BRIEF REPORT

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On demand use of anakinra for attacks of familial Mediterranean fever (FMF)

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Abstract

To evaluate the efficacy of on-demand use of anakinra in patients with crFMF. The Gazi FMF cohort was established in the year 2010, and from that date, 689 patients with FMF diagnosed according to the Tel Hashomer criteria were registered. Attack type, duration, severity, and their impact on life were collected either by disease diaries or a mobile phone application (FMF AIDD, AppStore, and Playstore). A retrospective cohort analysis was made from records of patients who have ever been treated with IL-1 inhibitors. A total of 78 patients were treated with IL-1 inhibitors in our cohort. Among these, 15 patients were identified who received on-demand anakinra. Rationale for on-demand use was prominent prodrome or trigger for attacks and patient's personal claim. Six patients were switched from regular use and nine were directly started as on-demand use. All were using background colchicine in maximum tolerated doses. None of the patients had evidence of persistently elevated acute phase reactants or proteinuria. The median duration of on-demand anakinra use was 6 (3–36) months. Pre- and post- on-demand anakinra periods were compared. Patient reported attack severity ($p = 0.002$), duration ($p = 0.001$), frequency ($p = 0.001$), absenteeism ($p = 0.002$), and presenteeism ($p = 0.002$) were significantly improved. On-demand anakinra prevented progression of prodromes to full-blown attacks which was demonstrated by decrease in the rate of attack/prodrome ratio ($p = 0.02$). On-demand anakinra can be continued in ten subjects on long-term. On-demand anakinra significantly improved FMF attacks in certain patients which suggest this approach would be of benefit in daily practice in selected patients.

Keywords Anakinra · Familial Mediterranean fever · On demand

Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease characterized by recurrent febrile episodes of peritonitis, pleuritis, arthritis, and erysipelas-like erythema [1–4]. FMF attacks are self-limited, typically lasting in 1–3 days with a crescendo-decrescendo course, and usually have a trigger [5] and/or a prodromal period [6]. FMF reduces quality of life and work productivity

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and predisposes patients to secondary amyloidosis which is the most dreaded complication causing mortality and morbidity [7]. FMF is caused by mutations in the *MEFV* gene which encodes pyrin, an inflammasome constructing protein. Pyrin is crucial in the regulation of interleukin caspase-1 and nuclear factor-κB (NF-κB) pathways, and malfunctioning pyrin results in overproduction of Interleukin (IL)-1β which is the principal cytokine that drives typical attacks of FMF [8].

The goals of FMF treatment are improvement of the quality of life by reducing frequency, severity and duration of attacks, and prevention from development of amyloidosis. Colchicine, the mainstay of FMF treatment, has been considered as safe and effective in reaching these goals in the majority of patients. However, up to 5–10% of FMF patients do not respond well to colchicine despite the highest tolerable doses [9–11]. IL-1 antagonists: anakinra, canakinumab, and rilonacept have been shown to be effective in reducing FMF attacks by injections with regular time intervals in patients with colchicine-resistant FMF (crFMF) [12, 13]. Anakinra is a short-acting

recombinant human IL-1 receptor antagonist administered as daily painful injections [14]. However, high cost, side effects, and patient incompliance limit its use which might be overwhelmed by on-demand use of it which has not been reported in FMF patients.

FMF attacks are managed with palliative care and there is no treatment for impending or emerging attacks. Substantial number of FMF patients report a prodromal period that they can exactly anticipate attacks many hours before its onset [6]. Therefore, prodromal periods might be a window of opportunity for the prompt treatment of pending attacks. Moreover, some patients report only attacks which are generated by obvious triggers. Therefore, use of IL-1β blockers before such triggers or in prodromal period might abrogate or reduce the severity of attacks in patients with FMF. There are a few case reports about "on-demand" (starting at first symptom of attacks) use of anakinra in other autoinflammatory diseases such as TRAPS or HIDS [15–17]. The purpose of this retrospective study is to assess the utility of "on-demand" anakinra in FMF patients.

