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Original article

Anakinra for colchicine refractory familial Mediterranean fever: a cohort of 44 patients

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Abstract

Objective. FMF is an autoinflammatory disease of genetic origin. Colchicine is the mainstay of treatment for the prevention of attacks and long-term complications but 5–10% of FMF patients are resistant to colchicine therapy. The aim of our study was to investigate the real-life safety and efficacy of anakinra in a cohort of patients with colchicine-resistant FMF.

Methods. In this retrospective study, patients treated with anakinra for colchicine-resistant FMF between 2010 and 2018 were identified using the computerized database of Sheba Medical Center and enrolled in the study. Data from structured clinical files were analysed to evaluate the efficacy and safety outcomes. To assess efficacy, we used the Global Assessment Score (GAS), a measure comprised of three different domains: number of attacks per month, duration of attacks and number of sites involved in the attacks. Reported adverse events were compiled.

Results. A total of 44 patients (24 female) were treated with anakinra. Of these patients, 75% were homozygous for the M649V mutation. The mean duration of treatment was 18 months. The GAS decreased significantly from 6.6 (IQR 5.3–7.8) before treatment to 2 (IQR 0–4.2) while on treatment ($P < 0.001$). During anakinra treatment, six hospitalizations were reported (three due to related adverse effects). In addition, 11 patients suffered from injection site reactions (5 ceased treatment). Twelve patients reported mild side effects.

Conclusion. Treatment with anakinra is beneficial for the majority of colchicine-resistant FMF patients and is relatively safe.

Key words: anakinra, FMF, autoinflammatory, colchicine, MEFV, inflammosome

CLINICAL SCIENCE

Rheumatology key messages

- The study describes a larger cohort and longer treatment duration than previously published.
- Anakinra treatment resulted in a significant reduction in the frequency, severity and duration of FMF attacks.
- Exclusion criteria eliminated confounders hampering the interpretations of the results.

Introduction

FMF is an autosomal recessive, auto-inflammatory disease that is estimated to affect 150 000 patients worldwide [1]. FMF mainly manifests with painful, febrile serositis attacks that involve peritonitis, pleuritis and arthritis [2–4]. Mutations in the *MEFV* gene were described in the late 1990s as associated with FMF when inherited in a recessive manner [5]. These mutations result in an abnormal pyrin protein, leading to caspase-1 activation in the pyrin inflammasome. This promotes IL-1β production, which mediates systemic inflammation [6, 7]. Since 1972, colchicine, a

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tricyclic neutral alkaloid, has been the mainstay of FMF treatment; until late 2016 it was the only approved medication for the disease [8]. Colchicine prevents attacks and amyloidosis in the majority of FMF patients [9], however, 5–10% of patients are either resistant to colchicine or intolerant to it due to adverse effects [10].

The finding that IL-1 was involved in the pathophysiology of FMF led to the use of new therapeutic agents in the treatment of FMF [11, 12]. Anakinra is an IL-1 inhibitor that has been shown to reduce FMF flares and decrease inflammatory markers [10, 13, 14]. A recent double-blind randomized controlled trial demonstrated a beneficial effect of anakinra for patients with colchicine-resistant FMF. In this trial, which was conducted on 25 FMF patients, the number of FMF attacks was reduced from ~5 to 1.7 attacks per month with anakinra treatment [15]. The aim of the current study was to investigate the safety and efficacy of anakinra in a larger cohort of patients with colchicine-resistant FMF who received anakinra for >2 months.

Patients and methods

Study population, intervention and data abstraction

We screened the database of the national centre for FMF at the Sheba Medical Center to identify patients who were treated with anakinra between 1 January 2010 and 31 December 2018. We began to use anakinra in our centre in January 2010 when reports that anakinra was beneficial for FMF patients started to appear. Anakinra was used as an add-on treatment to colchicine in patients unresponsive to a daily dose of 3 mg colchicine or in patients treated with a lower dose of colchicine due to intolerance to the drug. Due to financial constraints, the number of patients who received anakinra over the study period was limited.

Clinical and laboratory data obtained before and during anakinra treatment, ere retrieved from patients' medical records documented in the computerized system of the Sheba Medical Center. We extracted data regarding the following manifestations reflecting FMF flares: episodic abdominal, pleuritic and leg joint pain, exertional leg pain and fever-alone attacks. In addition, we obtained the ESR, CRP and urinary protein levels at study entry and on study termination (end of follow-up). Information on adverse effects, their relatedness to anakinra (based on the recorded discretion of the treating physician) and their outcome with respect to hospital admission and anakinra treatment cessation, as well as discontinuation due to inefficacy of anakinra was also retrieved. Missing data, particularly regarding anakinra adverse effects, were retrieved through telephone interviews. The study was approved by the Institutional Review Board for Human Experimentation at the Sheba Medical Center, which waived the requirement for signed informed consent of the participants (Declaration of Helsinki 4098-17-SMC).

