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Original Article

Efficacy of anti-interleukin-1 treatment in colchicine-resistant arthritis in patients with familial Mediterranean fever

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Abstract

Objective: In the familial Mediterranean fever (FMF) clinic, arthritis is among the most common symptoms, and it generally responds well to colchicine treatment. However, cases of patients with chronic prolonged colchicine-resistant arthritis have been reported, and there are inadequate studies on the treatments to be used for such patients.

Methods: This study included 18 patients diagnosed with FMF who had colchicine-resistant chronic arthritis and received anti-interleukin (IL)-1 treatment for at least 1 year. The clinical and laboratory data of the patients were retrospectively retrieved from the database of our hospital.

Results: Remission was achieved in arthritis attacks in 16 of 18 patients who started anti-IL-1 therapy because of colchicine-resistant chronic arthritis. The clinical and laboratory values of the other 2 patients improved, but complete remission could not be achieved. The treatment dose of colchicine was reduced with anti-IL-1 therapy. In addition to the improvement in arthritis symptoms, remission was achieved in other clinical findings of FMF by anti-IL-1 therapy. In this study, with an average follow-up time of 33 months, no adverse effects requiring discontinuation were observed in any patient.

Conclusion: Anti-IL-1 therapy is effective and reliable in the treatment of colchicine-resistant chronic FMF arthritis. The efficacy of anti-IL-1 therapy was realized without concomitant disease-modifying antirheumatic drug therapy, despite the reduction in colchicine dose.

Keywords: Anti-interleukin-1 antagonist protein, arthritis, familial Mediterranean fever

Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent, self-limited attacks of fever and serositis (1). Attacks usually last for 1-3 days, and fever is most often accompanied by abdominal pain caused by peritonitis (2). Other major clinical findings are arthritis, chest pain, myalgia, and skin rash, which often appears on the back of the foot (3). Clinical characteristics, duration of attacks, and severity of the disease may differ among individuals and ethnic groups and particularly affect those of Eastern Mediterranean origin (Turkish, Arab, Armenian, and Jewish) more often (1, 4).

In 1997, the discovery of the Mediterranean fever gene (MEFV) localized on the short arm of the 16th chromosome (16p13.3) has been a turning point in elucidating the etiopathogenesis of the disease. The MEFV gene encodes a protein known as pyrin with 781 amino acids (5, 6). Malfunctioning of pyrin causes the activation of caspase-1 that is responsible for the onset of inflammation and overexpression of interleukin (IL)-1ß (7).

Arthritis in the FMF clinic is one of the most common symptoms (8). Articular involvement of FMF is usually in the large joints of the lower extremities in the form of acute monoarthritis (9). The attacks of acute arthritis usually heal without causing permanent deformity, whereas severe, prolonged form of chronic arthritis can last for months or even years and result in persistent deformity (10). Arthritis may be the first clinical finding of FMF, but there are cases of FMF that occur only with arthritis attacks (11). Like other clinical findings of FMF, the prevalence of arthritis differs among ethnic groups (12). In addition, M694V mutation causes more frequent and severe arthritis involvement compared with other mutations (13, 14).

Although colchicine therapy, which is used to prevent FMF attacks, prevents the development of amyloidosis with regular use, it is not always effective in treating chronic prolonged arthritis. Therefore, some dis-

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ease-modifying antirheumatic drugs (DMARDs) and anti-tumor necrosis factor (anti-TNF) treatments have been used (15, 16). Although anti-IL-1 therapies are effective in preventing FMF attacks in cases of colchicine-resistant FMF, there are inadequate studies that have investigated its efficacy for treating FMF-related and colchicine-resistant arthritis (17).

In this study, we aimed to investigate the prevalence of arthritis in a single-center FMF cohort, clinical characteristics of patients with arthritis, and efficacy of IL-1 inhibitors in the treatment of colchicine-resistant arthritis.

Methods

Patients diagnosed with FMF who visited our Department of Rheumatology between March 01, 2013 and January 31, 2020 were included in the study. Livneh and Tel-Hashomer classification criteria were used as the diagnostic criteria (18). This retrospective study was approved by the Ethics Committee of Ondokuz Mayıs University (Approval Date: June 11, 2020; Approval Number: 2020/412). The patient data were scanned in our hospital's electronic database, and the results were recorded. The patients' sex and age, age of onset of symptoms, age of diagnosis, family history, clinical symptoms (fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, erysipelas-like erythema, vasculitis, and amyloidosis), laboratory results, MEFV gene analysis, and treatments they received were recorded.

