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ORIGINAL RESEARCH ARTICLE

Canakinumab in Children with Familial Mediterranean Fever: A Single-Center, Retrospective Analysis

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Abstract

Introduction Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by interleukin (IL)-1 overproduction. Colchicine is the mainstay drug in the treatment of FMF; however, a minority of patients do not respond despite the highest tolerated doses. We aimed to share our experience with canakinumab, a human monoclonal antibody against IL-1β, in pediatric FMF patients.

Methods This historical, single-cohort study retrospectively evaluated the disease characteristics, indications, and treatment responses of 14 pediatric FMF patients treated with canakinumab in our pediatric rheumatology department.

Results The median age at onset and diagnosis of 14 FMF patients (9 females, 5 males), were 3.5 (range 0.5–10) years and 6 (range 3–16) years, respectively. Indications for canakinumab treatment were renal amyloidosis ($n=1$), colchicine resistance ($n=11$), and persistent arthritis ($n=2$). Only two (14.3%) patients had colchicine intolerance. Complete response was obtained in 10/14 (71.5%) among all patients and 10/12 (86%) in patients with typical phenotype. The patient with chronic oligoarthritis had a complete response, whereas the patient with rheumatoid factor (RF)-positive polyarthritis demonstrated an initial partial response to canakinumab treatment. We found that attack frequency, proteinuria, and acute phase reactants, including erythrocyte sedimentation rate and C-reactive protein, were significantly decreased after canakinumab treatment in children with FMF.

Conclusion Canakinumab may be an effective treatment option for pediatric FMF patients with colchicine resistance, renal amyloidosis, and chronic oligoarthritis. Further studies are needed to clarify the efficacy of canakinumab in patients with a second disease, RF-positive polyarticular juvenile idiopathic arthritis.

Key Points

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by interleukin-1β overproduction.

Canakinumab is a reliable and safe treatment option for pediatric FMF patients with colchicine resistance, renal amyloidosis, and chronic oligoarthritis.

1 Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease worldwide, characterized by self-limiting attacks of systemic inflammation. Patients have fever lasting approximately 1–3 days,

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accompanied by abdominal pain, arthralgia/arthritis, chest pain, and less frequently, erysipelas-like erythema [1, 2]. Colchicine is the mainstay treatment since it alleviates clinical attacks and subclinical inflammation that may lead to secondary amyloidosis and renal failure, the most devastating complication of FMF [3]. The majority of patients clinically benefit from colchicine therapy; however, 3.9–6.6% of them do not respond to the highest tolerated doses [2, 4].

FMF is a monogenic disease but there are other genetic and environmental factors that play an additional role in the pathogenesis and that modify disease presentation and course. In the last two decades, pathogenetic mechanisms of FMF have been elucidated, initially by the discovery of the MEditerranean FeVer (*MEFV*) gene, which encodes pyrin, and subsequently by understanding the function of pyrin, which acts as an intracellular regulator of interleukin-1β (IL-1β) production [5]. Most of the *MEFV* mutations affect the B30.2/SPRY domain of pyrin, which binds apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain (ASC) and leads to caspase 1 activation and subsequent IL-1β maturation [6, 7]. Therefore, anti-IL1 agents became the area of interest in colchicine-resistant FMF in recent years. Anakinra competitively inhibits IL-1 receptor and rilonacept is a trapping molecule that binds and neutralizes IL-1. The long-acting inhibition of IL-1β specifically is now available with canakinumab, a human IgG_1 monoclonal antibody against IL-1β [8].

The efficacy and safety of canakinumab on colchicine-resistant patients is less known than for other anti-IL1 agents since the evidence is particularly based on case series, only two open-label studies, and one randomized controlled study [9–17]. Therefore, we aimed to share our experience with canakinumab in pediatric FMF patients.

