Long-term safety and efficacy of anakinra and canakinumab in patients with familial Mediterranean fever: a single-centre real-life study with 101 patients

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ABSTRACT

Objective. *Anakinra and canakinumab are the most commonly used agents in colchicine resistant/intolerant patients. In this study we investigated long-term efficacy and safety of anakinra and canakinumab.*

Methods. *In this retrospective study, we enrolled 101 adult patients with familial Mediterranean fever (FMF). Clinical and laboratory parameters before and after treatment with anakinra/canakinumab and the side effects observed during the treatment were recorded. All patients received anakinra initially and switched to canakinumab, in case of inadequate response/intolerance.*

Results. *The median (IQR) duration of treatment with anti-IL-1 agents was 35 (24-47.5) months. 101 patients were treated with anakinra and 27 patients with canakinumab. The autoinflammatory diseases activity and attacks decreased with both anakinra and canakinumab. Anakinra was effective in decreasing proteinuria and canakinumab was not effective in decreasing proteinuria in anakinra unresponsive patients. The modified FMF score was achieved in 76.2% of anakinra and 88.9% of canakinumab group. Injection site reactions (ISRs, n:15) was the most common reason of discontinuation of anakinra and most of ISRs developed in first 3 months of treatment. One severe skin rash, two anaphylactic reactions and one severe neutropenia were observed with anakinra; in the first, eighth, twelfth and fiftieth months, respectively. No severe side effects or side effect-related discontinuation of canakinumab were observed.*

Conclusion. *Anakinra and canakinumab seem to be effective in long-term management of FMF patients. Canakinumab had a favourable safety/tolerability profile. Anakinra is also generally safe, but the serious side effects that may be observed in the short and long-term use should be taken into account.*

Introduction

Familial Mediterranean fever (FMF) is the most frequent hereditary autoinflammatory disease in the world. Although FMF is most frequently seen in Mediterranean populations, especially Turkish, Arab, non-Ashkenazi Jews and Armenians, it has a worldwide distribution (1). FMF results from mutations of MEFV gene which encodes for a regulatory protein, pyrin. Mutations impair regulation of pyrin and result in activation of caspase-1 which, in turn, mediates the release of pro-inflammatory IL-1β from its inactive precursor and pyroptosis via the Gasdermin D pathway (2). FMF is characterised by self-limited attacks of fever, serositis, arthritis, and erysipelas like erythema along with elevated acute phase reactants (3). In attack-free periods, patients are asymptomatic, but some of patients suffer from chronic complications of disease. Amyloidosis and related end-stage renal disease are the most devastating complications of disease (4).

Colchicine is the mainstay of treatment given that it reduces frequency, duration and severity of attacks and also prevent from amyloidosis. The definite mechanism of action of colchicine is unknown, however it has multiple inhibitory functions on microtubule polymerisation, neutrophil chemotaxis/migration, and inflammasome assembly that activate interleukin (IL)-1β (5). However, about 5–10% of patients do not respond sufficiently to the colchicine, despite regular

use of highest therapeutic doses (6). In addition, effective doses of colchicine cannot be maintained in up to 20% of patients due to its side effects (7, 8). Many therapeutic options have been used in colchicine-intolerant/unresponsive patients, including intravenous colchicine, interferon alpha, thalidomide, tumour necrosis factor inhibitors, azathioprine and corticosteroids (9-12). None of these treatments had sufficient benefit in controlling disease.

The discovery of the critical role of interleukin-1ß in the pathogenesis of FMF and its pharmacologic blockade made a breakthrough in the management of colchicine-resistant (CrFMF) and colchicine-intolerant (CiFMF) patients and also those who suffer from complications of disease (2,13). IL-1 antagonist treatments have been evaluated in many studies and randomised controlled trials (14-19). However, most of these studies were conducted with small number of patients with considerably short study duration. Anakinra and canakinumab are the most commonly used IL-1 antagonists in CrFMF patients and they have been used by thousands of CrFMF/CiFMF patients, but data on their long-term utility and safety is largely lacking.

In this study we aimed to investigate characteristics of patients receiving anakinra and canakinumab and define long-term efficacy and safety of these two agents on a relatively large number of patients.

