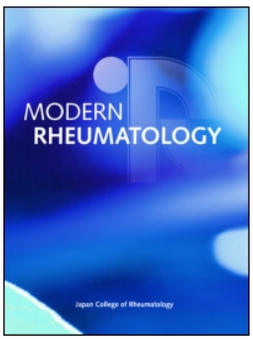

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REVIEW ARTICLE

Biologic therapy in familial Mediterranean fever

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Abstract

Familial Mediterranean fever (FMF) is the most common autoinflammatory hereditary disease characterized by self-limited attacks of fever and serositis. Although colchicine is the gold standard treatment for the attacks ~10% of cases of FMF are resistant or intolerant to effective doses of colchicine. In such cases, however, there are increasing numbers of case reports or clinical trials treated by biologic agents which directly target the proinflammatory cytokines. Anti-interleukin-1 (IL-1) treatment has proven beneficial in improving the inflammation in terms of clinical manifestations and laboratory findings in clinical trials. Furthermore, anti-tumor necrosis factor treatment has also revealed the efficacy and safety in patients with colchicine-resistant FMF. More recently, cases of successful treatment with IL-6 inhibitor, tocilizumab (TCZ), has been reported from Japan and Turkey. Of note, TCZ may be preferable in the treatment as well as the prevention of secondary amyloidosis of FMF patients since it significantly suppresses acute inflammatory response. In the present review, we summarize the literatures regarding the efficacy of biologic therapy in colchicine-resistant or -intolerant patients with FMF.

Keywords

Auto-inflammation, Familial Mediterranean fever, IL-1β inhibitor, IL-6 inhibitor, TNF inhibitor

History

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Introduction

Familial Mediterranean fever (FMF), the most common autoinflammatory hereditary disease, is characterized by recurrent attacks of fever with arthritis and serositis [1–3]. The goals of treatment for patients with FMF are to suppress the inflammation and provide an acceptable quality of life. In our daily practice, we introduce an FMF treatment to prevent attacks and normalize levels of acute-phase reactants such as C-reactive protein (CRP). Uncontrolled studies, including reports from clinical practices, have provided evidence that colchicine is efficient in preventing FMF attacks and the development of secondary amyloidosis [4]. However, 10% of FMF cases are resistant or intolerant to colchicine [5–7].

The mutation of *mediterranean fever* (*MEFV)* gene, which encodes pyrin, is closely associated with the pathogenesis of FMF [8]. Since pyrin is involved in the regulation of Nod-like receptor protein 3 (NLRP3) inflammasome, the dysfunction of pyrin leads to excess inflammation through the increased production of inflammatory cytokines including interleukin (IL)-1β and IL-18 [9]. These cytokines activate nuclear factor κB signaling pathways that lead to increased amounts of tumor necrosis factor-alpha (TNF-α) and IL-6 [10,11]. Thus, the blockage of these cytokines with biologic agents is considered to be a reasonable approach for the management of FMF.

Indeed, anti-IL-1 treatment has proven beneficial in improving the inflammation in terms of clinical manifestation and laboratory findings in FMF patients who are resistant or intolerant to colchicine [12,13]. In addition, anti-TNF treatment has revealed efficacy and safety in patients with colchicine-resistant FMF [12,14]. More recently, cases of successful treatment with an IL-6 inhibitor have been reported [15–18]. Of note, the IL-6 inhibitor has the potential for greater efficacy in the treatment of amyloid A (AA) amyloidosis since it can dramatically inhibit the production of serum amyloid A protein (SAA) [19].

In this review, we summarize the recent discussion about the treatment of FMF patients with biologic agents intended to inhibit the action of IL-1, TNF-α and IL-6.

Biologic therapy in FMF

IL-1 inhibitor

Since IL-1β, produced mainly by activated macrophages, is known as a potent mediator of the inflammatory response, an increased production of IL-1β causes a number of autoinflammatory diseases. Indeed, canakinumab, a human anti-IL-1β monoclonal antibody, was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) caused by mutations in *NLRP3* gene.

