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Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents

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Abstract Familial Mediterranean fever (FMF) is the most common autoinflammatory disease worldwide. Approximately 5–10 % of patients are unresponsive to colchicine. Aim of this study was to determine the short- and long-term efficacy and safety of anti-interleukin 1 (anti-IL1) and anti-tumor necrosis factor agents in colchicine-resistant FMF cases in Turkish children and adolescents. This is a single-center retrospective case series of colchicine-resistant FMF patients. The included patients were treated with biologics for either colchicine resistance or because of one of the following: (1) amyloidosis, (2) recurrent prolonged febrile myalgia and frequent need of steroid and (3) persistent arthritis. Colchicine resistance was defined as at least one attack per month for three consecutive months and elevated erythrocyte sedimentation rate or C-reactive protein or serum amyloid A in-between attacks despite taking adequate dose of colchicine. Response to biologicals was evaluated by the Autoinflammatory Diseases Activity Index (AIDAI) score sheet, patients/parents'/physicians' global assessment of disease severity and laboratory parameters every 3–6 months. Fourteen patients were included in the study. Three patients were treated with etanercept for median 7 months (range 3–11 months), and all patients had to be switched to anti-IL1 treatment because of adverse effects and/or partial response. Eleven patients were treated with anakinra with a median duration of 8 months (4–60 months). Nine patients responded to treatment at the third month, but four of them switched to canakinumab because of noncompliance, local side effects and active arthritis. Nine patients were treated with canakinumab, all responded. At follow-up, in two patients the dose had to be increased, and on the other hand, in three patients the interval was increased to every 12–16 weeks. In three patients, anti-IL1 treatment could be stopped and they are fine with colchicine. This case series describes the largest cohort of colchicine-resistant FMF patients in childhood and adolescence. Anti-IL1 treatment is a safe and effective therapy to control inflammation. The treatment should be modified and decided for each patient on an individual basis.

Keywords Familial Mediterranean fever · Colchicine · Child · Anti-IL1 · Canakinumab · Etanercept · Anakinra

Introduction

Familial Mediterranean fever (FMF) is a systemic autoinflammatory disorder characterized by recurrent episodes of fever and serosal, synovial or cutaneous inflammation. FMF is caused by recessively inherited mutations in MEFV, which encodes pyrin. Pyrin may form part of the NLRP3 inflammasome complex, and mutations in *MEFV* are associated with excess inflammation through increased interleukin-1 beta (IL-1β) production [1]. Colchicine is the mainstay of therapy: It decreases attack frequency and increases the quality of life and is the only proven treatment for the prevention of secondary amyloidosis [2]. Recently, Twig G et al. [3] have shown that the most important factor for increased mortality is reduced colchicine compliance or responsiveness causing renal amyloidosis. Approximately one-third of the patients treated with colchicine have a

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partial remission, and about 5–10 % are non-responders; another 2–5 % do not tolerate the drug mainly due to gastrointestinal symptoms [4]. Data from a large international registry (Eurofever) showed that almost 40 % of FMF patients display a partial response to colchicine, by means of persistent fever attacks or elevation of acute-phase reactants [5].

Since FMF is the most common autoinflammatory disease in Turkey, affecting estimated 1:1073 of the population [6], colchicine resistance or unresponsiveness is a problem for physicians. We would like to share our experience with the both short- and long-term efficacy of anti-IL1 and anti-TNF agents in colchicine-resistant FMF cases in childhood and adolescence and provide 'real-life' information.

Methods

This is a single-center retrospective case series of colchicine-resistant Familial Mediterranean fever patients who were treated with biological in Hacettepe Pediatric Nephrology and Rheumatology Departments between 2006 and 2013. Clinical characteristics, laboratory parameters and response to treatment were recorded. Diagnosis of patients was confirmed by genetic testing, and all patients are found homozygous or compound heterozygous of MEFV gene mutations. One patient was homozygous for mevalonate kinase (MVK) mutations and heterozygous for a MEFV mutation.

The indication for biologics was either colchicine resistance or one of the following: (1) amyloidosis, (2) recurrent prolonged febrile myalgia and frequent need of steroid and (3) persistent arthritis. Colchicine resistance was defined as at least one attack per month for three consecutive months and elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or serum amyloid A (SAA) in-between attacks despite taking adequate dose of colchicine [4]. Maximum dose of colchicine was 2 mg/day for adolescents and for younger children as the maximum tolerated dose. Colchicine-resistant patients were treated with anti-IL1 treatment and other biological agents after the patient used maximum colchicine dose for at least 3 months and having at least one attack per month along with increased acute-phase reactants (APR) for three consecutive months. The colchicine intake of the patients was monitored through the pill count or by their mothers. Initial dose of etanercept and canakinumab was 0.8 mg/kg/week and 2 mg/kg/8 week for patients below 40 kg and 150 mg/8 week for patients above 40 kg. Anakinra was used at dose of 2 mg/kg/day. Dose and frequency were adjusted according to patients' response to treatment. All patients continued colchicine treatment during biological agents.

