Review paper

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Efficacy and safety of anti-interleukin-6 treatment in familial Mediterranean fever: a systematic literature review

Olfa Saidane[1,2], Selma Bouden[1,2], Ameni Jerbi[3,4], Leila Rouached[1,2], Ines Mahmoud[1,2], Rawdha Tekaya[1,2], Aicha Ben Tekaya[1,2], Leila Abdelmoula[1,2]

[1]Department of Rheumatology, Charles Nicolle Hospital, Tunis, Tunisia
[2]Faculty of Medicine, University of Tunis El Manar, Tunisia
[3]Department of Immunology, Habib Bourguiba Hospital, Sfax, Tunisia
[4]Faculty of Medicine, University of Sfax, Tunisia

Abstract

Introduction: Biological treatments are indicated in familial Mediterranean fever (FMF) patients with colchicine resistance or intolerance. Interleukin-1 (IL-1) inhibitors may not yield sufficient efficacy and safety. Interleukin-6 inhibitors (tocilizumab – TCZ) have been suggested to be potentially beneficial. This systematic literature review aimed to evaluate the existing data on the efficacy and safety of IL-6 inhibitors in the treatment of FMF.

Material and methods: A systematic literature review was conducted using PubMed, Embase, Scopus, Web of Science, and the Cochrane Library to identify literature published until February 2024 on "Tocilizumab" OR "Interleukin-6 inhibitor" AND "Familial Mediterranean Fever". This study was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: A total of 11 studies were included, corresponding to 68 patients: 6 studies were case reports, 3 were case series, and 2 were randomized control trials. Tocilizumab was indicated mainly for amyloid A (AA) amyloidosis and resistance/intolerance to other drugs. Tocilizumab showed efficacy in controlling FMF attacks and disease symptoms including fever, abdominal pain, arthritis and arthralgia. Inflammatory markers including C-reactive protein and serum amyloid A protein decreased. A decrease in proteinuria levels was reported in 20 patients. Adverse events were recorded in one-third of patients and led to TCZ discontinuation in 5 patients. No deaths associated with anti-IL-6 treatment were documented within a median follow-up period of 13 months.

Conclusions: Although the duration of follow-up of TCZ was short, we concluded that TCZ might present an acceptable profile regarding efficacy and safety in adult FMF patients. Our data suggest that TCZ could be a good treatment option after IL-1 inhibitors and warrants further investigation.

Key words: anti-IL-6, colchicine resistance, familial Mediterranean fever, FMF, tocilizumab.

Introduction

Familial Mediterranean fever (FMF) is the most common hereditary monogenic auto-inflammatory recurrent fever. It mainly affects ethnic groups in the Middle East and around the Mediterranean [1].

Familial Mediterranean fever is the prototypical inherited autoinflammatory disease. The mutations occur in the Mediterranean fever gene *MEFV* that encodes the pyrin protein [2]. Pyrin controls the activation of caspase-1, leading to interleukin (IL)-1β production. Additionally, pyrin regulates the transcriptional nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), which in turn stimulates the production of other pro-inflammatory cytokines [3]. In physiological conditions, this protein inhibits inflammasome activity and helps in the downregulation of the innate immune response [2]. Therefore, mutations in the *MEFV* gene lead to disruption of the innate immune system. This abnormality occurs

Address for correspondence
Selma Bouden, Charles Nicolle Hospital, Avenue 9 Avril 1938, Tunis, Tunisia, 1070, e-mail: selma.bouden@gmail.com
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mainly in monocytes and neutrophils, and results in the abnormal secretion of certain pro-inflammatory cytokines such as IL-1β, IL-6, IL-18, and tumor necrosis factor [4]. This cytokine secretion leads to a non-specific increase in the proteins of the acute phase of inflammation (C-reactive protein [CRP], serum amyloid A protein [SAA], fibrinogen, etc.) and is responsible for the clinical signs of systemic inflammation (fever, muscle pain, and inflammation of serous membranes). Familial Mediterranean fever begins before the age of 20 in approximately 90% of patients. In more than half of them, the disease appears within the first 10 years of life.

The major long-term complication of FMF is amyloid A amyloidosis (AA amyloidosis). It mostly affects the kidneys and gastrointestinal tract, but it can also affect the liver, spleen, heart, and thyroid. It is a severe, life-threatening complication with a poor prognosis [5].

