A single dose of anakinra for arresting familial Mediterranean fever attacks: a proof-of-concept study

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Abstract

Objective

Familial Mediterranean fever (FMF) is characterised by painful inflammatory bouts, typically lasting one to three days. Analgesics, the only available treatment to alleviate acute attacks, are often ineffective in reducing pain and attack duration. This study evaluates the efficacy of a single dose of anakinra, administered at the onset of FMF attack, in arresting the attack.

Methods

This prospective self-controlled case series involved patients receiving a single prefilled syringe with 100 mg anakinra for self-administration at attack onset. The primary outcome was the duration of anakinra-treated attacks compared to baseline attack duration. Additional attacks were treated with self-procured anakinra and analysed separately.

Results

Twenty-three attacks experienced by 23 patients and treated with the furnished anakinra were analysed. Treated attacks were arrested within 5.4±6 hours from anakinra administration, and lasted 8.33±6.8 hours from onset, significantly shorter than the 56.3±16.8 hours reported at baseline (p=0.0001). Use of purchased anakinra (43 injections by 6 patients) attained equal outcome. Early administration of anakinra (within ≤4 hours of attack onset) resulted in attack termination within ≤4 hours from anakinra injection in 17 of 20 (85%) and 37 of 41 (90%) of the attacks treated with furnished and procured anakinra, respectively. Adverse events were limited to one patient experiencing an injection site reaction.

Conclusion

Acute FMF attacks are highly responsive to early anakinra administration with low safety cost.

Key words

familial Mediterranean fever, anakinra, arresting familial Mediterranean fever attacks, on-demand treatment

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Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disorder. It is mainly characterised by recurrent, severe attacks of febrile inflammatory serositis in the abdomen, chest and joints, and the development of amyloid A (AA) amyloidosis, associated with premature death (1).

Colchicine in a daily dose of 1–3 mg is the mainstay of FMF treatment. In the small subset of patients who are unresponsive or intolerant to colchicine (2, 3), continuous administration of interleukin 1 (IL-1) blockers, either anakinra or canakinumab, may be required for attack prophylaxis (4). Nonetheless, recurrent attacks of FMF still often occur, posing a challenge, as no effective treatments currently exist to prevent attack progression. Consequently, treatment is palliative, aiming at pain control through the use of non-steroidal anti-inflammatory drugs, standard analgesics, or opioids if necessary (5, 6).

On-demand treatment with IL-1 blockers has been suggested as an alternative to continuous administration (7, 8). This approach raises concerns: it increases the risk for AA amyloidosis, unless strict follow-up measures are taken and exposes patients to more attacks without remedies to curtail or relieve them. Hence, some clinicians view this strategy as unsafe. However, studies on on-demand treatment indicate that patients receiving one or several anakinra injections during the prodrome or shortly after an attack onset may benefit by abating the attack (7, 9, 10). Nonetheless, no studies have prospectively assessed this advantage.

Therefore, the aim of the present study is to prospectively assess the efficacy of a single anakinra dose, administered at the onset of an FMF attack, in arresting attack progression, in a patient population experiencing recurrent FMF attacks

Materials and methods

Overview

We conducted a prospective, self-controlled case series trial, to investigate the impact of a single dose of anakinra, administered at the onset of an acute FMF attack. The study, carried out from January 2021 through October 2022 at the FMF clinic of our medical centre, included patients who served as their own controls. The study was approved by the institutional review board, and all patients provided informed consent.

Patients

Patients followed and treated in our FMF clinic and meeting the Tel Hashomer criteria for the diagnosis of FMF (11), were eligible for inclusion in the study. Recruitment began on January 1, 2021, and concluded on December 31, 2021. The follow-up period ended on October 31, 2022. Patients were enrolled if they satisfied all the following criteria:

1. carried at least one pathogenic FMF gene (MEFV) mutation, 2. had experienced at least two FMF peritoneal or pleural attacks in the year preceding enrolment, 3. declined or were unable to escalate colchicine or initiate continuous anti-IL-1 treatment.

