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ORIGINAL ARTICLE

Nationwide Experience With Off-Label Use of Interleukin-1 Targeting Treatment in Familial Mediterranean Fever Patients

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Objective. **Approximately 30–45% of patients with familial Mediterranean fever (FMF) have been reported to have attacks despite colchicine treatment. Currently, data on the treatment of colchicine-unresponsive or colchicine-intolerant FMF patients are limited; the most promising alternatives seem to be anti–interleukin-1 (anti–IL-1) agents. Here we report our experience with the off-label use of anti–IL-1 agents in a large group of FMF patients.**

Methods. **In all, 21 centers from different geographical regions of Turkey were included in the current study. The medical records of all FMF patients who had used anti–IL-1 treatment for at least 6 months were reviewed.**

Results. **In total, 172 FMF patients (83 [48%] female, mean age 36.2 years [range 18–68]) were included in the analysis; mean age at symptom onset was 12.6 years (range 1–48), and the mean colchicine dose was 1.7 mg/day (range 0.5–4.0). Of these patients, 151 were treated with anakinra and 21 with canakinumab. Anti–IL-1 treatment was used because of colchicine-resistant disease in 84% and amyloidosis in 12% of subjects. During the mean 19.6 months of treatment (range 6–98), the yearly attack frequency was significantly reduced (from 16.8 to 2.4; $P < 0.001$), and 42.1% of colchicine-resistant FMF patients were attack free. Serum levels of C-reactive protein, erythrocyte sedimentation rate, and 24-hour urinary protein excretion (5,458.7 mg/24 hours before and 3,557.3 mg/24 hours after) were significantly reduced.**

Conclusion. **Anti–IL-1 treatment is an effective alternative for controlling attacks and decreasing proteinuria in colchicine-resistant FMF patients.**

INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by self-limited episodes of febrile serosal inflammation (1). The disease is most frequently seen in Turks, non-Ashkenazi Jews, Armenians, and Arabs. Amyloid deposition and the development of end-stage renal disease are the most severe complications of FMF. Since 1972, colchicine has become the mainstay of treatment for patients with FMF because continuous colchicine treatment is not only effective in prevention and amelioration of FMF attacks (2,3), but also in decreasing the frequency of amyloidosis (4). However, approximately 30–45% of FMF patients have been reported to have had attacks despite colchicine treatment

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Significance & Innovations

- Anti–interleukin-1 treatment is an effective alternative, with an acceptable safety profile, for controlling attacks in colchicine-resistant familial Mediterranean fever patients.
- Anti–interleukin-1 treatment also reduces urinary protein levels in colchicine-resistant familial Mediterranean fever patients.

(1,5). Currently, data on the treatment of colchicine-unresponsive or colchicine-intolerant FMF patients are limited. Although in a previous open pilot study of 21 attacks in colchicine-resistant FMF patients we observed that interferon might ameliorate acute attacks (6), we could not definitively demonstrate the effects of a single administration of interferon during an FMF attack in a subsequent double-blind placebo-controlled study (7). Azathioprine, tumor necrosis factor inhibitors, thalidomide, and corticosteroids have been used to control the disease with varying degrees of success.

Previous observations suggest that interleukin-1β (IL-1) may have a critical role in the pathogenesis of FMF (8). The gene responsible for FMF, called *MEFV* (9,10), is located on the short arm of chromosome 16 and encodes a protein termed pyrin. FMF-associated missense mutations in the B30.2 domain of pyrin may decrease the binding of regulatory proteins that block the pyrin inflammasome and cause an increase in IL-1 release (11). Anakinra, which is a recombinant human IL-1 receptor antagonist (IL-1Ra), and canakinumab, a fully human anti–IL-1β monoclonal antibody, are anti–IL-1 agents available for off-label use to treat FMF in Turkey. There have been several case reports and small case series regarding the efficacy of anti–IL-1 therapy. However, only 2 placebo-controlled studies have evaluated the efficacy of rilonacept, which is a complex protein consisting of the extracellular domains of humanized IL-1 type I receptor and IL-1 receptor accessory protein fused with the Fc portion of IgG1 (12), and anakinra (13) in colchicine-resistant FMF patients. Therefore, we conducted a nationwide retrospective study to describe the indications for anti–IL-1 therapy among Turkish rheumatologists and to obtain data regarding the efficacy and safety of the off-label use of these agents in patients with FMF.