Patients and methods

The study was conducted in the rheumatology clinic of Gazi University Hospital which is a tertiary care center. The Gazi FMF cohort was established in the year 2010, and from that date, 689 patients with FMF diagnosed according to the Tel Hashomer [18] criteria were registered as of March 2018. Demographic features, comorbidities, clinical manifestations, detailed attack characteristics, attack frequency, severity, triggers, duration, prodrome and treatment response of each manifestation, disease complications, family history, *MEFV* mutations (if available), and laboratory results were recorded. Patients were monitored for the frequency, duration, severity of each type of attacks, laboratory features, patient global assessment of disease activity, auto-inflammatory disease activity index scores (AIDAI, after year 2015) [19], compliance and side effects of therapy, prodrome, or triggers of attacks as well as work productivity as absenteeism and presenteeism on each visit with a 3- to 6-month interval. Disease activity and drug compliance data were collected either by printed FMF diaries (since 2010) or a mobile phone application named FMF-AIDD (available in Google Play and AppStore) since September 2016.

Rationale for use of on-demand anakinra were at least monthly attacks despite highest tolerated dose of colchicine, prominent prodrome and/or trigger for the attacks, and patients' own claim. Patient with marked prodrome used on-demand anakinra for subsequent 2 to 3 days when they felt a prodrome. On condition at least two consecutive days, duration of the on-demand anakinra protocol determined as the duration of patient's own attacks in pre-anakinra period.

Only one patient with marked prodrome had attack duration of 4 days. This patient was advised to use on-demand anakinra for 4 days. But he stated that 3 days of use was enough. Patients with well-defined attack trigger used on-demand anakinra just before and during exposure to the defined trigger, such as consecutive 5 days use of on-demand anakinra during menstruation. Background colchicine was continued in all subjects at highest tolerated dose. None of the patients had laboratory signs of persistent subclinical inflammation, proteinuria, and amyloidosis.

Statistical analysis

The data was analyzed with "Statistical Package for the Social Science (SPSS) version 21.0 for Windows". All continuous data were presented as median and minimum-maximum colchicine, and colchicine plus on-demand anakinra periods were compared with Wilcoxon rank test. A p value equal or less than 0.05 was considered as statistically significant.

Results

A total of 78 patients were treated with IL-1 inhibitors in our cohort, and 60 of them used anakinra due to either frequent attacks or amyloidosis. Among these, 15 patients were identified who received on-demand anakinra protocol. Median age of patients was 34.0 ± 9.5 years and 9 (60%) patients were female. Patients were using colchicine for median 100 (36–372) months. The median duration of on-demand anakinra use was 6 (3–36) months. Median use of on-demand anakinra by the patients with marked prodrome has been found as 8 (4–12) injections in a 3-month period. Six patients were switched from regular daily use (patient nos. 1–6) and nine were directly started as on-demand use. Ten patients had marked prodrome and three had prominent trigger (menstruation in one, long travel in one, and long travel or cold exposure in one). The detailed clinical and attack characteristics of the patients are summarized in Table 1.

Pre- and post- on-demand anakinra periods were compared (Table 2). Patient reported attack severity ($p = 0.002$), duration ($p = 0.001$), frequency ($p = 0.001$), absenteeism ($p = 0.002$), and presenteeism ($p = 0.002$) were significantly improved but C-reactive protein (CRP) remained in the same levels. The prodrome frequency of the patients and the conversion rates of these prodromes to the attacks were investigated. Prodrome frequency was variable between patients. However, by use of on-demand anakinra, progression of prodromes to full-blown attacks was abrogated; attack/prodrome ratio was significantly improved in all patients except for patients nos. 3, 12, and 15 ($p = 0.02$). Prophylactic on-demand use of anakinra in patients with prominent triggers was

