Rheumatology International (2018) 38:879–885
https://doi.org/10.1007/s00296-018-3993-5

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Canakinumab treatment in children with familial Mediterranean fever: report from a single center

Fatma Yazılıtaş[1] · Özlem Aydoğ[2] · Sare Gülfem Özlü[3] · Evrim Kargın Çakıcı[1] · Tülin Güngör[4] · Fehime Kara Eroğlu[4] · Gökçe Gür[4] · Mehmet Bülbül[4]

Received: 20 November 2017 / Accepted: 5 February 2018 / Published online: 15 February 2018

Abstract

Familial Mediterranean fever (FMF), the most common hereditary autoinflammatory disorder is characterized by recurrent episodes of fever, serositis, arthritis. The major long-term result is amyloidosis. Colchicine remains the principle of the treatment; it not only prevents the acute attacks but also prevents the long-term complications such as amyloidosis; 5–10% of the patients are unresponsive to treatment. Recently new therapeutic options as anti-interleukin 1 agents are successfully used for the patients who do not respond to colchicine treatment. In this study, we retrospectively evaluated 11 pediatric colchicine-resistant FMF patients who were treated with canakinumab. Three of the patients had amyloidosis and two had uveitis. Based on our results, we suggest that canakinumab may be a safe and effective therapy in patients who are resistant to colchicine and even in the patients with amyloidosis. We also suggest that canakinumab might be a safe option for the patients with uveitis.

Keywords Amyloidosis · Canakinumab · Childhood · Familial Mediterranean fever · Uveitis

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic systemic autoinflammatory disease [1]. FMF is caused by point mutations in *the Mediterranean Fever* (*MEFV*) *gene* located on the short arm of chromosome 16 [2]. The mutated gene encodes the protein pyrin (also known as marenostrin), which is expressed in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts [3–5]. Pyrin mediates regulation of caspase-1 activation and NLRP3 inflammasome, an intracellular complex required for conversion of precursor IL-1β (pro IL-1β) into mature IL-1β [6–9]. IL-1β is a cytokine released by cells of the immune system that have potent inflammatory and immunomodulatory effects, and is the key mediator of the immune response. IL-1β plays a role in T-cell activation, chemotaxis of polymorphonuclear leukocytes and monocytes, release of proteases from tissue macrophages, stimulation

✉ Fatma Yazılıtaş
fmeryemesra@yahoo.com

Özlem Aydoğ
ozlem_erdogan65@yahoo.com

Sare Gülfem Özlü
saredr@gmail.com

Evrim Kargın Çakıcı
evrimkargin@gmail.com

Tülin Güngör
tulingungor84@gmail.com

Fehime Kara Eroğlu
fehimekara@yahoo.com

Gökçe Gür
dr.gokcecan@gmail.com

Mehmet Bülbül
mbbjkank@yahoo.com.tr

1 Pediatric Nephrology Department, Ankara Dr. Sami Ulus Maternity and Children Hospital, Babur Caddesi No. 44, Altındağ, 06080 Ankara, Turkey

2 Pediatric Nephrology and Rheumatology Department, Ondokuz Mayıs University, Samsun, Turkey

3 Pediatric Nephrology Department, Medical School, Yildirim Beyazit University, Yenimahalle, Ankara, Turkey

4 Pediatric Nephrology and Rheumatology Department, Ankara Dr. Sami Ulus Maternity and Children Hospital, Babur Caddesi No. 44, Altındağ, Ankara, Turkey

of fibroblast proliferation, and activation of chondrocytes [9–12]. Mutated forms of pyrin cause oversecretion of Il-1β, leading to inappropriate neutrophil activation and a burst of systemic inflammation [11, 12]. Furthermore, IL-1 is an inducer of serum amyloid A (SAA), which contributes to the development of amyloidosis, the most serious complication of FMF [12, 13]. Recent advances in our understanding of the pathogenesis of FMF have led to the discovery of new drugs specific to the pathogenesis. As IL-1β is the primary factor in the process of inflammation, inhibition of IL-1β by newly discovered biological agents that block IL-1β signaling may provide significant advantages in the targeted treatment of FMF [12, 15–17]. Canakinumab is a complete human IL-1β monoclonal antibody that works via neutralization of IL-1β signaling. It binds to IL-1β with high selectivity, without interfering with other pathways activated by IL-1 [18, 19]. Few studies have investigated canakinumab treatment in patients with colchicine-resistant FMF (cr-FMF) and FMF-related amyloidosis, especially pediatric patients [17, 20, 21]. In addition, findings related to canakinumab use in patients with amyloidosis due to autoinflammatory diseases are unsatisfactory [22, 23].