Patients were excluded if:

1. experienced atypical attacks (defined as shorter than 6 hours or longer than a week, afebrile, or lacking manifestations consistent with peritonitis or pleuritis), or 2. displaying ongoing inflammation (determined by continuously elevated C-reactive protein, or/and erythrocyte sedimentation rate, or/and serum AA), thereby excluding patients who may benefit from continuous IL-1 blockers.

Data on baseline characteristics were extracted from patient files. For baseline attack duration we considered patients' statement on the length of their most recent typical attack, as recorded in their charts. Identification of the attacks treated with anakinra, and assessment of their duration were based on the patients' discretion.

Intervention and data collection

Patients were provided with a single prefilled syringe of anakinra 100 mg (distributed by Swedish Orphan Biovitrum AB (Sobi), Stockholm, Sweden), and instructed to administer it subcutaneously at the first signs of an attack. Detailed guidance on medication handling, storage, and administration was provided, with an emphasis on early use. Information on possible

adverse effects and methods to manage them was likewise provided.

Patients were asked to document: 1. The site of the attack; 2. The time elapsed between the onset of the attack and anakinra administration; 3. The time from anakinra injection to symptoms resolution; and 4. Any adverse events experienced. Data on the anakinra-treated attacks were collected through telephone calls, conducted at least twice within 6 to 12 months from the enrolment visit. Patients were also encouraged to treat additional attacks with self-procured anakinra and record each treated attack using the documentation method outlined above. To avoid potential selection bias, the outcomes of attacks treated with self-procured anakinra, were analysed separately.

Study outcomes

The primary outcome was the duration of the attacks treated with the furnished anakinra compared to the duration of the attack reported at baseline. Secondary outcomes included: 1. the duration of the attacks treated within 4 hours from onset, 2. the proportion of the attacks resolved within 24 hours from onset, and 3. treatment adverse effects, defined as any medical event occurring within a week from anakinra injection.

Statistical analysis

Based on our own and published experience (9), we expected anakinra treatment to significantly reduce the mean attack duration by at least 50%. Using a paired t-test, with adjustments made for intra-patient correlation, we determined that a sample size of at least 15 participants was required to detect 50% reduction in the duration of the attacks, lasting 48 hours at baseline, with 80% power and a two-tailed significance level of 0.05.

Study outcomes were determined by comparing the mean ± standard deviations (SD) values between baseline and anakinra-treated attacks. Wilcoxon signed-rank test or paired t-test were used to analyse non-parametric and parametric continuous data respectively, and Wilcoxon rank-sum test was used for unpaired non-parametric variables. Normal distribution was determined by Shapiro-Wilk test. Linear regression was used to estimate the effect of the timing of anakinra administration relative to attack onset on the duration of FMF attacks. Statistical analyses were performed using SAS software, v. 9.4 (SAS Institute), with a two-sided significance level set at $p \leq 0.05$.

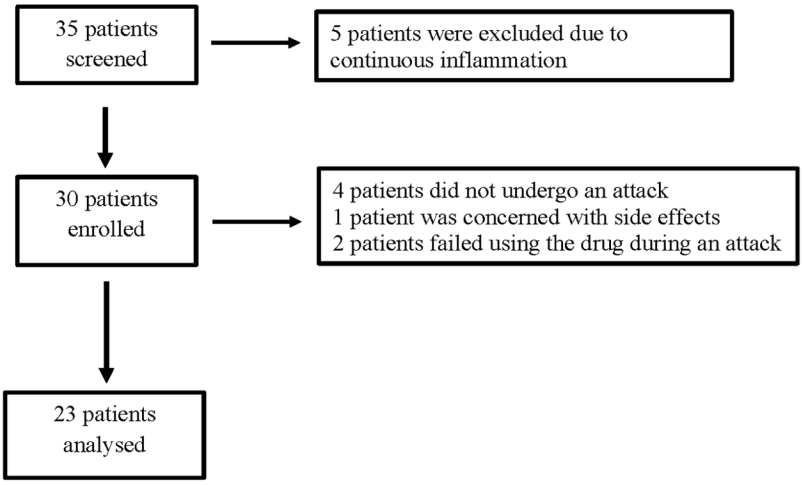

Fig. 1. Flowchart from enrolment to analysis.