Response to treatment was evaluated by Autoinflammatory Diseases Activity Index (AIDAI) score sheet or attack diary, patients/parents' global assessment of disease severity (10 cm VAS), physicians' global assessment of disease severity (10 cm VAS) (higher scores represent more severe disease activity) and laboratory parameters every 3–6 months. AIDAI is a patient-based symptom diary and scores fever >38 °C (0–1), abdominal pain (0–3), arthralgia or myalgia (0–3), swelling of joints (0–3), chest pain (0–3) and skin rash (0–3). AIDAI score sheet was used after January 2012, and scores over nine were accepted as active disease [7]. This score sheet was filled by parents in those patients below 12 years old and by the patient if older than 12 years old. At the last visit, response to anti-IL1 treatment (biological) was evaluated by the FMF50 score. FMF50 score includes percentage change in the frequency of attacks with the treatment, percentage change in the duration of attacks with the treatment, patients/parents' global assessment of disease severity [10-cm visual analog scale (VAS)], physicians' global assessment of disease severity (10-cm VAS), percentage change in arthritis attacks with the treatment, percentage change in C-reactive protein, ESR or SAA level with the treatment and at least 50% improvement in five of six criteria, without worsening in any one defined response to treatment [8].

For the compassionate use of anti-IL1 and anti-TNF treatment, permission was granted from the Turkish Ministry of Health. Since this was within routine clinical practice, approval from the local ethics committee (Hacettepe University Ethics Committee) was obtained for anonymous retrospective case notes review (GO13/280-36).

Results

Fourteen patients were included in the study. The median age of the patients was 13.2 ± 6.8 years (2–24 years), and the mean follow-up time from diagnosis was 7.43 ± 4.6 years (2–16 years). The most common symptoms were fever and abdominal pain; patient 2 had chronic arthritis of shoulder and sacroiliitis, and patients 9 and 10 had recurrent protracted febrile myalgia and high AFR between attacks. All patients except one had homozygous or compound heterozygous exon ten mutations. One patient was compound heterozygous of M694V/E148Q and also had homozygous MVK V377I mutation. However, the clinical phenotype of this patient was more compatible with FMF with recurrent fever and abdominal pain lasting for 3–4 days without rash or lymphadenopathy.

All patients were taking adequate dose of colchicine for their age before treatment with a median dosage of 0.035 ± 0.01 mg/kg/day (0.03–0.06 mg/kg/day).

Etanercept was started at a dose of 0.8 mg/kg/week in three children and continued for median 7 months (range 3–11 months). Patient 1 had to be switched to IL1 treatment because of nonresponse and patient 3 because of neutropenia. Patient 2, who had chronic arthritis and CRFMF, had partial benefit.

Eleven patients were treated with anakinra with a median duration of 8 months (4–60 months). Nine patients responded to treatment with decreased AIDAI score and acute-phase reactants in the third month of treatment; however, two patients (patient 3 and patient 6) had initial inadequate response (Table 1). In patient 6, the dose was increased to 3 mg/kg/day, and in patient 3, it was increased to 5 mg/kg/day (500 mg/day), but they continued to have attacks and increased APR. Therefore, they were switched to canakinumab.

Patient 1, patient 4 and patient 5 initially responded to anakinra; however, they were switched to canakinumab because of urticaria and injection side pain. Patient 2 initially responded to anakinra, but after 6 months of therapy, she began to have active arthritis with increased AFR and was switched to canakinumab (reported also in ref. [10, 11]). At last visit, four patients were receiving anakinra, with decreased attack frequency and acute-phase reactants. Patient 11 who also reported before had incomplete Behcet's disease and kidney amyloidosis, using anakinra for 60 months. Still she has normal kidney function without proteinuria (reported also in ref. [12]). In patient 14, anakinra could be stopped after 6 months of treatment and she is free of attacks and with normal laboratory features at 16 months of follow-up. Patient 12 who had recurrent PFM and high APR in-between attacks was treated with anakinra and responded well with normal APR at last visit.

Overall nine patients were treated with canakinumab, and four of them (patients 1, 2, 3 and 6) were unresponsive to other biologics as previously mentioned. All patients responded to canakinumab at the third month with decreased AIDAI scores and acute-phase reactants. However, the dose was increased, and/or the interval was shortened to 4 weeks in two patients (patients 2 and 6) since they had increased AIDAI scores after around the sixth month of treatment. On the other hand, in three patients (patients 1, 4 and 5) dose intervals were increased to every 12–16 weeks.

