

The role of Adalimumab in the Treatment of Colchicine-Resistant Familial Mediterranean Fever

CASE REPORT

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Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disorder. Articular manifestations are the second most common presentation in FMF patients after abdominal pain. Colchicine remains the gold standard of therapy for the different aspects of the disease. However, about 5-15% of patients experience resistance to colchicine. Therefore, physicians were encouraged to try different medications and treatment modalities. Biologic agents were used in several FMF patients with various clinical presentations including articular involvement. In the majority of those, there was a good clinical response with improvement in the quality of life. Adalimumab is an anti-TNF alpha agent used conventionally in inflammatory bowel disease and rheumatologic disorders. To date only five cases were reported in the literature using adalimumab for severe refractory FMF.

Our case report details a young female with severe disabling colchicine-resistant FMF associated with significant articular inflammation. She was treated with adalimumab with remarkable clinical improvement and complete response.

Introduction

Familial Mediterranean fever (FMF) is one of the hereditary auto-inflammatory recurrent fever syndromes [1]. Typical FMF attacks manifest as recurrent self-limiting episodes of fever, pleuritis, peritonitis, and arthritis [1, 2]. Secondary amyloidosis is the most serious complication in FMF and usually leads to proteinuria and possibly chronic renal failure [3].

FMF-associated arthritis is a symmetric mono-oligoarthritis that shows a self-limiting course and resolves without sequelae [4]. However, in less than 10% of patients arthritis runs a more complicated pro-

Keywords

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tracted course leading to functional disability and potentially prosthetic joint replacement [5-7]. There is a well-established link between FMF and ankylosing spondylitis (AS) where sacro-iliitis prevalence is estimated to be 7% in those with musculoskeletal manifestations [8]. The exact role of HLA-B27 in the development of sacro-iliitis is still controversial [8, 9]. On the other hand, it has been established that M694V mutation is associated with the most severe clinical form of FMF. Additionally, it has also been linked to the occurrence of arthritis [8, 10, 11].

Colchicine remains the mainstay of therapy in FMF patients, except for the 5-15% of patients who appear to be resistant to this therapy [12, 13]. Biologic agents have shown significant impact on symptoms improvement as well as a positive effect on the quality of life. In addition, they appear to play a role in amyloidosis prevention [14-20]. We hereby present a patient who had severe manifestations of FMF and arthritis despite treatment with anti-inflammatory agents and colchicine, but showed a dramatically positive response upon administration of adalimumab.

Case report

A 34-year-old Palestinian female patient homozygous for M694V mutation in the MEFV gene, diagnosed with FMF at the age of 24 presented to our care. She reported severe myalgias and arthralgias with large joint arthritis involving mainly the back and the knees. She was maintained on colchicine 1mg three times daily and naproxen 500mg three times daily, plus paracetamol 1gm three times daily and as needed. The patient had tried multiple short courses of steroids which provided her with only minimal transient relief.

Despite all those medications, she continued to experience recurrent attacks of severe abdominal pain, chest pain, and high grade fever each lasting 2-3 days, with a frequency of up to 6 times per month. In addition, she reported daily arthralgia

and joint stiffness mainly around the large joints. Her biochemical inflammatory profile showed significant elevations in ESR and CRP and mild anemia (**table 1**). She was noted to be depressed, in constant low mood due to a severe uncontrollable disease which significantly affected her social life and daily tasks. After consulting with her rheumatologist we decided to attempt treatment with adalimumab. She was started on 40mg subcutaneous injections every 2 weeks and both colchicine and naproxen doses were reduced. At week 8 she reported a significant decrease in the number of FMF episodes, joint stiffness and arthralgia. So, the treatment was maintained and both colchicine and naproxen were further decreased to once daily. 6 months later general improvement was subjectively reported to be 85% and she was able to move freely with minimal joint stiffness and she mentioned a total of 4 mild episodes of pain and fever. During all that period she was also off naproxen and her biochemical profile revealed a substantial decrease in acute phase reactants. At 1 year of treatment her medical insurance ceased financial coverage of her medication and the patient was forced to stop her regimen and go back to the previous drugs. Her medical status deteriorated fast and within 2 months she was back to her pre-treatment condition. The laboratory findings of the patient at different stages of follow-up are shown in **Table 1**.

Table 1. The laboratory results of the patient during different stages of follow-up..