Results

Study enrolment and patient characteristics

A total of 35 patients were screened for the study, 30 enrolled, but the attacks of only 23 were analysed (one attack per patient), as detailed in the study flowchart (Fig. 1). Table I provides the baseline demographic, genetic and clinical characteristics of the 23 participants. There were 15 females (65.2%). The mean age was 39.5±13.7 years, and a mean disease duration of 27.0 ±15.5 years. The mean colchicine dose was 1.54±0.64 mg/day, and the mean attack duration was 56.3 ±16.8 hours. Twenty patients carried the M694V MEFV mutation, with seven being homozygous. All patients experienced abdominal attacks, but 11 also had chest attacks, and two had joint attacks. The reasons for study inclusion were infrequent attacks in 19 patients (83%) and reluctance or inability to receive continuous anti-IL-1 treatment in four.

Effect of treatment with furnished anakinra and study outcomes

Table II displays the results of each attack treated with furnished anakinra, all of which were abdominal, except for two chest attacks. Table III outlines the results of the primary and secondary study outcomes. As shown for the primary outcome, the mean duration of anakinra-treated attacks was 8.33±6.8 hours, significantly shorter than the baseline attack duration ($p<0.001$).

Regarding the secondary study outcomes, 20 of 23 attacks (87%), treated within 4 hours from their inception, lasted 6.8±5 hours significantly shorter than their matched baseline attacks ($p<0.001$). Seventeen of these 20 early-treated attacks (85%) were arrested within 4 hours from anakinra injection, suggesting that anakinra may act as a curative treatment for FMF attacks. Late administration (after 4 hours of attack onset) resulted in longer attack duration (18.3±7, $p<0.005$ compared to the duration of earlier treated attacks), though still shorter than their baseline duration (64±11.3 hours, $p=0.005$). Table III also shows that all but two treated attacks (21 attacks, 91%) lasted ≤24 hours from onset. One of these relatively 'prolonged attacks' occurred despite early dosing (≤4 hours from onset). Finally, Adverse events were rare and limited to an injection site reaction in one patient.

Results of treatment with self-procured anakinra

Over the study period, only six patients used self-procured anakinra. Seventeen of the 23 patients did not purchase anakinra and used only the drug supplied by

Table I. Baseline demographic genetic and clinical characteristics of study participants.

Patient	Sex	Age at enrolment (years)	Genotype	Disease duration (years)	Colchicine dose (mg)	Attack duration (hours)	Main site of attacks	Indication for enrolment
1	F	18	M694V/V726A	16	1.5	72	Chest, abdomen	refused canakinumab
2	F	20	V726A/V726A	7	0.5	24	Abdomen	infrequent attacks
3	F	23	M694V/M694V	16	1	48	abdomen	infrequent attacks
4	F	26	M694V/V726A	17	1.5	48	Chest, abdomen	infrequent attacks
5	M	28	M694V/E148Q	19	1	48	Chest, abdomen	infrequent attacks
6	F	31	M694V/-	10	1	24	Abdomen	infrequent attacks
7	M	32	M694V/E148Q	23	2	48	abdomen	infrequent attacks
8	F	32	V726A/-	10	1	72	Abdomen	infrequent attacks
9	F	33	M694V/M694V	31	1	72	Abdomen	infrequent attacks
10	F	35	M694V/M694V	28	1.5	24	Chest, abdomen	infrequent attacks
11	F	36	M694V/V726A	30	1.5	72	Chest, abdomen	refused canakinumab
12	M	37	M694V/V726A	27	3	72	Chest, abdomen	infrequent attacks
13	F	38	M694V/-	15	1.5	48	abdomen	infrequent attacks
14	F	41	M694V/M694V	38	1.5	72	Chest, abdomen	infrequent attacks
15	M	43	V726A/R653H	8	1	48	Chest, abdomen	infrequent attacks
16	M	47	M694V/M694V	44	2	48	Abdomen	refused canakinumab
17	M	47	M694V/M694V	44	2	72	Abdomen	canakinumab contra-indicated
18	M	48	M694V/-	16	1	48	Joints, abdomen	infrequent attacks
19	F	49	M694V/E148Q	18	2	72	Joints, abdomen	infrequent attacks
20	F	57	M694V/E148Q	51	3	72	Chest, abdomen	infrequent attacks
21	M	53	M694V/-	50	1	48	Chest, abdomen	infrequent attacks
22	F	56	M694V/V726A	38	1.5	72	Abdomen	infrequent attacks
23	F	79	M694V/M694V	65	2.5	72	Chest, abdomen	infrequent attacks

