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Ruby Haviv & Philip J. Hashkes

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Drug Evaluation:

Canakinumab Investigated for Treating Familial Mediterranean Fever

Ruby Haviv, MD, Pediatric Rheumatology Fellow, Shaare Zedek Medical Center, Jerusalem & Meir Medical Center, Kfar Saba, Israel

Philip J. Hashkes, MD, MSc, Head, Pediatric Rheumatology Unit, Shaare Zedek Medical Center, Associate Professor of Pediatrics, Hebrew University Medical School, Jerusalem, Israel

Corresponding author:

Philip J Hashkes, MD, MSc

Head, Pediatric Rheumatology Unit

Shaare Zedek Medical Center

PO Box 3235

Jerusalem, 9103102

Israel

Phone: +972 2 6666242

Fax: +972 2 6555750

Email: hashkesp@szmc.org.il ruby.haviv@clalit.org.il

Abstract

Introduction: Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory syndrome. The treatment of choice is colchicine. However, ~40% of patients are only partial responders and 5-10% are non-responders. Advances in the understanding of the role of pyrin in the regulation of interleukin (IL)-1β activation, has led to use of anti-IL-1 agents for colchicine resistant FMF.

Areas covered: The authors performed a literature search of anti-IL-1 treatment for FMF, particularly canakinumab, a humanized IL-1β antibody, by searching PubMed/Medline/Scopus since 2001 and proceedings of major rheumatologic conferences since 2011 for unpublished studies.

Expert opinion: Many reports of successful treatments with anti-IL-1 agents were published since 2007. In 2011, the first case reports of successful treatment with canakinumab were reported. Successful phase II trials reported in 2014 and 2015 led to a double-blind, randomized, placebo-controlled phase III trial in patients with colchicine-resistant FMF. Significantly more canakinumab treated patients attained the very stringent primary outcome measure and secondary outcomes vs. those treated with placebo. The safety profile was similar to canakinumab trials for other indications. Canakinumab appears to be an excellent alternative for the vast majority of patients with colchicine resistant FMF with an adequate safety profile.

Keywords: amyloidosis, anakinra, canakinumab, colchicine, familial Mediterranean fever, interleukin-1, pyrin, rilonacept, treatment

Sources of support: None

List of Abbreviations:

Familial Mediterranean fever:	FMF
Interleukin:	IL
Tumor necrosis factor:	TNF
C-reactive protein:	CRP
Erythrocyte sedimentation rate:	ESR
Serum amyloid A:	SAA
Adverse events	AE
Serious adverse events	SAE
Food and Drug Administration	FDA
European Medicines Agency	EMA
Cryopyrin-associated periodic syndromes	CAPS
Pharmacokinetics	PK
Child Health Questionnaire - Parent Form 50	CHQ-PF50
SF-36: short-form twelve-item health survey	SF-36
Physician global assessment	PGA
Health-related quality of life	HRQoL
Autoinflammatory Diseases Activity Index	AIDAI
Intravenous immunoglobulin	IVIg
Non-steroid anti-inflammatory drug	NSAID
Mevalonate kinase	MVK

1. INTRODUCTION

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory (periodic fever) syndrome [1, 2]. FMF occurs most frequently among Sephardic Jewish, Arab, Armenian and Turkish populations [1, 3], with an estimated 120-150,000 cases worldwide [*4].

FMF is characterized by recurrent febrile attacks of short duration, usually lasting 12 to 72 hours. Attacks involve serosal inflammation (peritoneum, pleura, scrotum and occasionally pericardium), arthritis, myalgia and erysipelas-like skin rash [*5, 6-8]. Approximately 5% of FMF patients develop chronic arthritis, mainly of the sacroiliac joints and hips [9]. The most important complication of untreated FMF is the development of AA amyloidosis, usually presenting with proteinuria. FMF also decreases patients' health-related quality of life, and is associated with a higher prevalence of fibromyalgia, depression and anxiety than the general population [10].

FMF results from mutations in the *MEFV* gene, located on chromosome 16p13.3, with most disease causing mutations occurring on exon 10 in the highly conserved carboxy-terminal B.30.2 domain [1, 2].

