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CASE BASED REVIEW

Tofacitinib for the treatment for colchicine-resistant familial Mediterranean fever: case-based review

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Abstract

Familial Mediterranean fever is characterized by self-limited attacks of serositis and arthritis. However, substantial number of patients suffer from chronic complications of this disease, primarily involving musculoskeletal system. Treatment for these complications is challenging due to limited evidence. Interleukin-1 (IL-1) antagonists, tocilizumab and anti-tumor necrosis factor (anti-TNF) agents are off-label treatment options for the management of chronic manifestations of FMF, such as secondary (AA) amyloidosis, chronic arthritis and sacroiliitis. This paper presents a case series of four FMF patients who are refractory to IL-1 antagonists, anti-TNF agents and tocilizumab, who responded well to tofacitinib. The authors also conducted a comprehensive literature search for studies investigating tofacitinib use in FMF patients. Although still limited, current data suggest that tofacitinib could be a useful treatment option for FMF patients with associated inflammatory comorbid conditions and chronic manifestations of disease.

Keywords Familial Mediterranean fever · Auto-inflammatory disease · Spondylarthritis · Tofacitinib · Janus kinase (JAK) inhibitor

Introduction

Familial Mediterranean fever (FMF) is a hereditary, prototypic auto-inflammatory disorder characterized by recurrent, self-limiting episodes of polyserositis, fever, erysipelas-like erythema (ELE) and arthritis. FMF attacks usually resolve spontaneously within days. However, they can significantly impair quality of life, particularly in patients with frequent attacks. Although FMF is recognized as an episodic disease, a substantial number of patients suffer from intractable chronic manifestations, complications or associated comorbid conditions, including chronic arthritis, enthesis, spondylarthritis, psoriasis, vasculitis and inflammatory bowel disease [1]. While further studies are needed to investigate all of these FMF-associated conditions, about 10% FMF patients have spondylarthritis and 5% develop chronic deforming arthritis, unlike typical non-erosive transient lower extremity arthritis [2].

Colchicine is the mainstay of FMF treatment due to its proven efficacy for reducing frequency, duration and severity of attacks and preventing of secondary (AA) amyloidosis. AA amyloidosis is the most devastating complication of FMF; it causes severe morbidity and mortality, usually affecting patients that are treated inadequately. About 5–10% of FMF patients are resistant to colchicine (crFMF), which is defined as having frequent attacks despite the use of maximal tolerated dose of colchicine [3]. Interleukin-1 (IL-1) inhibitors have been shown to be very effective in the prevention of acute FMF attacks; however, their efficacy has not been proven in the treatment for chronic or non-classical manifestations of FMF.

Little is known about the pathogenesis and molecular pathways leading to chronic, non-classical and comorbid conditions associated with FMF, and their treatment. Very few articles have reported on the use of IL-1 inhibitors, anti-tumor necrosis factor (anti-TNF) agents and tocilizumab in chronic arthritis and amyloidosis. Tofacitinib is a Janus kinase (JAK) inhibitor that was initially approved by the United States Food and Drug Administration (FDA) to treat moderate to severe

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rheumatoid arthritis and then for the psoriatic arthritis and ulcerative colitis. This paper presents a series of four crFMF cases in which the patients, who are refractory or intolerant to IL-1 inhibitors, anti-TNF agents and tocilizumab, responded well to tofacitinib.

Case-1

A 18-year-old male patient who had a diagnosis of FMF with attacks of fever, peritonitis, pleuritis and arthritis starting at the age of 3 years, admitted to our clinic at 2009. He had homozygous M694V mutation and family history of FMF. At 2011, at the age of 20, patient started to have frequent serositis and right ankle arthritis attacks despite 2 mg/day of colchicine. A comprehensive workup for possible comorbid inflammatory disease was performed. His rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), anti-nuclear antibodies (ANA) and HLA-B27 were negative. Several synovial fluid analyses revealed neutrophilic joint inflammation. The addition of standard recommended doses of azathioprine and methotrexate (MTX) yield no benefit. In 2013, his colchicine dose was increased to 3 mg/day, and, subsequently, anakinra 100 mg/day was begun. The anakinra dose was increased to 200 mg/day due to the inadequate response. In 2015, he developed proteinuria, and kidney biopsy revealed AA amyloidosis. He was taken off anakinra and switched to canakinumab, 150 mg/month. Canakinumab was up-titrated gradually to 450 mg/month due to persistence of frequent attacks. Since the patient denied non-compliance with his medication, an extensive workup was performed for possible co-morbid diseases; the results did not show the presence of any additional disease. In March 2018, while the patient under treatment with ramipril 10 mg/day, colchicine 3 mg/day and canakinumab 450 mg/month, his urinary protein loss was 4.8 g/day, which increased to 11.2 g/day by July 2018. He was taken off canakinumab and given tocilizumab 12 mg/kg per month. After the fourth infusion, the proteinuria worsened to 23.1 g/day, so tocilizumab was discontinued and he was given infliximab, which caused a severe acute allergic reaction with an extensive skin rash. In January 2019, at the age of 28, when tofacitinib (5 mg bid) was prescribed, 1 month after the last dose of tocilizumab, patient had a proteinuria of 36.6 g/day. In April 2019, after 3 months of tofacitinib use, proteinuria was decreased from 36.6 to 11.2 g/day, and his FMF attacks were controlled without any treatment-related side effects (see Table 1).

