Anti-Interleukin 1 Treatment for Patients with Familial Mediterranean Fever Resistant to Colchicine

SEZA ÖZEN, YELDA BILGINER, NURAY AKTAY AYAZ, and MERAL CALGUNERI

ABSTRACT. ***Objective.*** Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disorder characterized by recurrent attacks of fever and serositis. Although colchicine is the standard therapy for preventing attacks and suppressing inflammation, 5%–10% of compliant patients are colchicine-resistant. We report the effect of anti-tumor necrosis factor therapy (etanercept) and anti-interleukin 1 (IL-1) treatment (anakinra) in 6 cases resistant to colchicine therapy.

Methods. Five children and an adult patient (3 female, 3 male) who were experiencing at least 2 attacks per month and had consistently elevated C-reactive protein levels despite regular colchicine therapy were given either etanercept or anakinra.

Results. Although etanercept lowered the number of attacks (from 3–4 attacks per month to 2 attacks per month), attacks still recurred and acute-phase reactants remained high in 2 patients; thus etanercept was considered ineffective. All 4 patients were switched to anakinra. In 2 patients anakinra completely resolved clinical and laboratory findings. The other 4 patients have been switched to anakinra recently; to date anakinra has reduced the number of attacks (to < 1 per month) and lowered the levels of acute-phase reactants.

Conclusion. In this small series, anakinra was succesful in suppressing inflammation and decreasing the number of attacks in FMF. This may be explained by the role of pyrin in the regulation of IL-1ß activation. (First Release Dec 15 2010; J Rheumatol 2011;38:516–18; doi:10.3899/jrheum.100718)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEV ANAKINRA RESISTANT ETANERCEPT

Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disease characterized by recurrent episodes of serositis and fever[1]. In this disease the Mediterranean fever gene (MEFV) encodes the protein pyrin (from the Latin word for "fever"). Elegant studies in recent years have suggested that mutations in the MEFV gene lead to uncontrolled production of interleukin 1 (IL-1) and exaggerated inflammatory response[2].

Acute-phase reactants are increased during attacks of FMF and they may remain so in untreated patients or in those with inadequate disease control. The main complication of uncontrolled inflammation in FMF is amyloidosis. Colchicine is the most effective treatment for preventing attacks and amyloidosis, but 5%–10% of cases are refractory[3]. Alternative treatment options (thalidomide, etanercept, infliximab, interferon, and anakinra) have been used as second-line agents for resistant cases, with varying success[4,5,6,7].

We describe the use of etanercept and anakinra in 5 children and one adult with the diagnosis of FMF who were nonresponders to colchicine therapy.

MATERIALS AND METHODS

We describe children (3 female and 2 male) and one adult diagnosed as colchicine-refractory and one adult male patient followed up in our center. Clinical response was monitored through the number of attacks and days of school loss, whereas laboratory inflammation was monitored through erythrocyte sedimentation rate, C-reactive protein (CRP), and serum amyloid A (SAA) concentrations. Colchicine resistance was defined as at least 2 attacks/month along with CRP and SAA levels above normal range between attacks. Patients' colchicine intake was monitored through the pill count and by their mothers. The colchicine dose was increased to 2 mg/day before they were considered colchicine-resistant.

Etanercept was given at a dose of 0.8 mg/kg/week. Anakinra was given at a dose of 1–2 mg/kg/day.

RESULTS

The median age of the patients was 16 years (range 11–25) and the median followup time from the onset of disease was 84 months (range 72–120). Three children had been initially responsive to colchicine. Five patients had 3–4 attacks and one had at least 2 attacks per month. Four were homozygous for the M694V mutation, one was homozygous for the M680I mutation, and one was a compound heterozygote for M694V/M680I mutations. Four children had complained of

From the Pediatric Nephrology and Rheumatology Unit, Faculty of Medicine, Hacettepe University, Ankara; Bakirkoy Maternity and Children Education Hospital, Istanbul; and Department of Rheumatology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

S. Özen, MD; Y. Bilginer, MD, Pediatric Nephrology and Rheumatology Unit, Faculty of Medicine, Hacettepe University; Nuray Aktay Ayaz, MD, Bakirkoy Maternity and Children Education Hospital; M. Calguneri, MD, Department of Rheumatology, Faculty of Medicine, Hacettepe University.

Address correspondence to Prof. S. Özen, Pediatric Nephrology and Rheumatology Unit, Hacettepe University Faculty of Medicine, Ankara, Turkey. E-mail: sezaozen@hacettepe.edu.tr

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severe abdominal pain and joint pain, while 2 also had chest pain during attacks. One adult patient also had arthritis in his attacks. The attacks were lasting usually for 4 days (minimum 2 to maximum 4 days).