Table 1 Clinical characteristics and detailed attack features of patients

Patient no	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age, (years)	29	33	45	20	32	19	34	35	35	45	36	39	31	57	31
Sex	M	F	M	F	F	F	F	F	F	F	M	F	M	M	M
MefV gene mutation	M694V E148Q	M694V M694V	M680I V726Q	M694V V726A	M694V M694V	M694V V726A	M694V M694I	M694V M694V	E148Q	V726A	M680I M680I	M694V M694V	M694V V726A	M694V M694V	V726A
Disease duration,(years)	6	20	23	9	27	12	32	32	10	10	12	35	14	55	9
Colchicine dose	2 mg	1 mg	1.5 mg	1.5 mg	2 mg	2 mg	2 mg	2 mg	1.5 mg	2 mg	2 mg	2 mg	2 mg	1.5 mg	2 mg
Attack type	MS	All	All	PP	MS	PP	PP	All	PP	PP	PP	PP	All	PP	PP
Anti-IL-1 Tx indication	R	I	R	I	R	R	R	R	R	R	R	R	R	I	R
On-demand reason	P	P	P	P	T	OW	OW	T	T	P	P	P+OW	P	P	P
Colchicine period/continuous anakinra period/on-demand anakinra period*						Colchicine period/on-demand anakinra period*									
Attack severity, (VAS)	8/6/6	10/6/8	10/7/8	10/10/10	10/0/10	10/8/10	8/3	10/6	10/8	8/4	8/6	10/5	8/5	10/0	7/5
Prodrome frequency**	4/4/5	4/1/4	4/2/3	8/1/3	NA	NA	NA	NA	NA	3/3	4/2	9/3	3/2	3/3	3/2
Attack frequency**	4/1/3	4/1/3	4/2/3	8/1/1	5/0/2	5/3/5	9/5	3/1	3/1	3/1	4/1	9/3	3/1	3/0	3/2
Attack to prodrome ratio	1/0.3/0.6	1/1/0.8	1/1/1	1/1/0.3	NA	NA	NA	NA	NA	1/0.33	1/0.50	1/1	1/0.5	1/0	1/1
Attack duration, (hours)	48/36/36	48/36/48	96/24/48	72/48/48	96/0/72	120/72/120	96/24	72/36	120/72	72/24	48/24	48/24	48/24	72/0	72/12
Absenteeism	8/2/3	5/0/2	3/2/3	23/2/3	10/0/2	9/2/9	18/4	NA	8/1	4/1	3/0	9/2	3/1	2/0	6/1
Presenteeism	13/2/4	7/0/2	5/2/5	30/3/4	13/0/5	13/3/13	27/5	NA	10/4	5/2	6/2	10/3	4/1	4/0	9/1
AIDAI	8/2/2	16/3/11	32/3/24	34/3/3	18/0/7	34/14/27	100/8	18/6	40/5	5/2	12/2	38/4	18/3	8/0	14/3
Tx durations, (months)	60/12/12	120/6/3	180/3/3	84/40/6	72/9/5	84/6/6	168/25	360/36	96/6	36/3	100/16	372/12	120/9	360/24	84/6
Final Tx	CA	CA	CA	ODA	CA	CA	ODA	ODA	ODA	ODA	ODA	ODA	ODA	ODA	ODA

*Data presented as colchicine/anakinra (if applicable)/on-demand anakinra, **Frequencies adjusted for a 3-month period, attack duration represented as days, disease and Tx duration represented as months. MefV Mediterranean fever, IL-1 Interleukin-1, CRP C-reactive protein, VAS 0–10 cm visual analog scale, patient-reported attack severity, AIDAI autoinflammatory disease activity index, PP plevritis-peritonitis, MS musculoskeletal, All both plevritis-peritonitis and musculoskeletal, R resistance, I = intolerance, P prodrome, T trigger, OW own will, NA not applicable, Tx treatment, CA continuous anakinra, ODA on-demand anakinra

Table 2 Comparison of attack characteristics before and after on-demand anakinra protocol

