Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.22039

The Characteristics of Pediatric Patients with Familial Mediterranean Fever Treated with Anti-Interleukin-1 Treatment

Pınar Özge Avar Aydın, Zeynep Birsin Özçakar, Fatma Aydın, Hatice Dilara Karakaş, Nilgün Çakar, Fatoş Yalçınkaya

Department of Pediatric Rheumatology, Ankara University Faculty of Medicine, Ankara, Turkey

What is already known on this topic?

- *Interleukin-1 (IL-1) inhibitors are used in colchicine-resistant patients with FMF.*
- *Interleukin-1 inhibitors are effective in reducing clinical attacks and subclinical inflammation in FMF.*

What this study adds on this topic?

- *Interleukin-1 inhibitors are used in a relatively small number of pediatric patients with FMF.*
- *Pediatric FMF patients presenting with earlier disease onset, acute arthritis, chest pain, and erysipelas-like erythema and carrying pathogenic exon 10 mutations of the MEFV gene show a higher need for IL-1 inhibitors.*

ABSTRACT

Objective: Interleukin-1 inhibitors are effective agents used in colchicine resistance or intolerance during the treatment of familial Mediterranean fever. This study aims to review the characteristics of patients treated with interleukin-1 inhibitors and their long-term follow-up in a large pediatric cohort of familial Mediterranean fever patients.

Materials and Methods: The study was conducted in a pediatric rheumatology reference center. The patients treated with interleukin-1 inhibitors for at least 6 months were included and compared to other patients with familial Mediterranean fever. Clinical and laboratory characteristics of the cohort were recorded.

Results: Among 542 patients with familial Mediterranean fever, 6.1% (n = 33) were treated with interleukin-1 inhibitors. Colchicine resistance was the reason in 82.8% and renal amyloidosis in 17.2% of the patients. Patients with interleukin-1 inhibitors had earlier disease onset and higher frequencies of acute arthritis, chest pain, and erysipelas-like erythema with pathogenic exon 10 mutations of the *MEFV* gene (all $P < .04$). All patients diagnosed with renal amyloidosis also received interleukin-1 inhibitors. Six patients were switched from anakinra to canakinumab or vice versa to control ongoing disease activity. Attack frequency was reduced in all patients.

Conclusion: Interleukin-1 inhibitors are used in a relatively small number of pediatric patients with familial Mediterranean fever. Patients presenting with earlier disease onset, acute arthritis, chest pain, and erysipelas-like erythema and carrying pathogenic exon 10 mutations of the *MEFV* gene may show a higher need for interleukin-1 inhibitors. In pediatric familial Mediterranean fever patients who are resistant to colchicine, interleukin-1 inhibitors seem to be highly effective agents.

Keywords: Anakinra, canakinumab, familial Mediterranean fever, IL-1 inhibitors, pediatrics

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease, mostly seen in Eastern Mediterranean populations and characterized by attacks of fever, chest pain, abdominal pain, and arthritis lasting for 0.5-3 days. Secondary amyloidosis is the major cause of morbidity and mortality that is caused by excessive inflammation.[1] The main goal of treatment in FMF is to decrease disease attacks and to prevent renal amyloidosis by controlling subclinical inflammation, thus increasing the survival and quality of life of the patients. Colchicine has been found effective to achieve these goals by its inhibitory effects on microtubules and pyrin inflammasome.[2] Despite maximum tolerated doses of colchicine, approximately 5-10% of the patients may show insufficient response to colchicine and additional therapeutics may be needed.[3]

Corresponding author:
Fatoş Yalçınkaya
fatos.yalcinkaya@medicine.ankara.edu.tr
Received: February 10, 2022
Accepted: April 1, 2022

Cite this article as: Avar Aydın PÖ, Özçakar ZB, Aydın F, Karakaş HD, Çakar N, Yalçınkaya F. The characteristics of pediatric patients with familial mediterranean fever treated with anti-interleukin-1 treatment. *Turk Arch Pediatr.* 2022;57(4):448-452.