Pyrin (marenostrin in Europe), the mutated protein, is a 781 amino-acid product of the *MEFV* gene and is expressed almost exclusively in the cytoplasm of cells of the myeloid lineage [11]. Pyrin has an important role in regulating various cytoplasmic inflammasomes. It is still unclear whether mutations in pyrin results in loss of function (compatible with autosomal recessive inheritance) or gain of function (dominant or co-dominant inheritance). Recent evidence from mice models seem to support the latter hypothesis; mutated pyrin can activate various inflammsomes [**12, *13]. Mutations may also result in the decreased binding of the inhibitory protein 14-3-3 to pyrin, thus increasing inflammsome activity and IL-1β activation [**14].

The treatment of choice is colchicine, first reported by Goldfinger in 1972 [*15]. Numerous controlled trials and longitudinal studies have established that colchicine significantly reduces the attack rate and also prevents the development of amyloidosis [16, *17]. There are several hypotheses on the mechanism of action of colchicine. Recently it was shown that colchicine suppresses the activation of caspase-1, blocking conversion of pro-IL-1β to IL-1β [18].

2 OVERVIEW OF THE MARKET

Even with colchicine treatment, nearly 40% of patients continue to have some attacks and 5-10% of patients are considered non-responders. Another ~5% are intolerant to colchicine, mainly due to gastrointestinal adverse effects [*19].
Until recently, there were no proven alternatives to colchicine, including use of thalidomide [*19, 20], tumor necrosis factor (TNF) inhibitors [*19, 20, 21] and interferon-α [*17, 22].

Advances in understanding the role of pyrin in the regulation of IL-1β activation, have led to the therapeutic breakthroughs described in this paper. The first cases of using anti-IL-1 therapy in FMF were reported in 2007, with the use of the IL-1 receptor antagonist anakinra in a colchicine resistant patient [23]. Many case reports and series have since been published [24-43]. The first controlled study published was of rilonacept, a soluble IL-1 receptor that "traps" IL-1 [10, *44]. Since 2011, case reports on the use of canakinumab, a humanized IL-1β antibody, were published [37, 39, 41, 42, 45-47]. These were followed by two phase 2 trials, one in children and one in adults [**48, **49]. Finally, controlled studies on the use of anakinra and canakinumab have been completed but their results have yet to be fully published [50, *51, **52, *53, *54].

3 LITERATURE SEARCH

We performed a literature search for manuscripts of anti-IL-1 treatment for FMF by searching PubMed/Medline/Scopus since 2001 (when anakinra was commercialized) and the references of published articles. We also searched abstract proceedings of major rheumatologic meetings since 2011 for controlled studies yet to be fully published. We used the key words of amyloidosis, anakinra, canakinumab, FMF, IL-1, pyrin and rilonacept. Figure 1 details the manuscript search of canakinumab for the treatment of FMF according to the PRISMA guideline.

4 ANTI-IL-1 THERAPY IN COLCHICINE RESISTANT FMF

4.1 Anakinra

Anakinra is a recombinant 153 amino-acid residues homolog of the human IL-1 receptor antagonist. Because of its very short half-life (2-4 hours), anakinra is administrated daily, by subcutaneous injection. Anakinra binds to both IL-1α IL-1β, and is a competitive inhibitor of the type 1 IL-1 receptor [55].

The most common indication for anakinra use was frequent attacks despite appropriate colchicine treatment (1.5-3 mg/day) [23-30]. Other indications included colchicine intolerance, persistent acute phase reactant elevations, arthritis and renal amyloidosis, even after transplantation [29, 31-32]. Anakinra was also useful in treating co-morbidities associated with FMF, including protracted febrile myalgia, pneumonitis and leukocytoclastic vasculitis [34].

In most cases, anakinra had a dramatic effect within hours or days; acute phase reactants normalized within a week. However, not all patients responded completely. The French MAIL1 (Maladies Auto-inflammatoires et Anti-IL-1) study reported a partial response rate of 46.2% [39]. In the case series published by Eroglu et al, 2 of 11 patients continued to have attacks and another developed arthritis after 6 months of treatment [42]. Only two serious adverse events (SAE) were reported; angioneurotic

edema [39] and pneumonia caused by Klebsiella pneumoniae, after which anakinra treatment was resumed [40]. Most adverse events (AE) were related to injection site reactions, some severe with pain ± local erythema, especially at the initiation of therapy [38, 42].