Materials and methods

Patients and study design

In this study, we enrolled adult patients (≥18 years) with FMF, followed at the tertiary rheumatology clinic of Gazi University Hospitals. The diagnosis of FMF was made according to the Tel Hashomer criteria (20). The study was approved by both Gazi University ethical committee (approval no 2018-674) and Turkish Medicines and Medical Devices Agency of the Turkish Ministry of Health (no. 75642246-000-E.222002). Informed consent was obtained from all participants. We retrospectively reviewed the computer-based medical records of all FMF patients who had received anti-IL-1 treatment. Face-to-face or telephone interview was done for missing data about any history of amyloidosis in second degree relative of 12 patients and the frequency of anakinra treatment in 4 patients.

Demographic characteristics, comorbidities, the age at onset of disease and diagnosis, attack characteristics, presence of amyloidosis, colchicine resistance/intolerance and persistent inflammation, MEFV gene mutations (if available), duration of disease (years), family history of FMF and amyloidosis, attack characteristics (recorded quarterly) and laboratory parameters; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin and creatinine and 24-hour urinary protein excretion before and after anti-IL-1 treatment were recorded. Obtained data on IL-1 antagonists included reasons for starting and switching from anakinra to canakinumab or vice versa, the dose, dosing interval and duration of therapy and safety data as adverse drug reactions, hospitalisations, malignancy, any permanent organ damage or death.

Colchicine resistance was defined as experiencing more than one attack per month despite maximal tolerated dose of colchicine (6). Persistent inflammation was defined as increased CRP levels measured during the attack-free periods (at least ≥2 weeks apart from the attacks) and evident in ≥75% of measurements at all follow-up visits, while not using targeted biologic therapies.

Evaluation of quality of life and disease activity

The impact of anti-IL-1 therapy on quality of life (QoL) and disease activity was evaluated with patient global assessment (PGA) using a 0-10-point numerical rating scale (NRS, 0=no disease activity, 10=the worst disease activity) and Auto-Inflammatory Diseases Activity Index (AIDAI), respectively. The AIDAI components were comprised the following; fever (≥38°C), abdominal pain, chest pain, swelling of the joints, arthralgia or myalgia and skin rash. Each item is scored as no (0=absence of symptom) or yes (1=presence of symptom), the final AIDAI score is the sum of all items. All daily scores in 1 month are added and a cumulative activity score is obtained (21). The AIDAI scores before IL-1 antagonists and the last were recorded. PGA was available for all patients, while AIDAI was available for patients who received anti-IL-1 therapy after 2014. At the last visit, efficacy of anti-IL-1 treatments were evaluated with the modified FMF50 score (15) which include 4 criteria and to consider an improvement, 3 of 4 criteria should be fulfilled; ≥50% decrease in all attacks, ≥50% decrease in joint attacks, ≥50% decrease in the levels of CRP or serum amyloid A, ≥50% increase in QoL.

All patients were considered for evaluation of adverse drug reactions, but only who received anti-IL-1 therapy for ≥3 months were evaluated for impact of anti-IL-1 therapy on clinical and laboratory parameters. All patients were treated with anakinra initially and then switched to canakinumab in case of inadequate response, intolerance or intolerable adverse events.

Statistical analysis

Statistical analyses were performed by SPSS software v. 15.0 (Chicago, IL, USA). The numerical variables were investigated by using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro Wilk's test) for evaluating the normality distribution. Categorical variables were presented as numbers and percentages, and continuous variables were presented with mean ± standard deviation or median (range or interquartile range (IQR) (25^{th}–75^{th}) values. Paired Students' t- or Wilcoxon tests were used for comparison of pre- and post-treatment values. A p-value ≤0.05 was considered statistically significant in all analyses.

