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Adherence to best practice consensus guidelines for familial Mediterranean fever: a modified Delphi study among paediatric rheumatologists in Turkey

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Abstract

Background Although not validated fully, recommendations are present for diagnosis, screening and treatment modalities of patients with familial Mediterranean fever (FMF).

Objective To review the current practices of clinicians regarding FMF and reveal their adherence to consensus guidelines.

Methods Fifteen key points selected regarding the diagnosis and management of FMF were assessed by 14 paediatric rheumatologists with a three-round modified Delphi panel.

Results Consensus was reached on the following aspects: genetic analysis should be ordered to all patients when clinical findings support FMF, but its result is not decisive alone. In the absence of clinical features, colchicine should be commenced when two pathogenic alleles and family history of amyloidosis are present. Serum amyloid A testing at each visit is recommended in patients resistant to colchicine, with subclinical inflammation and family history of amyloidosis. Consensus was reached on both the definition of colchicine resistance and starting biologic in resistant cases. Cost, efficiency, ease of use, treatment adherence, accessibility and emergence of adverse events are the factors affecting the choice of biologic agents. In patients without any attack and evidence of subclinical inflammation within the last 6 months following initiation of biologics, treatment dose intervals can be prolonged.

Conclusion A consensus was achieved regarding the routine diagnosis and screening and treatment of FMF patients. The definition of colchicine resistance was made and a protocol was created for prolongation of treatment intervals of biologic agents. We anticipate that the results of the study reveal real-life data on the approach to patients in clinical practice.

Keywords Familial Mediterranean fever · Children · Delphi technique · Colchicine · Colchicine resistance · Biological agents

Introduction

Familial Mediterranean fever (FMF) is the most prevalent inherited autoinflammatory disease and is considerably common among people from the Mediterranean basin such as Turks, Arabs, non-Ashkenazi Jews and Armenians, but is increasingly being reported from other countries not related to this region [1]. It is characterized by recurrent inflammatory attacks of fever and serositis, and increased risk of amyloidosis [2]. Colchicine is the standard treatment and is endorsed effective in preventing attacks and development of amyloidosis [3]. Biologic treatments such as interleukin-1 (IL-1) blocking agents are considered as a treatment of choice for colchicine resistant patients [3–5].

Highly variable phenotypes exist among FMF patients due to the differences in gene penetration, the impact of environmental factors and presence of modifier genes influencing the development of amyloidosis [6]. The heterogeneous

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course of disease complicates the diagnostic and therapeutic approaches of the physicians. Two sets of diagnostic criteria, the classic Tel Hashomer criteria and more recent Livneh criteria, have been developed for the diagnosis of FMF in adult patients to provide convenience and standardization in diagnosis [7]. In 2009 a new criteria for paediatric patients was put forward by a Turkish group [8], and validated in French children and in different ethnic groups in Europe and eastern Mediterranean basin [9, 10]. Most recently, the new Eurofever/Paediatric Rheumatology International Trials Organisation (PRINTO) criteria was introduced in 2019, which combined clinical manifestations with genotype for the first time [11] (Supplementary document). Although there are diagnostic criteria, diagnosis of FMF depends mainly on clinical basis and on the level of experience of the clinician, and there are some conflicting issues such as atypical clinical findings with the presence of a positive genetic test [12]. Furthermore, response to treatment with colchicine or IL-1 blocking agents differ among patients and there is still no consensus for the definition of inadequate response to colchicine for switching the treatment to IL-1 blocking agents [13].