Case-2

A 58-year-old woman who had diagnosis of rheumatoid arthritis (RA) since 2000. She had erosive polyarthritis and consistent serological tests (RF: 414 IU/mL, anti-CCP: 1000 U/mL, ANA and HLA-B27: negative). She admitted to our clinic with complaints of painful, and reddish ankle arthritis attacks differ from her usual joint complaints. She was treated with several disease-modifying antirheumatic drugs (DMARDs), including MTX, leflunomide (LEF) and sulfasalazine (SSZ). During follow-up, she described self-limiting recurrent episodes of chest pain, myalgia, stomach pain, vomiting and fever accompanied by markedly elevated C-reactive protein levels (CRP) levels. She was suspected of FMF, based on the presence of typical attacks and a positive family history for the disease. MEFV gene analysis revealed single heterozygous M694V mutation. She was started on colchicine 1.5 mg/day. Her serositis attacks remarkably improved; however, febrile arthritis and myalgia still remained bothersome. Therefore, she was treated with anakinra, which is indicated RA and FMF. After 1 month of taking anakinra, she developed leukopenia; however, that completely resolved with discontinuation of the medication. Because it was not possible to control her FMF attacks with adalimumab and, later, with tocilizumab, we prescribed tofacitinib 5 mg bid 1 month after the last dose

Table 1 Summary of published clinical manifestations of FMF patients and their pre- and post-tofacitinib clinical evaluations

	Case #5 Gök et al. [6]	Case #6 Garcia-Robledo et al. [7]
Age	27	NA
Gender	Female	NA
MEFV mutation	M694/R202Q	E148Q/-
Peritonitis	+	+
Fever	+	+
Pleuritis	-	-
Arthritis	+	-
Pre-tofacitinib CRP (mg/L)	79.9	NA
Post-tofacitinib CRP (mg/L)	3.17	Decrease
Pre-tofacitinib ESR (mm/h)	65	NA
Post-tofacitinib ESR (mm/h)	5	Decrease
PGA pre-tofacitinib (VAS)	9	NA
PGA post-tofacitinib (VAS)	0	NA
Pre-tofacitinib AIDAI	NA	NA
AIDAI at 3 months of tofacitinib	NA	NA
Drugs prior to tofacitinib	SSZ, HQ, MTX	Steroid
Duration of tofacitinib treatment	12 months	NA

ADA adalimumab, *AIDAI* auto-ınflammatory diseases activity ındex, *ANA* anakinra, *CAN* canakinumab, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ETA* etanercept, *HQ* hydroxy chloroquine, *INF* infliximab, *LEF* leflunomide, *MEFV* Mediterranean fever gene, *MTX* methotrexate, *PGA* patient global assessment of disease assessment, *SSZ* sulfasalazine, *TZC* tocilizumab, *VAS* visual analog scale of rated on 0–10 cm line

of tocilizumab. After 3 months of tofacitinib, patient was attack-free. She did not report any kind of FMF-related attacks (see Table 2).

Case-3

A 64-year-old female patient, who had a history of severe and resistant seronegative rheumatoid arthritis, admitted to our clinic in 2016. She also had diabetes mellitus and hypertension. Previous records showed the use of MTX, SSZ, hydroxychloroquine, LEF and cyclosporine. All of these drugs were discontinued due to inefficacy, except LEF, which was discontinued due to skin rash. Between 2010 and 2014, she was treated with adalimumab, which was also discontinued due to gradual loss of its initial efficacy. After adalimumab, she was treated with abatacept for a couple of months, which was then discontinued due to formation of warts on her hands and forearms. Consequently, she declined further biologic drug use and continued taking conventional DMARDs. She was off-therapy on hospital admission after having recently undergone knee replacement surgery for both knees. At that time, she had marked synovitis of both wrists, her left ankle, and right heel and a pelvic appendectomy scar. She had limited movement in both wrists, elbows and in her left ankle. Her pelvic X-ray was consistent with bilateral grade 2 sacroiliitis. Magnetic resonance imaging (MRI) confirmed the diagnosis with bone marrow edema. The RF, anti-CCP, ANA and HLA-B27 tests were negative. Since she had a robust acute phase response and a history of appendectomy, MEFV gene analysis was conducted; M694V/M680I complex heterozygous mutation was found. She was treated with colchicine 1.5 mg/day and nonsteroidal anti-inflammatory drugs (NSAIDs). Due to non-response, anakinra was added, resulting in a partial benefit with a reduction in CRP; however, treatment did not improve her arthritic symptoms. Tofacitinib 5 mg bid was initiated 1 day after of termination of anakinra; it improved her arthritis symptoms and acute phase responses. Her wrist and ankle swelling and tenderness completely resolved, but joint restriction in her ankle and elbows did not resolve completely, possibly due to joint damage. No side effects were observed during follow- up period.