Interleukin-1 (IL-1) is the main proinflammatory cytokine in FMF. The gain-of-function mutations in the *MEditerranean FeVer* (*MEFV*) gene cause a decrease in the activation threshold of the pyrin inflammasome. Aberrant pyrin inflammasome activity triggers the release of IL-1β and IL-18 and the magnitude of this response is dependent on a gene-dosage effect.[4,5] On the other hand, reduced expression of IL-1 receptor antagonist (IL-1Ra) in patients with FMF causes a deteriorated anti-inflammatory capacity, regardless of colchicine treatment.[6] The use of IL-1 inhibitors has been found effective in the treatment of FMF since the evident role of IL-1 in pathogenesis.[7] Today, anakinra (a recombinant IL-1Ra), canakinumab (human monoclonal antibody against IL-1β), and rilonacept (a soluble decoy receptor of IL-1β) are used in colchicine resistance or intolerance. They are generally added to colchicine because their efficacy in the prevention of renal amyloidosis is not clear although suppressing aberrant inflammation may prohibit this lethal complication.[8] Current data on the long-term follow-up of pediatric FMF patients using IL-1 inhibitors are still limited.

This study aims to present the characteristics of patients treated with IL-1 inhibitors, their long-term follow-up, and differences from other patients in a pediatric cohort of FMF patients.

MATERIALS AND METHODS

Study Population

Patients with a diagnosis of FMF who were followed in our pediatric rheumatology outpatient clinic in the last 5 years (2016-2021) were included in this retrospective cohort study. The inclusion criteria were: (1) a diagnosis of FMF according to Turkish pediatric criteria,[9] (2) a follow-up of FMF for at least 6 months, and (3) the usage of IL-1 inhibitors for at least 6 months for patients using IL-1 inhibitors. The study complies with the Declaration of Helsinki and the study protocol was approved by Ankara University Faculty of Medicine Human Research Ethics Committee (number: i8-540-20).

Study Procedures

Electronic medical records of the patients were used to register the demographic, clinic, and laboratory data. Colchicine was initiated with a dosage of 1.00 mg/m^2/day for a maximum dose of 2 mg/day after the diagnosis of FMF. Subclinical inflammation was defined as increased acute phase reactants (APRs: serum C-reactive protein, erythrocyte sedimentation rate, and fibrinogen) in between FMF attacks under regular colchicine treatment.[10,11] Further, when defining subclinical inflammation in the cohort, there were no other reasons such as infections or FMF-associated inflammatory diseases that might also increase APRs. Colchicine resistance was accepted as ongoing disease activity characterized by frequent FMF attacks (1 or more clinical attacks monthly over 3 months) or subclinical inflammation for patients receiving a maximum tolerated dose of colchicine.[12] The presence of symptoms related to the use of colchicine that prevented reaching an effective dose defined colchicine intolerance.[12] Starting dose of anakinra was 1-2 mg/kg/day with a maximum dose of 100 mg/day and a dose of 2-4 mg/kg for every 4-6 weeks with a maximum of 150 mg/dose for canakinumab was used. An increase in dosage of these agents had been done before switching to the other agent when recurrent attacks continued despite the initiated IL-1 inhibitor. The disease remission to discontinue IL-1 inhibitors had been accepted as an attack-free period for at least 1 year. Exon 10 mutations of the *MEFV* gene were studied by direct sequencing of the PCR-amplified fragments and exon 2 mutations by PCR-restricted fragment polymorphism protocol including at least 6 mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, and p.E148Q) were noted.

Statistical Analysis

The IBM Statistical Package for the Social Sciences (SPSS) Statistics 21.0.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY, USA: IBM Corp) was used for statistical analysis. The characteristics of the study population were presented with descriptive statistics: continuous variables by mean ± standard deviation or median (minimum-maximum) and categorical variables by frequency (n) and percentage (%). The Kolmogorov–Smirnov test or the Shapiro–Wilk test and distribution graphs were performed to test normal distribution. The categorical variables between groups were compared by the chi-square test and the Fisher's exact test while the Mann–Whitney *U* test was used for continuous variables. The statistical significance level was $P \leq .05$.