Treatment mainly aims to prevent disease outbreaks and reduce inflammation to prevent complications such as amyloidosis. First-line treatment has been based on colchicine since the 1970s with proven effectiveness in preventing and treating amyloidosis as well as managing acute FMF attacks [5]. However, 5 to 15% of patients with FMF are resistant and/or intolerant to colchicine and must be given alternative treatment options [6].

Recently, biological therapies, notably IL-1 antibody (anti-IL-1) medications including anakinra, canakinumab, and rilonacept, have been proven to be effective and safe in managing recurrent episodes and persistent inflammation among FMF patients. These treatments selectively target immune system components such as IL-1 to regulate the inflammatory cascade and mitigate disease severity [2, 5, 7–10].

Although anti-IL-1 medications are biological first-line treatment alternatives for FMF patients with colchicine resistance or intolerance [2], they may not yield sufficient efficacy, particularly in amyloidosis, or may be contraindicated due to adverse events [11, 12]. In this particular case, anti-IL-6 inhibitors have been suggested to be potentially beneficial [13].

Tocilizumab (TCZ), a humanized monoclonal antibody that blocks the action of IL-6 receptors, has been approved for the treatment of many autoimmune/inflammatory diseases such as rheumatoid arthritis [14], giant cell arteritis [15], and cytokine release syndrome [16], with acceptable safety and effectiveness. Numerous studies have revealed encouraging outcomes in managing FMF attacks and amyloidosis using TCZ.

While many reviews assessing the efficacy and safety of drugs are available [17], notably the effectiveness and safety anti-IL-1 drugs in FMF [2], systematic reviews analyzing the available evidence of anti-IL-6 drugs regarding the effectiveness and safety in FMF are lacking.

This systematic literature review aimed to evaluate the efficacy and safety of TCZ in the treatment of FMF.

Material and methods

Data sources and strategy search

The present systematic literature review was conducted according to the updated Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18]. Two authors (S.O., B.S.) independently performed the search using the PICO (Patient, Intervention/Exposure, Comparison, Outcome) strategy. The following online databases were searched: PubMed, Embase, Scopus, Web of Science, and the Cochrane Library, for literature published until February 2024. Medical Subject Headings (MeSH) used were: "Tocilizumab" OR "Interleukin-6 inhibitor" AND "Familial Mediterranean Fever". Manual research was also performed by reviewing the references of the retained articles.

Study selection

Eligible articles were clinical trials, cohort studies, cross-sectional studies, case series, and case reports including adult patients (≥ 18 years) with FMF treated by TCZ. The selected languages were English and French.

The same two authors (SO, BS) independently screened all the articles generated, according to title, abstract, and full text. Redundant articles were removed, and those that did not satisfy the eligibility criteria were excluded. Selection discrepancies were resolved through discussion and consensus. All authors agreed on the final decision of the studies to be included.

Data extraction

A standardized data collection form was used, and the following information was collected:

- study characteristics: design of the study, country, year, number of patients,
- population characteristics: age, sex,
- data related to FMF characteristics: duration, organ involvement,
- data related to TCZ treatment: dose, administration schedule, duration, associated treatments,
- data related to the efficacy of TCZ: clinical and laboratory data,
- data related to the safety of TCZ: short-term and long-term side effects were assessed.

Study quality assessment

Each included article was critically appraised for methodological quality using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized clinical trials (RCTs) [19]