Case-4

A 43-year-old female patient was diagnosed with FMF with a family history of FMF, past medical history of appendectomy, single heterozygous V726A MEFV mutation and typical febrile serositis attacks. She was also diagnosed with spondyloarthropathy with inflammatory back pain, knee and

Table 2 Clinical manifestations of FMF patients and their pre- and post-tofacitinib clinical evaluations in our patients

	Case #1	Case #2	Case #3	Case #4
Age	28 years	58 years	64 years	43 years
Gender	Male	Female	Female	Female
MEFV mutation	M694v/M94v	M694v/-	M694V/M680I	V726a/-
Peritonitis	+	+	−	+
Fever	+	+	+	+
Pleuritis	−	+	−	−
Arthritis	+	+	+	+
Pre-tofacitinib CRP (mg/L)	12.4	14	98	23
Post-tofacitinib CRP (mg/L)	6	4	11	11.6
Pre-tofacitinib ESR (mm/h)	57	37	76	54
Post-tofacitinib ESR (mm/h)	35	13	34	32
PGA pre-tofacitinib (VAS)	9	9	7	8
PGA post-tofacitinib (VAS)	4	3	3	3
Pre-tofacitinib AIDAI	52	60	22	19
AIDAI at 3 months of tofacitinib	6	5	3	3
Drugs prior to tofacitinib	AZA, MTX, ANA, CAN, INF, TCZ	SSZ, MTX, LEF, ANA, ADA, TCZ	SSZ, MTX, LEF, HQ, CsA, ADA, ABA, ANA	SSZ, ADA, ETA, ANA
Duration of tofacitinib treatment	3 months	3 months	4 months	3 months

ADA adalimumab, *AIDAI* auto-ınflammatory diseases activity ındex, *ANA* anakinra, *CAN* canakinumab, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ETA* etanercept, *HQ* hydroxy chloroquine, *INF* infliximab, *LEF* leflunomide, *MEFV* Mediterranean fever gene, *MTX* methotrexate, *PGA* patient global assessment of disease assessment, *SSZ* sulfasalazine, *TZC* tocilizumab, *VAS* visual analog scale of rated on 0–10-cm line

hip arthritis and bilateral grade 2 sacroiliitis on plain pelvis X-ray. HLA-B27 was negative. A comprehensive workup for possible comorbid inflammatory disease was done. RF, anti-CCP and ANA were negative. There were no signs of inflammatory bowel disease. She was started on colchicine 2.5 mg/day, SSZ, NSAIDs and low-dose corticosteroids. She did not gain a clear benefit from this treatment; she still has persistent acute phase elevation. She was also unresponsive to adalimumab and etanercept after using each for a minimum of 3 months. Therefore, anakinra 100 mg/day was added to the dose of colchicine. Her clinical symptoms, including back pain and peripheral arthritis, were remarkably improved after 3 months. However, leukopenia (3100/mm^3) developed. Increasing the dose intervals to one injection in every other day did not resolve leukopenia; thus, anakinra was discontinuation. Her leukocyte counts normalized one week after discontinuation of anakinra then tofacitinib 5 mg bid was begun. After 3 months of use, patient was attack-free. She did not report any kind of FMF-related attacks.

Literature search

We performed literature search of studies investigating the use of tofacitinib in FMF patients. MEDLINE, EMBASE, Scopus, Web of Science and Google scholar were searched. We included all papers (case reports, controlled trials, case control, cross-sectional or cohort studies) related to FMF and tofacitinib. Exclusion criteria were: manuscripts that are not accessible in full-text, publication in non-English languages. After analysis, we identified 2 papers about tofacitinib treatment in FMF. Both of them were case reports. In addition to our study, we included these two case reports in the final analysis.