	Colchicine period	Colchicine plus On-demand anakinra period	p
Attack severity, (VAS)	10 (7–10)	6 (0–10)	0.002
Duration, (days)	3 (2–5)	1.5 (0–5)	0.001
Frequency*, (number)	4 (3–9)	2 (0–5)	0.001
CRP (mg/L) (n = 14)	5.1 (2.4–12.5)	4.2 (2.7–14.4)	0.58
AIDAI	18 (5–100)	4 (0–27)	0.001
Attack/prodrome ratio, (n = 10)**	1	0.6 (0–1)	0.02
Absenteeism*, days (n = 14)	7 (2–23)	2 (0–9)	0.002
Presenteeism*, days (n = 14)	9 (4–30)	3.5 (0–13)	0.002

*Attack frequency and work productivity parameters are adjusted for a 3-month interval. **Ten of patients have prodrome. *VAS* visual analog scale, *CRP* C-reactive protein, *AIDAI* autoinflammatory disease activity index

successful in two patients (patient nos.8 and 9, one with menstruation and another with cold and long-travel provoked). On-demand anakinra can be continued in ten subjects on long-term but continuous treatment was required in five subjects.

Patients who were prone to leukopenia after the start of anakinra (patient nos. 3 and 9), were given 1.5 mg of colchicine although they were not intolerant. One of the patients (patient no. 5) wanted to use anakinra continuously with the purpose of complete attack control although on-demand use provides effective attack control.

Discussion

In our study, we found that on-demand anakinra is effective in selected patients with inadequate response to colchicine. However, it should be noted that we only used this approach in patients with prominent attack prodromes or triggers, and none of our patients had persistent inflammation which is determined by elevated levels of CRP.

The efficacy of various IL-1 blockers has been clearly demonstrated in preventing FMF attacks. For this effect, they should be continuously used with regular injections which cause substantial costs and loss of patient compliance by time. IL-1 inhibitors are relatively new drugs for the treatment of FMF, and there are many unanswered questions such as their long-term benefits, dose tapering, and duration of treatment. In our study, we found that on-demand use was successful in selected patients but failed in five patients who had mainly musculoskeletal attacks.

Most of FMF attacks result in bed-confinement impair quality of life and cause workforce-loss. Studies on IL-1 blockers are conducted on crFMF patients with frequent attacks, and there is still an unmet need for the treatments that abrogate an impending attack in colchicine responsive patients who have occasional attacks. On-demand anakinra use has been reported in other autoinflammatory disorders for this indication in two patients, one with mevalonate kinase deficiency and the other with TNF receptor-associated periodic syndrome, with success [15–17]. FMF attacks are usually preceded by a prodromal period which is well-recognized and perfectly characterized by FMF patients [6]. Therefore, prodromal period could be a window of opportunity for halting or alleviating symptoms of an impending attack. We observed that use of anakinra in this period would be a reasonable approach which is indicated by improvement in AIDAI, workforce loss of patients, and at least 80% reduction of anakinra usage compared with continuous use. All prodromal symptoms of the patients might not reflect an apparent full-blown attack. However, the frequency of full-blown attack significantly reduced after on-demand use of anakinra. This observation can be regarded as an objective proof that at least a group of prodromal symptoms of the patients was the first sign of an early full-blown FMF attack.

We have several limitations in our study. The major limitation is its retrospective design, and a prospective study may help to show more clearly efficacy of on-demand anakinra therapy. Serum amyloid A (SAA) which is a preferred marker for the assessment of subclinical inflammation in patients with FMF is lacking in our study [11]. Other major limitations are potential benefits or harms of long-term on-demand therapy which are not answered in our study.

In conclusion, use of anakinra in pre-attack prodromal period could help to abrogate or decrease the severity of an impending attack which needs confirmation in prospective controlled studies. Another advantage of this approach would be reducing cost and adverse effects of continued use of IL-1β antagonists in selected patients with marked prodrome or triggers and low risk of amyloidosis.

Compliance with ethical standards

Disclosures None.

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