FMF-associated mutations of pyrin abnormally activate the NLRP3-ASC (apoptosis associated speck-like protein containing a caspase activation and recruitment domain CARD)-Caspase-1 inflammasome leading to the aberrant production of IL-1β [20]. Functional studies [21–23], a number of case reports, and a literature review [13,24–37] describing the successful treatment of FMF patients with canakinumab or anakinra, a human IL-1 receptor antagonist (IL-1RA), suggest that IL-1 is involved in the pathogenesis of FMF and that the use of anti-IL-1 drugs achieved remission in the majority of FMF patients, including cases with end-stage renal failure caused by secondary AA amyloidosis.

More recently, a small placebo-controlled study from USA confirmed the efficacy of rilonacept, an IL-1 decoy receptor, in

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Table 1. Overview of reported FMF cases treated with TNF inhibitor.

Authors	Year	Age /sex	*MEFV* gene mutation	Disease duration (years)	Previous therapy	Complication	Amyloidosis	TNF inhibitor	Response	Response in FMF attacks	Response in AA amyloidosis	Persistent response (months)	Side effects
Metyas et al. [52]	2004	30/M	N/A	10	MTX	None	+	IFX	Good	Normalized CRP Free of attack	Improvement of the proteinuria	24	None
Daysal et al. [48]	2005	21/F	M694V/M694V	3	Colchicine	None	–	IFX	Good	Normalized CRP Improvement of arthritis	–	2	None
Seyahi et al. [43]	2006	35/F	N/A	30	Colchicine	None	–	ETA	Good	Decreased frequency	–	8	Injection site reaction
		42/M	N/A	40	Thalidomide	None	–	ETA	Good	Decreased frequency	–	10	None
		49/M	N/A	37	Thalidomide	None	–	ETA	Good	Decreased frequency	–	6	None
Sakalliouglu et al. [44]	2006	15/M	E148Q/–	5	Colchicine PSL	None	–	ETA	Good	Normalized CRP Improvement of arthritis	–	4	None
Yuksel et al. [54]	2006	12/F	M694V/M680I	8	Colchicine	None	+	IFX	Good	Free of attack Improvement of arthritis	Improvement of the proteinuria	22	None
Mor et al. [45]	2007	35/M	V726/–	10	Colchicine	None	–	ETA	Good	Decreased frequency	–	36	None
Nakamura et al. [49]	2007	20/F	M694I/E148Q	13	Colchicine	None	–	IFX	Good	Free of attack	–	12	None
Kaya et al. [55]	2010	27/M	M694V/V726A	8	Colchicine PSL	JIA	–	ETA	Good	Free of attack Improvement of arthritis	–	12	None
Bilgen et al. [47]	2011	42/M	M694V/M694V	N/A	Colchicine	None	–	ADA	Good	Free of attack Improvement of arthritis	–	5	None
		29/F	M694V/M680I	N/A	Colchicine	None	+	IFX	Partial	Decreased frequency	Improvement of the proteinuria	N/A	None
		40/F	E148Q/E148Q	N/A	Colchicine	SpA	–	ETA	Partial	Decreased frequency	–	N/A	None
		42/F	M694V/M680I	N/A	MTX	None	–	ETA	Good	Free of attack Improvement of arthritis	–	N/A	None
		31/M	M694V/M694V	N/A	Colchicine	None	+	ETA	Good	Free of attack Improvement of arthritis	Improvement of the proteinuria	N/A	None
		20/F	M694V/V726A	N/A	Colchicine	None	–	IFX	Good	Free of attack Improvement of arthritis	–	N/A	None
		27/F	M694V/–	N/A	Colchicine	None	+	IFX	Good	Free of attack Improvement of arthritis	Improvement of the proteinuria	N/A	None
		20/M	–	N/A	MTX	SpA	–	ETA	Good	Free of attack Improvement of arthritis	–	N/A	None
		25/M	M694V/M680I	N/A	MTX	SpA	–	ETA	Good	Free of attack Improvement of arthritis	–	N/A	None
		25/M	M694V/M694V	N/A	Colchicine	None	–	IFX	Good	Free of attack Improvement of arthritis	–	N/A	None
Ozgocmen et al. [46]	2011	37/M	M694V/M694V	33	Colchicine PSL	None	+	IFX	Good	Free of attack Improvement of arthritis	Improvement of the proteinuria	36	None
		24/F	M694V/M694V	17	Colchicine PSL	SpA	–	ETA	No	No improvement	–	6	None
		31/F	M694V/V726A	13	MTX	SpA	–	ADA	Partial	Decreased frequency	–	4	None
Erten et al. [51]	2012	35/M	M694V/M694V	15	Colchicine	None	–	IFX	Good	Normalized CRP Free of attack	–	48	None
Ozcakar et al. [53]	2012	13/F	N/A	11	Colchicine	None	+	IFX	Partial	Free of attack Improvement of arthritis	No improvement of the proteinuria	12	None
		12/M	N/A	6	Colchicine	None	+	IFX	Good	Free of attack	Improvement of the proteinuria	15	None
		15/F	N/A	7	Colchicine	None	+	IFX	Partial	Free of attack	No improvement of renal function	24	None
		12/F	N/A	7	Colchicine	None	+	IFX	Good	Free of attack	Improvement of the proteinuria and creatinine level	30	Anaphylactic reaction
Kosmidou et al. [50]	2014	33/M	M694V/R761H	15	Colchicine	CD	–	IFX	Good	Free of attack	–	6	None