RESULTS

Patient Characteristics

Among 542 patients with FMF, 6.1% (n = 33) of the patients were found to receive IL-1 inhibitors. Four patients who were on IL-1 inhibitors for less than 6 months or left follow-up while on IL-1 inhibitors were excluded from group analysis. The demographic and clinical features of the patients treated with IL-1 inhibitors are presented in Table 1 and their comparison to other patients in the cohort in Table 2.

Table 1. The Demographic, Clinical, and Genetic Features of Patients Diagnosed with Familial Mediterranean Fever and Treated with IL-1 Inhibitors

	n = 29 (%) or Mean ± Standard Deviation
Female	17 (58.6)
Age at diagnosis of familial Mediterranean fever, years	6.10 ± 4.40
Follow-up, years	10.77 ± 4.03
Familial Mediterranean fever-associated diseases	
Inflammatory bowel disease*	2 (6.9)
Sacroiliitis	2 (6.9)
Chronic nonbacterial osteomyelitis*	1 (3.4)
Undifferentiated vasculitis	1 (3.4)
Juvenile idiopathic arthritis	1 (3.4)
Familial history	
Familial Mediterranean fever	20 (69.0)
Renal amyloidosis	6 (20.7)
MEditerranean FeVer gene mutations	
M694V/M694V	23 (79.3)
M694V/M680I	3 (10.3)
M694V/V726A	1 (3.4)
M694V/R761H	1 (3.4)
M694V/-	1 (3.4)

*One patient had both inflammatory bowel disease and chronic nonbacterial osteomyelitis.

Table 2. The Comparison of Clinical and Genetic Features of Patients Treated with IL-1 Inhibitors and Other Patients with a Diagnosis of FMF

	Patients Treated with IL-1 Inhibitors (n = 29)	Other Patients in the Cohort (n = 509)	*P*
Female	17 (58.6)	266 (52.3)	.505[a]
Age at onset of familial Mediterranean fever, years	2.72 ± 2.36	3.76 ± 3.69	**.024**[b]
Clinical findings of familial Mediterranean fever			
Fever	29 (100)	470 (92.3)	.256[c]
Abdominal pain	27 (93.1)	445 (87.4)	.561[c]
Acute arthritis	15 (51.7)	122 (24.0)	**.002**[c]
Chest pain	13 (44.8)	118 (23.2)	**.013**[c]
Other findings related to familial Mediterranean fever			
Erysipelas-like erythema	6 (20.7)	41 (8.1)	**.032**[c]
Protracted febrile myalgia	2 (6.9)	8 (1.6)	.097[c]
Familial Mediterranean fever-associated diseases	6 (20.7)	52 (10.2)	.113[c]
MEditerranean FeVer gene mutations			
Biallelic exon 10 mutations	28 (96.6)	280 (55.0)	**<.001**[a]
M694V/M694V	23 (79.3)	137 (26.9)	**<.001**[a]

n (%) or mean ± standard deviation.
[a]Chi-square test,
[b]Mann–Whitney *U* test, or
[c]Fisher's exact test were used.
The statistical significance level was accepted at $P \leq .05$.

Indications of IL-1 Inhibitors

The reason to initiate IL-1 inhibitor was colchicine resistance in 82.8% (n = 24) of the patients whereas 17.2% (n = 5) received it for renal amyloidosis. Colchicine intolerance as an indication of IL-1 inhibitors was not identified in the cohort. Before anti-IL-1 therapy, these patients used colchicine for 6.89 ± 4.00 years. All patients were compliant to colchicine when IL-1 inhibitors were initiated. The mean age at the initiation of IL-1 inhibitors was 13.52 ± 3.40 years and 75.9% (n = 22) of the patients were over 10 years old at the start of therapy. Subclinical inflammation was present in 62.1% (n = 18) of the patients. All patients with renal amyloidosis had proteinuria on admission and they were diagnosed with FMF after that. Two patients with renal amyloidosis received anti-tumor necrotizing factor-alpha agents before the emergence of IL-1 inhibitors.