In 2015, recommendations for genetic diagnosis of FMF were introduced by "Single Hub and Access point for paediatric Rheumatology in Europe" (SHARE). The following year, "European League Against Rheumatism" (EULAR) introduced the recommendations for diagnosis and management of FMF [12, 14]. Turkey is one of the countries with the highest prevalence of FMF estimated as 1/1000 [1, 15], so it's of interest both to document the clinical practices of the experienced paediatric rheumatologists dealing with a huge patient population and their adoption to existing formal recommendations and current guidelines, as real-life data. A consensus based on the real-life data obtained from an FMF prevalent country might be a model for the clinicians dealing with the diagnosis and management of FMF. This study aims to reveal adherence of clinicians to existing guidelines and document the current clinical practices of field experts from tertiary centres in Turkey, regarding the diagnosis and management of FMF. Another objective of the study is to settle a consensus based protocol for prolongation of biologic treatment dose intervals when patients are accepted to be in remission.

Methods

Study participants

The study was conducted by the Paediatric Rheumatology Academy-Research Group (PeRA-RG). The members of the PeRA-RG are paediatric rheumatologists (PRs) working in regional tertiary centres in different cities of Turkey [16]. The invitation mails for the study were sent to 20 PRs who are members of PeRA-RG. Fourteen PRs accepted to participate in the study and six PRs denied to participate either due to their busy working schedule or due to COVID-19 pandemics. The Delphi panel consisting of 14 panellists from 11 centres was established. All participants are expert in diagnosis, follow-up and management of FMF and number of FMF patients seen per week by each PRs was at least 40. (Supplementary document).

Delphi method

Delphi is a method for structuring a group communication process to deal with a complex problem [17]. It is conducted via multi-step questionnaires preserving participant anonymity, and by providing feedback information to participants between steps. It has been widely used across many disciplines including rheumatology, to elicit consensus on a topic, but it is also used to investigate a wide range of opinions without achieving a consensus. Since the Delphi technique does not require face-to-face meetings, it allows group communication between people in different geographic areas [18, 19].

In the first stage of the Delphi exercise of this study, a detailed literature search was performed by a paediatric rheumatology fellow (GKK) and a review of the literature was carried out and a shortlist of 15 key points were selected by three paediatric rheumatologists (NAA, BS, HES). These key points comprised of; (1) clinical and laboratory parameters for diagnosis and initiation of colchicine therapy, (2) requesting genetic analysis, (3) the impact of the result of genetic analysis on commencing colchicine treatment, (4) follow-up frequency of patients, (5) monitorization of the patients by laboratory parameters during follow-up, (6) evaluation of FMF attacks, (7) utilization of outcome measurements, (8) adjustment of colchicine dosage, (9) evaluation of the response to colchicine, (10) decision making for resistance to colchicine therapy, (11) indications for commencing biologic treatment, (12) factors affecting biologic drug selection, (13) evaluation of the response to biologic treatment, (14) convenience of prolongation of biologic treatment dose intervals when the patient is in remission, and (15) settling a protocol for prolongation of the intervals between biologic doses.

A three-round modified Delphi panel was assessed by all panellists by answering questionnaires sent via an e-mail. In the first round of the Delphi exercise, panellists were requested to answer open-ended questions to define their general opinions and stimulate the generation of new ideas. In the second round, key points were converted to statements with a 9-point Likert scale (1 = strongly disagree, 9 = strongly agree). In the third round, the statements that could not be reached consensus in the previous round were

asked again. A summary of the previous answers of the entire group was provided before each round and the panellists were requested to re-evaluate their answers.

Ethics

Approval was obtained for the study protocol from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved: 31/08/2020- 145479). The study was carried out complied with the Declaration of Helsinki.

Data management and statistical analysis

Data from each statement was collected using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS 17.0 (IBM, Armonk, NY) for the survey analysis. Descriptive statistics including mean, mode, median, percentage and interquartile ranges were conducted for each statement.

A statement was deemed consensual in agreement if it was voted 7–9 on the Likert scale by at least 75% of the participants, and the mean of all responses were greater than 7 for this statement. A statement was deemed consensual in disagreement if it was voted 1–3 on the Likert scale by at least 75% of the participants, and the mean of all responses were less than 3 for this statement.