We included patients with chronic arthritis whose arthritis continued despite colchicine therapy and who, therefore, received anti-IL-1 therapy for at least 1 year. In our clinic, patients with planned anti-IL-1 therapy are screened for malignancy, tuberculosis, hepatitis, and other infections before the treatment is initiated.

Statistical analysis

Statistical Package for Social Sciences software version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for performing statistical analysis. Using descriptive statistics, the average value, standard deviations, and percentages, were calculated for each clinical finding. Spearman's chi-squared test was used for the evaluation of categorical data, and paired t-test was used for binary comparison of linear data. A p value of <0.05 was considered statistically significant.

Main Points

- Anti-IL-1 therapies are successful in the treatment of colchicine-resistant chronic arthritis in patients with FMF.
- Anti-IL-1 therapies do not need concomitant disease-modifying antirheumatic drug therapy in patients with FMF arthritis.
- Arthritis has been the most common clinical symptom that accompanied fever after peritonitis.

Results

Arthritis involvement was detected in 303 patients (36%) in our cohort of 837 patients diagnosed with FMF. The clinical findings that frequently accompanied arthritis, such as amyloidosis, erysipelas-like erythema, and M694V mutation, were more common in these patients (Table 1). In contrast, peritonitis and pleuritis attacks were less frequent in patients with FMF with arthritis.

Table 2 summarizes the data of 18 patients with chronic arthritis who were resistant to colchicine treatment and who, therefore, received anti-IL-1 therapy for at least 1 year. While 10 patients were administered anakinra 100 mg/day, 8 were on canakinumab 150 mg/month therapy. The major risk factor for chronic colchicine-resistant arthritis was M694V homozygous mutation (Table 3). The period from the diagnosis to the start of anti-IL-1 therapy was 151 (minimum 6 to maximum 360) months. The duration of anti-IL-1 therapy was an average of 33 months. No patient received DMARD in addition to anti-IL-1 therapy. All the patients received colchicine treatment, and the colchicine dose was reduced after anti-IL-1 therapy (Table 3).

Malignancy, tuberculosis, and hepatitis B reactivation did not occur in any patient who received anti-IL-1 therapy, and there were no side effects that resulted in drug discontinuation. Only 1 patient developed pneumonia twice with an interval of 10 months, and this patient is still undergoing anti-IL-1 therapy.

Discussion

The prevalence of arthritis, symptoms accompanying arthritis, risk factors for arthritis development, and efficacy of anti-IL-1 therapy in cases of colchicine-resistant arthritis were investigated in a single-centered FMF cohort study including 837 patients. The prevalence of arthritis in our FMF cohort was 36%, and amyloidosis, erysipelas-like erythema, and M694V mutation were more frequent in patients with arthritis attacks. Overall, 18 patients underwent anti-IL-1 therapy because of colchicine-resistant arthritis, 16 achieved remission, and 2 showed partial response.

In previous studies and our study, arthritis has been the most common clinical symptom that accompanied fever after peritonitis (8, 9). In the majority of cases, the arthritis pattern is acute monoarticular, and the patients recover without spontaneous deformity in a short period of time (19). However, cases of patients with prolonged and colchicine-resistant chronic arthritis have also been reported (20). Although M694V mutation is an important risk factor for the development of arthritis, (21) the major risk factor in our study that predicted the development of colchicine-resistant arthritis has been M694V homozygous mutation.

FMF-associated arthritis most often responds to colchicine treatment. However, some colchicine-resistant patients do not respond to other DMARD treatments, and the studies about this have remained inadequate. There are case reports on the efficacy of sulfasalazine (21), methotrexate (22), and anti-TNF (23)

Table 1. Comparison of patients with FMF with and without arthritis.

	Arthritis (n: 303)	Non-arthritis (n: 534)	p
Gender (female/male)	204/99	311/223	>0.05
Family story	184 (60%)	294 (55%)	>0.05
Amyloidosis	22 (7%)	25 (5%)	0.011
Early start	191 (63%)	322 (60%)	>0.05
IL-1 treatment	31 (10%)	32 (6%)	0.019
Peritonitis	261 (86%)	502 (94%)	<0.001
Erysipelas-like erythema	58 (19%)	30 (5%)	<0.001
Pericarditis	23 (7%)	46 (8%)	>0.05
Pleuritis	124 (40%)	254 (47%)	0.048
M694V positivity	227 (74%)	324 (60%)	<0.001

FMF: familial Mediterranean fever.