2 Patients and Methods

In this study, we included 14 patients from our cohort of 714 children diagnosed with FMF, who were administered canakinumab and followed up in our department between April 2016 and April 2019. Two patients were 19 years old at canakinumab initiation, thus 12 pediatric patients and 2 adult patients were reported. All patients were diagnosed according to Tel-Hashomer criteria [18]. Age at last visit and disease onset, symptoms, *MEFV* gene results, treatment prior to canakinumab, indication for canakinumab treatment (colchicine resistance, renal amyloidosis, persistent arthritis), presence of colchicine intolerance, administration interval and dosage of canakinumab, side effects, response to treatment, and timing of response were recorded retrospectively from medical files of the patients. Acute phase reactants (APRs), including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), studied before canakinumab administration and monthly thereafter, were also collected from medical records.

Colchicine resistance was defined as having one or more attacks each month despite compliance to maximally tolerated dose for the last 6 months. Colchicine intolerance was determined as the presence of at least one of the drug-related symptoms, including transient or persistent abdominal pain, hyperperistalsis, vomiting, and diarrhea, that interrupt treatment compliance [3].

A complete response to canakinumab was achieved with the absence of even a single attack plus normal levels of APRs [19]. Partial response was defined as a favorable decrement in severity, frequency, and duration of attacks, without complete response after canakinumab treatment.

Adverse events such as infections, including upper respiratory tract infections, pneumonia, urinary system infections, gastroenteritis, cellulitis, tuberculosis and sepsis, injection-site reactions, and anaphylaxis, were recorded from medical files of the patients that were based on description of symptoms, physical examination, and laboratory parameters at each outpatient visit. Local injection-site reactions were defined as having redness, itching, pain, swelling, and/or burning at the injection site.

All analyses were performed using Statistical Package for the Social Sciences (SPSS) 20.0, statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as median and minimum–maximum. The distribution of continuous variables was tested by histogram, stem-and-leaf and Kolmogorov–Smirnov tests for normality. We utilized the non-parametric paired test, Wilcoxon signed-rank test for comparison of dependent variables, including attack frequency, proteinuria, and acute phase reactant levels before and after two doses of canakinumab treatment in the same cohort.

Informed consents were obtained from both patients and parents of the patients before the present study, which was ethically approved by the local ethics committee of our medical faculty according to the Declaration of Helsinki–Ethical Principles.

3 Results

A total of 14 FMF patients, 9 (64.3%) females and 5 (35.7%) males, were included in the present study. The median ages at onset and diagnosis were 3.5 (range 0.5–10) years and 6 (range 3–16) years, respectively. The median follow-up duration from diagnosis to the last visit and age at initiation of canakinumab were 7.5 (range 1–17) years and 11 (range 4–19) years, respectively. Demographic features, genotypes, indications, and features of canakinumab administration are described in Table 1. Indications for canakinumab treatment

Table 1 Demographic features, genotypes, indications and features of canakinumab administration in children with familial Mediterranean fever

Patient	Gender	Age at symptom onset (years)	Age at diagnosis (years)	Follow-up duration (years)	*MEFV* genotype	Reason for CAN	Additional diagnosis	Colchicine continuation	Age at CAN administration	Previous therapies	Dosage of CAN (mg/kg)	Dose interval (months)	Total number of CAN
1	M	2	5	11	M694V/M694V	CR	nd	Yes	15	C	3	2	7
2	F	4	10	8	M694V/M694V	CR	nd	Yes	14	C	3	2	17
3	F	4	6	8	M694V/M694V	Persistent arthritis	Oligo JIA	Yes	12	C, Mtx, E	4	2	8
4	F	2	3	7	M694V/M694V	CR	nd	Yes	7	C, A	3	2	12
5	M	7	16	4	M694V/M694V	CR	nd	Yes	19	C	2.5	2	6
6	F	0.5	3	3.5	M694V/M694V	CR	nd	Yes	5	C	3	2	10
7	M	10	14	4	M694V/M694V	Renal amyloidosis	nd	Yes	15.5	C	3	1*	20
8	F	3	9	6	M694V/M694V	CR	nd	Yes	13.5	C	4	2	13
9	M	4	7	10	M694V/M694V	CR	nd	Yes	9	C	3	2	31
10	F	1	3	10	M694V/M694V	CR + CI	nd	Yes	8	C	2	2	28
11	F	2	3	1	P369S/R202Q	CR	nd	Yes	4	C	4	2	2
12	F	4	7	17	M694V/M694V	Persistent arthritis	RF + poly JIA	Yes	19	C, Mtx, E, P	3	1*	60
13	M	2	3	3	R202Q/R202Q	CR + CI	nd	Yes	6	C	4	2	2
14	F	5	6	6	R202Q/-	CR	nd	Yes	10	C	4	2	3

