

Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature

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Introduction: In 5%–10% of patients with familial Mediterranean fever (FMF), colchicine is not effective in preventing inflammatory attacks. Another 5%–10% of patients are intolerant to effective doses of colchicine and experience serious side effects. Treatment with anti-interleukin-1 (IL-1) drugs may be an alternative for these patients, although it is not reimbursed for this indication in many countries.

Methods: We systematically searched PubMed, Web of Science, and Scopus for reports of anti-IL-1 treatment in FMF patients.

Results: Out of 284 potentially relevant articles, 27 eligible reports were identified and included in the data analysis.

Conclusion: A complete response to therapy without a single attack during treatment was reported in 76.5% of patients on anakinra treatment and in 67.5% of patients during canakinumab treatment. In patients with established type AA amyloidosis, anti-IL-1 treatment can reverse proteinuria. Anti-IL-1 therapy seems to be a safe and effective alternative for patients with FMF who do not respond to or cannot tolerate colchicine.

Keywords: familial Mediterranean fever, interleukin-1, amyloidosis, colchicine

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever. Fevers typically last 12 hours–3 days and are accompanied by serositis, such as peritonitis, pleuritis, pericarditis, and arthritis.¹ There is a subgroup of patients, mostly with a M694V homozygous genotype, who have a more severe phenotype and also suffer from inflammation in between attacks.² Colchicine has been shown to be effective in controlling inflammation in the majority of patients. However, an estimated 5%–10% of patients do not respond to colchicine.³ Furthermore, another 5%–10% of patients are intolerant to effective doses of colchicine and experience serious side effects, including severe diarrhea, neuropathy, rhabdomyolysis, and bone marrow suppression.⁴ For these patients, a therapeutic alternative for colchicine is needed.

In recent years, it has been shown that interleukin-1 (IL-1) plays a central role in the pathogenesis of inflammation in most autoinflammatory diseases.⁵ Inhibiting the action of IL-1 is therefore a logical step in controlling inflammation in these autoinflammatory diseases. Indeed, IL-1 blocking drugs have been proven successful in inhibiting inflammation in several autoinflammatory diseases, including cryopyrin-associated periodic syndrome,^{6,7} tumor necrosis factor receptor-associated periodic syndrome,^{8,9} and hyper-Immunoglobulin D syndrome.^{10,11}

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Currently, three anti-IL-1 drugs are available.¹² Anakinra is a recombinant homolog of the human IL-1 receptor that competitively inhibits binding of IL-1-alpha and -beta to its receptor. It is administered as a daily subcutaneous injection. Canakinumab is a human IgG antibody directed against IL-1-beta. It is administered subcutaneously every 4–8 weeks. Riloncept is a dimeric fusion protein consisting of the extracellular portions of the human IL-1 receptor and the Fc region of human IgG1 that binds and neutralizes IL-1. Although adding anti-IL-1 treatment seems promising when colchicine causes serious side effects or is ineffective, there is currently no reimbursement in Belgium for FMF patients. Recently, the Belgian Network for Auto-Inflammatory Diseases was founded (www.bnaid.be). The Belgian Network for Auto-Inflammatory Diseases consists of a network of physicians who have expertise in diagnosing and treating patients with autoinflammatory diseases. In order to make a statement on the optimal treatment of patients with colchicine-resistant FMF and FMF patients with serious side effects of colchicine, we performed a systematic review of the literature that aimed to summarize all available evidence of anti-IL-1 therapies in patients with FMF.

Methods

We followed a protocol using the methodological approaches outlined in the Agency for Healthcare Research

and Quality's Methods Guide for Effectiveness and Comparative Effectiveness Reviews and applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹³ The systematic literature review aimed to include all studies published until October 1, 2015, reporting on anti-IL-1 therapy in FMF patients. We searched Medline, Web of Science, and Scopus using the following syntax: (anakinra OR anti-IL-1 OR canakinumab OR Riloncept) AND (familial Mediterranean fever OR FMF) in all fields.

Study selection

The selection was performed by one investigator (JH). We included randomized controlled trials, nonrandomized trials, retrospective analysis of these trials, cohort studies or cross-sectional studies, case reports, and case series. There were no language restrictions. We excluded in vitro and animal studies, review articles, and congress abstracts. We assessed all titles and abstracts identified by our search. Publications were considered eligible for the analysis if they contained data on any of the anti-IL-1 therapies in patients with FMF as defined by the Tel Hashomer criteria.¹⁴ Full-length articles were retrieved from all published papers. The flow diagram is depicted in Figure 1.