Table 2. Clinical features of patients who started anti-IL-1 therapy in this study.

Patient	Age/Sex	MEFV mutations	Anti-IL-1 treatment	Period of anti-IL-1 treatment	Previous treatment	Remission
1	29/F	M694V/ M694V	Anakinra	22 months	Methotrexate Sulfasalazine	Yes
2	29/F	M694V/ M694V	Canakinumab	37 months	Sulfasalazine Leflunomide	Yes
3	29/F	M694V/ M694V	Canakinumab	39 months	Methotrexate Adalimumab Prednisolone	Yes
4	39/M	M694V/ M694V	Anakinra	17 months	-	Yes
5	31/M	M694V/ M680I	Canakinumab	47 months	Methotrexate	Yes
6	19/M	M694V	Anakinra	59 months	Etanercept Methotrexate Sulfasalazine	Yes
7	53/F	M694V/ M694V	Canakinumab	23 months	Infliximab	Yes
8	61/F	M694V	Anakinra	25 months	Sulfasalazine Methotrexate	No
9	47/M	M694V/ M694V	Anakinra	16 months	-	Yes
10	43/F	M694V	Canakinumab	27 months	Sulfasalazine Methotrexate Prednisolone	Yes
11	36/M	M694V/ M694V	Anakinra	49 months	-	Yes
12	31/M	M694V/ M694V	Canakinumab	18 months	Methotrexate	No
13	27/F	M694V/ M694V	Anakinra	55 months	-	Yes
14	22/F	M694V/ M694V	Anakinra	22 months	-	Yes
15	22/M	M694V/ M694V	Anakinra	17 months	-	Yes
16	21/F	M694V	Anakinra	39 months	-	Yes
17	21/F	M694V/ M694V	Anakinra	39 months	-	Yes
18	19/M	M694V/ M694V	Canakinumab	51 months	-	Yes

F: female; M: male; MEFV: Mediterranean fever gene; IL-1: interleukin-1.

Table 3. Clinical and laboratory data before and after anti-IL-1 therapy.

	Before anti-IL-1 treatment	After anti-IL-1 treatment	p
Attack frequency	5.23±1.13	1.23±0.56	<0.001
Sedimentation (mm/h)	58±28	21±20	<0.001
C-reactive protein (mg/L)	51±47	6±8	<0.001
Fibrinogen (g/L)	4.5±3.2	2.2±1.7	<0.001
Colchicine dose (mg)	1.78±0.33	1.15±0.47	<0.001

IL-1: interleukin-1.

treatments in these difficult-to-treat patients and a series of cases that included less number of patients. However, the efficacy of anti-IL-1 therapy, which is effective in controlling colchicine-resistant FMF attacks, is unknown in the treatment of colchicine-resistant arthritis. Only 2 of the 18 patients who started anti-IL-1 therapy because of prolonged colchicine-resistant arthritis had arthritis attacks, whereas the other 16 patients achieved dramatic improvement and remission in terms of arthritis.

The efficacy of anti-TNF treatments has been investigated in a study by Bilgen et al. (23) conducted on 10 patients with colchicine-resistant chronic arthritis and/or sacroiliitis. In this study, in addition to anti-TNF therapy, 3 patients were administered sulfasalazine plus methotrexate, and 1 was administered only sulfasalazine. Remission was achieved in 7 of the 10 patients, whereas partial response was obtained in 3 patients. In our study, patients with arthritis and FMF attacks achieved remission with anti-IL-1 therapy, although no patient received DMARD therapy in addition to the anti-IL-1 therapy. Moreover, colchicine doses were reduced in these patients.

The major limitation of our study is its retrospective nature. Another limitation is the small number of cases. In the literature, there are a few case reports on colchicine-resistant arthri-

tis treatment in patients with FMF; therefore, further studies are needed in this area. We believe that our work is valuable in this respect.