Two adolescent patients (patients 7 and 8), who had triggered attacks due to emotional stress, were directly treated with canakinumab and they responded excellently. Since they did not have frequent attacks after the single dose of canakinumab, they were not given a second dose. They are fine with colchicine after 9 and 16 months, respectively.

Patient 9, who had frequent attacks of protracted febrile myalgia and needed steroid, was treated with two doses of canakinumab 8 months apart (at each attack of febrile myalgia) and responded in 2 days without need of steroid treatment.

At the last visit, all patients who were treated with canakinumab had an FMF50 response, but two patients (patients 2 and 6) had active AIDAI score (>9) and CRP levels above normal. Also all patients who were treated with anakinra had FMF50 response at last visit.

As for serious side effects, one patient had severe pneumonia during canakinumab treatment and required hospital stay. Other side effects are shown in Table 1.

Discussion

This case series describes the largest cohort of colchicine-resistant FMF patients in childhood and adolescence. At the time of enrollment of these patients, the universally accepted definition for colchicine resistance was not available. However, the criteria used for the indication for biological agents in these patients have been clearly outlined. We have also used the validated AIDAI score and VAS for the assessment of disease activity [7]. In the final analysis, we have also used the FMF50 score which was initially proposed by Ben Chetrit et al. [9] according to annual rate of attacks but improved and validated by Ozen et al. [8] to assess outcome to therapy.

One of the major problems in the definition is the assessment of compliance. We have tried to evaluate compliance through the pill counts. Furthermore, the bioavailability of the drug is another concern, and there is no consensus on method and which blood compartment should be used to measure colchicine level. Studies of factors affecting bioavailability such as MDR gene polymorphisms and concentration of colchicine in lymphomonocytes, polymorphonuclear cells or plasma have contradictory results [13–15]. However, the colchicine dose was increased to upper limits in all our patients and they did not respond.

The majority of colchicine-resistant FMF cases in the literature as well as in our study have two penetrant mutations which was associated with a more severe phenotype [16]. Recently, Omenetti et al. [17] have showed that IL1 secretion increased with both the number and penetrance of mutations, confirming the studies showing increased requirement of colchicine dosage and unresponsiveness in patients with homozygous M694V [18, 19].

Etanercept has been the biological to use before anti-IL1. Good responses have been reported in selected cases in the literature [16], especially in patients with chronic arthritis. However, in our patients, etanercept did not provide any sustained response.

The use of anti-IL1 treatment in colchicine-resistant FMF has been the extrapolation of the experience from the bench to bed side. Anakinra is generally favored as an initial approach due to its short half-life, to test effectiveness [2]. Eleven patients used anakinra at a dose of 2–5 mg/kg/