A Anakinra, *MEFV* Mediterranean FeVer, *C* colchicine, *CAN* canakinumab, *CI* colchicine intolerance, *CR* colchicine resistance, *E* etanercept, *Mtx* methotrexate, *nd* not defined, *Oligo JIA* oligoarticular juvenile idiopathic arthritis, *P* prednisolone, *RF + poly JIA* rheumatoid factor-positive juvenile idiopathic arthritis

*Patients with renal amyloidosis (Patient 7) and RF + poly JIA (Patient 12) were treated with canakinumab monthly for the first 6 months and 2-monthly thereafter

were renal amyloidosis ($n=1$), colchicine resistance ($n=11$), and persistent arthritis ($n=2$). Only two (14.3%) patients had colchicine intolerance, both of whom were colchicine resistant. Patients with persistent arthritis were treated with methotrexate and etanercept without clinical response before canakinumab. Anakinra was chosen in only one patient (Patient 4) prior to canakinumab in this cohort. The remaining patients and parents considered the local side effects and discomfort associated with daily administration of anakinra to be unacceptable.

Eleven (75.8%) patients were homozygote for M694 V, while three patients had P369S/R202Q compound heterozygosity, one patient had R202Q homozygosity, and one had R202Q heterozygosity for the *MEFV* gene (Table 1).

Median dosage of canakinumab was 3 (range 2–4) mg/kg with an interval of 2 months except for one case with rheumatoid factor (RF)-positive polyarticular juvenile idiopathic arthritis (JIA) and one with amyloidosis, both treated with monthly canakinumab for the first 6 months and bimonthly thereafter. A median of 11 (range 2–60) doses of canakinumab were administered throughout the follow-up. In 9 (64.3%) of the 14 patients, APRs were normalized after the first dose of canakinumab. However, four (28.5%) patients required two doses and one patient (7.2%) required six doses of canakinumab to normalize APRs. A complete response to canakinumab was achieved in 10 out of 14 patients (71.5%) overall. Moreover, when we excluded the cases with chronic arthritis, whose management could be more challenging, complete response was achieved in 10 (86%) of 12 patients with classical FMF. Clinical response to canakinumab and changes in APRs are summarized in Table 2. Median annual attack number was 24 (range 12–36)

Table 2 Clinical response to canakinumab and acute phase reactants before and after two doses of canakinumab treatment in patient with familial Mediterranean fever

Patient	Attacks per year before CAN therapy	Attacks per year during CAN therapy	ESR (mm/h) level before CAN treatment	ESR (mm/h) after two doses of CAN	CRP (mg/dL) level before CAN treatment	CRP (mg/dL) level after two doses of CAN	Response to CAN treatment
1	24	0	50	37	3.4	0.26	Complete
2	18	0	41	15	4.5	0.18	Complete
3	12	1	85	16	11.9	0.83	Partial
4	24	0	40	2	1.54	0.1	Complete
5	24	0	95	28	16.7	0.52	Complete
6	18	0	40	2	3.4	0.1	Complete
7	18	0	40	17	4	0.32	Complete
8	24	1	42	15	2.6	0.4	Partial
9	24	0	33	12	6.6	0.16	Complete
10	24	0	68	22	3.65	0.32	Complete
11	24	1	15	2	1.94	0.32	Partial
12	12	0	85	23	8.7	0.48	Partial
13	24	0	62	43	1.26	0.42	Complete
14	36	0	6	2	0.31	0.2	Complete