Results

Patient characteristics

In this study, 101 patients with FMF who had received anti-IL-1 treatments were included. While anakinra was initial agent in all 101 patients, 27 of them switched to canakinumab (Fig. 1). The mean age was 37.3 (±10.9) years and 58 (57.4%) patients were female. Demographic and clinical characteristics of patients were described in Table I. The

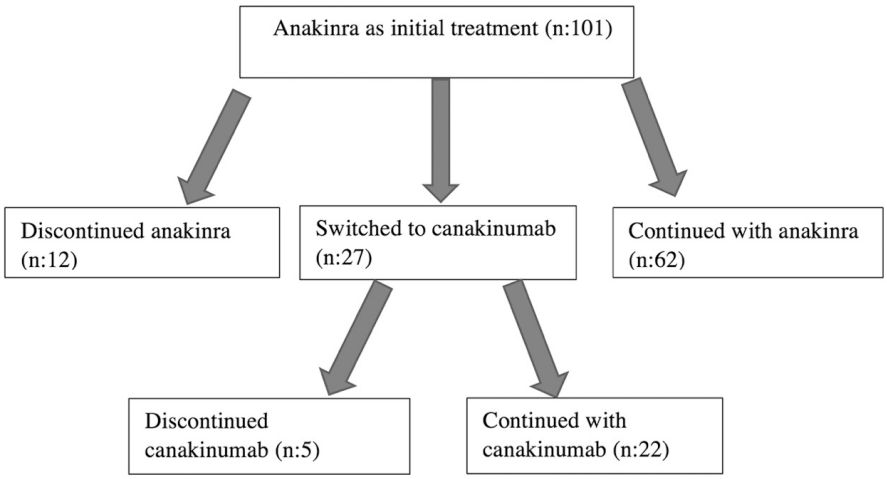

Fig. 1. Flow diagram of patients treated with anakinra and canakinumab.

Table I. Demographic and clinical features of FMF patients treated with anakinra/canakinumab.

Clinical characteristics of patients (n=101)	
Age, mean (S.D.), years	37.3 (±10.9)
Female/Male	58/43
M694V/M694V homozygous*	52 (56)
M694V heterozygous* (complex/single heterozygous)	8/25 (8.5/27)
Age at symptom onset, years	8 (5-12)
Age at diagnosis, years	20 (11-28)
Time since diagnosis, years	15 (10-21)
Age at onset of anti-IL-1 therapy, years	30 (25-38.5)
Time between diagnosis and anti-IL-1 therapy, years	11 (5-17)
Fever	63 (62.4)
Peritonitis	84 (83.2)
Pleuritis	49 (48.5)
Pericarditis	3 (3)
Arthritis	82 (81.2)
Erysipelas like erythema	26 (25.7)
Myalgia	31 (30.7)
Protracted febrile myalgia	4 (4)
Orchitis	1 (1)
Family history of FMF	61 (60.4)
First degree relative	50 (49.5)
Second degree relative	35 (34.7)
Family history of amyloidosis	8 (7.9)
First degree relative	7 (6.9)
Second degree relative	2 (2)
Colchicine dose before anti-IL-1 treatment (mg/day), mean (S.D.)	1.7 ± 0.4
Duration of anti-IL-1 therapy, median (range), months	35 (1-108)
Duration of anakinra, median (range), months	30 (1-108)
Duration of canakinumab, median (range), months	28 (6-57)
Duration of anakinra before canakinumab switch, months	7 (1-18)
Comorbidities	
Spondyloarthritis	15 (14.8)
Chronic peripheral arthritis	10 (9.9)
IBD	4 (4)
Behçet's syndrome	1 (1)
Vasculitis	3 (3)
Psoriasis	8 (7.9)
Amyloidosis	33 (32.7)
The reasons for starting anti-IL-1 therapy	
Colchicine resistance	63 (62.3)
Amyloidosis/proteinuria	27 (26.7)
Colchicine intolerance/side effects	5 (5)
Persistent inflammation	7 (7)

*Mutation data are available for 93 patients. Values are presented as n (%) or median (interquartile range, 25th-75th), unless stated. IBD: inflammatory bowel disease.

median (IQR) age at onset of anti-IL-1 therapy was 30 (25–38.5) years and the median (IQR) duration between diagnosis and anti-IL-1 therapy was 11 (5-17) years. Median duration of anti-IL-1 therapy was 35 (range: 1–108) months. Median duration of anakinra and canakinumab treatment was 30 (range, 1–108) and 28 (range: 6–57) months, respectively. Genotype data was available for 93 patients and *M694V* was the most common variant (52 homozygous and 33 heterozygous). Amyloidosis which was confirmed by biopsy was present in 33 patients (Table II) and amongst 6 patients were on regular haemodialysis and 3 patients had had renal transplantation. Two patients had had renal transplantation before and one patient after anakinra treatment. Spondyloarthritis (n=15) was the most common inflammatory comorbidity.