The present study aimed to determine the clinical effects, safety, and tolerability of canakinumab in pediatric patients with cr-FMF, and FMF patients with coexisting amyloidosis, chronic renal insufficiency, and uveitis.

Materials and methods

The study was conducted at Dr. Sami Ulus Children's Hospital, Pediatric Nephrology and Rheumatology Departments, Ankara, Turkey, between January 2012 and January 2017. The study included 11 pediatric cr-FMF patients aged 6–17 years (median 14 years) that had been followed-up for ≥ 3 months while receiving canakinumab treatment [subcutaneous dose 2 mg/kg, monthly (maximum dose 150 mg)]. Patients that had been using canakinumab for < 3 months were excluded from the study.

FMF was diagnosed according to Tel-Hashomer criteria [24], with the support of routine diagnostic genetic testing. FMF attacks were confirmed by the presence of fever (≥ 38 °C), clinical findings (peritonitis, pleuritis, or monoarthritis), and an elevated acute phase reactant level. The diagnosis of amyloidosis was confirmed via kidney biopsy. Demographic and clinical data, genetic analysis of *MEFV* mutations results, laboratory parameters, including acute phase reactants, and response to treatment and adverse reactions were recorded. All patients were treated with colchicine together with canakinumab at the maximal dose for age and weight.

Colchicine resistance was defined as ≥ 1 FMF attacks per month for three sequential months and/or a high level of any acute-phase reactant between attacks despite taking the maximum dose of colchicine according to the degree of renal insufficiency, age, and weight [25]. Lidar et al. [26] defined non-responders as patients that do not respond to colchicine, patients with > 1 FMF clinical attacks every 3 months despite treatment with colchicine 2 mg/day. In addition, the FMF50 score, which was improved and validated by Ozen et al. [27], was used to assess treatment outcome. The primary outcome measure was to evaluate the percentage of patients with ≥ 50% reduction in FMF 50 score during the treatment period. Secondary outcome measures were acute phase reactants of patients, and recovery of serum creatinine, albumin, urinary protein excretion and findings associated with FMF.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate normality of data. Descriptive analyses were presented as median and range (minimum–maximum) for continuous variables.

Results

Among the patients, seven (cases 1–7) had cr-FMF, three (cases 8–10) had FMF and chronic kidney disease (CKD), FMF secondary amyloidosis, and nephrotic syndrome, of which one (case 10) also had bilateral uveitis, and one (case 11) had cr-FMF and bilateral uveitis. Patients aged between 6 and 17 years (median 14.0 years). The median duration of use of canakinumab was 21 months (5–49). Genetic analysis showed homozygous M694V mutations in exon 10 in all the patients. Demographic data, clinical and laboratory findings, attack frequency, and treatment response are shown in Table 1.

Complete clinical, laboratory, and FMF50 response to canakinumab treatment was achieved in all the cr-FMF patients. In all, three patients (case 8, 9, and 10) had FMF-associated amyloidosis, nephrotic syndrome, and CKD, of which two (case 9 and 10) had clinical improvement with canakinumab and one (case 8) had partial response. Among the patients only one case (case 8) died in 2014; 1 year after canakinumab cessation due to sepsis related with mixed fungal and staphylococcal peritonitis. Nine of our patients currently continue to receive canakinumab treatment. Demographic, clinical, and laboratory features of the patients with FMF-associated amyloidosis are given in Table 2.

Only one patient developed pneumonia following upper respiratory tract infection as an adverse effect. Macrophage activation syndrome and anaphylactic reaction were not observed in any of the patients.