CAN canakinumab, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

Table 3 Comparison of proteinuria and acute phase reactant levels before and after two doses of canakinumab treatment in patients with familial Mediterranean fever

Parameters	Before canakinumab treatment	After two doses canakinumab treatment	*p* value
Proteinuria (mg/day), median (range)	139.5 (86–4956)	98 (52–443)	0.004
ESR (mm/1st h), median (range)	40.5 (6–95)	15.5 (2–43)	0.001
CRP (mg/dL), median (range)	3.52 (0.31–16.70)	0.32 (0.10–0.83)	0.001

Kolmogorov–Smirnov tests for normality showed *p*-values of 0.001 and 0.003 for proteinuria, 0.018 and 0.020 for the first and second ESR values, and 0.011 and 0.032 for the first and second CRP levels, respectively. Therefore, the non-parametric paired test, Wilcoxon signed-rank test was used for comparison of dependent variables

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate

and 0 (0–2) before canakinumab administration and at last visit, respectively ($p = 0.001$). We also compare the data, including proteinuria and acute phase reactant levels, of FMF patients before and after two doses of canakinumab treatment in Table 3.

Proteinuria disappeared after six doses of monthly canakinumab treatment in a patient with renal amyloidosis, and bimonthly canakinumab was administered thereafter.

A patient with oligoarticular involvement (Patient 3) was successfully treated with canakinumab. However, another patient (Patient 12) had both RF-positive polyarticular JIA and FMF. She had been having recurrent fever attacks accompanied by arthralgia since she was 4 years old. At 7 years of age, she was admitted to our department with symmetric polyarthritis of both hands and wrists and morning stiffness. She had both RF positivity and M694 V homozygosity in *MEFV* gene. Once the RF-positive polyarticular JIA diagnosis had been made, subcutaneous methotrexate and low-dose systemic prednisolone were initiated with partial clinical response. She had been concomitantly treated with colchicine and the intensity and frequency of the inflammatory attacks were significantly decreased after that. Arthritis worsened at 15 years of age, so etanercept was initiated and resulted in satisfactory improvement in clinical manifestations. While she was under colchicine, methotrexate, and etanercept treatment for 3 years, systemic prednisolone was gradually ceased. However, arthritis and recurrent fever episodes did recur after 6 months off systemic prednisolone. Since APRs remained high despite low-dose systemic prednisolone initiation, etanercept was switched to canakinumab. Attacks and APRs improved after the first two doses of canakinumab in this patient, but disease relapsed with destructive arthritis and elevated APRs after 6 months, and low-dose prednisolone was added to her treatment; canakinumab was switched to tocilizumab thereafter.

Throughout the follow-up, we did not observe any adverse events, including infections, injection-site reactions, cytopenia, or anaphylaxis in any of the 14 patients.

4 Discussion

In the present study, we report a complete response in 86% of FMF patients with typical clinical manifestations, but RF-positive polyarticular JIA as a second comorbid disease restricted the favorable response in one patient. We found that attack frequency, proteinuria, and APRs, including ESR and CRP, were significantly decreased after canakinumab treatment in children with FMF. Improvement of these parameters was also shown in recent studies including adult FMF patients receiving anti-IL1 agents [20, 21]. In comparison with our results, previous studies demonstrated a complete response to canakinumab in 65–76.5% of colchicine-resistant patients [17, 19, 20]. Similar to the literature, the most common *MEFV* mutation was M694 V homozygosity in our study, suggesting that the M694 V phenotype is linked to a more severe disease course [9–17]. The major indication was colchicine resistance in our study, similar to previous literature [8–17].