Follow-Up of Patients Using IL-1 Inhibitors

Anakinra was initiated in 23 patients and 18 of them switched to canakinumab because of the discomfort of daily injections in ten patients, local injection reaction in four patients, and recurrent attacks under anakinra treatment in four patients. Two patients reswitched from canakinumab to anakinra because of the ongoing FMF attacks with canakinumab. Canakinumab was used as the first-line agent in six patients. The median attack number was 0 (0-6.00) during the first and 0 (0-2.00) during the second 6 months of treatment. Twenty-one patients had no attacks while on treatment and all patients experienced a reduction in attack frequency with normalized APRs during follow-up. After the initiation of the IL-1 inhibitor, all patients continued regular colchicine with a mean dosage of 1.24 ± 0.16 mg/m^2/day.

The mean duration of anti-IL-1 therapy was 39.89 ± 26.71 months during follow-up in our pediatric rheumatology clinic. Excluding patients with renal amyloidosis, IL-1 inhibitors were discontinued due to remission in 50% (n = 12) of the patients. Two of them carrying M694V homozygous mutation restarted IL-1 inhibitors after 12 and 18 months because of frequent FMF attacks. Four patients with amyloidosis received kidney transplantation during childhood and continued IL-1 inhibitor after that. Adult rheumatology transfer was achieved in 44.8% (n = 14) of the patients including all patients with renal amyloidosis while on IL-1 inhibitors.

DISCUSSION

This study demonstrated that in a large pediatric cohort of FMF patients, approximately 5% of the patients were treated with IL-1 inhibitors. Patients who needed anti-IL-1 therapy had earlier disease onset and higher frequencies of acute arthritis, chest pain, and erysipelas-like erythema. Further, all patients diagnosed with renal amyloidosis received anti-IL-1 therapy. Strikingly, the majority of the patients carried homozygous M694V mutation and all had at least 1 M694V mutation.

Familial Mediterranean fever is characterized by episodes of exaggerated inflammatory response that can be stimulated by pro-inflammatory environmental triggers such as infections or stress. Most of the patients do not show enhanced inflammation in between these episodes with undetectable levels of IL-1β.[4] The disease dynamic in this group of patients is termed "hyperinflammatory state".[13] Although FMF is an autoinflammatory disease that generally shows hyperinflammatory dynamics, some patients may experience an "autonomous inflammatory state" with frequent clinical attacks or subclinical inflammation in between attacks despite the maximum tolerated dose of colchicine.[14] Biologic agents that block IL-1 activity may stabilize the disease course and patients with frequent FMF attacks or subclinical inflammation may achieve a good response to colchicine again.[13] In accordance with these

terms, around 5% of the patients in the current study needed IL-1 inhibitors and the major reason was colchicine resistance which constituted more than 80% of the reasons. The second reason to use IL-1 inhibitors was renal amyloidosis. Colchicine intolerance was not identified in the cohort. More than half of the patients in need of IL-1 inhibitors demonstrated subclinical inflammation. Although these patients had earlier onset of FMF, they were followed with colchicine for almost 7 years before IL-1 inhibitor therapy, more than 75% of them were in the pubertal period and were compliant to colchicine when IL-1 inhibitors were initiated. This result may reflect the heightened inflammatory state along with stressful events during puberty and point to an increasing need for IL-1 inhibitors in this critical period of life.