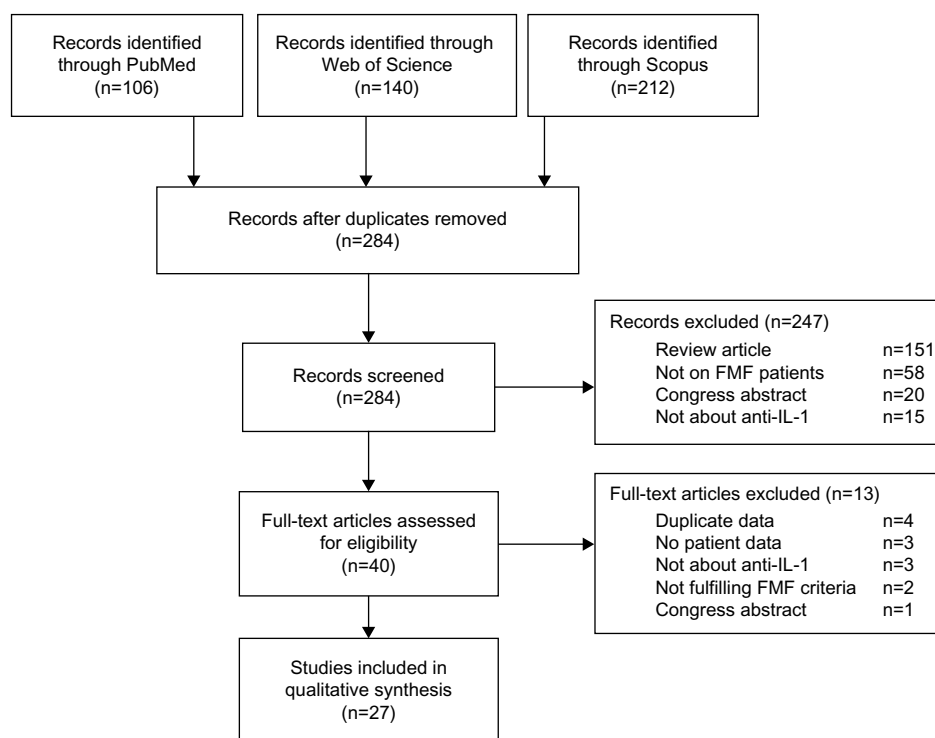


Figure 1 Selection of literature.

Note: Databases were last consulted on October 15, 2015.

Abbreviations: FMF, familial Mediterranean fever; IL-1, interleukin-1.

Data extraction

Using a standardized data extraction sheet, the following data were collected from the articles: lead author, publication year, study design, sample size, reason for anti-IL-1 use, MEFV-mutation, presence of type AA amyloidosis, the response to therapy, and follow-up since the start of anti-IL-1 treatment. In addition, the following baseline characteristics were extracted: age of the patients and the number and proportion of male patients. Patients were considered to have a complete response if there was not a single attack while on anti-IL-1 medication.

Results

The literature search yielded 27 studies that reported on the effect of anti-IL-1 treatment in FMF patients. Twenty-four were case reports or case series, two were open-label prospective trials,^{15,16} and one was a placebo-controlled prospective trial.¹⁷

Eighteen reports contained data on treatment with anakinra,^{18–35} four on treatment with canakinumab,^{15,16,36,37} and four on patients treated with either anakinra or canakinumab.^{38–41} In addition, there is one study that reports on the use of riloncept.¹⁷

Effects of anakinra

Since 2006, there have been 22 publications reporting on the effect of anakinra that included 64 patients from ten different countries. The data are presented in Table 1. The cumulative follow-up was 885 months. A complete response during treatment was reported in 76.5% of patients. An additional 18.8% of patients had a decrease in attack frequency and inflammation. Only in three patients, there was no clinical response to anakinra. Two of the three patients switched to canakinumab with favorable clinical response. Data on MEFV genotype were available for 51 patients; 72.5% were homozygote for *M694V* mutation.

Nineteen of the 64 patients who were treated with anakinra already had type AA amyloidosis at the start of treatment. Four patients had nephrotic syndrome.^{35,38–40} In all four patients, a decrease in proteinuria was observed after initiation of anakinra. In five patients, anakinra was started after patients received a renal transplantation, with no recurrences of AA amyloidosis in the kidney transplant reported. Eight patients had end-stage renal disease when anakinra was started. Three of these patients underwent renal transplantation while on anakinra treatment. No recurrence of amyloidosis was reported under anakinra treatment.

Table 1 Effect of anakinra

Study	Patients included (N)	Sex (male), (N)	Age (adult), (N)	Type AA amyloidosis (N)	Reason for starting anti-IL-1 (resistance/toxicity)	Complete response (N)	Follow-up (months)
Chae et al ²⁰	1	1	1	1	0/1	1	6
Belkhir et al ³³	1	0	1	1	1/1	1	5
Gattringer et al ²²	2	0	2	0	2/0	2	4.5
Kuijk et al ²¹	1	0	0	0	1/0	1	9
Calligaris et al ³²	1	0	0	0	1/0	0	15
Mitroulis et al ²³	1	1	1	0	1/0	1	6
Roldan et al ²⁵	1	1	0	0	1/0	1	6
Moser et al ²⁴	1	1	1	1	1/0	1	20
Petropoulou et al ²⁷	1	1	1	0	1/0	1	4
Meinzer et al ⁴¹	6	4	0	0	5/1	5	73
Özen et al ²⁸	3	2	0	0	3/0	1	48
Alpay et al ²⁶	1	1	1	1	0/1	1	2
Hennig et al ¹⁸	1	1	1	1	1/0	1	NR
Stankovic Stojanovic et al ³⁰	4	1	4	4	4/0	4	56
Estublier et al ²⁹	1	1	1	0	1/0	1	12
Soriano et al ¹⁹	1	1	1	0	0/1	1	17
Celebi et al ³¹	1	0	1	1	1/0	1	8
Mercan et al ³⁴	2	0	2	0	2/1	2	3
Özçakar et al ³⁹	10	4	3	6	10/1	8	179
Cetin et al ⁴⁰	12	7	10	1	12/1	7	198
Eroglu et al ³⁸	11	NR	NR	1	11/1	7	172
Sevillano et al ³⁵	1	1	1	1	1/1	1	42

Abbreviations: IL-1, interleukin-1; NR, not reported.