Results

A total of 14 PRs from 11 paediatric rheumatology centres were involved to the study. All participants completed the survey. It was reported that 6 PRs were examining 80–120, 6 PRs were examining 40–80, 2 PRs were examining 120–160 children with the diagnosis of FMF per week. The frequency of colchicine resistance among patients they followed was asked to the panellists; 10 PRs reported the frequency as 5–10%, 3 PRs as 10–14% and 1 PR as 15–20%.

Turkish paediatric FMF criteria is used by all panellists, Eurofever/PRINTO criteria is used by 9 panellists, Tel Hashomer criteria is used by 7 panellists and Livneh criteria is used by 1 panellist.

Consensus reached statements

The statements that reached a consensus regarding to diagnosis of FMF, colchicine therapy, management of the patients with FMF, evaluation of response to colchicine and biologic treatment are presented in the Table 1.

For diagnosis; a consensus was reached for the following aspects: FMF should be diagnosed according to certain classification criteria, genetic analysis should be ordered when clinical findings support FMF, the result of genetic testing alone cannot be considered decisive for diagnosis (Table 1).

For colchicine treatment; a consensus was reached for the following aspects: colchicine therapy should be initiated at the time of diagnosis, colchicine therapy should be initiated when two pathogenic alleles and family history of amyloidosis are present, colchicine therapy should be started at low doses and dose should be increased to receive a response without side effects until the maximum dose recommended for the patient's age is reached and presence of subclinical inflammation is an indication for increasing colchicine dose (Table 1).

For follow-up; a consensus was reached for the following aspects: screening periods of patients with FMF should not be longer than 6 months of duration, the newly initiated treatment of the patients should be monitored at least every 3 months, until the disease is stable (Table 1).

To evaluate colchicine response; a consensus was reached for the following aspects: decrease in duration and number of attacks is confirmative for defining response to colchicine treatment, colchicine resistance is defined as the presence of six or more attacks per year or ≥ 3 attacks in a 4–6-month period or elevation of two or more of the acute phase reactants in incomplete attacks, or evidence of subclinical inflammation between attacks (Table 1).

For biologic treatment; a consensus was reached for the following aspects: biologic agents should be commenced in resistant FMF patients and patients with amyloidosis, decrease in duration and number of attacks and cease of subclinical inflammation are accepted as response to biologics, prolongation of treatment intervals of biologic agents should be considered, in patients without any attack and laboratory evidence of subclinical inflammation within the last 6 months following initiation of biologics, the treatment intervals can be prolonged to twice the original dose intervals, after the prolongation of treatment intervals, in patients without any attack and laboratory evidence of subclinical inflammation within the last 1 year, the treatment intervals can be prolonged to three times the original dose intervals (Table 1).

Indecisive statements

Responses were indecisive (insufficient to form a consensus in neither direction), regarding the following aspects: initiating colchicine therapy to patients with a positive genetic testing with two pathogenic alleles but without the typical features of FMF, routine testing of serum amyloid A (SAA) or protein/creatinine in spot urine at each visit, formal scoring systems such as Auto-Inflammatory Diseases Activity Index (AIDAI), visual analogue scale (VAS) and FMF50 scoring as applicable at each visit, erythrocyte sedimentation rate (ESR) testing during an FMF attack, the use of formal scoring systems to evaluate the response to colchicine

Table 1 The statements that reached a consensus with the median scores and the numbers of participants who agreed