FMF patients were enrolled in the study if their FMF diagnosis was consistent with the Tel Hashomer criteria for diagnosis of FMF [16], their age was ≥18 years and they were treated with anakinra for at least 2 months for colchicine-resistant or intolerant FMF [14]. To meet the definition of colchicine resistance or intolerance, patients had to experience at least one attack or episode of activity per month in any of the five FMF sites (abdomen, chest, leg joints, fever-only and exertional leg pain) for at least 1 year despite being treated with colchicine at a dose of ≥2–≤3 mg/day or a lower dose if unable to tolerate this dose due to adverse events (most often diarrhoea).

Patients were excluded if they failed to fulfil the inclusion criteria, received treatment with anakinra for any indication other than FMF or had comorbidities or received treatment with medications that could have interfered with the interpretation of anakinra's effect. The use of NSAIDs and other analgesics did not lead to exclusion of patients, because these drugs were prescribed on an 'as needed' basis (PRN) and they are not considered capable of preventing attacks or affecting the course of FMF.

Evaluation of anakinra's effect

The Global Assessment Score (GAS), constructed for the current study, was used to evaluate outcomes of anakinra treatment. The GAS combines three different meaningful and easily determinable domains, each scored from 1 to 5 into one measure that reflects disease severity. These include the number of attacks per month (1 point for each attack per month, where a score of 5 denotes ≥5 attacks), the duration of attacks (1 point for each day, where a score of 5 indicates an attack of ≥5 days) and the number of sites involved in attacks along the course of the disease (1 point for each site, where a score of 5 denotes all five possible sites). For the pre-anakinra period, the GAS accounted for all the attacks that occurred during 1 year preceding initiation of anakinra. For the under-anakinra phase, the GAS considers the whole anakinra treatment interval. For each individual patient, a total GAS was computed by summing up the scores of the three components divided by 3 (giving a maximal score of 5) and multiplied by 2 in order to convert the score to a 1–10 scale. It should be considered a qualitative rather than a precise quantitative index.

The primary outcome was the difference in the GAS between study entry and the end of follow-up. Several secondary outcomes were additionally evaluated. We determined the difference between study entry and end of follow-up in the number and duration of attacks, the number of sites involved in the disease along the disease course, the number of attacks at each site separately (i.e. chest, abdomen and joints), the levels of inflammatory markers (ESR and CRP) and the proportion of patients experiencing leg pain.

Statistical analysis

The duration of treatment was evaluated using the reverse censoring method. Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distribution using a histogram and Q-Q plot. Normally distributed continuous variables were reported as mean (S.D.), while skewed variables and ordinal variables were reported as median and interquartile range (IQR). Comparison of pretreatment and during treatment was performed using the Wilcoxon signed rank test. All statistical tests were two-tailed and $P < 0.05$ was considered statistically significant. SPSS software was used for all statistical analyses (version 25; IBM, Armonk, NY, USA).

Results

Baseline characteristics

A total of 44 patients were enrolled in the study (24 females). Table 1 displays the patient demographic data. The mean age was 44.02 years (S.D. 13.3) and the mean disease duration at onset of anakinra treatment was 34 years (S.D. 14). In our cohort, 75% were homozygous and 11% heterozygous for the M649V mutation and 43% were of Moroccan Jewish descent on at least one parental side. Thirteen patients had proteinuria of some degree prior to treatment with anakinra, among them seven with amyloidosis proven by biopsy. In addition, six had an overlap of FMF with Behçet's disease. The mean colchicine dosage prior to treatment with anakinra was 2.09 mg/day (S.D. 0.66). A total of eight patients received additionally ($n = 6$) or alternatively ($n = 2$) i.v. colchicine 1 mg once a week. Anakinra was indicated in the majority of the patients ($n = 36$) for colchicine-resistant disease and in 8 for colchicine intolerance. The mean treatment duration with anakinra was 18 months (IQR 9–24). Forty-one patients received anakinra at a dose of 100 mg/day and three were treated with a dose of 50 mg/day. All patients continued treatment with colchicine during anakinra treatment.