Table 1 Patients' characteristics, attack frequency, and treatment response

Case	Sex	Age (years)	Age at diagnosis (years)	Family history of FMF	CM	Can duration (months)	SAA (mg/dL)		CRP (mg/L)		ESR (mm/h)		Attack frequency per year		Adverse effect with can	Baseline clinical characteristics
							Before can	After can	Before can	After can	Before can	After can	Before can	After can		
1	F	16	4	Yes	Yes	13	6.29	0.79	95.0	< 3.3	75	22	> 12	0	No	Fever, abdominal and joint pain
2	M	11	6	No	No	21	0.23	< 0.07	109	< 3.3	47	5	12	0	No	Fever, abdominal and chest pain
3	M	17	3	Yes	No	15	15.7	1.05	35.2	< 3.3	64	3	6	0	No	Fever, abdominal, joint and chest pain
4	M	15	1	Yes	Yes	43	107	0.1	34.8	< 3.3	48	10	> 12	0	No	Fever, abdominal and joint pain
5	M	15	4	Yes	No	49	N/A	0.2	143	< 3.3	120	6	> 12	0	No	Fever, abdominal and joint pain
6	M	8	2	Yes	Yes	13	N/A	0.39	96.5	< 3.3	38	5	> 24	0	No	Fever, abdominal and joint pain
7	M	13	9	No	No	5	N/A	4.1	91.8	7.9	74	12	6	0	No	Fever, abdominal and joint pain, arthritis
8	F	14	5	Yes	No	24	N/A	N/A	99.1	16.1	132	77	> 12	[a]	Sepsis peritonitis	Fever, abdominal and joint pain[b]
9	F	12	7	Yes	Yes	31	1.2	< 0.07	47	< 3.3	126	27	12	0	No	Fever, abdominal and joint pain[b]

Table 1 (continued)

Case	Sex	Age (years)	Age at diagnosis (years)	Family history of FMF	CM	Can duration (months)	SAA (mg/dL)		CRP (mg/L)		ESR (mm/h)		Attack frequency per year		Adverse effect with can	Baseline clinical characteristics
							Before can	After can	Before can	After can	Before can	After can	Before can	After can		
10	F	17	5	No	No	41	N/A	N/A	13.9	< 1.4	52	10	12	0	No	Fever, abdominal and joint pain, uveitis[b]
11	F	6	2	Yes	Yes	11	13.4	2.39	16.8	< 3.3	35	11	12	0	URTI, pneumonia	Fever, abdominal and joint pain, uveitis

CM consanguineous marriage, *can* canakinumab, *SAA* serum amyloid A, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *F* female, *M* male, *N/A* not available, *URTI* upper respiratory tract infection

[a]It could not be assessed because she has been complaining of abdominal pain, fatigue, diarrhea, arthralgia and chest pain continuously due to severe gastrointestinal and other organ amyloidosis

[b]FMF-associated amyloidosis, nephrotic syndrome and chronic kidney disease

Table 2 Patients' characteristics with FMF-associated amyloidosis

Case	Time[a]	BUN (mg/dL)	Cre (mg/dL)	Albumin (g/dL)	Hb (g/dL)	Spot urine proteinuria	24 h urinary protein excretion	Treatment	Clinical characteristics at onset	Adverse effect with can	Age at amyloidosis (years)
8	Previous	83	7.7	1.1	8.3	++++	Not calculated because of oliguria	CAPD, colchicine and infliximab	GDR, hypothyroidism, NS, severe gastrointestinal and renal amyloidosis, CKD	Sepsis peritonitis	9
	Later	46	5.3	2.2	7.7	++		CAPD, colchicine			
9	Previous	49	2.8	1.1	9.3	++++	450 mg/m^2/h	CAPD, colchicine	NS, amyloidosis, CKD	No	8
	Later	32	1.8	4	10.8	+	21 mg/m^2/h	Colchicine	CKD		
10	Previous	19	1.16	2.1	9.1	++++	103 mg/m^2/h	Colchicine	NS, amyloidosis, CKD bilateral anterior uveitis	No	5
	Later	11	0.7	4.2	11.3	+	18 mg/m^2/h	Colchicine	No		

BUN blood urea nitrogen, *Cre* creatinine, *Hb* hemoglobin, *can* canakinumab, *CAPD* continuous ambulatory peritoneal dialysis, *GDR* growth and developmental retardation, *NS* nephrotic syndrome, *CKD* chronic kidney disease

