP	0.595	2.83 (1.97, 4.06)	<0.001
Attack frequency/SAA/S100A12	0.596	4.12 (2.38, 7.11)	<0.001
Attack frequency/SAA/S100A8/9	0.587	4.06 (2.13, 7.72)	<0.001
Attack frequency/CRP/S100A12	0.599	3.87 (2.30, 6.53)	<0.001
Attack frequency/CRP/S100A8/9	0.593	3.81 (2.05, 7.10)	<0.001
Attack frequency/S100A8/9/S100A12	0.590	3.80 (2.06, 7.02)	<0.001
CRP/SAA/S100A12	0.566	2.86 (1.79, 4.57)	<0.001
CRP/SAA/S100A8/9	0.562	2.88 (1.62, 5.14)	<0.001
SAA/S100A8/9/S100A12	0.542	2.89 (1.65, 5.07)	<0.001
CRP/S100A8/9/S100A12	0.564	2.78 (1.63, 4.75)	<0.001
Combination of four			
Attack frequency/CRP/SAA/S100A12	0.601	4.31 (2.49, 7.43)	<0.001
Attack frequency/CRP/SAA/S100A8/9	0.598	4.26 (2.23, 8.12)	<0.001
Attack frequency/SAA/S100A8/9/S100A12	0.596	4.51 (2.37, 8.59)	<0.001
Attack frequency/CRP/S100A8/9/S100A12	0.599	4.26 (2.29, 7.92)	<0.001
SAA/CRP/S100A8/9/S100A12	0.573	3.11 (1.77, 5.48)	<0.001
Combination of five			
Attack frequency/SAA/CRP/S100A8/9/S100A12	0.604	4.66 (2.46, 8.85)	<0.001

AUC: area under the curve; OR: odds ratio; SAA: serum amyloid-A protein.

range of prescribed dosages circumvents the use of the body surface area as a single parameter for prediction of the colchicine dosage. One reason (among others discussed in the present study) is the wide range of colchicine bioavailability [25].

In the present study, we were able to demonstrate that the highest impact of an increase in colchicine on attack frequency and inflammation can be observed when increasing a rather low dose, for example, from 1 to 1.5 mg colchicine/day. In contrast, a substantial number of patients did not benefit from an increase from 1.5 to 2 mg colchicine/day. Given that colchicine therapy is well tolerated even when applied in higher dosages, this still encourages the use of higher doses in individual patients.

One goal of treatment in FMF is the prevention of frequent painful attacks by application of an adequate colchicine dosage. Current treatment regimens recommend a dosage increase in patients with persistent attacks and/or inflammation [6, 8], thus patients have already experienced an increase in clinical symptoms. Patients presenting with mild disease at diagnosis measured by the Mor-Score were initially treated with lower colchicine dosages and were at higher risk of a dosage increase in the first 24 months. Thus, as soon as the diagnosis of FMF is established, appropriate colchicine dosages should be applied irrespectively of the disease severity.

In line with previous studies that demonstrated the high sensitivity of S100 molecules in the detection of inflammation in FMF [17, 26, 27], our data prove the clinical relevance of increased S100 serum concentrations in the prediction of a dosage increase in FMF patients already being treated. Furthermore, these data suggest that SAA and CRP are correlated very well with each other; thus, a combined analysis of these parameters does not increase the accuracy of prediction of a dosage increase.

Another reason for prophylactic colchicine application is the prevention of amyloid deposition. Early disease onset [28], the M694V genotype [29, 30], a positive

family history, male sex [31] and environmental factors [32] are predictors for the occurrence of amyloidosis. In this group of patients, it seems to be especially important to limit periods of short-term high and long-term subclinical inflammation by appropriate adjustment of the colchicine dosage. Thus, in this group the predictors for an upcoming dosage increase should be evaluated carefully. But given that a recently performed meta-analysis could not identify any inflammation marker that is superior over the others in order to predict long-term outcome, it is not possible to define a limit of acceptable subclinial inflammation [7].

In summary, this work comprehensively analysed factors influencing colchicine therapy in children and adolescents with FMF and demonstrated the usefulness of S100 molecules as biomarkers for dosage increases of colchicine. Although colchicine dosage will still be guided mainly by the occurrence of clinical symptoms and inflammation, the risk factors described will help to adapt the treatment intensity individually in order to prevent disease exacerbation in the upcoming months and years.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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