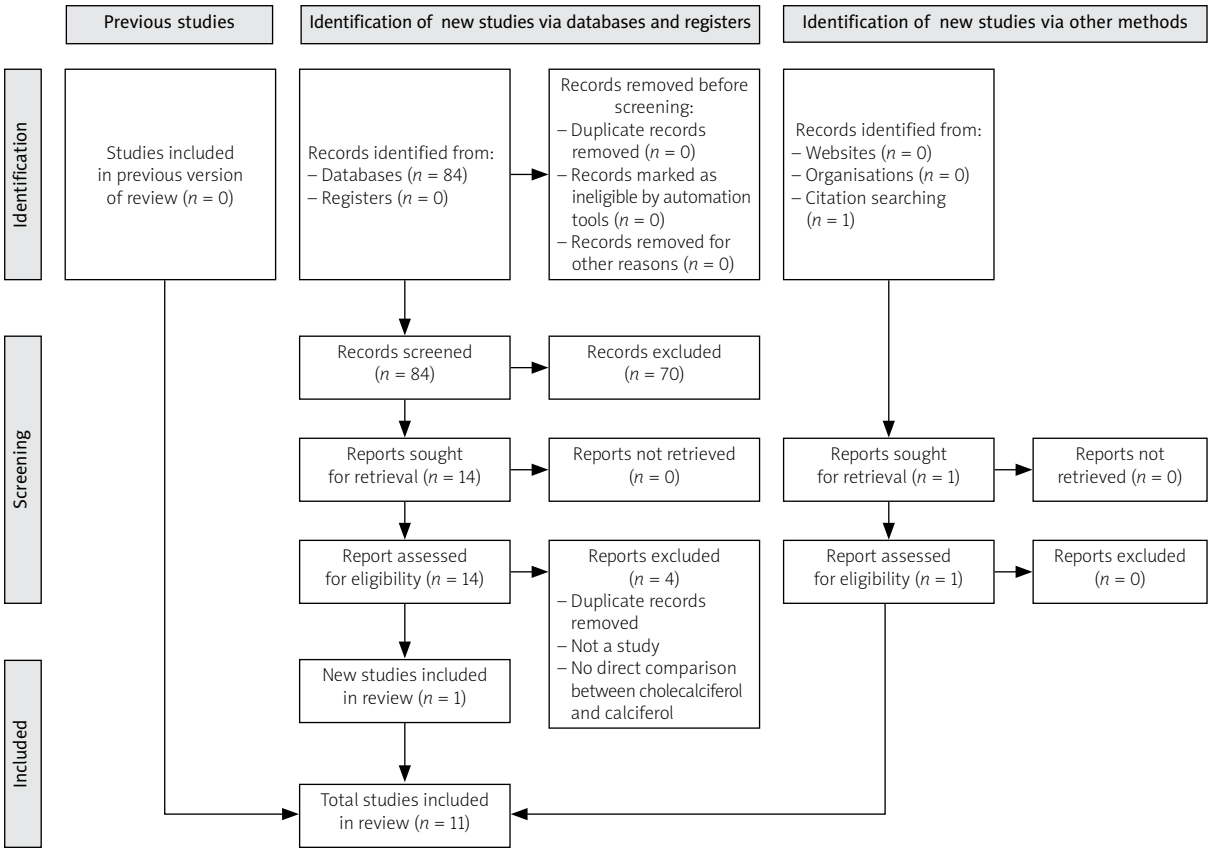

Fig. 1. PRISMA 2020 flow diagram of included studies.

and the Newcastle–Ottawa Scale for non-RCTs and observational studies [20]. One author (BS) appraised the quality of eligible studies.

Results

Retrieved articles

The systematic search identified initially 84 potentially eligible publications. Then, 60 studies were excluded based on title screening (primary exclusion) and a further 10 studies were excluded after abstract screening (secondary exclusion). Four duplicates were removed and one study was added through hand research.

Finally, we included a total of 11 eligible studies in our systematic review [21–31]. The PRISMA flow diagram for the review selection process is shown in Figure 1.

Studies and population characteristics

Of the collective 11 studies, 6 were case reports [21, 23, 24, 26, 28, 30], 3 were case series [22, 29, 31] and 2 were RCTs [25, 27]. The studies were conducted in Japan (6) [21, 23, 24, 26, 27, 30], Turkey (3) [22, 29, 31], Germany (1) [25] and Greece (1) [28]. The total number of participants receiving TCZ was 68 patients. Studies and population characteristics are summarized in Table I.

Tocilizumab indications

Tocilizumab has been used in FMF for different indications (Table II). First, TCZ was introduced for treating AA amyloidosis in 7 studies [21, 22, 24, 26, 28, 29, 31]. In these studies, amyloidosis was confirmed by histopathological findings of biopsies mostly from renal and/or gastrointestinal origins. The second most frequent indication was for an active disease with disease activity defined by the occurrence of at least one fever attack in 3 months (2 studies) [25, 27]. In one study, TCZ was initiated to treat a resistant case of myositis [30]. Finally, in the study of Fujikawa et al. [23], it was introduced to treat a case of erysipelas-like erythema associated with periodic fever and polyarthralgia that was mistaken for adult-onset Still disease.