F: female; M: male.

Table II. Duration of acute FMF attacks from onset to resolution in individual study participants treated with furnished anakinra.

Patient	Type of attack	Time interval from the onset of the attack to anakinra administration (hours)	time interval from anakinra injection to attack resolution (hours)	Duration of the attack from onset (hours)
1	abdominal	3	3	6
2	abdominal	3	4	7
3	abdominal	6	3	9
4	chest	3	3	6
5	chest	1	3	4
6	abdominal	3.5	4.5	8
7	abdominal	2	4	6
8	abdominal	6	24	30
9	abdominal	3	24	27
10	abdominal	2	8	10
11	abdominal	3	3	6
12	abdominal	8	8	16
13	abdominal	1.5	1.5	3
14	abdominal	0.25	2	2.25
15	abdominal	2	2.5	4.5
16	abdominal	2	4	6
17	abdominal	1	1	2
18	abdominal	4	4	8
19	abdominal	2	3	5
20	abdominal	3	4	7
21	abdominal	3	5	8
22	abdominal	3	3	6
23	abdominal	2	3	5

us. Of these 12 did not experience additional attacks, three could not afford the cost of anakinra, one started treatment with a continuous IL-1-blocker, and for one patient, the reason for not using anakinra again is unknown. The six patients who used self-procured anakinra treated an additional 43 attacks. The outcomes of these attacks are detailed in Table IV. The mean duration of the additional attacks was 8.4±10.7 hours, similar to the duration of the attacks treated with the anakinra provided by us (p=0.97), substantiating the primary outcome of the study. Most additional attacks (41 of 43, 95%), were treated within 4 hours from attack onset, resulting in a mean attack duration of 7.9±10 hours, comparable to the duration achieved by early treatment with the anakinra provided by us (p=0.65).

Timing of anakinra administration and related attacks duration

Linear regression analysis demonstrated a significant correlation between the timing of anakinra injection and the duration of the treated attacks (p=0.002) (Fig. 2), but failed to reveal a significant correlation between these variables for the purchased anakinra (p=0.12). However, by excluding one attack that unexpectedly lasted 75 hours, despite the administration of anakinra 3 hours from the initiation of the attack (last attack of patient 16) (Table IV), the linear regression analysis became highly significant (p<0.0001). The outlier attack could have resulted from an overlooked technical flaw in anakinra administration. Noteworthy, linear regression of

Table III. Results of the primary and secondary study outcomes.

Outcome type	Outcome measure	Finding	*p*-value	Comment
Primary tion:	Duration of treated attacks, mean ±SD, hours	8.33 ±6.8*	<0.0001**	• 23 attacks with baseline duration of 56.3 ± 16.8 hours • Mean time interval from attack onset to anakinra administra- 2.9 ± 1.7 hours • Mean time interval from anakinra administration to attack resolution: 5.4 ± 6 hours
Secondary	Duration of attacks treated within 4 hours from onset, mean ±SD, hours	6.8 ±5*	<0.0001**	• 20 attacks with a baseline duration of 55.2 ±17.1 hours were treated • Mean time interval from attack onset to anakinra administration: 2.36 ± 0.92 hours • Mean time interval from anakinra administration to attack resolution: 4.8 ± 4.7 hours
	Proportion of attacks resolving within 24 hours from onset, n, (%)		21/23 (91)*	<0.001**
	Adverse events, n (%)	1 (4%)		• Injection site reaction

SD: standard deviation. *Computed from data presented in Table II. **Analysed, compared to baseline data, presented in Table I.

the pooled 66 attacks treated with furnished or purchased anakinra, again demonstrated a significant correlation (p=0.007), achieved by diluting the effect of the deviant attack.