	Median (Minimum–maximum)	Number of participants who agreed (*n*)
1. Diagnosis of FMF		
FMF should be diagnosed according to certain classification criteria	9 (9–9)	14
Genetic analysis should be ordered to all patients when clinical findings support FMF	9 (2–9)	12
The result of genetic testing alone cannot be considered decisive for diagnosis	9 (3–9)	12
2. Initiation of colchicine therapy		
Colchicine is the first choice of treatment for FMF patients	9 (9–9)	14
Colchicine therapy should be initiated at the time of diagnosis	9 (9–9)	14
Colchicine therapy should be initiated when two pathogenic alleles and family history of amyloidosis are present, even in the absence of typical features	9 (2–9)	13
3. Adjustment of colchicine dose		
Colchicine therapy should be started at low doses (0.5 mg/day) and dose should be increased until the maximum dose for the patient (based on the calculation depends on age/body surface area/body weight of the patient) (maximum 2 mg/day) for receiving a response without emergence of side effects	9 (9–9)	14
Colchicine dose is calculated based on the age of the patients in routine clinical practice ($\leq$0.5 mg for $<$5 years of age, 1 mg for 5–10 years of age, 1.5 mg for $>$10 years of age)	9 (1–9)	12
Laboratory evidence of subclinical inflammation is an indication for increasing colchicine dose	9 (7–9)	14
Colchicine dose should be reduced if the liver enzymes were 2 times higher than normal levels	9 (5–9)	13
4. Screening periods		
Screening periods of patients with FMF should not be longer than 6 months of duration	9 (7–9)	14
The newly initiated treatment of the patients should be monitored at least every 3 months, until the disease is stable	9 (2–9)	12
Colchicine-resistant patients should be monitored at least every 3 months	9 (5–9)	13
5. Evaluation of laboratory parameters		
Complete blood count testing should be performed at each visit	9 (9–9)	14
CRP testing should be performed at each visit	9 (9–9)	14
ESR testing should be performed at each visit	7.5 (4–9)	12
SAA testing should be performed at each visit in patients resistant to colchicine	9 (1–9)	13
SAA testing should be performed at least once per year nevertheless the disease is stable	9 (8–9)	14
SAA testing should be performed in patients with elevation in other acute phase reactants	9 (5–9)	12
SAA testing should be performed in patients with a positive family history of amyloidosis	9 (3–9)	12
Liver and kidney function tests should be performed at each visit	9 (9–9)	14
Urinalysis should be performed at each visit	9 (9–9)	14
If proteinuria is detected in the urinalysis, it should be confirmed with quantitative tests in 24-h urine	9 (9–9)	14
6. Evaluation of FMF attacks		
During an FMF attack, complete blood count testing should be performed	9 (9–9)	14
During an FMF attack, CRP testing should be performed	9 (9–9)	14
During an FMF attack, urinalysis should be performed to exclude other causes which would mimic an attack	9 (3–9)	13
7. Evaluation of response to colchicine		
Decrease in number of attacks is indicative of a response to colchicine treatment	9 (3–9)	13
Decrease in duration of attacks is indicative of a response to colchicine treatment	8 (3–9)	13
Cease in subclinical inflammation is indicative of a response to colchicine treatment	9 (7–9)	14
8. Definition of colchicine resistance		
Colchicine resistance is defined as the presence of six or more attacks per year or $\geq$3 attacks in a 4–6 month period or elevation of two or more of the acute phase reactants in incomplete attacks, or evidence of subclinical inflammation between attacks	9 (8–9)	14
Failure to achieve an adequate improvement in quality of life scales is indicative for colchicine resistance	7 (5–9)	11
Less than 50% reduction in FMF 50 scoring for 5 out of 6 criteria is indicative of colchicine resistance	7 (7–9)	14

Table 1 (continued)