Effects of canakinumab

Eight studies including 40 patients reported on the treatment of canakinumab in FMF (Table 2). The cumulative follow-up period was 427 months. In 67.5% of patients, a complete response was reported. In the remaining 32.5%, a partial response with reduced attack frequency and inflammation was noticed. There were no reports of treatment failure of canakinumab. One patient treated with canakinumab had type AA amyloidosis. A significant decrease in urinary protein excretion after canakinumab (25.6–12 mg/m²/h) was recorded.⁴² Data on MEFV genotype were available for 31 patients; 77.4% were homozygote for M694V mutation. Seven patients had used anakinra before they started with canakinumab. In four patients, anakinra was stopped because of side effects. None of these patients had reported side effects while on canakinumab. In two patients, anakinra was unsuccessful in controlling inflammation. In both patients, canakinumab resulted in a complete response.

Effects of rilonacept

The effect of rilonacept has been studied in a randomized, double blind, placebo-controlled trial including 14 patients. A complete remission during the 3-month rilonacept course was reported in two patients. Eight patients had a partial response, while in four patients, there was no significant reduction in attack frequency.

Safety of anti-IL-1 treatment

Serious side-effects warranting the discontinuation of anakinra were reported in five patients. This included four patients with injection site reactions, one patient with injection site reactions, and one patient who developed interstitial pneumonia possibly related to anakinra use. There were no adverse events reported requiring the cessation of canakinumab or rilonacept. Notably, there were no cases of

neutropenia or serious infections necessitating the discontinuation reported.

Discussion

The current systematic review indicates that anti-IL-1 treatment is effective for patients with colchicine-resistant FMF and for patients who are unable to tolerate colchicine. All three currently available anti-IL-1 drugs were effective in suppressing inflammatory attacks. In the majority of patients, a complete remission with absence of even a single attack was reported.

Because FMF severely affects quality of life, prevention of attacks is important.⁴³ In addition, the ability to control inflammation is directly related to the risk of type AA amyloidosis.^{44,45} If inflammation cannot be controlled, type AA amyloidosis develops in up to three-quarter of patients during life.⁴⁶ It is therefore essential to suppress inflammation in order to prevent this severe complication. In patients with already established nephrotic syndrome caused by type AA amyloidosis, a significant reduction in proteinuria was consistently observed. Furthermore, in patients with renal transplantation, no recurrences of amyloidosis were seen when patients were on anti-IL-1 treatment.

The optimal treatment of colchicine-resistant FMF remains unclear and largely based on low-quality evidence. The current literature does not allow to make a statement about optimal dosing. The lack of high-quality evidence also precludes judgment about superiority of one of the anti-IL-1 treatments over another. In addition, since most reports in our review are case reports or case series, there is a potential risk of publication bias.

However, despite the fact that colchicine resistance and colchicine toxicity in FMF are rare complications of a rare disease, results of 27 publications representing >100 patient-years of follow-up are available. The results of anti-IL-1

Table 2 Effect of canakinumab

Study	Patients included (N)	Sex (male), (N)	Age (adult), (N)	Type AA amyloidosis (N)	Reason for starting anti-IL-1 (resistance/toxicity)	Complete response (N)	Follow-up (months)
Meinzer et al ⁴¹	2	1	0	0	2/0	2	9
Mitroulis et al ³⁷	1	0	1	0	1/0	1	24
Brik et al ¹⁵	7	5	0	0	7/0	3	42
Özçakar et al ³⁹	3	0	2	0	3/0	0	56
Alpa and Roccatello ³⁶	1	0	1	0	1/0	0	24
Cetin et al ⁴⁰	8	4	6	0	8/0	6	137
Eroglu et al ³⁸	9	NR	NR	1	9/0	7	108
Gül et al ¹⁶	9	7	NR	0	9/0	8	27

Abbreviations: IL-1, interleukin-1; NR, not reported.

treatment are remarkably consistent and show a dramatic clinical response with a favorable safety profile in the majority of patients with a hitherto very difficult to treat condition without therapeutic alternatives.

Prospective placebo-controlled trials are currently being performed both for anakinra⁴⁷ and canakinumab ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02059291) identifier: NCT02059291).

Conclusion

Based on the results of the current review, anti-IL-1 therapy seems to be a safe and effective alternative for patients with FMF who do not respond to or cannot tolerate colchicine.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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