Discussion

In this trial, we demonstrated that a single dose of anakinra significantly reduced the attack duration (p< 0.001) (Table III). The timing of intervention was positively correlated with attack duration (Fig. 2). Administration of anakinra within 4 hours from attack inception led to resolution in 17 of 20 (85%) of the attacks within 4 hours (Table II). The results were confirmed in a second set of attacks treated with self-procured anakinra, further validating of the effectiveness of the treatment (Table IV). These findings offer a valuable treatment option for acute attacks of FMF, which are currently only poorly palliated by administration of analgesics.

Presently, the main objective in the management of FMF is the prevention of disease activity. However, in real-life, various factors may contribute to prophylaxis failure, resulting in acute attacks with debilitating pain, associated with work or school absenteeism and decreased quality of life (12). The treatment approach offered here has the potential to change this course and its consequences. It involves a readily accessible syringe prefilled with 100 mg anakinra and the ability to recognise the onset of an attack, a skill possessed by most patients.

Table IV. Duration of acute FMF attacks from onset to resolution in individual study participants treated with self-procured anakinra.

Patient	Time interval from onset of the attack to anakinra administration (hours)	Time interval from anakinra injection to attack resolution (hours)	Duration of the attack from onset (hours)
8	3 1	12 6.5	15 7.5
11	3 (in each of 2 attacks) 3 (in each of 26 attacks) 8 12	4 3 4 12	7 (2 attacks) 6 (26 attacks) 12 24
13	1.5 (in each of 2 attacks)	3	4.5 (2 attacks)
16	2 (in each of 3 attacks) 3 (in each of 2 attacks) 3	4 4 72	6 (3 attacks) 7 (2 attacks) 75
17	2	3	5
23	2 3.5	3 5	5 8.5

Adverse events that are well established in continuous anakinra administration, such as immunosuppression, leukopenia, headache gastrointestinal discomfort and injection site reactions (13), are expected to occur rarely and to be more easily manageable in intermittent intervention. Indeed, our trial involved injection site reaction, in a single patient as the only side effect.

It is important to highlight that the study did not test and therefore does not support on-demand treatment as an alternative to continuous IL-1 blocker administration in FMF patients with colchicine failure or intolerance. The study did find that in FMF attacks for any reason, either due to non-compliance or despite being on full and appropriate treatment, a single injection of anakinra is a salvage tool that may quickly terminate the attacks and thereby reduce the associated suffering without significant safety cost. Consequently, for using occasional anakinra to abort FMF attacks, AA amyloidosis, a potential long-term complication with on-demand treatment instead of continuous anakinra, is not a consideration.

Published studies on attack-based treatment with anakinra for FMF are sparse and differ from our study by one or