[a]Previous: before use of canakinumab; later: after use of canakinumab

Discussion

In FMF patients inflammatory attacks that typically last 1–3 days are usually self-limiting, but in some FMF patients continuous chronic subclinical inflammation causes secondary amyloidosis, which has a negative effect on quality of life, and is associated with renal failure and death [1, 2, 28, 29]. Colchicine prevents both FMF attacks and amyloid deposition, but not in all patients [12, 28–30]. The majority of patients that do not get receive this benefit from colchicine have homozygous M694V mutations, which are also associated with a more severe FMF phenotype [13, 31]. The present study included 11 patients given canakinumab for the treatment of cr-FMF. All of the presented patients had homozygous M694V mutations, as reported earlier.

Amyloidosis, the most serious life-threatening complication of FMF, and is more common in FMF patients with homozygote M694V mutation; three of the present study's patients with FMF associated amyloidosis had a homozygote M694V mutation. It is critically important to decrease the number and frequency of FMF attacks in patients that do not respond to colchicine, so as to avoid renal failure due to secondary amyloidosis [13, 32]. Elevated IL-1 secretion is correlated with both the number of *MEFV* mutated monocytes and a high-degree of mutation penetration [33, 34]; therefore, IL-1β blockers might be an option for achieving successful treatment in patients with cr-FMF and FMF-associated amyloidosis [17, 20, 35]. The first use of anti-IL-1 therapy for cr-FMF was reported in a pediatric patient in 2007 [15]. Subsequently, anti-IL1 treatment was shown to be highly successful in pediatric patients with cr-FMF by other researchers [16, 36, 37]. Canakinumab, which was first used in an adult FMF patient [19], is preferred over other IL-1 blockers due to its specificity to IL-1β and its long half-life. Moreover, canakinumab can improve renal function, decrease protein excretion, and partially decrease amyloid deposition [20–23, 35]. Clinical experience about canakinumab is particularly limited in childhood [20, 38, 39]. Canakinumab was used in the present study due to the important role of IL-1 in the pathogenesis of cr-FMF and FMF-associated amyloidosis.

Complete clinical remission and a decrease in the laboratory parameters of active inflammation were achieved using canakinumab in all seven of the presented patients with cr-FMF (without amyloidosis). Published findings regarding use of canakinumab to treat amyloidosis due to autoinflammatory diseases are inconsistent. Topaloğlu et al. [22] reported that amyloid deposition decreases in response to IL-1β blockade. Other studies reported that amyloidosis associated with FMF can be successfully treated with canakinumab in children [20, 21, 35]. In the present study adequate response to canakinumab was observed in two of three FMF patients with secondary renal amyloidosis and nephrotic syndrome. The progression of amyloidosis and nephrotic syndrome were arrested, and renal function improved in two (case 9 and 10) of three patients with FMF-related amyloidosis, nephrotic syndrome, and CKD in response to canakinumab treatment; during follow-up there were no subsequent FMF attacks and the decreases were observed in acute phase reactants. Complete response to canakinumab treatment was not achieved in case 8. She had underwent persistent continuous ambulatory peritoneal dialysis (CAPD) treatment due to end stage renal disease (ESRD) and severe multiorgan amyloidosis. She died due to sepsis and peritonitis 1 year after cessation of canakinumab treatment. Though the present study's patient sample was small, we think the findings indicate that canakinumab treatment has favorable effects on FMF-associated amyloidosis. In our study; we detected pneumonia following an upper respiratory tract infection in patient 11 as an adverse effect; she was treated with appropriate antibiotics successfully and we did not have to stop treatment. In a recent study carried out in 13 adults revealed different adverse affects as anxiety (1/13), headache (4/13), hidradenitis (1/13), pruritis(1/13), tooth infection (1/13), upper respiratory tract infection (2/13) and vomiting (1/13) [40]. Based on our results and the aforementioned literature we concluded that canakinumab might be a safe and tolerable choice in the treatment of cr-FMF patients.