Table 1 Demographic and genetic data

Gender, *n*		
Male	20	
Female	24	
Age (years), mean (S.D.)	44 (13.3)	
Jewish ethnicity	Parental (%)	Maternal (%)
Morocco	43	36
Tunisia	7	16
Libya	18	16
Iran	2	2
Iraq	7	7
Ashkenazi	2.2	2.2
Other	20.8	20.8
FMF mutation	Heterozygous (%)	Homozygous (%)
M694V	11	75
V726A	9	2
Other	4	

Efficacy

The median frequency of attacks was 1 per month (IQR 0–2) during treatment with anakinra compared with 4 per month (IQR 2–5) before treatment ($P < 0.001$) (Fig. 1). The median duration of an attack was 1 day (IQR 0–2.7) during treatment compared with 3 days (IQR 3–3) before treatment ($P < 0.001$) and the number of sites involved in attacks also decreased upon treatment to 1 (IQR 0–2) from 4 (IQR 3–4) before treatment ($P < 0.001$) (Fig. 1). The GAS declined from 6.6 (IQR 5.3–7.8) before treatment to 2 (IQR 0–4.2) upon treatment ($P < 0.001$) (Fig 1) and was zero (free of attacks) in 16 patients. In 29 patients CRP (normal 0–5 mg/l) decreased from 15 mg/l (IQR 3–71) prior to treatment to 2 mg/l (IQR 0.5–13) upon treatment ($P < 0.001$) and in 21 patients ESR (normal 20 mm/h) also decreased, from 37 mm/h (IQR 11–54) to 17 mm/h (IQR 11–14) ($P < 0.021$).

A significant decrease was also seen in the proportion of patients suffering attacks in each of the disease sites ($P < 0.0001$). Approximately 56% of patients reported leg pain on exertion prior to treatment with anakinra, while on treatment only 15.9% reported pain. A similar significant decline was seen regarding arthritis, with a reduction from 81.8% to 15.9%. A decrease from 84% to 47.7% was reported for abdominal attacks, 65.9% to 25% for pleuritis attacks and 52.2% to 15.9% for fever-only attacks. Of the 13 patients with proteinuria at baseline, 5 remained stable, 4 improved, 1 worsened and in the remaining the effect of anakinra could not be assessed (due to IgA nephropathy, dialysis or spontaneous improvement just before initiation of anakinra, each in one patient). Overall, the decrease in proteinuria from 2.5 (S.D. 2.7) to 2.2 (S.D. 3.3) g/24 h was not significant. None of the patients stopped anakinra treatment due to lack of efficacy.

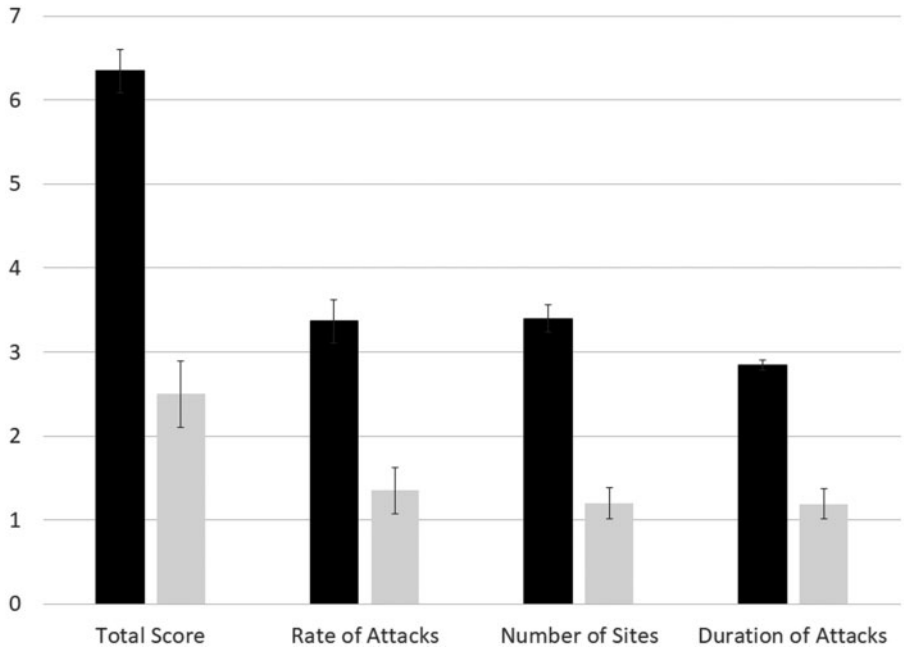
Safety

Of the 44 patients in the cohort, 20 reported 29 adverse effects (Table 2). Among the adverse events, six were defined as serious, requiring hospitalization, yet none had long-term sequelae. Of these, only three were drug-related, while the other three were unrelated to anakinra and treatment was continued without worsening. Eleven patients suffered from injection site reactions (ISRs), five of which were severe enough to cause treatment cessation. Mild side effects were reported in 12 patients (Table 2).

Discussion

In the present study we evaluated the efficacy and safety of anakinra for the treatment colchicine-resistant FMF. In line with previous studies, anakinra treatment resulted in a substantial clinical response with a significant decrease in the rate and duration of the FMF attacks, the number of the sites involved in the attacks, the level of the inflammatory markers and the GAS. As

FIG. 1 GAS total and domain scores before and during treatment with anakinra



Plot of scores before anakinra treatment (black bars) and during treatment (grey bars). Differences are significant with $P < 0.0001$ for each parameter studied. The total score is the sum of the means of the three measurements multiplied by 2.