MTX, methotrexate; PSL, prednisolone; SpA, spondyloarthritis; CD, Crohn's disease; IFX, infliximab; ETA, etanercept; ADA, adalimumab; N/A, not available.

Table 2. Overview of reported FMF cases treated with tocilizumab.

Authors	Year	Age/sex	*MEFV* gene mutation	Disease duration (years)	Previous therapy	Amyloidosis	Response	Response in FMF attacks	Response in AA amyloidosis	Persistent response (months)	Side effects
Fujikawa et al. [15]	2013	19/F	M694I/–	12	PSL	–	Yes	Normalized CRP Free of attack	–	N/A	None
Hamanoue et al. [16]	2015	51/M	E148Q/M694I	41	Colchicine	+	Yes	Normalized CRP Free of attack	Improvement of the proteinuria Reduction of amyloid deposits in gastric biopsy	41	None
Yilmaz et al. [17]	2015	34/F	M694V/M694V	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	16	None
		22/M	M694V/M680I	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	8	None
		76/M	M694V/M680I	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	15	None
		46/M	M694V/M694V	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	6	None
		39/M	M694V/M694V	N/A	Colchicine	+	Partial	Free of attack	No improvement of the proteinuria	12	None
		34/M	–	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	15	None
		43/M	M694V/M694V	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	11	None
		24/M	M694V/M694V	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	3	Mild thrombocytopenia
		23/M	M694V/M694V	N/A	Colchicine	+	No	No improvement	No improvement of the proteinuria	N/A	None
		32/M	E148Q/E148Q	N/A	Colchicine	+	Partial	Free of attack	No improvement of the proteinuria	3	None
		45/M	M694V/M694V	N/A	Colchicine	+	Yes	Free of attack	Improvement of the proteinuria	4	Mild thrombocytopenia
Umeda et al. [18]	2015	64/F	E148Q/–	7	Colchicine	–	Yes	Normalized CRP Free of attack	–	9	None

PSL, prednisolone; N/A, not available.

patients with colchicine-resistant FMF [38,39]. International clinical trials of canakinumab in colchicine-resistant FMF patients are currently ongoing. These prior and early findings indicate that the blockage of IL-1 is a promising therapeutic strategy for the treatment of severe FMF.

TNF inhibitor

Tumor necrosis factor-alpha is also known as a monocyte/macrophage-derived cytokine that accelerates inflammatory responses. It was demonstrated that TNF-α produced by activated macrophages can promote IL-1β secretion through the NLRP3-ASC-Caspase-1 inflammasome in the absence of microbial infection [40]. It was also reported that blocking TNF-α represents the decreased IL-1β production by synovial cells in both human and animal models [41,42].