To our knowledge there are only few case reports in the literature about FMF-associated uveitis [41, 42]. Two of our patients with uveitis were evaluated for accompanying vasculitis, Behçet and also juvenile idiopathic arthritis; neither these diseases nor any other underlying condition responsible for uveitis could be detected. Also uveitis may be an idiopathic finding not associated with FMF. In a recent report of Salehzadeh the authors concluded that in the areas with high prevalence of FMF, it could be considered as an underlying cause of uveitis [41]. Because our country is an endemic area for FMF and there is no other possible causative disease; we thought that uveitis is associated with FMF in these two patients. It is already known that IL-1 inhibitors [43] and canakinumab therapy [44, 45] have been successfully used to treat uveitis in patients with Behcet's disease. Brambill et al. [46] reported that canakinumab successfully treated idiopathic uveitis and juvenile idiopathic arthritis. Hirano et al. [47] reported that chronic, infantile neurologic, cutaneous, and articular syndrome (CINCA) was successfully treated using canakinumab, and Simonini et al. [48] noted that canakinumab successfully treated Blau syndrome-related uveitis. To the best of our knowledge the literature is devoid of any information regarding the efficacy of IL-1 inhibitors or

canakinumab in the treatment of uveitis in pediatric FMF patients as well as adults.

Uveitis in case 10 was successfully treated using canakinumab, without reactivation. Unfortunately, in 1 cr-FMF patient with uveitis (case 11), uveitis reactivated during canakinumab treatment (after 10 months) despite full remission of clinical and laboratory manifestations of FMF and canakinumab was withdrawn due to uveitis reactivation. To the best of our knowledge, this is the first report to describe administration of canakinumab in an FMF patient with bilateral anterior uveitis. Inhibition of IL-1β via canakinumab might be another option for management of FMF with bilateral anterior uveitis.

The main limitations of this study are the retrospective design and the small sample size. We could also stop treatment at a certain time and evaluate the period between the discontinuation of treatment and attack. This could provide an important contribution to the literature for the duration of treatment.

Conclusion

Canakinumab has favorable results in the management of pediatric patients with cr-FMF, FMF-associated renal amyloidosis, and is well tolerated. The duration of the treatment is still a matter of debate so it warrants further investigations.

Author contributions Study conception and design: FY and OA. Acquisition of data: contribution of all authors. Analysis and interpretation of data: FY and SGÖ. Drafting of manuscript: FY and MB. Critical revision: contribution of all authors.