	Median (Minimum–maximum)	Number of participants who agreed (*n*)
9. Commencing biologic treatment		
Biologic agents should be commenced in colchicine resistant FMF patients	9 (7–9)	14
Biologic agents should be commenced in patients with amyloidosis	9 (4–9)	13
Colchicine treatment should not be discontinued in patients ongoing biological therapy	9 (7–9)	14
Factors effecting the choice of biologic agents are		
Cost	7 (2–9)	11
Efficiency	9 (9–9)	14
Ease of use	9 (7–9)	14
Treatment adherence	9 (7–9)	14
Accessibility	8.5 (7–9)	14
Presence of adverse events during biologic agent treatment	9 (6–9)	13
10. Evaluation of response to biologic treatment		
Decrease in number of attacks is indicative of a response to biologic treatment	9 (5–9)	13
Decrease in duration of attacks is indicative of a response to biologic treatment	8.5 (5–9)	13
Cease in subclinical inflammation is indicative of a response to biologic treatment	9 (6–9)	13
Outcome measurements such as AIDAI, VAS and FMF50 scoring should be performed at each visit to evaluate response to biologics	7 (4–9)	11
11. Prolongation of treatment intervals of biologics		
In patients whose attacks are in remission under biologics, prolongation of treatment intervals of biologic agents should be considered	9 (3–9)	12
Patients without any attacks and laboratory evidence of subclinical inflammation within the last 6 months following initiation of biologics, treatment intervals can be prolonged to twice the original dose intervals	7 (2–9)	11
After the prolongation of treatment intervals, patients without any attacks and laboratory evidence of subclinical inflammation within the last 1 year, treatment intervals can be prolonged to three times the original dose intervals	7.5 (1–9)	13

AIDAI auto-inflammatory diseases activity index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FMF* familial Mediterranean fever, *SAA* serum amyloid A, *VAS* visual analogue scale

treatment, accepting adverse reactions to colchicine as a basis for initiating biologics.

Discussion

This study revealed the current real-life trends in the diagnosis and management of FMF from a country where the disease is highly prevalent. Since the survey was assessed by clinicians dealing with a large population of FMF patients, the results suggest a practical approach. Diagnosis and treatment patterns of the panellists mostly followed the current guidelines. As for the controversial issues of the literature such as evaluation of response to colchicine, or laboratory tests in the management of patients, a consensus was reached on many statements.

The diagnosis of FMF is based on the use of diagnostic criteria with the support of genetic testing. The initial implementation of genetic testing has brought a new perspective to diagnostic practices of FMF, and genetic testing is worthwhile both as a diagnostic adjunct and for predicting the severity of the disease and the patients' predispositions to comorbidities, since some mutations were found to be associated with a severe disease course in various studies [20–24].

Whether treatment should be commenced to asymptomatic patients with a positive genetic testing remains controversial in the literature. Various studies have indicated that environmental factors, type of the mutation in *MEFV* gene and genetic changes other than *MEFV* gene may be involve in the development of amyloidosis [25–27]. Current guidelines recommend following these patients closely and considering initiation of treatment if there are risk factors for amyloidosis such as country of residence, family history of amyloidosis and persistently elevated acute phase reactants [12, 14]. The percentage of patients with amyloidosis and severity of the disease have been decreasing in Turkey [28, 29], therefore residing in Turkey alone was not considered to be associated with an increased risk of amyloidosis in asymptomatic patients by the panellists, and a consensus

could not be reached in neither direction on initiation of colchicine treatment in asymptomatic patients, but it seems necessary to follow these patients closely. However, presence of a positive family history for amyloidosis is considered to be an indication to start colchicine in asymptomatic patients with two pathogenic alleles due to the possibility of additional genetic factors that may influence the development of amyloidosis.

With respect to colchicine dose adjustment, the evidence for optimum colchicine dose to prevent attacks in children is scarce. Our study revealed that in routine practice colchicine dose is adjusted mostly according to the patient's age. However, especially for young children, dose adjustment based on body surface area or body weight would be more effective. A recent study also revealed that the best correlation of colchicine intake with a positive response was calculating the dose according to body surface area [30, 31]. The dose can be increased up to 2 mg for receiving a response without emergence of side effects.

During routine follow-up various laboratory tests are beneficial to evaluate drug effectiveness, side effects and subclinical inflammation; however, the evidence supporting monitorization of FMF with any acute phase reactant over the others is still limited [32]. The panellists prefer CRP and ESR testing in every visit due to their availability, but SAA testing at least once a year to every patient, and at each visit in patients who are resistant to colchicine, having other evidence of subclinical inflammation and having a family history of amyloidosis considering its role in the pathogenesis of AA amyloidosis [33].