A recent genotype-phenotype study of a large pediatric FMF cohort from Turkey clearly distinguished that homozygous M694V mutation carried strikingly higher risks for early-onset disease, chest pain, arthritis, erysipelas-like erythema (ELE), protracted febrile myalgia, and secondary amyloidosis compared to other mutations.[15] These findings were similarly reported by several studies.[16–19] Further, a gene-dosage effect was shown by significantly higher levels of IL-1β in patients with homozygous M694V mutations compared to heterozygous M694V mutations.[4] In this study, almost all patients treated with IL-1 inhibitors had biallelic exon 10 mutations with a predominance of M694V homozygosity. Several clinical differences were also found between patients treated with IL-1 inhibitors and others in the cohort. The frequencies of acute arthritis, chest pain, and ELE were more frequently seen in patients using IL-1 inhibitors. The presence of these clinical features may help to identify the patients with excessive inflammation earlier. Besides, all patients with renal amyloidosis were treated with IL-1 inhibitors and all had proteinuria at the diagnosis of FMF. Although the effect of IL-1 inhibitors on the prevention of renal amyloidosis is not clear and it is suggested to use them in combination with colchicine, the decreased prevalence of secondary amyloidosis in recent years may have resulted from their effect on suppressing exaggerated and subclinical inflammation. In the current study, IL-1 inhibitors were continued together with colchicine in patients with renal amyloidosis through the adult transition, even after kidney transplantation.

There is no consensus on the preference among different IL-1 inhibitors. Reimbursement conditions of the country, the price of the agent, and the social and living conditions of the patients affect the choice of IL-1 inhibitors. Anakinra has been used as the first agent when patients need IL-1 inhibitors in Turkey. Allergic reactions to anakinra and living conditions of the patients (living in a dorm, not being able to do daily injections, etc.) permit the use of canakinumab. Hence, the majority of the patients with IL-1 inhibitors in the study were treated with anakinra at the beginning. The discomfort of daily injections and local injection reactions were the main reasons for switching to canakinumab. Further, around 15% of the patients who continued to have frequent FMF attacks while on anakinra were also switched to canakinumab and the disease attacks were successfully controlled by this agent. Besides, 2 patients whose attacks were under control with anakinra and switched to canakinumab were treated again with anakinra due to the emergence of frequent FMF attacks under canakinumab. This conflict might have been caused by different mechanisms of action of both agents. Overall, almost 75% of the patients experienced a complete response without any FMF attacks with IL-1 inhibitors and all patients had a decrease in attack frequency during follow-up. These results delineate that anti-IL-1 inhibitors, anakinra, and canakinumab have high efficacy in colchicine-resistant pediatric patients with FMF.

The major limitation of the study was its retrospective design. Although many patients were transferred to adult rheumatology while on IL-1 inhibitors and these follow-up data were missing, this study provides demographic, clinical, and genetic features of pediatric FMF patients treated with IL-1 inhibitors with a relatively long follow-up till adulthood in a reference center.

In conclusion, IL-1 inhibitors are needed in a relatively small number of pediatric patients with FMF. Patients presenting with acute arthritis, chest pain, and ELE in early ages of childhood may have a higher need for IL-1 inhibitors. Additionally, pathogenic exon 10 mutations of the *MEFV* gene are more common in these patients. Although there is no superiority data among currently available IL-1 inhibitors, patients' conditions and legal regulations of the country may assign the agent. In pediatric FMF patients who are resistant to colchicine, IL-1 inhibitors seem to be highly effective agents.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara University Faculty of Medicine (Approval No: i8-540-20).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.Ö.A.A., Z.B.Ö., F.A., N.Ç., F.Y.; Design – P.Ö.A.A., Z.B.Ö.; Supervision – Z.B.Ö., F.A., N.Ç., F.Y.; Funding – None; Data Collection and/or Processing – P.Ö.A.A, D.K.; Analysis and/or Interpretation – P.Ö.A.A., Z.B.Ö.; Literature review – P.Ö.A.A., Z.B.Ö., F.A., N.Ç., F.Y.; Writing – P.Ö.A.A., Z.B.Ö.; Critical Review – Z.B.Ö., F.A., N.Ç., F.Y.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet*. 1998;351(9103):659-664. [CrossRef]
2. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum*. 2015;45(3):341-350. [CrossRef]
3. Özçakar ZB, Özdel S, Yılmaz S, Kurt-Şükür ED, Ekim M, Yalçınkaya F. Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. *Clin Rheumatol*. 2016;35(2):441-446. [CrossRef]
4. Jamilloux Y, Lefeuvre L, Magnotti F, et al. Familial Mediterranean fever mutations are hypermorphic mutations that specifically decrease the activation threshold of the pyrin inflammasome. *Rheumatology (Oxford)*. 2018;57(1):100-111. [CrossRef]

