Efficacy of anti-interleukin-1 treatment in colchicine-resistant arthritis in patients with familial Mediterranean fever
Demet Yalçın Kehribar¹, Metin Özgen²

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)-1β (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-
ease-modifying anti-rheumatic 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 Mayis 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.

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 reactions 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.
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 arthritis.
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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 Mayis University (Approval Date: June 11, 2020; Approval Number: 2020/412).

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

Conflict of Interest: The authors have no conflict of interest to declare.

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