White blood cell count and CRP testing were considered convenient to evaluate acute phase response during an attack by the panellists. In a study evaluating the laboratory parameters of 168 FMF patients, a correlation between CRP and SAA was found during FMF attacks, therefore the authors concluded that checking for SAA during an FMF attack is not required [33].

The rate of colchicine resistance is reported as 5–10%, and partially response rate is reported as 30–40% in the previous studies [34, 35]. Colchicine resistance was reported 5–15% by 92.86% of our panellists similar to the literature, but 7.14% of the panellists reported higher rates. There is no universally accepted tool for evaluating the response to colchicine and determining colchicine resistance in the literature. Ben-Chetrit et al. proposed to use a scoring system based on percentage reduction in number of attacks [36]. Hentgen et al. defined colchicine resistance as suffering from either more than six typical FMF attacks per year or more than three typical FMF attacks within 4–6 months. In case of incomplete attacks, an increase in at least two out of three acute phase reactants (CRP, ESR and SAA) between attacks is considered mandatory for defining a patient as unresponsive to colchicine [35]. In the recent EULAR recommendations colchicine resistance is defined as having one or more attacks each month despite receiving the maximally tolerated dose of colchicine for at least 6 months [14]. The panellists defined colchicine resistance as the presence of six or more attacks per year or ≥ 3 attacks in a 4–6 month period or elevation of two or more of the acute phase reactants in incomplete attacks, or evidence of subclinical inflammation between attacks, or failure to achieve an adequate improvement in quality of life scales or less than 50% reduction in FMF 50 scoring [37] for 5 out of 6 criteria.

Favourable results have been reported for anti-IL-1 treatments and it has become first choice in patients resistant to colchicine therapy although its long term efficacy and safety has not been yet clarified [38–44]. The panellists accepted the colchicine resistance as an indication for the anti-IL-1 therapy and they reported that they continue colchicine on anti-IL-1 therapy, it's also recommended in the current guidelines as colchicine is the only proven medication in preventing secondary amyloidosis [14, 35].

One of the most noticeable results of the study was the consensus among the panellists that, after a while, treatment intervals could be extended. This opinion was based on the clinical observation that some patients who discontinued anti IL-1 treatment did not experience an attack for a long time, even though they had frequent attacks before initiation of biologic treatment. This could be explained by resetting the autonomous inflammatory state with IL-1 blocking [45]. The protocol for prolonging the biologic treatment intervals was solely determined subjectively by the participants and is needed to be confirmed by controlled studies.

Owing to its interactive, iterative and systematic nature, we believed that the Delphi technique provided more clarified data on controversial aspects compared to a conventional survey. However, our study has some limitations. All participants come from the same country and the number of the participants are limited. Turkey is a country where FMF is highly prevalent and all paediatric rheumatologists in Turkey deal with a large number of FMF patients in their routine clinical practice. The fact that all participants are coming from Turkey may be considered as a limitation, but this might also have led to more uniform results. An international study is also in the future plans of the authors. Another limitation of the study was the lack of a consensus on some aspects as reported in the literature. We believe a stronger scientific evidence is needed on these aspects to form a uniform agreement.

In conclusion, in this study a consensus was achieved regarding the routine screening periods of FMF patients with the convenient laboratory parameters. Recommendations for the initiation of colchicine treatment in asymptomatic patients were made and adjustment of colchicine treatment dose in routine practise was revealed. The definition of colchicine resistance was made and a protocol was created for

prolongation of treatment intervals of biologic agents. We anticipate that the results of the study reveal real-life data on the approach to patients in clinical practice. An international survey may enable us to reach an agreement on issues that we did not reach a consensus.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval Approval was obtained for the study protocol from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved: 31/08/2020- 145479). The study was carried out complied with the Declaration of Helsinki.

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