Colchicine resistance and amyloidosis/proteinuria were the main reasons for starting anti-IL-1 therapy. Anakinra was switched to canakinumab in 27 patients. Proportions of FMF manifestations in patients treated with canakinumab were peritonitis 23 (85.2%), arthritis 23 (85.2%), fever 17 (63%), pleuritis 14 (51.9%), erysipelas-like erythema (ELE) 9 (33.3%), myalgia 6 (22.2%) and pericarditis 1 (3.7%). The median (IQR) duration of anakinra treatment before canakinumab switch was 7 (1-18) months. Anakinra related side effects (n=16) and insufficient response to anakinra (n:11) were the reasons for switching to canakinumab. Anakinra 100 mg single injection was given daily to 48 patients, twice daily to four, thrice daily to one, every other day to 23 patients, once every three days to 9 patients and as on demand (22) to the rest of the patients. Canakinumab 150 mg was administered monthly to 21 patients, bimonthly to 3 patients and quarterly to one patient. One patient received 300 mg and the other received 450 mg canakinumab monthly. One patient who received canakinumab was switched back to anakinra due to insufficient clinical response. 88 patients were treated with anakinra for ≥3 months and all patients (n=27) received canakinumab were treated for ≥6 months. Therefore 88 patients received

Table II. Clinical characteristics of FMF patients with amyloidosis.

Patients with amyloidosis (n=33)	
Age, mean (S.D.)	43.3 (±12.2)
Female/Male	17/16
MEFV variants*	
M694V/M694V homozygous	21 (63.6)
M694V single heterozygous	2 (6)
M694V/V726A	3 (9)
M694V/M680I	3 (9)
M680I/M680I	2 (6)
M694I/V726A	1 (3)
Age at symptom onset, years	8 (5.5-20.5)
Age at diagnosis, years	24 (12.5-31)
Time since diagnosis, years	16 (10-26.5)
Age at onset of anti-IL-1 therapy, years	37 (28-51.5)
Fever	18 (54.5)
Peritonitis	28 (84.8)
Pleuritis	17 (51.5)
Arthritis	26 (78.8)
Erysipelas like erythema	7 (21.2)
Myalgia	5 (15.2)
Protracted febrile myalgia	1 (3)
Current treatment	
Anakinra	21 (63.6)
Canakinumab	10 (30.3)
Adalimumab	1 (3)
Certolizumab	1 (3)

*Mutation data are available for 32 patients.
Values are presented as n (%) or median (interquartile range, 25th-75th), unless stated.

anakinra and 27 received canakinumab were included to evaluate the impact of anti-IL-1 therapy on clinical and laboratory parameters.

Efficacy

Anakinra. Total attack frequency decreased significantly from 3.25 attacks per 3 months (range: 0–15) to 1 attack per 3 months (range: 0–9) with anakinra ($p<0.001$). All attack types decreased significantly, of note 3 patients with pericarditis and 4 patients with febrile myalgia resolved immediately soon after introduction of anakinra. The median ESR and CRP levels decreased significantly after anakinra treatment. Both disease activity and PGA improved significantly (Table III). The modified FMF50 score was available for 84 patients and achieved in 64 (76.2%) patients at the last visit. Twenty-two patients with proteinuria were included to evaluate the impact of anakinra on proteinuria. Patients with end-stage renal disease/oligouria were not included for analysis. The median (IQR) 24-hour urinary proteinuria before treatment was 3126 mg (1262–5450) and decreased to 1750 mg (759–3891) at the third month ($p=0.006$), 1355 mg (396–3830) at the sixth month ($p<0.001$) and 730 mg (303–3120) at the last visit ($p=0.001$). The median (IQR) time between the measurement of proteinuria before and at the last visit after anakinra was 18.5 (12-37) months.