Table 1 Treatment review of patients

Patient	Indication of biological	Biological treatment	Dose	Duration of treatment	Before switch of treatment			At the third month			Last visit			Adverse effect
					AIDAI[b]	CRP/SAA	PtVAS/PhVAS	AIDAI[b]	CRP/SAA	PtVAS/PhVAS	AIDAI[b]	CRP/SAA	PtVAS/PhVAS	
1[a]	CRFMF	ETA	0.8 mg/kg/week	3 m	NA	SAA: 599	NA	NA	SAA: 360	NA				None
		ANA	2 mg/kg/day	4 m	NA	SAA: 360	7/6	6	SAA: 3.7	4/3				Urticarial skin reaction
		CAN	2 mg/kg/8–16 week	17 m	43	CRP: 2.3	7/6	0	CRP: <0.1	1/1	7	CRP: 0.4	4/3	None
2[a]	CRFMF/chronic arthritis and sacroileitis	ETA	0.8 mg/kg/week	7 m	NA	CRP: 5	NA	NA	CRP: 1.4	NA				None
		ANA	1–2 mg/kg/day	19 m	NA	CRP: 3.5	NA	NA	CRP: 0.5	NA				None
		CAN	2 mg/kg/4–8 week	30 m	20	CRP: 10	7/7	8	CRP: 0.7	4/3	10	CRP: 0.99	6/5	None
3	CRFMF	ETA	0.8 mg/kg/week	11 m	NA	SAA: 130	NA	NA	SAA: 6	NA				Neutropenia
		ANA	2–5 mg/kg/day	44 m	NA	SAA: 172	NA	NA	SAA: 316	NA				None
		CAN	2 mg/kg/8 week	18 m	23	SAA: 460	7/6	2	SAA: 3	2/2	5	CRP: 0.42	2/1	None
4	CRFMF	ANA	2 mg/kg/day	5 m	20	CRP: 12	8/7	9	CRP: 0.6	4/3				Injection side pain
		CAN	2 mg/kg/8–12 week	9 m	7	CRP: 3.2	4/3	3	CRP: 0.1	2/3	5	CRP: 0.77	2/3	
5	CRFMF	ANA	2 mg/kg/day	4 m	36	CRP: 1.0	8/7	9	CRP: 0.7	8/5				Injection side pain
		CAN	2 mg/kg/8 week	10 m	9	CRP: 0.7	8/5	1	CRP: <0.1	1/1	5	CRP: 0.53	3/3	None
6	CRFMF/poor growth and splenomegaly	ANA	2–3 mg/kg/day	8 m	59	CRP: 7.3	8/7	20	CRP: 4.4	6/6				None
		CAN	2–3 mg/kg/4–8 week	24 m	52	CRP: 19	8/8	3	CRP: 0.3	1/1	15	CRP: 1.48	3/4	Pneumonia
7	CRFMF	CAN	2 mg/kg/dose	1 dose	35	CRP: 4.4	7/5	2	CRP: 0.2	2/2	7	CRP: 0.1	4/3	None
8	CFMF	CAN	2 mg/kg/dose	1 dose	25	SAA: 140	7/6	2	SAA: 6	2/2	3	CRP: 0.21	2/2	None
9	Recurrent PFM	CAN	2 mg/kg/dose	2 dose	40	CRP: 4.8	8/8	2	CRP: 0.1	1/1	2	CRP: 0.12	2/2	None
10	Recurrent PFM	ANA	2 mg/kg/day	8 m	30	CRP: 12	8/7	4	CRP: 0.1	2/2	3	CRP: 0.4	2/2	None
11[a]	CRFMF/incomplete Behcet/amyloidosis	ANA	2 mg/kg/day	60 m	NA	CRP: 6.4	NA	NA	CRP: 0.1	NA	3	CRP: 0.2	2/2	None
12	CRFMF/elevated LFT	ANA	2 mg/kg/day	6 m	9	SAA: 43	4/3	12	SAA: 6	2/2	NA	CRP: 0.14	NA	None
13	CRFMF	ANA	2 mg/kg/day	8 m	9	CRP: 1.0	4/3	7	CRP: 1.2	4/3	3	CRP: 0.3	2/2	None
14	CRFMF	ANA	2 mg/kg/day/stopped	6 m	15	CRP: 2.3	7/6	NA	CRP: 0.1	NA	NA	CRP: 0.3	NA	None

CRP (C-reactive protein): upper limit of normal 0.8 mg/dl; SAA (serum amyloid A): upper limit of normal 7 mg/L

CRFMF colchicine-resistant Familial Mediterranean fever, *ANA* anakinra, *CAN* canakinumab, *ETA* etanercept, *NA* not available

[a] These cases are reported also in reference [10–12]

[b] AIDAI score sheet is used after January 2012, and scores over nine are accepted as active disease

day, and all patients except two initially responded with decreased attacks and normalized acute-phase reactants. Two patients (cases 1 and 5) who failed to respond anakinra in 3 months are now well with canakinumab. In one of these patients, the dose was increased up to 500 mg/day. This finding supports experience of Kuemmerle-Deschner et al with CAPS patients failing to respond to anakinra but having a good response to canakinumab [20].

The disappearance of proteinuria and the normal kidney function in our only amyloidosis patient is promising. There is no evidence that anti-IL1 treatment can reverse the amyloid deposits, however, halting the process may enable the remaining nephrons to function adequately.

We have continued colchicine in these patients and have attempted to stop anti-IL1 treatment once the inflammation was under control, and the response was sustained after a certain period. In fact anti-IL1 treatment of two patients on canakinumab and one patient on anakinra could be stopped. Thus, anti-IL1 treatment needs to be a patient-tailored therapy in FMF patients. Short courses of treatment may suffice in bouts of acute inflammation such as febrile myalgia. On the other hand, there are a group of patients who need more continuous treatment for a satisfactory quality of life. In patients requiring more persistent treatment, dosage intervals of canakinumab were adjusted according to clinical and laboratory features of every patient.

In conclusion, the reported series shows that in colchicine-resistant patients, anti-IL1 treatment is a safe and effective therapy to control inflammation. We suggest colchicine to be continued along with biological treatment. Personalized medicine is clearly indicated, and the response of each patient should be assessed. The treatment should be modified and decided for each patient on an individual basis.

Conflict of interest Seza Ozen has received consultancy fees from Novartis and SOBI. Fehime Kara Eroglu has no conflictsof interest.

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