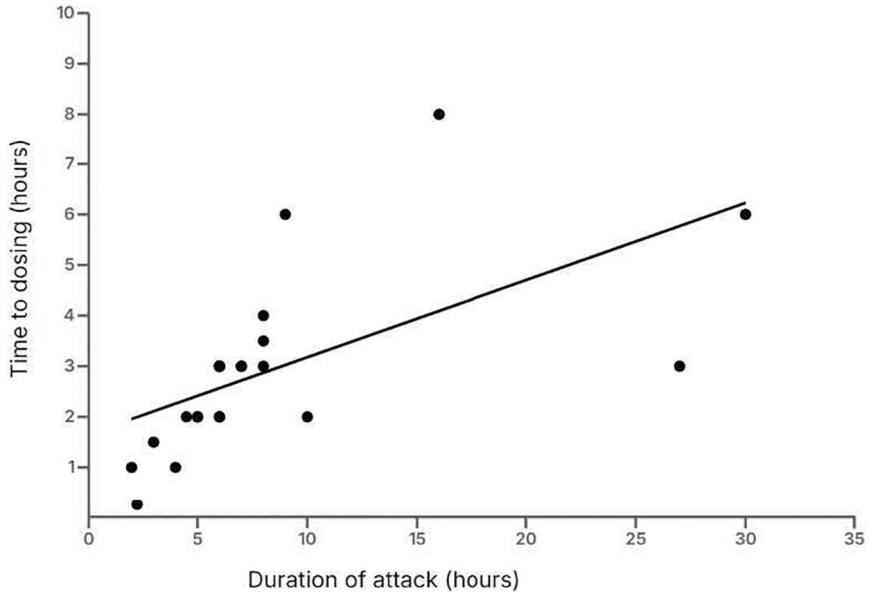

Fig. 2. Association between the timing of anakinra application and the duration of the treated attacks. Linear regression analysis shows a significant correlation between the time interval from attack onset to anakinra administration and the duration of FMF attacks (p=0.002).

more of the following aspects: being retrospective, pursuing an alternative to continuous IL-1 blocker prophylaxis, applying treatment during a prodrome which is not customary or familiar to all FMF patients, or during a recognised trigger, using multiple injections (3-4) over several days, or reporting on only one or some patients (7, 9, 10, 14-18). In contrast our study is prospective, in a cohort of 23 patients, aiming at fast suppression of acute FMF attacks, with only a single injection of anakinra, administered at the onset of the attack, which is more practical than at the prodrome. Nevertheless, despite these differences, the findings of previous reports are consistent with ours, particularly regarding the shortening of attack duration, further strengthening our results. Thus, it appears that on-demand use of anakinra is effective for both: as a treatment strategy alternative for continuous drug administration in selected FMF patients, highlighted by earlier publications, and as a remedy for suppressing acute attacks, demonstrated here, and also in some previous studies.

The favourable results of early single anakinra dosing might rest on the pathogenesis of an acute FMF attack. It begins with the assembly of the pyrin inflammasome (19, 20), which leads to the secretion of IL-1 beta and IL-18, followed by the production of many cytokines and mediators, driving an inflammatory response (21-23). Early administration of anakinra may disrupt the evolution of this cascade in its very beginning. Thus, the effectiveness of timely anakinra injection in mitigating an attack might suggest that several hours after the onset of the attack, IL-1 is no longer generated or shaded, or is naturally suppressed in most patients.

Our study has certain limitations. First, it has a small sample size and an open-label design. However, it can be considered a proof-of-concept trial, providing a foundation for future blinded, placebo-controlled trials. Additionally, due to technical considerations, the study focused on abdominal and chest attacks. Nonetheless, based on our own and published experience (7, 9), a similar approach may benefit attacks in other sites as well. Another challenge is the dependence on patients' identification of the attack, self-administration of anakinra, and judgement on the length of the attack. However, these patients, with long standing FMF, were well experienced with FMF attacks, and were thoroughly trained in anakinra administration, which minimised possible deviations from the protocol. Moreover, objective verification of the onset and end of attacks through laboratory tests is impractical in this type of study as well as in real-life scenarios due to the lack of a tight clinical and laboratory correlation. Finally, most participants in the study (19 patients ~ 80%) had mild FMF with infrequent attacks, and four patients (~ 20%) were undertreated, refusing or unable to use continuous IL-1 blockers. Nevertheless, based on published experience (16), This treatment modality might be comparably effective for patients on full treatment with colchicine or continuous IL-1-blockers, who still experience occasional attacks. In conclusion, we present a proof-of-concept prospective study demonstrating a safe and effective strategy for managing acute FMF attacks, using subcutaneous injection of anakinra 100 mg at the onset of the attack. We are now initiating a randomised controlled trial to substantiate the findings of this study. Our goal is to make timely application of anakinra for FMF attack suppression an advised and accessible salvage treatment for all FMF patients, whether at home or emergency points of care.

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