PATIENTS AND METHODS

This study was conducted through the Turkish Multi-Centered Investigations Platform in Rheumatology, and 21 centers from different geographic regions were included in the study. The Turkish Ministry of Health granted the compassionate use of anti–IL-1 drugs for FMF patients, and every patient who planned to use this treatment signed an informed consent form. Therefore, this study was performed after the approval of both the local ethical committee (#181/2016) and the Turkish Medicines and Medical Devices Agency of the Turkish Ministry of Health (#7564 2246-000-72309). After approval, the medical records of all FMF patients who had used anti–IL-1 treatment for at least 6 months were reviewed. The following data were collected using a web-based structured questionnaire: 1) demographic characteristics (age, sex, smoking status, weight, height, and body mass index), 2) age at onset of attacks, 3) age at diagnosis, 4) cumulative clinical features of FMF, including presence of amyloidosis, 5) prior treatment history before anti–IL-1 agent(s) (colchicine use, colchicine dose), 6) family history of FMF and amyloidosis, 7) presence of comorbid conditions (hypertension, diabetes mellitus, cardiovascular disease, heart failure, chronic kidney disease, and vasculitis), 8) the reason for starting anti–IL-1 therapy (colchicine-resistant disease, colchicine intolerance, or the development or progression of amyloidosis), 9) the type and the dose of anti–IL-1 agent, 10) yearly attack frequency before and after treatment, and 11) the development of any serious adverse drug reactions (adverse event requiring hospitalization or prolongation of hospitalization, life or organ threatening, or causing disability or death). Laboratory data (serum levels of C-reactive protein [CRP], erythrocyte sedimentation rate, and 24-hour urinary protein excretion before and after treatment) and patients' *MEFV* gene status (if it existed) were also recorded.

Unless otherwise stated, values are presented as means and ranges (minimum–maximum) or percentage. Because most of our data were not normally distributed, Wilcoxon's signed rank test was used to compare repeated measurements, and Spearman's rank correlation was used to evaluate related variables with treatment response. For all measurements, P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software, version 13.0.

RESULTS

In total, 172 FMF patients (83 [48%] female, mean age 36.2 [range 18–68] years) who had used anti–IL-1 agents for >6 months were included in the analysis. The demographic and some clinical characteristics of the patients are summarized in Table 1. The frequencies of peritonitis, pleuritis,

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Table 1. Demographic and some clinical characteristics of the study group in comparison with previously described Turkish FMF patients*

Characteristic	Current group	Previous patients
Age, mean (range) years	36.2 (18–68)	35.3 (17–78)
Female, no. (%)	83 (48)	575 (49.2)
Body weight, mean (range) kilograms	67.3 (37–121)	NA
Body mass index, mean (range) kg/m^2	23.9 (16.0–40.9)	NA
Age at symptom onset, mean (range) years	12.6 (1–48)	14.9 (0–60)
Fever	159/171 (93)	1,063/1,092 (97)
Peritonitis	138/169 (82)	1,085/1,135 (96)
Pleuritis	79/165 (48)	726/1,135 (64)
Arthritis	116/169 (69)	585/1,135 (52)
Pericarditis	15/165 (9)	NA
Erysipelas-like erythema	63/165 (38)	340/1,119 (30)
Protracted febrile myalgia	6/151 (4)	185/1,127 (16)
Family history for FMF	107/155 (69)	616/1,131 (55)
Family history for amyloidosis	21/145 (15)	66/959 (7)
Presence of *M694V* mutation	126/149 (85)	566/824 (69)
Presence of amyloidosis	52/169 (31)	93/1,054 (9)
Presence of chronic renal disease	31/171 (18)	NA
Regular colchicine usage	162/171 (95)	916/1,015 (90)
Colchicine dosage, mean (range) mg	1.7 (0.5–4.0)	1.4 (0–5)