Funding No funding.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Ozen S, Bilginer Y (2014) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol 10(3):135–147. https://doi.org/10.1038/nrrheum.2013.174
2. Sarı I, Birlik M, Kasifoğlu T (2014) Familial Mediterranean fever: an updated review. Eur J Rheumatol 1(1):21–33
3. French FMF Consortium (1997) A candidate gene for familial Mediterranean fever. Nat Genet 17(1):25–31
4. The International FMF Consortium (1997) Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 90(4):797–807
5. Chae JJ, Wood G, Richard K, Jaffe H, Colburn NT, Masters SL et al (2008) The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment. Blood 1 112(5):1794–1803. https://doi.org/10.1182/blood-2008-01-134932
6. Dinarello CA (1996) Biologic basis for interleukin-1 in disease. Blood 15(6):2095–2147 (2187)
7. Bozkurt Y, Demir A, Erman B, Gül A (2015) Unified modeling of familial Mediterranean fever and cryopyrin associated periodic syndromes. Comput Math Methods Med 2015:893507. https://doi.org/10.1155/2015/893507
8. Chae JJ, Aksentijevich I, Kastner DL (2009) Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. Br J Haematol 146(5):467–478. https://doi.org/10.1111/j.1365-2141.2009.07733.x
9. Wang DQH, Bonfrate L, de Bari O, Wang TY, Portincasa P (2014) Familial Mediterranean fever: from pathogenesis to treatment. J Genet Syndr Gene Ther 5:248. https://doi.org/10.4172/2157-7412.1000248
10. Brough D, Rothwell NJ (2007) Caspase-1-dependent processing of pro-interleukin-1 beta is cytosolic and precedes cell death. J Cell Sci 1 120 (Pt 5):772–781
11. Stojanov S, Kastner DL (2005) Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr Opin Rheumatol 17(5):586–599
12. Grattagliano I, Bonfrate L, Ruggiero V, Scaccianoce G, Palasciano G, Portincasa P (2014) Novel therapeutics for the treatment of familial mediterranean fever: from colchicine to biologics. Clin Pharmacol Ther 95(1):89–97
13. Bilginer Y, Akpolat T, Ozen S (2011) Renal amyloidosis in children. Pediatr Nephrol 26(8):1215–1227. https://doi.org/10.1007/s00467-011-1797-x
14. Duzova A, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S, Ozaltin F et al (2003) Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheum 21(4):509–514
15. Kuijk LM, Govers AM, Frenkel J, Hofhuis WJ (2007) Effective treatment of a colchicineresistant familial Mediterranean fever patient with anakinra. Ann Rheum Dis 66(11):1545–1546
16. Meinzer U, Quartier P, Alexandra JF, Hentgen V, Retornaz F, Koné-Paut I (2011) Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum 41(2):265–271. https://doi.org/10.1016/j.semarthrit.2010.11.003
17. Eroglu FK, Beşbaş N, Topaloglu R, Ozen S (2015) Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents. Rheumatol Int 35(10):1733–1737. https://doi.org/10.1007/s00296-015-3293-2
18. Haviv R, Hashkes PJ (2016) Canakinumab investigated for treating familial Mediterranean fever. Expert Opin Biol Ther 16(11):1425–1434
19. Mitroulis I, Skendros P, Oikonomou A, Tzioufas AG, Ritis K (2011) The efficacy of canakinumab in the treatment of a patient with familial Mediterranean fever and long standing destructive arthritis. Ann Rheum Dis 70(7):1347–1348. https://doi.org/10.1136/ard.2010.146878
20. Özçakar ZB, Özdel S, Yılmaz S, Kurt-Şükür ED, Ekim M, Yalçınkaya F (2016) Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clin Rheumatol 35(2):441–446. https://doi.org/10.1007/s10067-014-2772-2
21. Sozeri B, Gulez N, Ergin M, Serdaroglu E (2016) The experience of canakinumab in renal amyloidosis secondary to familial Mediterranean fever. Mol Cell Pediatr 3(1):33. https://doi.org/10.1186/s40348-016-0058-2
22. Topaloglu R, Batu ED, Orhan D, Ozen S, Besbas N (2016) Anti-interleukin 1 treatment in secondary amyloidosis associated with autoinflammatory diseases. Pediatr Nephrol 31(4):633–640. https://doi.org/10.1007/s00467-015-3249-5