Canakinumab. All attack types decreased significantly with canakinumab except myalgia ($p=0.068$) and one patient with pericarditis resolved after introduction of canakinumab. ESR and CRP levels decreased significantly with canakinumab. Additionally, disease activity and PGA improved significantly (Table III). The modified FMF50 score was achieved in 24 (88.9%) patients at the last visit. Eight patients with proteinuria were treated with canakinumab. Anakinra was ineffective in decreasing proteinuria in 6 of eight patients. The median (IQR) 24-hour proteinuria before and after canakinumab was 1622 mg (760–4042) and 1725 mg (622–4310), respectively ($p=0.753$). The median time between the measurement of proteinuria before and at the last visit after canakinumab was 8.5 (range: 6–21) months. The other two patients developed anakinra related side effects in first month of treatment, hence switched to canakinumab. Twenty four-hour proteinuria decreased from 7012 mg to 5859 mg and 6400 mg to 3800 mg in these two patients in their last visits, after 30 and 31 months of treatment with canakinumab, respectively.

Safety

Anakinra. Side effects were observed in 41 (40.6%) patients treated with anakinra. Injection site reactions (ISRs, n:22) were the most common side effect, followed by skin rash (n:12) and weight gain (n:8). Among them, four serious side effects were observed, including two anaphylactic reactions (hospitalisation required), one severe neutropenia (<500/μL) and one hospitalisation required diffuse skin rash (Table IV). Anakinra was discontinued

Table III. Change of clinical and laboratory parameters with anakinra and canakinumab.

	Before anakinra (n=88)	After anakinra (n=88)	*p*	Before canakinumab (n=27)	After canakinumab (n=27)	*p*
Total attacks/per 3 months	3.25 (2.25-4.94)	1 (0.25-1.95)	**<0.001**	2.5 (1-5)	0.5 (0.25-1)	**<0.001**
Fever	0.75 (0-1.5)	0 (0-0.25)	**<0.001**	0.75 (0-4.5)	0 (0-0.25)	**<0.001**
Peritonitis	2 (0.5-3)	0.25 (0-0.75)	**<0.001**	0.5 (0.25-4)	0 (0-0.5)	**<0.001**
Pleuritis	0 (0-1.25)	0 (0-0.25)	**<0.001**	0 (0-0.75)	0 (0-0)	**0.002**
Arthritis	1 (0.25-2.5)	0.25 (0-0.5)	**<0.001**	0.5 (0.25-2)	0 (0-0.25)	**<0.001**
ELE	0 (0-0.2)	0 (0-0)	**<0.001**	0 (0-0.5)	0 (0-0)	**0.007**
Myalgia	0 (0-0.7)	0 (0-0)	**<0.001**	0 (0-0)	0 (0-0)	0.068
ESR, mm/hour	33.5 (19.25-46)	13.2 (8.2-22.7)	**<0.001**	28 (15-40)	13 (8-20)	**<0.001**
CRP, mg/liter	24 (12-44)	9 (3-14)	**<0.001**	24 (11-46)	4 (3-12)	**<0.001**
Creatinine, mg/dl	0.69 (0.6-0.9)	0.71 (0.6-0.9)	0.2	0.69 (0.62-0.88)	0.71 (0.62-0.85)	0.265
Albumin, mg/dl	4.3 (3.9-4.5)	4.4 (4.2-4.6)	**0.001**	4.3 (3.8-4.4)	4.4 (4.1-4.4)	0.132
AIDAI	14 (8.75-19.25)	2.5 (0-4)	**<0.001**	11 (6.5-19.5)	0 (0-3)	**<0.001**
PGA (NRS 0-10)	8 (6-8)	2.5 (2-4)	**<0.001**	6 (5-8)	2 (1-3)	**<0.001**

Values are presented as median (interquartile range, 25th-75th).
AIDAI: auto-inflammatory diseases activity index; CRP: C-reactive protein; ELE: erysipelas like erythema; ESR: erythrocyte sedimentation rate; NRS: numerical rating scale; PGA: patient global assessment.

in 20 patients due to side effects (Table V). There was no skin rash related discontinuation of anakinra, except one severe skin rash, while 68% (n=15) of ISRs resulted in cessation of treatment with anakinra. The time of development of ISRs which led to discontinuation of anakinra treatment was as following; 7 in first month, 4 in second month, 2 in third month, 1 in 10th and 1 in 18th month. Severe skin rash developed in first month, increased liver enzymes in 12th month, anaphylactic reactions in 8th and 14th months. Severe neutropenia was observed in 50th month of anakinra treatment.