* Values are the number/total number (%) unless indicated otherwise. FMF = familial Mediterranean fever; NA = not available.

and protracted febrile myalgia were lower in our study group than in ordinary Turkish FMF patients whom we have described previously (1). However, age at symptom onset was somewhat earlier and the presence of the *M694V* allele, a family history of FMF, and amyloidosis were more frequent in patients who used anti–IL-1 therapy (Table 1). Of our patients, 95% were reported to be regularly taking colchicine median dosage of 1.7 mg/day. Genetic analyses were available for 149 patients, and *M694V* was the leading mutation (126 [85%]). In addition, 20 patients (13%) were carrying *M680I*, 7 (5%) were carrying *V726A*, and 2 (1%) were carrying *M694I*.

At the time of data entry, 24 FMF patients (14%) had hypertension, 5 (3%) had diabetes mellitus, 4 had cardiovascular diseases, and 1 had congestive heart failure. In all, 151 patients (88%) were treated with anakinra, and the rest (21 patients [12%]) were treated with canakinumab. Anakinra was administered as a subcutaneous injection of 100 mg/day in 96.4% of patients; the remaining patients received 50–300 mg/day. Overall, 67% of the patients received 150 mg subcutaneous injection of canakinumab at 4 weeks, 24% received 150 mg at 8 weeks, and 9% received 150 mg at 12 weeks. The reason for starting anti–IL-1 treatment was reported in 171 patients (Table 2); 117 patients (68%) started due to colchicine-resistant disease, and the other 28 (16%) started due to the development/progression of amyloidosis in addition to colchicine-resistant disease. In 20 patients (12%), the only reason for anti–IL-1 usage was the presence or progression of amyloidosis. During the mean treatment period of 19.6 (range 6–98) months, yearly attack frequency, serum levels of CRP, erythrocyte sedimentation rate, and 24-hour urinary protein excretion were significantly reduced ($P < 0.001$) in our study group (Table 3).

Among the 145 patients who were reported to have colchicine-resistant disease, the attack frequency was significantly reduced ($P < 0.001$) from 16.8 attacks/year (range 1–60) to 2.4 attacks/year (range 0–36). In addition, 61 patients (42.1%) were attack free, and 71 patients (49.7%) were reported to have attack frequencies of <6 per year during data collection. In the remaining 11 patients (8%), the attack rate did not change during anti–IL-1 therapy. The other 2 patients' data for attack frequency after treatment were missing. Univariate analyses showed no significant associations between nonresponse to anti–IL-1 treatment and any of the demographic, disease-related clinical, and laboratory data or the presence of comorbidities other than the baseline attack frequency ($r = -0.224$, $P = 0.003$).

Baseline data showed that 47 patients had urinary protein excretion of >500 mg/24 hours before the anti–IL-1 agent was begun. Anti–IL-1 treatment caused a significant reduction of urinary protein levels among those patients (from baseline 5,458.7 mg/24 hours [range 550–19,610] to 3,557.3 mg/24 hours [range 0–18,500]) after treatment. At the end of the observation period, 24-hour urinary protein excretion had decreased in 36 of 47 patients (77%), and 10 patients (21%) had no significant proteinuria at all. Although serum levels of creatinine had also improved

Table 2. Reported reasons for starting interleukin-1 blocking therapy in 171 patients

Reason	No. (%)
Colchicine resistance	117 (68)
Colchicine resistance and development/progression of amyloidosis	28 (16)
Development/progression of amyloidosis	20 (12)
Other*	6 (4)

* Including 3 patients with colchicine intolerance.

Table 3. Change of disease-related clinical and laboratory parameters during anti–interleukin-1 treatment*

Parameters	Before treatment	After treatment	*P*
Attacks/year	16.2 (0–96)	2.3 (0–36)	< 0.001†
CRP level, mg/liter	49.4 (0.0–220)	9.3 (0–110)	< 0.001†
ESR, mm/hour	43.2 (2–129)	18.7 (0–154)	< 0.001†
24-hour urinary protein, mg	5,458.7 (550–19,610)	3,557.3 (0–18,500)	< 0.001†
Serum creatinine, mg/dl	1.2 (0.3–10.2)	1.1 (0.4–7.7)	0.907

* Values are the mean (range) unless indicated otherwise. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
† Significant.

after anti–IL-1 treatment, this improvement did not reach statistical significance (Table 3).