Discussion

The main goals of FM F treatment are improving quality of life by reducing frequency of attacks and the prevention of complications of disease, particularly the formation of amyloidosis. Colchicine is very effective for achieving these goals in most patients, at a lower cost than other drugs. However, it is more difficult to manage the chronic manifestations and complications of FMF due to the lack of evidence. Management of these manifestations is largely based on clinical experience with other rheumatic diseases. Moreover, there are a limited number of on-label drugs for treating FMF due to the limited number of reports. Case studies in the present paper are on the successful use of tofacitinib in four cases of crFMF, who were resistant or intolerant to anti-TNF, IL-1 antagonists and tocilizumab. Tofacitinib was found to be effective for both serosal inflammation and musculoskeletal manifestations of the disease. Although the follow-up duration of these case studies is short, tofacitinib was found to significantly lower proteinuria in an amyloidotic patient.

FMF is a genetic disease caused by mutations of the MEFV gene, which encodes for pyrin, a critical protein involved in NLRP3 and other inflammasome complexes that regulate inflammatory and apoptotic pathways. The inflammasome-dependent aberrant production of IL-1β triggers short-lived attacks of FMF [4]. However, pathogenetic mechanisms leading to chronic manifestations and co-morbid conditions in FMF, which are largely IL-1 independent, need to be identified. A recent study showed significant alterations in serum cytokine profiles of FMF patients' comparison to healthy subjects, including IL-4, IL-6, IL-8, IL-10, IL-12p40, IL-17, IL-18 and IFN—however, no clear explanation was reported [5]. Moreover, it was shown that the activation of the nuclear factor-kB signaling pathway in FMF results in increased production of TNF-alpha (TNF-α) and IL-6.

A significant number of FMF patients suffer from FMF-associated chronic manifestations or comorbid inflammatory conditions, including deforming arthritis, spondylarthritis, vasculitis, inflammatory bowel disease and psoriasis. It is currently unknown whether these conditions are directly linked to the canonical pathway of FMF or whether they are due to the aberrant activation of auxiliary molecular pathways [5]. Therefore, these pathways constitute potential targets in the treatment for chronic manifestations or comorbid conditions observed in FMF. Several studies have reported on the uses of tocilizumab and anti-TNF agents (ADA, ETA, IFX) as add-on treatment options with colchicine, showing variable success for chronic manifestations of FMF, such as AA amyloidosis, chronic arthritis and sacroiliitis. There are two reported uses of tofacitinib in patients with FMF in the literature. In a recent paper, tofacitinib was found to effectively suppress attacks in a patient with FMF. However, to some extent, the clinical presentation of this case conflicted with the well-known clinical pattern of FMF. Another study reported on a case in which the patient had RA and crFMF that patient's FMF attacks and disease activity were controlled after treatment with tofacitinib [6, 7].

Tofacitinib is a pan-JAK inhibitor with the greatest potency of inhibition on Jak3, followed by Jak1, Jak2 and Tyk2 [8]. The JAK family of tyrosine kinases is located on downstream pathways of important inflammatory mediators, such as IL-2, IL-6, IL-7 and IL-21 [9, 10]. Tofacitinib also inhibits granulocyte macrophage colony-stimulating factor (GM-CSF)–stimulated IL-1β secretion by blocking NLRP3 inflammasome, which plays a pivotal role in auto-inflammatory diseases. Although JAKs does not involve in the downstream pathway of IL-17, tofacitinib was found to suppress

the increased IL-17 levels upon the injection of CD4 in animal models. Supporting the findings reported in these studies, it has been demonstrated that tofacitinib is effective in treating spondyloarthropathy spectrum diseases, psoriatic arthritis and inflammatory bowel disease [11] which are also FMF- associated inflammatory comorbid diseases. In the four cases presented in this paper, the observed benefits of tofacitinib might be explained by the above-mentioned multifaceted effects of the drug. Although we suggest the beneficial use of tofacitinib in crFMF patients, we cannot rule out publication bias. Thus, systematic studies are needed to recommend tofacitinib use in crFMF patients.

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Compliance with ethical standards

Conflict of ınterest AT is Consultant for: Novartis and Abdi Ibrahim, Speaker Bureau of: Novartis, Pfizer and UCB with no conflict related to this study. AT is editorial board member of two international journals and reviewer for 3 international journals and research funding bodies. None of the authors have conflict of interest and non-financial relationships with agencies promoting tofacitinib.

Informed consent Written informed consent was obtained from all subjects. Permissions was taken from regulatory agencies for off-label uses of drugs. For each patient, we applied for permission of use and shared our Patient files with Medical Devices Agency of the Turkish Ministry of Health. The Turkish Ministry of Health granted the compassionate use of tofacitinib for FMF patients with special permission.

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