5. Chae JJ, Cho YH, Lee GS, et al. Gain-of-function pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice. *Immunity*. 2011;34(5):755-768. [CrossRef]
6. Mortensen SB, Hansen AE, Mogensen TH, et al. Pyrin inflammasome activation abrogates interleukin-1 receptor antagonist, suggesting a new mechanism underlying familial Mediterranean fever pathogenesis. *Arthritis Rheumatol*. 2021;73(11):2116-2126. [CrossRef]
7. Ugurlu S, Ergezen B, Egeli BH, Selvi O, Ozdogan H. Anakinra treatment in patients with familial Mediterranean fever: a single-centre experience. *Rheumatology (Oxford)*. 2021;60(5):2327-2332. [CrossRef]
8. Hentgen V, Vinit C, Fayand A, Georgin-Lavialle S. The use of interleukine-1 inhibitors in familial Mediterranean fever patients: a narrative review. *Front Immunol*. 2020;11:971. [CrossRef]
9. Yalçınkaya F, Özen S, Özçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology (Oxford)*. 2009;48(4):395-398. [CrossRef]
10. Tunca M, Kirkali G, Soytürk M, Akar S, Pepys MB, Hawkins PN. Acute phase response and evolution of familial Mediterranean fever. *Lancet*. 1999;353(9162):1415. [CrossRef]
11. Korkmaz C, Özdogan H, Kasapçopur O, Yazici H. Acute phase response in familial Mediterranean fever. *Ann Rheum Dis*. 2002;61(1):79-81. [CrossRef]
12. Özen S, Sag E, Ben-Chetrit E, et al. Defining colchicine resistance /intolerance in patients with familial Mediterranean fever: a modified-Delphi consensus approach. *Rheumatology (Oxford)*. 2021;60(8):3799-3808. [CrossRef]
13. Gül A. Dynamics of inflammatory response in autoinflammatory disorders: autonomous and hyperinflammatory states. *Front Immunol*. 2018;9(2422):2422. [CrossRef]
14. Gül A. Approach to the patients with inadequate response to colchicine in familial Mediterranean fever. *Best Pract Res Clin Rheumatol*. 2016;30(2):296-303. [CrossRef]
15. Ayaz NA, Tanatar A, Karadağ ŞG, Çakan M, Keskindemirci G, Sönmez HE. Comorbidities and phenotype-genotype correlation in children with familial Mediterranean fever. *Rheumatol Int*. 2021;41(1):113-120. [CrossRef]
16. Tunca M, Ozdogan H, Kasapcopur O, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Med (Baltim)*. 2005;84(1):1-11. [CrossRef]
17. Grossman C, Kassel Y, Livneh A, Ben-Zvi I. Familial Mediterranean fever (FMF) phenotype in patients homozygous to the MEFV M694V mutation. *Eur J Med Genet*. 2019;62(6):103532. [CrossRef]
18. Duşunsel R, Dursun I, Gündüz Z, Poyrazoğlu MH, Gürgöze MK, Dundar M. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. *Pediatr Int*. 2008;50(2):208-212. [CrossRef]
19. Ozturk K, Cakan M. The analysis of genotype-phenotype correlation in familial Mediterranean fever. *Pediatr Int*. 2021;64(1):e15017. [CrossRef]