In 10 studies, TCZ was introduced as patients showed resistance or intolerance to colchicine used at the maximum tolerated dose (1.5–2 mg/day) [21, 22, 24–31], whereas, in the Fujikawa et al. [23] study, it was

Table I. Characteristics of studies and population

First author/ Year [Ref.]	Country	Study design	Number of patient	Sex/ sex ratio	Age/mean age ±SD/ Median (min.–max.) [years]	Disease duration/ mean duration ±SD/ Median (min.–max.) [years]	Heterozygous MEFV mutation [*n* (%)]
Aikawa et al. 2016 [20]	Japan	Case report	1	M	53	16	Genetic analysis was not mentioned
Colak et al. 2019 [21]	Turkey	Case series	15	3/12	42.07 ±14.37	25.73 ±10.86	11 (73.3)
Fujikawa et al. 2013 [23]	Japan	Case report	1	F	19	12	1
Hamanoue et al. 2016 [24]	Japan	Case report	1	M	51	21	1
Henes et al. 2022 [25]	Germany	RCT	13 TCZ 12 placebo	6/7 TCZ 5/7 placebo	33 (18–53) TCZ 28.5 (18–41) placebo	18 (2–44) TCZ 12.5 (0–29) placebo	8 (61.5) TCZ 5 (41.6) placebo
Inui et al. 2020 [26]	Japan	Case report	1	M	51	NR	1
Koga et al. 2022 [27]	Japan	RCT	11 TCZ 12 placebo	3/11 TCZ 6/6 placebo	37.5 (14.5) TCZ 45.9 (11.0)	NR	6 (86) TCZ 9 (75) placebo
Serelis et al. 2015 [28]	Greece	Case report	1	F	32	32	The type of mutation was not specified
Ugurlu et al. 2017 [29]	Turkey	Case series	12	6/6	35.2 ±10	6.43 ±6.90	8 (66.6)
Umeda et al. 2015 [30]	Japan	Case report	1	F	64	NR	1
Yilmaz et al. 2014 [22]	Turkey	Case series	11	1/10	37.9 (22–76)	NR	3 (27.2)

NR – not recorded, RCT – randomized clinical trial, SD – standard deviation, TCZ – tocilizumab.

resistance to methotrexate associated with prednisolone (1 mg/kg/day) that led to its use.

Notably, several patients experienced intolerance or resistance to synthetic disease-modifying drugs or biologics before receiving TCZ whether these treatments were indicated for treating FMF or another associated disease. These previous treatments included methotrexate (1 patient) [23], azathioprine (1 patient) [29], sulfasalazine (2 patients) [29], cyclophosphamide (2 patients) [29], anakinra (6 patients) [25, 29], canakinumab (4 patients) [29], infliximab (3 patients) [29] or etanercept (2 patient) [24, 29].

Route of administration

In 9 studies corresponding to 56 patients (82%), TCZ was administered intravenously every 4 weeks at a dose of 8 mg/kg [22–26, 28–31]. The subcutaneous route was used for 2 studies, at the dose of 162 mg every week [27] and 162 mg every 2 weeks [21] (Table II).

Concomitant treatment

In 8 studies among 11 corresponding to 62 patients (91%), patients were receiving a co-medication with colchicine [21, 22, 25, 27–31]. In the studies of Henes et al. [25] and Koga et al. [27], patients were also allowed to take a low dose of glucocorticosteroids (≤ 10 mg/day and ≤ 5 mg/day respectively) as long as these doses were stable throughout the studies. Particularly, in the study of Henes, non-steroid anti-inflammatory drugs that were allowed as a rescue treatment for attacks were used by 61.5% of patients [25].