Renal amyloidosis was the reason for canakinumab use in only one patient, as it is a late-term complication of FMF. In contrast, amyloidosis led to canakinumab prescription in 28–30% of the adult patients in case series [20, 21]. Proteinuria resolved after six doses of monthly canakinumab in our single patient with amyloidosis, adding to the evidence that canakinumab has benefits for patients with renal amyloidosis [12]. Renal amyloidosis may also be related to other diseases in addition to FMF. We recently described a child with deficiency of adenosine deaminase 2, who also carried an M694 V mutation in the *MEFV* gene, who was successfully treated with canakinumab [22]. We speculate that canakinumab may be considered as a treatment option in the presence of recalcitrant amyloidosis regardless of the primary disease.

Similarly, one of the 14 patients discussed here had RF-positive polyarticular JIA, a second disease that could have important genetic markers not yet identified and be related to canakinumab resistance. Furthermore, a recent study indicated that renal amyloidosis and coexisting diseases, including ankylosing spondylitis and adult-onset Still's disease, were related to colchicine resistance, which further necessitates the administration of an additional anti IL-1 agent [23].

There are several examples of difficulties in the management of chronic arthritis in patients with FMF in the literature. Three adult patients with chronic arthritis were successfully treated with canakinumab, whereas it was discontinued in two patients with recently developed axial spondyloarthropathy in a previous study [21]. In another study, two patients with chronic arthritis had a complete response to canakinumab while one required cessation of canakinumab and received anti-IL6 treatment due to the progression of chronic arthritis [24]. RF-positive polyarticular JIA is one of the subtypes of the JIA umbrella term and includes patients with characteristic involvement in the small joints of the hands (particularly proximal interphalangeal joints), APRs elevation, and destructive course. Several clinicians think that it represents the childhood equivalent of rheumatoid arthritis. Therefore, treatment should be more intensive with the early introduction of methotrexate and biologic agents [25]. A recent guideline recommended the tumor necrosis factor–alpha inhibitors, abatacept and tocilizumab, in refractory cases, but did not suggest anti-IL1 agents due to lack of relevant data in children [26]. In contrast, there is also growing evidence about the efficacy and safety of canakinumab in adult patients with rheumatoid arthritis, which is based on a phase II study [27].

In our study, the patient with chronic oligoarthritis had a complete response, whereas the patient with RF-positive polyarthritis demonstrated an initial partial response to canakinumab treatment.

Our study did not reveal any adverse events, including infections or tuberculosis activation. A recent study including 15 pediatric colchicine-resistant FMF patients from Turkey reported urinary tract infections, dental abscess, and bronchopneumonia during canakinumab treatment. In the same study, four patients had a positive tuberculosis skin test and received isoniazid prophylaxis for 6 months. Although none of these patients had been diagnosed as having tuberculosis or another serious infection, this study showed several side effects that were not often described previously [28]. Therefore, more comprehensive studies with longer follow-up duration should be performed to clarify the safety of canakinumab in pediatric patients.

The major limitations of our study were the retrospective design and lack of a large number of patients. Other limitations of the present study include the lack of a control group and a disease group taking colchicine. Nonetheless, we think that this will add to the studies emphasizing the need for multicenter comprehensive prospective works, and revealing real-life experiences in this field.

5 Conclusion

Canakinumab may be an effective and reliable treatment option for pediatric FMF patients with colchicine resistance and renal amyloidosis. Additionally, it may also be preferred in chronic arthritis that does not respond to immunosuppressive and other biologic drugs. Further comprehensive studies are needed to confirm the efficacy of canakinumab by comparing outcomes with colchicine- and canakinumab-naïve patients, and also in patients with a second disease such as RF-positive polyarticular JIA.

Compliance with Ethical Standards

Conflict of interest Dr Kisla Ekinci, Dr Sibel Balci, Dr Dilek Dogruel, Dr Derya Ufuk Altintas, and Dr Mustafa Yilmaz declare that they have no conflicts of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from parents of the participants included in the study.

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