	Before treatment	6 months Follow up	After stopping treatment
ESR	83	32	54
C-reactive protein (mg/l)	39	8	28
Hemoglobin (g/dl)	11.1	12.9	11.8
Platelets	332000	308000	392000
Creatinine (mg/dl)	1.1	1.0	1.0

Discussion

We reported a case of FMF with coexisting spondyloarthritis and large joint arthritis in a patient who suffered from severe abdominal pain attacks despite maximal use of colchicine and anti-inflammatory agents. Once adalimumab was started, marked improvement in her symptoms occurred. Her quality of life changed substantially with almost complete resolution of her articular pain and abdominal attacks. The therapy was considered to be efficacious, well tolerated, with no reported side effects.

It is estimated that 70-75% of FMF patients have articular involvement, with serositis as the most common manifestation [21]. The joint involvement subsides within days, however in about 5% of patients destructive arthritis involving mainly the large joints many ensue [22]. The mainstay medication for treatment of FMF and amyloidosis prophylaxis is colchicine at a dose of 1.5-2mg daily [23, 24]. However, in 5 to 15% of patients treatment fails and they get labeled as non-responders. In these patients compliance should be checked and reinforced as it may be the causative agent [12, 13, 23, 25]. Multiple genetic and pharmacological factors play a role in true non-responders and they are not well clarified yet [23, 26].

The pathogenesis of FMF starts from the MEFV gene mutation that leads to increased synthesis of mutated pyrin. As a consequence, an inappropriate full-blown inflammation occurs. The activation of IL-1 β is mediated by an inflammatory trigger leading to the induction of an inflammasome [27]. TNF-

alpha plays a role in the mediation of the inflammatory cascade. Consequently, blocking this factor might lead to the reversal of the inflammation [28]. Nonetheless, previous studies have shown variable levels of TNF-alpha in FMF patients confusing the picture. Thus, their exact role has not yet been well clarified [29, 30]. Despite these controversies, the efficacy and safety of anti-TNF alpha agents in the treatment of resistant FMF patients in different case reports and case series is an evidence of a potential major role of TNF-alpha in FMF pathogenesis [14-20].

Data derived from the efficacy of biologics in treatment of various rheumatological diseases had encouraged clinicians to use them in resistant FMF cases [14-20, 31]. There are several case reports to date that use anti-TNF agents in the treatment of FMF. The most commonly used agent is etanercept followed by infliximab. In all these cases, a favorable response with complete resolution of the clinical manifestations as well as normalization of the acute phase reactants was recorded [14-20].

Literature review yielded only five reported cases for the use of adalimumab in FMF patients [16, 17, 19]. Our case shares many of the characteristics with those cases including the age, the presence of peripheral arthropathy, the genetic mutation, the colchicine resistance, and the marked improvement upon the initiation of adalimumab. The personal characteristics of the published cases, clinical presentation, genetic backgrounds, as well as their disease course after starting adalimumab are listed in **Table 2**. It seems even patients with

Table 2. Characteristics of the reported cases in the literature.

Age	G	C R	S G	P A	MEFV	HLA B27	BASDAI*	BASDAI**	Disease course
42	M	+	3-4	-	M694V	-	5.9	1.3	Attacks duration & frequency decreased
31	F	+	2	+	M694V/V726A	+	7.1	2.0	Attacks disappeared
24	F	+	3	-	M694V	+	7.4	3.2	Attacks disappeared & arthritis improved
37	M	+	4	+	M694V	+	5.0	1.7	Attacks disappeared & arthritis improved
48	F	+	4	-	M694V/M680I	-	5.2	1.2	Attacks decreased & arthritis improved

G = gender, C R = colchicine resistance, S G = Sacro-iliitis grade, P A = peripheral arthritis, BASDAI* = before Rx, BASDAI** = 2 months on Rx.

bad prognostic phenotypes had a good chance of response to adalimumab.

Conclusion

Colchicine remains the only Food and Drug Administration approved medication for the treatment of different FMF patients. It is also the only approved medication against FMF complications and namely amyloidosis. Biologic agents appear to have a valid future role in the management of colchicine-resistant FMF cases. Several case reports and series had demonstrated the use of anti-TNF agents and alpha integrin blockers. Nonetheless, to be considered valid treatment options well designed randomized controlled trials are needed. Therefore until then and because of the serious side effects of these agents caution and selectivity must dictate their use.

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