23. Scarpioni R, Rigante D, Cantarini L, Ricardi M, Albertazzi V, Melfa L et al (2015) Renal involvement in secondary amyloidosis of Muckle–Wells syndrome: marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1β monoclonal antibody canakinumab. Clin Rheumatol 34(7):1311–1316. https://doi.org/10.1007/s10067-013-2481-2
24. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T et al (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40(10):1879–1885
25. Ozen S, Kone-Paut I, Gül A (2017) Colchicine resistance and intolerance in familial mediterranean fever: definition, causes, and alternative treatments. Semin Arthritis Rheum 47(1):115–120. https://doi.org/10.1016/j.semarthrit.2017.03.006
26. Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R et al (2004) Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum 33(4):273–282
27. Ozen S, Demirkaya E, Duzova A, Erdogan O, Erken E, Gul A et al (2014) FMF50: a score for assessing outcome in familial Mediterranean fever. FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR) and Turkish FMF study group. Ann Rheum Dis 73(5):897–901. https://doi.org/10.1136/annrheumdis-2013-204719
28. Cakar N, Yalçinkaya F, Ozkaya N, Tekin M, Akar N, Koçak H et al (2001) Familial Mediterranean fever (FMF)-associated amyloidosis in childhood. Clinical features, course and outcome. Clin Exp Rheumatol 19(5 Suppl 24):S63–S67
29. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J (1986) Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med 314(16):1001–1005. https://doi.org/10.1056/nejm198604173141601
30. Shohat M (2000) In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, Stephens K, Amemiya A, Ledbetter N (eds) GeneReviews® (internet), 1993–2017. University of Washington, Seattle (updated 15 Dec 2016)
31. Soylemezoglu O, Arga M, Fidan K, Gonen S, Emeksiz HC, Hasanoglu E et al (2010) Unresponsiveness to colchicine therapy in patients with familial Mediterranean fever homozygous for the M694V mutation. J Rheumatol 37(1):182–189. https://doi.org/10.3899/jrheum.090273
32. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G et al (2016) EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 75(4):644–651. https://doi.org/10.1136/annrheumdis-2015-208690
33. Omenetti A, Carta S, Delfino L, Martini A, Gattorno M, Rubartelli A (2014) Increased NLRP3-dependent interleukin 1β secretion in patients with familial Mediterranean fever: correlation with MEFV genotype. Ann Rheum Dis 73(2):462–469. https://doi.org/10.1136/annrheumdis-2012-202774
34. Yalcinkaya F, Ozcakar ZB, Tanyildiz M, Elhan AH (2011) Familial Mediterranean fever in small children in Turkey. Clin Exp Rheumatol 29(4 Suppl 67):S87–S90
35. Bilginer Y, Ayaz NA, Ozen S (2010) Anti-IL-1 treatment for secondary amyloidosis in an adolescent with FMF and Behçet's disease. Clin Rheumatol. 29(2):209–210. https://doi.org/10.1007/s10067-009-1279-8
36. Başaran Ö, Uncu N, Çelikel BA, Taktak A, Gür G, Cakar N (2015) Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients. Mod Rheumatol 25(4):621–624. https://doi.org/10.3109/14397595.2014.987437
37. Ozdogan H, Ugurlu S (2017) Canakinumab for the treatment of familial Mediterranean fever. Expert Rev Clin Immunol 13(5):393–404. https://doi.org/10.1080/1744666X.2017.1313116
38. Brik R, Butbul-Aviel Y, Lubin S, Ben Dayan E, Rachmilewitz-Minei T, Tseng L et al (2014) Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study (Hoboken, NJ). Arthritis Rheumatol (Hoboken NJ) 66(11):3241–3243. https://doi.org/10.1002/art.38777
39. Ozkan S, Atas B (2017) Canakinumab treatment in four children with colchicine resistant familial mediterranean fever. J Pak Med Assoc 67(6):945–947
40. Gül A, Ozdogan H, Erer B, Ugurlu S, Kasapcopur O, Davis N, Sevgi S. Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis Res Ther 17:243. https://doi.org/10.1186/s13075-015-0765-4
41. Salehzadeh F, Yasrebi O, Hosseini Khotbesara M, Hosseini Khotbesara M (2014) Idiopathic uveitis and familial Mediterranean fever: is there any relationship? Autoimmune Dis 2014:238931. https://doi.org/10.1155/2014/238931
42. Berestizschevsky S, Weinberger D, Avisar I, Avisar R. Episcleritis associated with familial Mediterranean fever. Isr Med Assoc J 10(4):318–319
43. Cantarini L, Vitale A, Scalini P, Dinarello CA, Rigante D, Franceschini R et al (2015) Anakinra treatment in drug-resistant Behcet's disease: a case series. Clin Rheumatol 34(7):1293–1301. https://doi.org/10.1007/s10067-013-2443-8
44. Ugurlu S, Ucar D, Seyahi E, Hatemi G, Yurdakul S (2012) Canakinumab in a patient with juvenile Behcet's syndrome with refractory eye disease. Ann Rheum Dis 71(9):1589–1591. https://doi.org/10.1136/annrheumdis-2012-201383
45. Fabiani C, Vitale A, Emmi G, Lopalco G, Vannozzi L, Guerriero S et al (2017) Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: a multicenter retrospective observational study. Clin Rheumatol 36(1):191–197. https://doi.org/10.1007/s10067-016-3506-4
46. Brambilla A, Caputo R, Cimaz R, Simonini G (2016) Canakinumab for childhood sightthreatening refractory uveitis: a case series. J Rheumatol 43(7):1445–1447. https://doi.org/10.3899/jrheum.160064
47. Hirano M, Seguchi J, Yamamura M, Narita A, Okanobu H, Nishikomori R et al (2015) Successful resolution of stromal keratitis and uveitis using canakinumab in a patient with chronic infantile neurologic, cutaneous, and articular syndrome: a case study. J Ophthalmic Inflamm Infect 5(1):34. https://doi.org/10.1186/s12348-015-0065-9
48. Simonini G, Xu Z, Caputo R, De Libero C, Pagnini I, Pascual V et al (2013) Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. ArthritisRheum 65(2):513–518. https://doi.org/10.1002/art.37776