Ben-Zvi et al conducted a 4-month double-blind randomized placebo-controlled trial of anakinra in 25 colchicine resistant FMF patients [*51]. The inclusion criteria were adult FMF patients (age 18–65 years), who met the Tel Hashomer criteria for the diagnosis of FMF, with 2 *MEFV* mutations, who continued to have at least one febrile attack per month despite receiving ≥2 mg/d of colchicine [50, *51]. Twelve patients received anakinra (100 mg/d) and 13 placebo. The attack rate, the primary outcome, was significantly less among the anakinra group versus placebo (1.7±1.7 versus 3.5±1.9 attacks per patient month, respectively, p=0.037). Seven patients, all who received placebo, prematurely discontinued the study. The quality of life, assessed by visual analog scale, was significantly better in the anakinra group (p=0.045). There were no significant differences in the AE rate and no SAEs were recorded.

4.2 Rilonacept

Rilonacept, also called IL-1 "trap", is an IL-1 receptor fusion protein, consisting of portions of the IL-1 receptor and the IL-1 receptor accessory protein linked to the Fc portion of human immunoglobulin G1 (IgG1). Rilonacept is highly specific and forms a very high affinity complex with IL-1β. The half-life ranges between 6.3 and 8.6 days. Thus, rilonacept is administered weekly, by subcutaneous injection [55].

The first controlled trial of anti-IL-1 therapy in FMF patients, who were colchicine resistant or intolerant, used rilonacept. The trial utilized an alternating treatment design. Patients were randomly assigned to receive two 3-month courses of

rilonacept (2.2 mg/kg/week, maximum 160 mg) and 2 of placebo. Among 12 patients who completed at least 2 treatment courses the median number of attacks per month was significantly less with rilonacept than placebo (0.77 vs. 2.00, respectively; p=0.027). The rilonacept-placebo attack risk ratio was 0.45 (equal-tail 95% credible interval, 0.26 to 0.77) [*44]. There were more treatment courses of rilonacept without attacks (29% vs. 0%; p=0.004) There was a significant improvement in the physical aspects of the health-related quality of life only when patients received rilonacept [10]. There were 2 SAEs: the development of pneumonia in a rilonacept treated patient and a lower respiratory infection in a placebo treated patient. Injection site reactions were more frequent among rilonacept treated patients.

4.3 Introduction to Canakinumab

Canakinumab (ACZ885, Ilaris®; Novartis Pharma, Basel, Switzerland) is a recombinant fully humanized selective anti-IL-1β monoclonal antibody. Canakinumab is currently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of cryopyrin-associated periodic syndromes (CAPS) and systemic juvenile idiopathic arthritis. Canakinumab is also approved by EMA to treat symptoms of gout arthritis, when other drugs are not tolerated, contraindicated or do not have an appropriate effect [55, 56].

4.3.1 Pharmacokinetics, Metabolism and Pharmacodynamics

Canakinumab binds to serum IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors. In the CAPS trial the peak serum concentration occurred approximately 7 days after subcutaneous administration of a single 150 mg dose (2 mg/kg in children ≤40 kg) with an observed half-life from 21.5 to 33 days in adults and 22.9 to 25.7 days in children [57]. The absolute bioavailability was 70%

and the expected accumulation ratio 1.3 fold following 6 months of subcutaneous dosing of 150 mg administered every 8 weeks. No gender- or age-related pharmacokinetic (PK) differences were observed after correction for body weight.

While the CAPS trial used a lyophilisate form of canakinumab, the FMF phase III trial used a solution for injection-liquid in vial formulation (LIVI). The PK and pharmacodynamics (mainly serum IL-1β levels) findings were published in abstract form [*53].