TABLE 2 Adverse events

Side effect	Patients, *n* (%)
Diarrhoea	2 (4.5)
Headache	4 (9)
Alopecia	3 (6.8)
Injection site reaction	11[a] (25)
Neutropenia	2 (4.5)
Leukopenia	1 (2.2)
Hospitalization	
Related	3[b] (6.8)
Unrelated	3[c] (6.8)

[a]Five stopped treatment due to ISRs.
[b]Adverse events related to anakinra treatment were respiratory tract infections ($n = 2$) and acute coronary syndrome followed by an infection with influenza A ($n = 1$).
[c]Unrelated adverse events included soft tissue bleeding ($n = 1$), acute kidney injury ($n = 1$), acute coronary syndrome ($n = 1$) and FMF flares ($n = 3$).

has been previously demonstrated [17], this favourable clinical outcome translated into improved quality of life for patients with FMF. Ben-Zvi *et al.* [13, 15] recently showed in a double-blind randomized controlled study that anakinra treatment is effective and safe for colchicine-resistant FMF. In another study that assessed 44 patients treated either with anakinra or canakinumab, a statistically significant increase in quality of life and improvement in attack parameters were also noted upon treatment with anakinra [17]. In addition, Kohler *et al.* [18] reported a rapid and persistent suppression of disease symptoms and inflammatory markers in 29 FMF patients who were treated with anakinra. Anakinra is effective in other inflammatory conditions as well, including pericarditis [19], crystal-induced arthropathy [20] and other periodic fever syndromes such as cryopyrin-associated periodic syndrome [21].

The present study is unique, as the cohort size was larger and the treatment duration was longer than previous studies. The 44 patients in our cohort were found to be homozygous for the M649V mutation at significantly higher rates than the overall Israeli FMF population (75% *vs* 36%) [22] and originated more commonly from a Moroccan Jewish ancestry (34% *vs* 19%) [23]. This is in keeping with previous data on the M694V *MEFV* mutation, which demonstrated the association, particularly in homozygous patients, with colchicine treatment failure [24]. In terms of safety, the overall adverse effects were similar to those reported previously [25], mostly ISRs and infections. In our study, six patients were hospitalized while being treated with anakinra, but three of these adverse events were unrelated to anakinra. In previous studies that investigated the safety of anakinra, patients were treated with additional agents, including steroids, which hampered the interpretation of unfavourable manifestations as related to anakinra alone. In the present study, the exclusion criteria eliminated patients with confounding medications.

AA amyloidosis remains the most serious and severe manifestation of FMF [15, 26, 27]. To prevent its occurrence, patients in our study were all treated with

colchicine, which is currently the only agent proven to prevent FMF amyloidosis [15]. Although the role of anakinra in the prevention of AA amyloidosis in FMF patients is yet to be determined, its efficacy in the treatment of already established amyloidosis, particularly amyloid nephropathy, has been disappointing in our practices (unpublished data).

For many patients in our cohort there was a significant reduction in the severity and duration of peritonitis and pleuritis attacks upon anakinra treatment, and improvement was even more dramatic for leg pain and arthritis. These findings are in line with previous studies showing a similar effect [14]. This suggests that anakinra treatment should be offered to patients suffering from severe and disabling leg pain and arthritis as a first-line treatment.

The most common side effect described in the literature regarding anakinra treatment is ISRs, which was shown to occur in up to 70% of patients, most of them mild to moderate in severity [28]. In our study, 25% of patients reported ISRs, with 11% reporting severe ISRs leading to treatment termination. The discrepancy in the overall percentage of ISR events may be related to the retrospective nature of the study, yet the rate of severe ISRs was in concert with that described in the literature.

One limitation of our study was the necessity in some cases to rely on patient recall. But this has occurred only infrequently and the overwhelming information was derived from the files. In addition, due to the retrospective nature of the study, measurements of inflammatory markers (ESR and CRP) were missing for some patients and thus the total mean value might be inaccurate. However, this limitation is reduced by the infrequent data deficiency and the highly statistically significant decline in the inflammatory markers induced by anakinra treatment. Although stability in proteinuria was attained, the effect of anakinra on amyloidosis or proteinuria remains an unaddressed concern. Yet, since AA amyloidosis is a slowly progressing disorder, exploring these issues requires much longer study duration and a larger study cohort, comparable to those described in the study on colchicine in the prevention of FMF-related amyloidosis (11 years and 1070 patients) [9]. Finally, the long-term efficacy and safety of anakinra in FMF could not be determined from this study, although by being the longest monitoring of FMF patients treated with anakinra to date, the current study further assures one of the already-known excellent safety and efficacy profiles of the drug.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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