The colchicine doses were adjusted according to the dose suggested for children and adolescents, and all received 2 mg/day before they were considered to be resistant[8]. Etanercept was started at a dose of 0.8 mg/kg/week in 3 children and one adult patient. Median duration of treatment was 3 months; however, they were all switched to anakinra due to insufficient clinical response and failure to achieve normal SAA levels. The other 2 patients were started initially on anakinra.

Three patients taking etanercept as initial therapy had decreased numbers of attacks, from 3–4 per month to 2 attacks per month; however, the clinical and laboratory response was not considered to be satisfactory. Acute-phase reactants and SAA remained high in 2 patients despite etanercept therapy. All 3 patients were then switched to anakinra; 2 of them had complete resolution of both clinical features and laboratory values at the end of the sixth month. Subsequently, anakinra was also given to the 25-year-old FMF patient, who had 2–4 attacks/month and very high acute-phase reactants despite receiving colchicine 2 mg/day. He continues his colchicine as well.

The 2 patients have only been switched recently (2 months), and already have experienced a good clinical response. The patients who received anakinra from the beginning also had a dramatic decrease in their attacks and the acute-phase reactants returned to normal ranges. Median duration of treatment with anakinra was 9 months (range 2–30; Table 1).

All patients continued taking colchicine 1.5 mg/day throughout the treatment period.

DISCUSSION

Our report confirms the efficiacy of anti-IL-1 treatment in a small series of patients with FMF who were resistant to colchicine. The effectiveness of this treatment in FMF represents the application of and may be regarded as the confirmation of the bench results. Although there are case reports on the use of anti-IL-1 therapy in such patients, our report represents the first case series[9,10,11].

FMF is a prototype of autoinflammatory diseases with monogenic inheritance. In this disease, mutations in the pyrin protein are associated with uncontrolled production of IL-1[12]. Another group of the monogenic autoinflammatory diseases are cryopyrin-associated autoinflammatory syndromes where the mutations in cryopyrin lead to an activation of caspase. Anti-IL-1 treatment has been shown to be effective and even curative in the treatment of the cryopyrinopathies[13].

Colchicine is the established treatment of FMF. We previously suggested doses of colchicine for FMF according to the body weight of the child[8]. Colchicine resistance is defined as the lack of clinical and laboratory response to colchicine. True colchicine resistance is not common. The physician must be sure of compliance before a patient is classified as having colchicine-resistant FMF. Indeed, in a recent review, Ben-Chetrit and Aamar[14] show that a significant portion of adult patients were not taking their colchicine regularly. In the cohort of FMF patients we describe, compliance was assessed strictly and we offer the definition of resistance accordingly.

The children described here were having attacks and persistent high levels of acute-phase inflammation in spite of adequate colchicine doses. The persistence of inflammation is accepted as predisposing to secondary amyloidosis, which is the most important complication of this disease. Therefore we decided to use anti-tumor necrosis factor (anti-TNF) and anti-IL-1 treatment to control inflammation in these children. Etanercept (anti-TNF) was our initial choice in children because of the favorable responses we have had in our limited number of patients classified as hyper-immunoglobulin D[15]. However, the response to anti-TNF therapy was inadequate. Thus we applied to the local health authorities for the use of anakinra. We observed a satisfactory response to anti-IL-1 treatment and achieved control of inflammation in our patients. We thus suggest that anti-IL-1 treatment should be an alternative in patients with FMF who are definitely resistant to colchicine therapy, and that anti-TNF treatment has not, in our limited experience, been effective.

Table 1. Characteristics of the 5 children with FMF.

Patient	Sex	MEFV	Disease Duration, mo	Attacks/mo	Anti-TNF Duration, mo	Anti-IL-1 Duration, mo	Attacks/mo After Anti-IL-1 Therapy
1	F	M694V/M694V	120	4	0	30	1*
2	M	M694V/M694V	108	4	0	9	0
3	F	M680I/M680I	84	2	3	2	0
4	M	M680I/M694V	72	4	6	7	1*
5	F	M694V/M694V	72	5	6	9	0

* In those who continued to have one attack/mo (decreased from 4/mo) the duration and severity of fever and pain decreased significantly.

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The duration of biologic therapy that is needed in these patients and whether therapy can be stopped after a certain suppression of inflammation remains to be clarified with longterm studies.

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