In line with these functional studies, the efficacy of TNF inhibitors including etanercept, infliximab and adalimumab in colchicine-resistant FMF patients has been reported [43–51]. Anti-TNF-α treatment has been shown to have benefits in patients with AA amyloidosis [52–55]. Of note, FMF patients with gene polymorphisms in the TNF-α promoter region are more susceptible to the development of amyloidosis and arthritis [56].

Table 1 shows the cases of FMF treated with TNF inhibitors. Among 29 patients, 10 patients developed AA amyloidosis in kidneys and/or the gastrointestinal tract at introduction of biologics. About 8 out of 10 patients improved the proteinuria after treatment. However, there was no case performed repeated biopsy to confirm the pathological improvement of amyloidosis. Among patients shown in Table 1, five patients complicated spondyloarthritis (SpA) and 1 patient complicated Crohn's disease. It is suggested that patients with FMF may present manifestations including ankylosing spondylitis [57], and inflammatory bowel disease (IBD) [58] and reported that colchicine treatment is not enough to control the disease activity of these patients [59]. Since TNF inhibitor is effective for theses condition [60], it might be better therapeutic option for FMF patients complicated with SpA or IBD.

TNF inhibitors thus seem to be an alternative treatment for FMF patients who are unresponsive or intolerant toward colchicine. However, there has been no controlled study evaluating the safety and efficacy of TNF inhibitors in patients with FMF.

IL-6 inhibitor

IL-6, secreted by T cells and macrophages upon the immune response, is a pro-inflammatory cytokine. In clinical settings, tocilizumab (TCZ), an IL-6 receptor blocker, has been widely used in the treatment of patients with rheumatoid arthritis (RA). More recently, three cases of successful treatment of FMF patients with an IL-6 inhibitor were reported from Japan [15,16,18].

Intriguingly, functional studies have shown that IL-6 in combination with other pro-inflammatory cytokines plays a critical role in the synergic induction of human SAA genes and that the inhibition of IL-6 is critical to achieve the complete suppression of SAA production [19]. These findings suggest that the blocking of IL-6 has the potential to regulate AA amyloidosis directly compared with the other biologic agents.

There have been some reports showing the efficacy of an IL-6 inhibitor in AA amyloidosis secondary to rheumatic diseases [61–63]. Okuda et al. [64] suggested that TCZ was of greater efficacy than anti-TNF therapy in Japanese patients with AA amyloidosis secondary to rheumatic diseases. Indeed, Yilmaz et al. [17] recently reported 11 cases with AA amyloidosis secondary to FMF successfully treated by TCZ. Among these 11 patients, 10 patients did not experience any attack during the course of TCZ treatment,

and no major adverse events were observed. Even though 8 patients had the decreased level of the proteinuria after treatment, there was no case confirmed the reduction of deposition of amyloid in any organ.

Table 2 summarizes the cases of FMF treated with TCZ. The patient reported by Fujikawa et al. [15] was treated with TCZ because of adult still disease-like manifestation including hyperferritinemia and skin rash. The patient reported by Hamanoue et al. [16] was initially treated with colchicine but the activity of FMF was not controlled and developed AA amyloidosis. In this case, the efficacy of TCZ on amyloid deposits was proven by repeated gastric biopsy. The patient reported by Umeda et al. [18], complicated with fasciitis and myositis, was also initially treated with colchicine but fasciitis and myositis were not improved. Taken together, we propose that TCZ is recommended toward FMF patients complicated with AA amyloidosis at earlier stage and those who are refractory to colchicine to prevent the development of AA amyloidosis. IL-6 inhibitors thus also seem to be an alternative treatment for severe FMF patients. However, the data for the use of IL-6 targeting drugs in FMF patients are currently limited to uncontrolled off-label use. Further studies are thus needed to evaluate the efficacy and safety of anti-IL-6 reagents.

Conclusion

Biologic agents including IL-1 inhibitors, TNF inhibitors and IL-6 inhibitors were effective in colchicine-resistant or -intolerant patients with FMF. Controlled trials are required to better evaluate the long-term efficacy and safety of biologics in the treatment of patients with FMF.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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