Adverse events were reported in 24 patients (17%) of the 143 for whom sufficient data were available (the adverse events of 22 patients were related to anakinra, and those of 2 were related to canakinumab). Four events were classified as serious by the attending physicians. We observed 1 anaphylactoid reaction, 1 serious neutropenia, and 1 pneumonia in patients using anakinra, and 1 fungal pneumonia in patients using canakinumab. The remaining 20 events were as follows: 17 injection-site reactions (1 with canakinumab and 16 with anakinra), 1 herpetic infection, 1 cellulitis, and 1 development of psoriasis. Anti–IL-1 agents were discontinued in 35 patients (after a mean of 19.2 [range 3–67] months of therapy): 11 due to adverse events, 5 and 8 due to primary and secondary failure (loss of efficacy), respectively, 3 due to patient preference, 2 due to pregnancy, and 6 due to other/unknown reasons. Anti–IL-1 therapy was switched in 20 patients (18 patients switched to canakinumab, and 2 patients switched to anakinra).

DISCUSSION

The results of our study confirm the results of the 2 previous randomized controlled studies (9,10) reporting that anti–IL-1 agents might prevent attacks in colchicine-resistant FMF patients when used continuously. In the present study, complete remission was achieved in 42% of patients who have FMF attacks despite relatively high doses of colchicine. A recent systematic review of published case reports and case series showed (14) a complete remission in 76.5% of patients treated with anakinra and in 67.5% of patients treated with canakinumab. Our data revealed complete remission rates of 40% and 65% and inefficacy rates of 8% and 6% for patients treated with anakinra and canakinumab, respectively. Although the response rates seem different between these 2 agents, this difference was not statistically significant ($P = 0.144$ and $\chi^2 = 3.872606$).

In a previous placebo-controlled trial (10), the difference between the anakinra and placebo groups was shown to be significant only for joint attacks, although the number of attacks in each serosal site was lower in the anakinra group. However, from our data, which type of attack responded better to anti–IL-1 therapy is not clear. Unfortunately, not all of our patients responded to IL-1–blocker therapy. Due to the observational nature of our work, one may think that the diagnosis of those patients may be wrong. However, among those 11 patients who had FMF attacks despite colchicine and did not respond to further anti–IL-1 treatment, 7 were homozygous for *M694V*, 1 was heterozygous for *K695R* and also carrying *R202Q* polymorphism, and 1 was heterozygous for *M680I*. Genotype data were not provided for a single patient with colchicine-resistant disease, and 1 was reported to have wild-type *MEFV*. One can also speculate that unresponsive patients might have responded better to dose escalation. This question cannot be answered in our work, as dose escalation was not tried in unresponsive patients, because of dose limitations in off-label use. However, interestingly, only 2 unresponsive patients were reported to have switched to another anti–IL-1 agent, and another 2 stopped the treatment. These data indicate that other mechanisms could be operative in colchicine-resistant FMF patients.

Up to now, there are only some case reports regarding the use of anti–IL-1 agents in patients with amyloidosis or proteinuria (15–20). However, the effects of this treatment on proteinuria have not previously been systematically evaluated. Our data reveal that IL-1–blocking therapy could reduce urinary protein excretion in colchicine-resistant FMF patients. However, we did not perform biopsies to prove the regression of amyloidosis.

The main limitation of the present study was its retrospective nature. It was not possible to use more recent or complex outcome measures or to assess the effects of anti–IL-1 treatment on quality of life in colchicine-resistant FMF patients, due to the study design. Likewise, we could not make any conclusions about the efficacy of on-demand use or dose modifications of anakinra or canakinumab in this indication. In summary, the results of this large observational study showed that anti–IL-1 treatment is an effective alternative, with an acceptable safety profile, for not only controlling the attacks, but also decreasing the proteinuria in colchicine-resistant FMF patients in routine clinical practice.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Akar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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