4.4 Clinical Efficacy

4.4.1 Case Reports and Series

Case reports were published since 2011 [37, 45-47] (Table 1). The age range was 7 to 30 years, almost all homozygous for the M694V mutation. All patients were treated with colchicine (1-2 mg/d). Some of the patients also received corticosteroids, anti-TNF agents and methotrexate without effect. All patients had active disease with elevated acute phase reactants between attacks, three had chronic arthritis, and one severe FMF-associated Henoch-Schonlein purpura. Four of the 5 patients were previously treated with anakinra, initially with a good response. However, patients switched to canakinumab due to injection-site reactions or a non-sustained response to anakinra.

Another 5 case series were published since 2014; many patients were treated with anakinra prior to canakinumab [39-43] (Tables 2a and 2b). Summarizing the data, canakinumab was an effective treatment option for the vast majority of patients. However, some patients had only a partial response, especially when canakinumab was administered less frequently than every 4 weeks. There was only one SAE, pneumonia requiring hospitalization [42]. Injection site reactions were minimal.

4.4.2 Phase II Studies

Phase II trials with canakinumab in colchicine resistant patients from Israel (children) and Turkey (primarily adults), were published in 2014 and 2015, respectively [**48, **49] (Table 3). These 6-month trials were open-label, single-arm studies. Inclusion criteria were diagnosis of FMF according to Tel-Hashomer criteria, two documented *MEFV* exon 10 mutations (except 2 heterozygous patients in the Turkish cohort) and attacks at a mean frequency of ≥1 per month during the 3 months prior to screening, despite treatment with ≥1–2 mg/day of colchicine, for at least 3 months. Following successful screening, participants experiencing ≥1 investigator-confirmed FMF attack during a 30-day run-in period were eligible to receive treatment. Participants received 3 subcutaneous injections of canakinumab (2 mg/kg, maximum 150 mg) every ~4 weeks, while continuing their usual colchicine treatment. The first injection was administered during an attack. Canakinumab dose was doubled to 4 mg/kg (maximum 300 mg), if another attack occurred between the first and second injections. Six of 7 patients in the Israeli study and all 9 patients in the Turkish study achieved the primary endpoint of ≥50% reduction in the frequency of attacks. The median 28-day time-adjusted attack rate decreased from 2.7 to 0.3 (89%) in the Israeli study and from 1.1 to 0 in the Turkish study. Eleven AEs were reported in 4 (57%) participants of the Israeli cohort, and 8 (89%) patients in the Turkish cohort had at least 1 AE. AEs were mild or moderate, with headache and local injection-site reaction the most frequent. No participants discontinued the study or missed an injection because of an AE. One Turkish patient became pregnant after the third canakinumab injection, and gave birth to a healthy son.

4.4.3 Phase III Trial

The design and results of the still active phase III umbrella trial of canakinumab in patients with hereditary periodic fever syndromes, including FMF, have yet to be published as a full manuscript. Thus we can only report the general qualitative results published in abstract/poster form [**52, *53, *54].

This international, randomized, double-blind placebo controlled study aimed to enroll >200 participants diagnosed either with mevalonate kinase deficiency, TNF-receptor associated periodic syndrome or colchicine resistant FMF under an umbrella protocol for the 3 diseases.

Key eligibility criteria regarding FMF, were patients from age ≥2 years, with at least one exon 10 mutation and with active disease despite colchicine therapy.
The study consisted of 4 epochs: screening period of up to 12 weeks, a pivotal randomized, double blind, placebo controlled, parallel arm phase of 16 weeks, a randomized withdrawal phase for responders of 24 weeks and an open-label treatment extension
In epoch 2, eligible patients were randomized 1:1 to receive 150 mg canakinumab (or 2 mg/kg for patients weighing ≤40 kg), or placebo every 4 weeks.

The primary outcome measure was comparison of the canakinumab and placebo groups for the proportion of participants with resolution (within 15 days) of the initial flare at treatment onset and absence of new flares within 16 weeks (using an intention to treat approach). Secondary outcomes included the proportion of patients with absent or minimal disease activity at week 16, proportion of patients with normal CRP and SAA levels at week 16 and safety assessments. The health-related quality of life was assessed using similar tools to the phase II studies.

Results are available only for the pivotal epoch 2. Significantly more patients treated with canakinumab attained the primary outcome and were considered

responders versus those who received placebo [**52]. All secondary objectives were attained and there was a clinically significant increase in both the physical and psychosocial/mental measures of health-related quality of life [*53].