Canakinumab. Side effects were observed in 7 (30.4%) patients treated with canakinumab. Weight gain which was developed in six of 27 patients was the main side effect (Table V). There were no severe side effects in patients treated with canakinumab and no side effect related cessation of canakinumab was observed in our study.

Reasons (other than side effects) for discontinuation of anakinra and canakinumab

Anakinra was discontinued in 39 (38.6%) patients. Insufficient response (n=14) to anakinra was the second most common reason of discontinuation after the anakinra related side effects. Anakinra was switched to anti-TNF drugs in two patients, due to dominancy of comorbid spondyloarthritis (Table V).

Canakinumab was discontinued in 5 (18.5%) patients. Insufficient response to canakinumab was the main reason for discontinuation. In two patients, canakinumab was switched to anti-TNF drugs, due to dominancy of spondyloarthritis.

Table IV. Anakinra and canakinumab related side effects.

Side effects	Anakinra treated n=41* (40.6%)	Canakinumab treated n=7 (30.4%)
ISRs	22	-
Skin rash	12	-
Neutropenia	4	-
Anaphylactic reaction	2	-
Increased liver enzymes	3	1
Weight gain	8	6

*Eleven patients experienced two different side effects, while 30 patients experienced only one type.
ISRs: injection site reactions.

Table V. Reasons for discontinuation of anakinra and canakinumab.

	Anakinra (n=101) n, %	Canakinumab (n=27) n, %
Patient preference*	4 (4)	
Insufficient response	14 (13.8)	3 (11.1)
High number of attacks	6	-
Increased proteinuria	6	1
Prevailing comorbid condition	2	2
Unintended pregnancy	1 (1)	2 (7.4)
Side effects	20 (19.8)	
ISRs	15	
Severe skin rash	1	
Increased liver enzymes	1	
Anaphylactic reaction	2	
Severe neutropenia	1	
Total	39 (38.6)	5 (18.5)

*Due to clinical and laboratory improvement.
ISRs: injection site reactions.

Discussion

In this study, we evaluated the long-term efficacy and safety of anakinra and canakinumab in a large population of FMF patients. To the best of our knowledge, this study has the longest median duration of anakinra and canakinumab treatment in adult FMF patients in published literature.

In our study, there was a long median diagnostic delay with 15 years. Another characteristic of our FMF patients was the high frequency of M694V homozygosity. More than half of the patients had M694V homozygosity and this ratio was 23% in our previous study with 971 patients (23). M694V homozygosity is associated with early-onset disease, poor prognosis and amyloidosis (24, 25). These characteristics of patients lead to severe disease phenotypes and may increase the need for anti-IL-1 agents.

In term of efficacy, the findings of our study were similar with previous studies and randomised controlled trials (15-18). In a previous small randomised, placebo-controlled trial, total attacks and joint attacks were decreased significantly with anakinra (15). In this trial, the attacks in serosal sites were also decreased with anakinra but decrease in these attacks was not statistically significant. The data of which attack type responded better to anakinra was not clear in other studies. In our study, we reported all attack types for anakinra and canakinumab separately and both agents were effective in decreasing total attacks. The use of AIDAI and the modified FMF 50 score in our study had the advantage of standardised assessment of disease activity and a more objective evaluation of drug efficacy. In our study, in addition to prevention of FMF attacks, the disease activity improved and the modified FMF 50 score was achieved in a satisfactory number of patients treated with anakinra and canakinumab at the last visit and considering the long treatment duration, both agents seem to maintain their efficacy for a long time.