Table II. Indications of tocilizumab, doses, concomitant and previous treatment

First author	Number of patients	Indication for treatment by TCZ	Dose	Number of infusions/ injections mean ±SD/Median (min.-max.)	Follow-up (months)	Co-medication	Previous DMARDS/ biologics before TCZ (*n*)
Aikawa et al. [20]	1	Gastrointestinal amyloidosis	162 mg every 2 weeks	NR	13	Colchicine	None
Colak et al. [21]	15	Amyloidosis	8 mg/kg bw monthly	12 (3–96) perfusions	12	Colchicine	None
Fujikawa et al. [23]	1	FMF attack with fever synovitis and erysipelas like erythema	8 mg/kg bw monthly	NR	NR	None	Methotrexate (*n* = 1)
Hamanoue et al. [24]	1	Gastrointestinal and renal amyloidosis	8 mg/kg bw monthly	NR	24	None	Etanercept (*n* = 1)
Henes et al. [25]	13	Active disease	8 mg/kg bw monthly	4 perfusions	4	Colchicine NSAIDS GC	Anakinra (*n* = 1) Canakinumab (*n* = 1)
Inui et al. [26]	1	Renal amyloidosis	8 mg/kg bw monthly	NR	108	NR	None
Koga et al. [27]	11	Active disease	162 mg weekly	NR	6	Colchicine GC	NR
Serelis et al. [28]	1	Renal amyloidosis	8 mg/kg bw monthly	NR	48	Colchicine	None
Ugurlu et al. [29]	12	Amyloidosis	8 mg/kg bw monthly	15.3 ±12.1 perfusions	17.5 ±14.7	Colchicine	Anakinra (*n* = 5) Canakinumab (*n* = 3) Infliximab (*n* = 3) Cyclophosphamide (*n* = 2) Etanercept (*n* = 1) Sulfasalazine (*n* = 2) Azathioprine (*n* = 1)
Umeda et al. [30]	1	Active disease with myositis	8 mg/kg monthly	NR	9	Colchicine	None
Yilmaz et al. [22]	11	Renal amyloidosis	8 mg/kg monthly	9 perfusions	NR	Colchicine	None

DMARDS – disease-modifying drugs, GC – glucocorticosteroid, NR – not recorded, NSAIDs – non-steroid anti-inflammatory drugs, SD – standard deviation, TCZ – tocilizumab.

Efficacy data

Familial Mediterranean fever attacks

The effect of TCZ on FMF attacks was recorded in 10 studies, corresponding to 57 patients (84%) [21–26, 28–31].

Tocilizumab showed efficacy in controlling fever (4 studies [21, 23, 24, 30]) abdominal pain (3 studies [22, 24, 26]) arthritis or arthralgia (5 studies [21, 23, 24, 26, 28]) myalgia or myositis (2 studies [22, 30]), erysipelas-like erythema (1 study [23]), chest pain (1 study [22]) and headache (1 study [22]).

Two studies focused on evaluating the efficacy of TCZ in reducing the frequency of attacks [27, 28]. Although the study of Koga et al. [27] showed no efficacy vs. placebo at the primary endpoint (24 weeks), attack recurrence was significantly lower in the TCZ group (hazard ratio = 0.457; 95% CI: 0.240–0.869) [27]. Additionally, it reported a tendency for fewer attacks in the long term (48 weeks) [27].

Inflammatory markers

Tocilizumab showed efficacy in controlling inflammatory markers. All 6 studies [24–27, 29, 30] reporting CRP variation under TCZ noted a decrease in levels, with 4 studies showing a fall to a normal range [24, 25, 27, 30] (Table III). Additionally, the study of Ugurlu et al. [29] that recorded erythrocyte sedimentation rate (ESR) variation noted a decrease from 48.7 ±3 mm/h to 27.3 ±mm/h.

Tocilizumab was also found to be efficient in controlling the levels of SAA [24, 25, 27] (Table III).

Renal function

Renal function in patients on TCZ was assessed in 5 studies, corresponding to 26 patients [24, 26, 28, 29, 31]. The effect of TCZ on renal function was inconsistent. A decrease in serum creatinine levels was reported by Hamanoue et al. [24] and Serelis et al. [28], while Inui et al. [26] observed an increase in its level. Conversely, the studies of Ugurlu et al. [29] and Yilmaz et al. [31] observed stabilization of serum creatinine levels in most patients.