The safety profile was similar to other canakinumab studies, including the phase II FMF trials [**52].

4.4.4 Long-Term Use of Canakinumab in FMF

Since canakinumab was first used in FMF only in 2011 there is very little data on long-term use (Table 2b). Hashkes et al. performed an extension study of the phase II Israeli cohort [58]. All 7 patients (no drop-outs) were followed for an additional median period of 17 months (range 13–25). Three patients experienced 6 attacks (0.05 attacks per patient month) and in 2 patients the dose of canakinumab was increased. The canakinumab dose was increased in 2 additional patients due to mild increases in the acute phase reactants not during an attack. The median dose of canakinumab was 3 mg/kg (range 1.8–4.8 mg/kg), with administration interval lengthened in 3 patients to every 7 weeks. The global physician assessment was rated as very good for all patients. The colchicine dose was reduced to 1 mg/day in three patients and self-discontinued by one.

11 AEs were recorded in 5 patients, all mild, and did not lead to medication discontinuation.

4.5 Safety and Tolerability

As previously described, there were no significant safety signals among the FMF patients treated with canakinumab, although the number of treated patients is small, with relatively short follow-up.

From larger studies and series of patients receiving canakinumab for related autoinflammatory diseases, e.g. CAPS, the safety profile is good and injections well tolerated [59]. The most common AEs were nasopharyngitis and gastrointestinal symptoms. Other common AEs included influenza and headache. Infections were

common, but usually treatable, with rare SAEs associated with hospitalization. In mouse models, IL-1 inhibition has led to an increased risk of Gram-positive bacterial infections, particularly pneumococcal, but this has yet to be confirmed in human studies.

In CAPS, there were no reported cases of malignancy or opportunistic infections, including mycobacterium. Also, there were no cases of autoantibody formation to canakinumab. No autoimmune/demyelinating AEs were reported. No significant differences in safety were noted between adult and pediatric patients and the safety profile did not change with long-term therapy. Two specific concerns in CAPS were the development of vertigo in about 10% of patients (severe CAPS is associated with inner ear inflammation) and severe local inflammatory reactions to pneumococcal vaccination [*60].

4.6 Regulatory affairs

Canakinumab has yet to be labeled by the FDA or EMA for FMF. In April 2016 the FDA granted a breakthrough drug designation for colchicine resistant FMF.

5. EXPERT OPINION

Following the completion of several controlled trials, it is clear at the highest level of evidence (IA) that anti-IL-1 therapy is effective for the vast majority of patients with colchicine resistant or intolerant FMF. Of the current three anti-IL-1 medications on the market, anakinra, rilonacept and canakinumab, it is most convenient to use canakinumab due to its long half-life and ease of use. This is especially true for a genetic disease that may necessitate lifelong treatment. Substantial and long-term immunosuppression by canakinumab is less of a concern in FMF compared to other diseases (e.g. systemic juvenile idiopathic arthritis) since there is some evidence that mutations in the *MEFV* gene may "protect" patients from

infections (positive selection) and colchicine does not suppress the immune system. On the other hand many medications used for the treatment of systemic juvenile idiopathic arthritis (corticosteroids, etc.) are immunosuppressive. Thus, if priced appropriately, canakinumab is likely to capture the majority of this market. Based on the epidemiology of FMF, it is possible that between 5,000 and 15,000 patients will need anti-IL-1 therapy. We are not aware of alternative effective therapies currently in the pipeline, but other anti-cytokine therapies (e.g. IL-18 or inflammasome inhibitors) have the potential to be effective. Utilizing gene editing to "cure" monogenic diseases may be available to treat patients with severe FMF someday in the future.

There are still many questions on the use of anti-IL-1 therapy.

The first question is who to treat? This may depend in part on the definition of colchicine resistance. It is crucial to achieve consensus on defining those patients needing these therapies, i.e. stratifying patients by severity of their disease, defining non-response to colchicine and agreeing on clear and meaningful outcome measures. Recently, an international consensus expert group published new criteria for the definition of disease severity [61]. Dependent on the cost of canakinumab, it is possible there will be different definitions of colchicine resistance for physicians as opposed to funders (governments, insurance).