In our study, anakinra reduced proteinuria. Serum albumin level also increased after anakinra, probably due to decreased urinary protein excretion and decreased inflammatory burden. Canakinumab was not effective in reducing proteinuria in 6 patients who did not responded to anakinra, but a decrease in proteinuria was observed in two patients who was not treated with anakinra due to side effects. Then, in case of worsening proteinuria under anti-IL-1 treatment, the data about which treatment options can be used is

limited. Whether increasing the daily dose of anakinra and canakinumab or switching to each other would be effective merits further investigation.

A recent study reported a decrease in proteinuria of FMF patients with amyloidosis (26). Akar *et al*. also reported improved proteinuria with anti-IL-1 antagonists (18), but in another study, the decrease in proteinuria was not found significant (27). In none of above-mentioned studies, the efficacy of anakinra and canakinumab in reducing proteinuria had not been evaluated separately. In our study, acute phase reactants (ESR and CRP) decreased significantly with both of anakinra and canakinumab. The decrease in ESR and CRP with IL-1 antagonists was reported in many other studies (16, 18, 26-28). Amyloidosis is the most devastating complication of FMF. There is no treatment for established amyloidosis, therefore the prevention of development of amyloidosis or further damage due to ongoing amyloidosis should be the main target of treatment. The role of colchicine in prevention of amyloidosis is well established (29), while the role in established amyloidosis has remained elusive. Anti-IL-1 agents are useful therapeutic options in FMF patients developed amyloidosis despite the use of maximum tolerated dose of colchicine. The beneficial effects of anti-IL-1 agents in amyloidosis can be explained by normalisation of acute phase reactants and suppressing chronic inflammation, halting further amyloid fibril deposition and inhibition of intrinsic toxicity of amyloid fibrils (30). Anakinra and canakinumab are new agents when compared to colchicine and their role in prevention of amyloidosis requires more data. Therefore, unless there was an absolute contra-indication to colchicine use it must be continued indefinitely, and anakinra/canakinumab must be added to colchicine.

In previous studies, the health-related quality of life which is another feature of the disease burden was improved with both anti-IL-1 agents (31, 32). In our study, in addition to clinical and laboratory improvement with anakinra and canakinumab, the PGA was also improved.

In patients treated with anakinra, the main side effect was ISRs and almost all of ISRs which lead to cessation of anakinra developed in first three months of treatment. All serious side effects, except neutropenia developed approximately during the first year of treatment. Therefore, although most of the serious side effects developed in the early stages of treatment with anakinra, it should be kept in mind that serious side effects may also develop in the long-term treatment. The main side effect of canakinumab treatment was weight gain and no ISRs and skin rash were observed with canakinumab. Weight gain which may result in additional health problems was also frequent in patients treated with anakinra. Therefore, FMF patients treated with IL-1 antagonists, particularly those with metabolic diseases, should be closely followed in terms of weight gain.

In previous studies, mild (15, 17, 33) and a few severe infections (18, 34, 35) were reported in FMF patients treated with anti-IL-1 antagonists. Most of FMF patients in this study experienced mild infections, mainly upper respiratory infections. We did not record mild infections in our study, because to make a direct connection between the use of anti-IL-1 antagonists and mild infections is difficult, due to high frequency of these infections in general population and long median duration of treatment. But the important point is that there was no opportunistic, hospitalisation and/or parenteral antibiotic required infection cases, which makes anakinra and canakinumab safe for severe infections in long-term use. No malignancies or deaths were reported in our study.

In the published literature, there is no head-to-head study for anakinra *versus* canakinumab. Our study is also not a comparative study. Therefore, the results of this study should be interpreted for the two drugs separately. Both drugs had advantages and disadvantages. Anakinra is administered as daily subcutaneous injections which makes patient compliance difficult, while canakinumab is administered as monthly subcutaneous injections. The current cost of canakinumab is higher than anakinra and the price may affect preference for the type of anti-IL-1 agent.

Our study has some limitations. First, our study has limitations of any retrospective study. Second, smaller number of patients were treated with canakinumab compared to anakinra and with higher number of patients, different results may be observed.

In conclusion, both anakinra and canakinumab seem to be safe and effective in long-term management of CrFMF and CiFMF patients and those with complications of disease. The decision on which anti-IL-1 agent to use in colchicine resistant/unresponsive FMF should be made by considering the efficacy, cost, safety and the ease of use.

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