In conclusion, anti-IL-1 therapy appears to be effective and reliable in the treatment of colchicine-resistant FMF arthritis without the need for additional DMARD therapy. Moreover, in addition to its efficacy in the treatment of arthritis, anti-IL-1 therapy allows for reduction in the colchicine dose and is effective in preventing FMF attacks and maintaining remission.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ondokuz Mayıs University (Approval Date: June 11, 2020; Approval Number: 2020/412).

Informed Consent: Informed consent was not obtained due to the nature of the study.

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References

1. Rigante D. The broad-ranging panorama of systemic autoinflammatory disorders with specific focus on acute painful symptoms and hematologic manifestations in children. Mediterr J Hematol Infect Dis 2018; 10: e2018067. [Crossref]
2. Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: An updated review. Eur J Rheumatol 2014; 1: 21-33. [Crossref]
3. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967; 43: 227-53. [Crossref]
4. Manna R, Rigante D. Familial mediterranean fever: Assessing the overall clinical impact and formulating treatment plans. Mediterr J Hematol Infect Dis 2019; 11: e2019027. [Crossref]
5. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997; 17: 25-31. [Crossref]
6. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 1997; 90: 797-807. [Crossref]
7. Chae JJ, Aksentijevich I, Kastner DL. Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. Br J Haematol 2009; 146: 467-78. [Crossref]
8. Garcia-Gonzalez A, Weisman MH. The arthritis of familial Mediterranean fever. Semin Arthritis Rheum 1992; 22: 139-50. [Crossref]
9. Uthman I, Hajj-Ali RA, Arayssi T, Masri AF, Nasr F. Arthritis in familial Mediterranean fever. Rheumatol Int 2001; 20: 145-8. [Crossref]
10. Bodur H, Ucan H, Seckin S, Gündüz OH. Protracted familial Mediterranean fever arthritis. Rheumatol Int 1999; 19: 71-3. [Crossref]
11. Lidar M, Kedem R, Mor A, Levartovsky D, Langevitz P, Livneh A. Arthritis as the sole episodic manifestation of familial Mediterranean fever. J Rheumatol 2005; 32: 859-62.
12. El-Shanti H, Majeed HA, El-Khateeb M. Familial Mediterranean fever in Arabs. Lancet 2006; 367: 1016-24. [Crossref]
13. Jarjour RA. Familial Mediterranean fever in Syrian patients: MEFV gene mutations and genotype-phenotype correlation. Mol Biol Rep 2010; 37: 1-5. [Crossref]
14. Olgun A, Akman S, Kurt I, Tuzun A, Kutluay T. MEFV mutations in familial Mediterranean fever: Association of M694V homozygosity with arthritis. Rheumatol Int 2005; 25: 255-9. [Crossref]
15. Langevitz P, Livneh A, Zemer D, Shemer J, Pras M. Seronegative spondyloarthropathy in familial Mediterranean fever. Semin Arthritis Rheum 1997; 27: 67-72. [Crossref]
16. Sakallioglu O, Duzova A, Ozen S. Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever. Clin Exp Rheumatol 2006; 24: 435-7.
17. Akar S, Cetin P, Kalyoncu U, Karadag O, Sari I, Cınar M, et al. Nationwide experience with off-label use of interleukin-1 targeting treatment in familial Mediterranean fever patients. Arthritis Care Res (Hoboken) 2018; 70: 1090-4. [Crossref]
18. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-85. [Crossref]
19. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: Results of a nationwide multicenter study. Turkish FMF Study Group. Medicine (Baltimore) 2005; 84: 1-11. [Crossref]
20. Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R, et al. Colchicine nonresponsiveness in familial Mediterranean fever: Clinical, genetic, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum 2004; 33: 273-82. [Crossref]
21. Bakkaloglu SA, Aksu T, Goker B, Unlusoy A, Peru H, Fidan K, et al. Sulphasalazine treatment in protracted familial Mediterranean fever arthritis. Eur J Pediatr 2009; 168: 1017-9. [Crossref]
22. Nakamura A, Matsuda M, Tazawa K, Shimojima Y, Ikeda S. Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever. Intern Med 2007; 46: 1247-9. [Crossref]
23. Bilgen SA, Kilic L, Akdogan A, Kiraz S, Kalyoncu U, Karadag O, et al. Effects of anti-tumor necrosis factor agents for familial mediterranean fever patients with chronic arthritis and/or sacroiliitis who were resistant to colchicine treatment. J Clin Rheumatol 2011; 17: 358-62. [Crossref]