It is necessary to define is the optimal dose and interval. In non- or partial responders it is possible that a dose increase or switch to another IL-1 inhibitor will be effective. The published controlled studies do not adequately address this question.

Similarly, current studies do not address this issue of how long to treat and how to wean. It is possible that the disease pathogenesis/immunology

may "reset" after using IL-1 inhibitors and be amenable again to use of colchicine.

Another important question that needs to be addressed is the continued use of colchicine in patients treated with IL-1 inhibitors? Currently, there is a consensus that it is still necessary to continue colchicine, since it's the only agent proven to prevent amyloidosis. It is possible, however, to administer a lower dose of colchicine proven to be effective in preventing amyloidosis (1 mg/day). It may take many years of longitudinal studies to assess whether anti-IL-1 agents are independently able to prevent amyloidosis.

Furthermore, the effect of anti-IL-1 agents in reversing existing amyloidosis, specifically improving proteinuria and renal function, is still unclear.

Despite our newly discovered ability to help the most severe FMF patients with anti-IL-1 therapy, including canakinumab, the cornerstone of FMF therapy for the vast majority of patients will remain colchicine.

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Declaration of Interest

Prof. Hashkes is a consultant and has received honoraria and research support from Novartis. Dr. Haviv has no conflicts of interest. Dr. Hashkes and Dr Haviv were investigators in the canakinumab phase III trial. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial

interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

DRUG SUMMARY BOX

Drug name: Canakinumab

Phase III

Indication: Colchicine resistant familial Mediterranean fever (FMF)

Mechanism of action: Monoclonal antibody to IL-1β

Route of administration: Subcutaneous injection

Pivotal trial: [52-54]

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Table 1: Summary of cases reports on the use canakinumab in patients with familial Mediterranean fever (FMF)									
Authors	**Patient's age (years), gender**	***MEFV* gene analysis**	**Colchicine dose (mg/d)**	**Trials with other drugs**	**Indications for anti-IL-1 therapy**	**Previous anakinra use**	**Reason for discontinuation of anakinra**	**Canakinumab dose**	**Effects of canakinumab**
Mitroulis, et al. [45]	25, female	M694V/M694V	2	Etanercept 25 mg X 2/week, Prednisone 5–7.5 mg/day, Methotrexate 10 mg/week	Chronic destructive arthritis	100 mg/day	Severe injection site reactions	150 mg every 6-8 weeks	Significant clinical improvement, reduction of acute-phase reactants, significant improvement in joint MRI findings
Meinzer, et al. [37]	7, female	M694V/M694V	1-2	No	Frequent and severe FMF attacks (3-4/month)	No	NA	2 mg/kg every 8 weeks	Complete remission
	7, male	M694V/M694V	1-2	Prednisone 2 mg/kg/day, IVIg 2 g/kg, 2 doses	FMF associated severe Henoch-Schonlein purpura	100 mg/day	Severe injection site reactions	2 mg/kg every 8 weeks	Complete clinical remission

Hacihamd-ioglu & Ozen [46]	>14, female	M694V/M694V	2	Continuous NSAIDs, anti-TNF, methotrexate, Prednisolone	Recurrent FMF attacks, sacroiliitis & chronic arthritis	1-2 mg/kg/day	Loss of initial response by 9 months	Dose not detailed, given every 70 days	Complete remission
Alpa & Roccatello [47]	30, female	M694V/I519T	Up to 2	No	Frequent FMF attacks, weight loss, chronic arthritis	100 mg/day for 10 days	Severe injection site reactions	150 mg every 8 weeks	Significant improvement in both clinical symptoms and HRQoL scores

IL: interleukin; NA: not applicable; IVIg: intravenous immunoglobulin; NSAID: non-steroid anti-inflammatory drug; TNF: tumor necrosis factor; HRQoL: health-related quality of life