Proteinuria

Urinary protein excretion in patients on TCZ was assessed in 5 studies, corresponding to 26 patients [24, 26, 28, 29, 31]. Overall, a decrease in proteinuria levels was reported in 20 patients (77%) (Table III). For instance, in their study, Yilmaz et al. [31] reported a decrease or normalization of 24-hour proteinuria in 7/11 patients. A reduction of 24-hour proteinuria was also observed in 10/12 patients in the Ugurlu et al. study [29].

Amyloidosis

Although 7 studies were conducted in patients with histologically proven AA amyloidosis corresponding to 43 patients [21, 22, 24, 26, 28, 29, 31], only 3 studies, corresponding to 3 patients, reported the effect of TCZ on amyloid deposition [21, 24, 26]. Interestingly, a reduction of amyloid deposition was confirmed in all 3 cases. This reduction was variable: from a 19% reduction [26] to a complete resolution [29].

Efficacy data in patients with resistance to anti-interleukin-1 biologics

Tocilizumab was used in 8 patients with known resistance to anti-IL-1 biologics.

Data were only available for the Ugurlu et al. study [29], corresponding to 6 patients, among whom 2 had had 2 anti-IL-1 biologics: anakinra and canakinumab. Tocilizumab administration was associated with a decrease in creatinine levels in 1 patient, stabilization in 3 patients, and an increase in 2 patients. Accordingly, glomerular filtration increased in 3 patients and decreased in 3 patients. Efficacy data on proteinuria were also inconsistent, as 4 patients experienced a decrease in their proteinuria levels, while 2 patients showed an increase.

Tolerance data

Tocilizumab tolerance data were reported in 5 studies, corresponding to 62 patients (91%) [22, 25, 27, 29, 31]. Overall, adverse events were recorded in 19 patients (30%; Table IV). Three serious adverse events were noted in 3 patients (13%) including ileitis, myocarditis, and headache [25, 27].

Interestingly, no serious or opportunistic infections were reported. Among adverse events of special interest, 2 cases of increased liver enzymes and a case of mild thrombocytopenia were noted [25, 31]. Infusion reactions were not observed. However, 2 patients presented an injection site reaction [27]. Notably, the study of Koga et al. [27] found no difference between patients and placebo in the number and severity of adverse events.

Adverse events led to TCZ discontinuation in 5 patients [25, 27, 29]. No deaths associated with anti-IL-6 treatment were documented in 4 studies that reported death occurrence, corresponding to 50 patients [22, 25, 27, 31].

The follow-up period was mentioned in 9 studies among 11, corresponding to 56 patients [21, 22, 24–30]. It varied between 4 and 108 months, with a median of 13 months.

Table III. Efficacy data of tocilizumab

First author	Number of patients	Response to TCZ (*n*)	Number of attacks under TCZ (*n*)/ Median (min.-max.)	CRP [mg/dl]	Renal function	Proteinuria	SAA	Amyloid deposits
Aikawa et al. [20]	1	1: no attacks	0	NR	NR	–	NR	Disappeared
Colak et al. [21]	15	8: no attacks 6: decreased attacks frequency 1: no response	0 (0–10)	–	–	–	–	NR
Fujikawa et al. [23]	1	1: no attacks	0	NR	–	–	–	–
Hamanoue et al. [24]	1	1: no attacks	0	Decreased to 0.0	Creatinine decreased to 1.6 mg/dl	Decreased to 0.3 mg/day	Decreased to 5.0 µg/ml	Marked reduction of amyloid deposits
Henes et al. [25]	13	2: responders 11: no response (primary endpoint: PGA score of < 2 and normalization of SAA and CRP and/or ESR)	NR	CRP < 0.5 for 69.2% of patients ($p < 0.011$)	–	–	SAA < ULN (10 mg/l) in 7 patients (53.8%) ($p < 0.015$)	NR
Inui et al. [26]	1	1: no attacks	NR	Decreased	Creatinine: increased from 1.9 to 2.3 mg/dl GFR: decreased from 31.1 to 24.1 ml/min	Decreased from 3.8 g/day to 1.4 g/day	–	Decrease of up to 19%
Koga et al. [27]	11	NR	11: TCZ 20: placebo ($p = 0.58$) Recurrence of attacks significantly lower with TCZ (HR = 0.457; 95% CI: 0.240–0.869)	Median CRP decreased from 0.70 (0.20–82) to 0.2 (0.20–0.80)	-	-	Median SAA decreased from 7.5 mg/l (2.5–1,100 mg/l) to 2.7 mg/l (2.5–41 mg/l) in TCZ group	-
Serelis et al. [28]	1	1: decreased attacks frequency	2 milder attacks/year	NR	Creatinine decreased from 2 to 1.2 mg/dl	Decreased from 9 g/day to 3.6 g/day	–	NR
Ugurlu et al. [29]	12	10: no attacks 1: less frequent and mild attacks 1: no response	NR	Mean CRP decreased from 18.1 ±19.5 to 5.8 ±7.1	Stable Mean creatinine: from 1.1 ±0.9 to 1.0 ±0.6 mg/dl mean GFR from 111.7 ±50.1 to 108.9 ±54.8 ml/min	Decreased from 6,537.6 ±6,526.0 mg/day to 4,745.5 ±5,462.7 mg/day (in 10 patients)	–	NR
Umeda et al. [30]	1	1: no attacks	0	Suppressed to the normal range	–	–	–	–
Yilmaz et al. [22]	11	10: no attacks 1: no response	NR	NR	Creatinine: Increased ($n = 1$) Stable/slightly increased ($n = 10$)	Decreased ($n = 7$) Stable ($n = 2$) Increased ($n = 2$)	–	NR

