EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.18190

Original Article

Treatment of familial mediterranean fever with canakinumab in patients who are unresponsive to colchicine

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common inherited monogenic autoinflammatory disease worldwide. It is caused by loss-of-function mutations in the MEFV gene, mostly affecting Eastern Mediterranean population. It is discussed if it should be considered an autosomal-dominant disease with variable penetrance, because heterozygosis mutations are associated with clinical autoinflammatory manifestations. Colchicine constitutes that the mainstay of FMF treatment should be preventing acute attacks and amyloidosis, and decreasing the chronic inflammation. In colchicine-resistant or intolerant patients, recent insights into the pathogenesis of FMF have made the anti-IL1 treatments important. We aimed to search for the retrospective results of canakinumab treatment in patients with FMF who are unresponsive to colchicine.

Methods: In this study, 22 (13 males and nine females) patients with FMF with colchicine resistance/intolerance, age ranging from 6 to 18 years, were included in Ege University Department of Pediatric Rheumatology. After clinical and genetic diagnosis, colchicine treatment with standard doses was started. After treatment with canakinumab, complete response to treatment was determined as no acute episodes and normal level of acute phase reactants.

Results: After canakinumab treatment, 22 patients with FMF who were colchicine-resistant were evaluated. After the treatment, no attack was observed in 19 patients, and the values of acute phase reactants were normal in 22 patients. In three patients, disease attack was observed 16 months after the first dose treatment. In all patients, the values of acute phase reactants were found at normal level during treatment. No drug-related side effects were observed in any patient.

Conclusion: Canakinumab is an effective and safe anti-IL1 agent to reduce attacks in patients with FMF with no response to colchicine and to reduce the level of high-level laboratory findings associated with FMF.

Keywords: Autoinflammation, familial Mediterranean fever, amyloidosis, colchicine-resistant disease, canakinumab

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Cite this article as: Berdeli A, Şenol Ö, Talay G. Treatment of familial mediterranean fever with canakinumab in patients who are unresponsive to colchicine. Eur J Rheumatol 2019; 6(2): 85-8.

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Submitted: 3 November 2018
Accepted: 18 January 2019

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease (AID), and it is characterized by spontaneous attack with fever, abdominal pain, and polyserositis. It is the most common monogenic periodic fever syndrome that affects the Mediterranean people (1). It is the most prevalent disease among the Armenians, Turks, Arabs, and Sephardic Jews. It has frequency between 1: 400 and 1: 1000, and has carrier rate between 1:3 and 1:5 (2). Two groups simultaneously and independently carried out the two most important steps in the study of FMF disease. The first one was use of colchicine for the FMF treatment in 1972, and the second was identification of the MEFV gene that was responsible for the disease in 1997. After identification of the gene that was responsible for the disease (MEFV gene), the recognition in other populations at different regions of the world has significantly increased (3, 4). The MEFV gene encodes a pyrin protein. This protein is a part of inflammasome that has an important role in the innate immune system and that causes an inflammatory response due to uncontrolled production of interleukin-1 when it is mutated (5). Pyrin is mainly expressed in neutrophils, dendritic cells, monocytes, and fibroblasts, but it is not expressed on lymphocytes. This explains the role of the natural immune system in FMF (6). Recently, it has been reported that pyrin acts as an inflammation sensor against bacterial toxins that modify GTPase RhoA. Studies show that the binding of mutant pyrine to regulatory proteins (14-3-3, PCN), which normally block the pyrin inflammasome by RhoA, is reduced and results in IL-1β activation. Most of the pyrin mutations

occur in the C-terminal B20.2-(SPRY) region of the protein where wild-type pyrin binds via this region to pro-caspase-1 directly and inhibits IL-1β activation. Therefore, patients with FMF who have mutant pyrin have a reduced inhibitory effect on caspase-1 (7-8).