Table 2a: Summary of data from familial Mediterranean fever (FMF) canakinumab case series (2015-2016) prior to use of canakinumab								
Authors & year of publication	**Number of patients**	**Patients' age range (years) & gender (male:female)**	**MEFV gene analysis**	**Colchicine dose (mg/d)**	**Trials with other drugs**	**Indications for anti-IL-1 therapy**	**Previous Anakinra use**	**Reason for discontinuation of anakinra**
Rossi-Semerano et al. 2015 [39]	4	Pediatric population, gender not specified	Not specified	Not specified (all received colchicine)	Unknown	Not specified	In 3 of 4 patients, doses not specified	Inefficacy or injection site reaction
Cetin, et al. 2015 [40]	8	14-20, 4:4.	M694V/M694V	1-2.5	Unknown	Colchicine resistance	No	NA
Başaran et al. 2015 [41]	4	11-19.5, 3:1.	M694V/M694V	2. Three of 4 patients discontinued therapy while on canakinumab, all had FMF symptoms	One patient received prednisolone (2 mg/kg/day) and etanercept	Colchicine resistance, persistent elevated acute phase reactants, optic neuritis, non-specific vasculitis	2 mg/kg/day (one patient 3 mg/kg/day)	Low compliance, inefficacy in 1 patient
Eroglu et al. 2015 [42]	9	2-24, gender not specified	All patients except one had homozygous or compound heterozygous exon 10 mutations. One patient was compound heterozygous for	2	Etanercept in 3 patients (0.8 mg/kg/week), corticosteroids in one patient.	Colchicine resistance, amyloidosis, recurrent protracted febrile myalgia, elevated acute phase reactants between attacks, persistent	6 of 9 patients (2-5 mg/kg/day)	Urticaria and injection site pain in 3 patients, inefficacy in 2 patients, 1 patient lost response (developed arthritis after 6

			M694V/E148Q and also had homozygous MVK V377I mutation			arthritis		months)
Özçakar et al. 2016 [43]	3	11-22, gender not specified	-M694V/M694V (2 patients) -M694V/M680I (1 patient)	2–3	Unknown	Colchicine resistance	No	No

IL: interleukin; NA: not applicable, MVK: mevalonate kinase

Table 2b: Summary of canakinumab treatment data from familial Mediterranean fever (FMF) case series (2015-2016)					
Authors & year of publication	**Canakinumab dose**	**Follow-up period (months)**	**Effects of canakinumab**	**Adverse events**	**Serious adverse events**
Rossi-Semerano, et al. 2015 [39]	2 mg/kg every 8 weeks (1 patient treated with 2 mg/kg/dose only during attack)	19.3-37.7	Complete response 2/4 (50%); partial response 2/4 (50%)	Not specified	None
Cetin, et al. 2015 [40]	150 mg every 8 weeks	4-25	Complete response in 4/8 (50%); Partial good response (~1 attack/year) in 4/8 (50%)	Not specified	None
Başaran, et al. 2015 [41]	2 mg/kg every month (maximum 150 mg)	24-28	Complete response: 1/4 (25%); partial response: 1/4 (25%, 3 mild attacks); lack of response: 1/4 (25%); good clinical but partial laboratory response: 1/4 (25%)	None	None
Eroglu, et al. 2015 [42]	Initially 2 mg/kg/dose every 8 weeks; 3 patients received only one or two doses. In 2 patients dose increased to 4 mg/kg, and/or the interval shortened to 4 weeks. In 3 patients dose intervals were increased to 12–16 weeks	Up to 30	Complete AIDAI and laboratory response in 8/9 (89%) by 3 months, 1/9 (11%) with chronic shoulder arthritis and sacroiliitis, and mildly elevated CRP	None	Pneumonia requiring hospitalization
Özçakar, et al. 2016 [43]	2–4 mg/kg every 6–8 weeks	16-20	Partial response in all: 2 (67%) patients had 4 attacks/year, 1 (33%) patient had 1 attack/year, 1 (33%) patient had elevated ESR between attacks (normal CRP)	None	None

AIDAI: Autoinflammatory Diseases Activity Index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