CI – confidence interval, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, GFR – glomerular filtration rate, HR – hazard ratio, NR – not recorded, PGA – patient global assessment, SAA – serum amyloid A protein, TCZ – tocilizumab, ULN – upper limit normal.

Table IV. Tolerance data of tocilizumab

First author	Number of patients	Serious adverse events (*n*)	Infections (*n*)	Liver enzymes alteration (*n*)	Blood count parameters abnormalities (*n*)	Infusion reaction/ injection site reaction (*n*)	Other adverse events (*n*)
Aikawa et al. 2016 [20]	1	–	–	–	–	–	–
Colak et al. 2019 [27]	15	None	None	None	None	None	None
Fujikawa et al. 2013 [21]	1	–	–	–	–	–	–
Hamanoue et al. 2016 [17]	1	–	–	–	–	–	–
Henes et al. 2022 [1]	13	1: ileitis	None	1: increased liver enzymes:	NR	NR	NR
Inui et al. 2020 [26]	1	–	–	–	–	–	–
Koga et al. 2022 [24]	11	2 (1: myocarditis 1: headache)	NR	NR	NR	2: injection site reactions	10 (8: hypofibrinogenemia 2: headache)
Serelis et al. 2015 [19]	1	–	–	–	–	–	–
Ugurlu et al. 2017 [22]	12	NR	1: non-complicated urinary tract infection 1: respiratory tract infection	None	None	None	1: transient diplopia 1: increased blood pressure
Umeda et al. 2015 [25]	1	–	–	–	–	–	–
Yilmaz et al. 2014 [23]	11	None	NR	1: increased liver enzymes	1: thrombocytopenia	NR	NR

NR – not recorded.

Discussion

In this systematic literature review, we assessed the efficacy and safety of TCZ in the management of FMF patients. This is the first systematic review to synthesize the available evidence about anti-IL-6 in FMF. Our results showed that TCZ is safe and effective for treating FMF, especially in terms of decreasing proteinuria and inflammatory markers. Three-quarters of the included patients experienced no FMF attacks or had a decreased frequency and/or severity of attacks under TCZ.

Familial Mediterranean fever attacks are usually associated with high levels of proteins of the acute phase of inflammation such as CRP. Our results showed that more than half of the patients had their CRP levels controlled and fell into the normal range. This seems to be directly linked to the physiopathological mechanism of action of IL-6 inhibitors. Interleukin-6 is a major pro-inflammatory cytokine known to prompt the liver to produce acute-phase proteins such as CRP. Therefore, by blocking the action of IL-6, anti-IL-6 inhibitors decrease CRP levels. This reduction in acute-phase proteins underscores the efficacy of anti-IL-6 treatment in modulating the immune response and mitigating inflammation in numerous otherinflammatory diseases [32].

Interestingly, SAA levels were also controlled in all patients on TCZ treatment. This holds major importance in FMF patients since, it may prevent organ amyloidosis.