Colchicine is still the main treatment for patients with FMF (9). It has a wide variety of mechanisms of action, and one of its important roles is to disrupt the cytoskeleton. Colchicine has anti-inflammatory effects by reorganizing the actin cell skeleton, and it leads to downstream Mediterranean fever (MEFV) gene expression in FMF (10-11). It reduces attacks, improves quality of life, and prevents amyloidosis. Colchicine is activator for RhoA, and therefore it reduces the activation of pyrin inflammasome that inhibits induction of caspase-1 and IL-1β (12). Colchicine administration (1–2 mg/day) is very effective in controlling the inflammatory attacks of FMF. It significantly reduces acute attacks in more than 90% of patients. Full drug response in 5%–10% of patients has still not been achieved. This is one of the limitations of colchicine on patients. Because of its toxic side effects, it should be lower than 7 ng/L in blood; dose above 10 ng/L limits the use of colchicine (13, 14). This negative feature is also associated with digestive intolerance that limits to increase the daily dose to achieve full therapeutic effect in patients with the most severe (inflammatory) phenotypes (15). Side effects such as increased liver or muscle enzymes, cytopenia, and neuromyopathy may, in rare cases, require a reduction or even cessation of colchicine in patients with amyloidosis (10). For these reasons, it leads to the use of new IL-1 agents especially in patients with FMF who are colchicine-resistant. Canakinumab is a fully human monoclonal anti-IL-1β antibody developed to treat various inflammatory disorders. It binds to IL-1β in circulation and blocks its interaction with the IL-1 receptor by neutralizing its activity, but does not interfere with the IL-1 signal (16, 17).

Table 1. Demographic and clinical features of the patients included in the study

Age (year)	13.8±4.0
Sex	
Male	59% (n=11)
Female	41% (n=9)
Mutation statue	
Homozygous	59% (n=13)
Compound heterozygous	27% (n=6)
Other	14% (n=3)
Years of disease (avg.)	5.1±2.6
Colchicine dose (mg/day) (avg.)	1.2±0.3
Total canakinumab number (avg.)	7.2±2.8
CRP (mg/dL) (avg.)	
Before canakinumab	6.8±4.1
After canakinumab	0.4±0.6
SAA (mg/L) (avg.)	
Before canakinumab	465.2±58
After canakinumab	5.1±2.6
Observation (month) (avg.)	15.9±8.8
Complete remission	100% (n=22)
Partial remission	0% (n=0)

Avg: average

The objective of this study was to evaluate the efficacy and safety of canakinumab, a fully human anti-IL-1β monoclonal antibody, that binds to human IL-1β and neutralizes its proinflammatory effects, in patients with FMF who are resistant or intolerant to higher doses of colchicine.

Method

In this study, 22 (13 males and nine females) patients with FMF with colchicine resistance or intolerance, age ranging from 6 to 18 years, were included in Ege University Department of Pediatric Rheumatology. FMF was diagnosed according to the diagnostic criteria of Tel Hashomer, Livneh, and Yalçınkaya (18-20). In addition to these criteria, the DNA sequence of the whole MEFV gene in each patient was performed by Sanger DNA sequencing method to support the clinical diagnosis. After clinical and genetic diagnosis, colchicine treatment with standard doses was started. The criteria of resistant and intolerance to colchicine treatment in a patient was defined by more than six typical episodes (fever, abdominal pain, arthralgia, joint swelling etc.) per year. In the case of incomplete episodes, if at least two of the three acute phase reactants (CRP,SAA) were high value in the inter-episode period, the criteria of resistant and intolerance to colchicine treatment were confirmed in patients who have typical attack in 4–6 months. The inclusion criterion of this study was that the patients should have clinical and genetic diagnosis of colchicine-resistant FMF according to above criteria. The exclusion criteria was that the patients had no history of hypersensitivity or malignancy of in any organ system and active or persistent/recurrent infections including positive tests for tuberculosis, hepatitis B, or hepatitis C infections, and significant medical diseases. Patients with digenic inheritance with gene mutations (NLRP3, TNFRSF1A, MVK, etc.) leading to other autoinflammatory diseases were excluded from the study. Canakinumab was subcutaneously administered to colchicine-resistant/intolerant patients for the first three doses of 4 mg/ kg/month and other doses were administered every 2 months. During the course of treatment with canakinumab, a constant dose (1.5–2 mg/day) of colchicine was administered to patients without any dose change.

After treatment with canakinumab, complete response over treatment was determined as no acute episodes and normal level of acute phase reactants. The partial response was defined as the decrease in the severity and the number of attacks and/or the decrease of the values of the acute phase reactants. All statistical analyses were performed with the Statistical Package for Social Sciences version 17.0 (SPSS Inc.; Chicago, IL, USA) program for Windows.

Results

The mean age of 22 patients in our study was 13.8±4.0 years, and there were nine females (41%) and 13 males (59%). The mean duration of onset of the disease was 5.1±2.6 years. In genetic findings, 13 patients (59%) had homozygous mutation (M694V/M694V) in 10 exons of the MEVF gene; six patients (27%) had compound heterozygote mutation; and three patients (14%) had other mutations. Patients were administered colchicine with average of 1.2±0.3 mg/day. The total dose of canakinumab was n=7.2±2.8. The mean observation of the patients was 15.9±8.8 months. After treatment with canakinumab, no attack was observed in any patient. The values of acute phase reactants were normal in 22 patients. The mean CRP value before canakinumab treatment was 6.8±4.1 mg/dL, and this value was 0.4±0.3 one month after the treatment. The mean SAA value was 465.2±58 mg/L before treatment and 5.1±2.6 mg/L one month after the treatment. Baseline demographic and clinical characteristics were summarized in Table 1.