Table 3: Summary of phase II trials of canakinumab treatment in familial Mediterranean fever (FMF)		
Authors & year of publication	**Brik R, et al. 2014 [**48]**	**Gül A, et al. 2015 [**49]**
Demographics		
Location	Israel	Turkey
Number of patients	7	9
Age range (years)	6.8–14.9	12-34
Gender: male:female ration	5:2	2:7
Inclusion criteria		
MEFV gene analysis	-M694V/M694V (5 patients) -M694V/V726A (1 patient) -M694V/M680I (1 patient)	-M694V/M694V (6 patients) -M694V/M680I (1 patient) -M694V heterozygous (1 patient) -M680I heterozygous (1 patient)
Colchicine dose (mg/d)	≥1–2 mg/day (based on age), for at least 3 months	2 mg/kg (7 patients) 1.5 mg/day (2 patients)
Number of attacks before screening	≥1 attack per month, within 3 months before screening	≥1 attack per month, within 3 months before screening
Number of attacks after screening	At least one attack in 30 days	At least one attack in 30 days
Canakinumab dose & follow-up period		
Primary canakinumab dose	<40 kg 2 mg/kg (≥40 kg 150 mg) every 4 weeks, up to 3 injections	150 mg every 4 weeks (3 injections)
Number of patients eligible for a canakinumab dose increase	Dose was doubled in 2 patients, due to a flare between day 1 and 29 after the first injection	No patient needed a dose increase
Follow-up period (days)	Treatment phase: 86 days Post-treatment phase: 40-74 days or until the next flare	Treatment phase: 86 days Post-treatment phase: ~ 60 days or until the next flare
Primary outcome measure	Proportion of participants with 50% reduction, or more, in time-adjusted frequency of FMF flares during the treatment period vs. the pretreatment period	

Proportion of patients achieved primary end point	6/7 (86%)		9/9 (100%)	
Median 28-day time-adjusted flare rate decrease	From 2.7 to 0.3 (89%)		From 1.1 to 0	
Number of patients experiencing flares after 2nd canakinumab injection	4 patients: 2 patients, who received dose increase, experienced 1 to 2 flares each after dose was doubled 2 patients treated with initial dose experienced moderate flare		1 patient (peritonitis, day 54)	
Secondary outcome measures	1. Proportion of patients with no flares in the treatment period 2. Acute-phase reactant levels 3. Health-related quality of life 4. Physician's global assessment of FMF control 5. Time to flare following the last canakinumab injection 5. Safety and tolerability of canakinumab			
Proportion of patients with no flares in the treatment period	3/7 (43%)		8/9 (89%)	
	Before canakinumab treatment	**Under canakinumab treatment**	**Before canakinumab treatment**	**Under canakinumab treatment**
Median CRP (mg/L)	74	2 on day 8 1.3 on day 86	58	2.5 on day 8 0.9 on day 86
Median ESR (mm/hour)	83	17 on days 29 & 86	34	-
Median SAA (mg/L)	>500	2.5 on day 57 12.2 on day 86	162	11.1 on day 57 9.6 on day 86
Health-related quality of life	**CHQ-PF50*** (higher is better)		**SF-36**** (higher is better)	
Median physical score	21	46 on day 86	30	90 on day 86
Median psychosocial/ mental score	31	40 on day 86	38	90 on day 86
Physician's global assessment of FMF control	Very poor-3 Poor-3 Fair-1	On day 86: Good-3 Very good-4	Very poor-1 Poor-8	On day 86: Good-1 Very good-8
Number of patients experiencing flares in the post-treatment phase	3 patients (43%)		5 patients (56%)	
Time to flare following the last canakinumab injection	32 to 57 days (median 34)		31 to 78 days (median 71)	

Safety and tolerability of canakinumab		
Number of patients study completers	7/7 (100%)	9/9 (100%)
Proportion of patients reporting at least 1 adverse event	4/7 (57%)	8/9 (89%)
^Total number of adverse events reported	11	13
Severity of adverse events reported	All mild, except 1 moderate group A *Streptococcal* tonsillitis	All mild-moderate, except 1 event of severe headache

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAA: serum amyloid A

* CHQ-PF50: Child Health Questionnaire - Parent Form 50

** SF-36: 36-item short-form health survey

^No serious adverse events

Figure 1: PRISMA flow diagram – canakinumab for the treatment of familial Mediterranean fever (FMF)