In this systematic review, the effect of TCZ on amyloid deposition was reported in 3 patients out of 43 with histologically proven amyloidosis, and all 3 of them experienced a decrease in amyloid deposition.

Colchicine is the gold standard for the treatment of FMF [33]. Its efficacy has been proven to control the frequency and severity of recurrent attacks and also decrease the risk of amyloidosis complications [33]. Nonetheless, 5 to 15% of FMF patients exhibit resistance and/or intolerance to colchicine [9, 34]. Biological therapies, notably anti-IL-1, have been proven as alternative treatment options. Kilic et al. [2] suggested that combining colchicine with IL-1 inhibitors is preferred to mitigate subclinical inflammation. The effectiveness of anti-IL-1 treatment in reducing the frequency and severity of attacks as well as in managing secondary amyloidosis in FMF patients has been demonstrated in many observational studies [11, 35]. Nonetheless, there is presently no evidence demonstrating the efficacy of anti-IL-1 treatment in preventing the onset of AA amyloidosis in FMF patients [2]. Additionally, IL-1 inhibitors do have certain inconveniences. First, daily anti-IL-1 subcutaneous administration, particularly anakinra, could be associated with eventual injection-site reactions. Moreover, the administration of IL-1 inhibitors, particularly canakinumab, is associated with higher costs compared to TCZ treatment [22].

It is worth noting that IL-1 triggers the transcription of IL-6 and is associated with a marked rise in serum IL-6 levels observed in FMF patients [36]. Therefore, targeting IL-6 could be a promising alternative treatment in IL-1-mediated diseases such as FMF. In the same context, the efficacy of TCZ was demonstrated in systemic-onset juvenile idiopathic arthritis, characterized by a distinct IL-1β signature [37].

Interestingly, our findings highlight promising results of IL-6 inhibitors in reducing amyloid deposition. However, the evidence supporting the efficacy of anti-IL-6 inhibitors in preventing or managing AA amyloidosis in FMF patients remains limited and requires further robust studies.

Proteinuria was controlled in most of our patients on TCZ. Conversely, data on renal function were inconsistent.

It is notable that we found heterogeneity in TCZ regimens. Most of the studies adopted monthly intravenous administration of an 8 mg/kg regimen of TCZ.

Additionally, 95% of patients in this review received simultaneously colchicine and TCZ. We agree with Klic et al. [2] that combined therapy of colchicine with IL-6 inhibitors could be more effective in controlling inflammation and disease activity.

Tocilizumab was indicated as a third line treatment in patients who experienced intolerance or resistance to synthetic disease-modifying drugs or biologics. Tocilizumab was prescribed to 8 patients who previously received IL-1 antagonists with no amelioration [29].

In our systematic review, TCZ was a safe treatment option within a median follow-up period of 13 months. Adverse events were reported in almost one-quarter of our patients, with only 3 cases with serious adverse events. Interestingly, no serious or opportunistic infections were reported. Adverse events led to TCZ discontinuation in 5 patients. No deaths associated with anti-IL-6 treatment were documented in our review.

Anti-IL-1 treatment is the preferred initial treatment option for colchicine-resistant FMF due to its effectiveness and approved status [25]. To the best of our knowledge, no studies have proven a direct comparison between anti-IL-1 and anti-IL-6 treatments in FMF patients. However, our results suggest that TCZ offers a safe and effective treatment option in FMF patients who are intolerant and/or resistant to colchicine and/or IL-1 blockers.

Study limitations

The limitations of this systematic review arise from its main reliance on case reports and small case series, resulting in missing data for several variables. Clinical trials with a long-term follow-up remain necessary to validate our findings and would further characterize the profile of efficacy and safety of TCZ in FMF patients.

Conclusions

Although the duration of follow-up of TCZ was short, our systematic literature review concluded that TCZ might present an acceptable profile regarding efficacy and safety in FMF adult patients, in reducing inflammatory markers, particularly CRP and SAA, and decreasing proteinuria. Data on renal function and amyloidosis need to be better clarified, but our data suggest that TCZ could be a good treatment option after IL-1 inhibitors. Further prospective studies or controlled clinical trials are necessary to establish definitive conclusions.

Disclosure

Conflict of interest: The authors declare no conflict of interest.
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Data availability: The data that support the findings of this study are available on request from the corresponding author (S.B.).

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