Drug Safety

There were no adverse effects of drug as well as non-infectious adverse events such as abdominal pain, headache, diarrhea, and arthralgia in patients. There were no opportunistic infections, cases of tuberculosis, or deaths observed in our patients.

Discussion

Familial Mediterranean fever is the result of mutations in the MEFV gene encoding pyrin that is a regulatory component of the intracellular in-

flammasome complex required for the conversion of pro-interleukin (IL)-1β into active IL-1β. Non-mutated wild-type pyrin inhibits the degradation of pro-IL-1β by active caspase-1 (21). In FMF, inflammatory attacks typically lasting 1–3 days are usually self-limited; but continuous chronic subclinical inflammation in some patients of FMF causes secondary amyloidosis that has a negative impact on quality of life and is associated with renal failure and death (22). Colchicine inhibits these lesions and accumulation of amyloidosis, but it is not effective in every patient. The majority of patients in whom colchicine treatment is ineffective have homozygous M694V mutations that are also associated with a more severe FMF phenotype. The IL-1 blocking agents have become important for patients who are unresponsive to colchicine by clarifying the pathogenesis of FMF (23). Recently, anti-interleukin-1 agents have been successfully used in patients who did not respond to colchicine treatment. The IL-1 blocking agents are anakinra, rilonacept, and canakinumab. Canakinumab is a human IgG1 monoclonal antibody that selectively binds IL-1β to IL-1β. Compared to other IL-1 blocking agents, canakinumab has the longest half-life of 21–28 days; therefore, it can be applied every 4–8 weeks. Retrospective studies have also reported that canakinumab is an effective and safe treatment for patients with colchicine-resistant FMF (24).

Babaoglu et al. (25) achieved complete remission after the canakinumab treatment in 14 out of 23 patients with colchicine- and anakinra-resistant FMF in 2010–2018 . Jesenak et al. (26) reported that in the first report in Eastern Europe, after the use of canakinumab, attacks were completely eliminated in patients with anakinra and colchicine-resistant FMF, and they reported that canakinumab was a safe and effective agent . Laskari et al. (27) reported that 11 out of 14 (79%) patients with colchicine-resistant FMF had complete remission following canakinumab treatment. In a case report in 2017, Ozkan et al. (28) reported that the treatment was successful after canakinumab that they used as IL-1β agent in four children with no response to colchicine. In a study conducted by Gül et al. (29) in 2010–2016, they reported success treatment after canakinumab in 13 patients with colchicine-resistant FMF. Yazılıtaş et al. (30) conducted a study in 2018 that included 11 patients with pediatric FMF who did not respond to colchicine. They reported that canakinumab treatment was safe and effective in patients not responsive to colchicine. In accordance with Akar et al. (31) multicenter study that was conducted in 2018, they evaluated 172 patients with FMF after canakinumab treatment who did not respond to colchicine. They reported that in 42% of the patients in their study, attacks were completely eliminated; and serum reactive protein, ESR, and 24-hour urine protein were significantly reduced, and the remaining patients had decreased attacks. In our study, 22 patients with colchicine-resistant FMF were evaluated after canakinumab treatment. After the treatment, no attack was observed in 19 patients. In three patients, disease attack was observed 16 months after the first dose treatment. In all patients, the values of acute phase reactants were found at normal level during treatment. And no drug-related side effects were observed in any patient.

Canakinumab is an effective and safe anti-IL1 agent to reduce attacks in patients with FMF with no response to colchicine and to reduce the level of high-level laboratory findings associated with FMF. There should be further investigations to explore its efficacy, safety, and optimum dosage and administration intervals in this subset of patients with FMF.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ege University School of Medicine (Date:14.07.2016 No:12-3.1/1)

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B., Ö.Ş.; Design - A.B.; Supervision - A.B. ; Resources - A.B., G.T.; Materials - A.B., Ö.Ş.; Data Collection and/or Processing - A.B., G.T.; Analysis and/or Interpretation - A.B., Ö.Ş.; Literature Search - Ö.Ş.; Writing Manuscript - Ö.Ş.; Critical Review - A.B.

Acknowledgements: We thank to all our patient who volunteer to include our study.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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