CASE SERIES

Canakinumab treatment in four children with colchicine resistant familial mediterranean fever

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Abstract

Familial Mediterranean Fever (FMF) is an autosomal recessive and autoinflammatory disease, characterized with inflammation of serous membranes such as peritoneum, pleura, synovium with fever and pain. Colchicine is the main treatment of FMF, but 5-10 % of patients are unresponsive to colchicine. We report using anti-interleukin-1 agents anakinra and canakinumab in four colchicine-resistant patients who were successfully treated. Three of the patients were siblings.

Keywords: Familial Mediterranean fever, Anakinra, Canakinumab.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive and autoinflammatory disease, characterized with inflammation of serous membranes such as peritoneum, pleura, synovium with fever and pain. It is an ethnic disease, most common among Jews, Arabs, Turks and Armenians.[1]

FMF is caused by inherited mutations in MEFV (MEditerranean FeVer) gene which encodes pyrin-marenostrin protein. This protein inhibits inflammation by suppressing the activation of neutrophils, part of the NLRP3 inflammasome complex, and mutations in MEFV are associated with excess inflammation through increased interleukin-1 beta (IL-1β) production.[2,3]

Colchicine is the main treatment for patients with FMF by preventing febrile attacks and amyloidosis. But 5-10% of patients are reported to be resistant to colchicine. IL-1 receptor antagonist (anakinra) and IL-1β monoclonal antibody (canakinumab) can be used as biological agents in resistant cases.[4,5] We report using anti-interleukin-1 agents anakinra and canakinumab in four colchicine-resistant patients three of whom were siblings. All patient's symptoms and laboratory markers of inflammation improved. Consent was taken from the parents of the childrens to publish the cases.

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Case Report

This study was performed with 4 patients with colchicine-resistant FMF diagnosis at the Necmettin Erbakan University School of Medicine Paediatric Nephrology Department. Three of them were siblings (case 1-3). Also colchicine-resistant FMF was diagnosed in sibling's mother. While 2 of the siblings had M694V homozygote mutation, the other had M694V heterozygote. Our fourth patient with colchicine-resistant FMF had M694V homozygote too. None of our patients had proteinuria or amyloidosis. Initially all patients were treated with maximum dosage of colchicine, before starting anti-IL-1 therapy. Firstly, anakinra was started with a dose of 2 mg/kg/day (subcutaneous (s.c.)) and seen clinical and laboratory remission except case 1, who had partial response to anakinra but full response to canacinumab. After 6 months of treatment, anakinra was switched to canakinumab (2 mg/kg/day, maximum 150 mg/monthly, s.c.), for the noncompliance of daily injection in patients.

Case One (Siblings)

A 16-year-old boy with FMF heterozygous for M694V mutation was admitted to our hospital because of the persistence of recurrent fever attacks 3 or 4 times in a month for 3 days, accompanied by chest and abdominal pain, myalgia, arthritis of the knees, headache, and aphthous lesion on his tongue with herpes labialis, despite taking maximum dosage of colchicine (2 mg/day). When he was 6, he was followed for 1 year with the diagnosis of acute rheumatic fever. He had been diagnosed with FMF and was given colchicine when he was 7 years old. On admission to our hospital acute phase reactants; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen and white blood cell (WBC) were high. There was no proteinuria. Anakinra was started at 2 mg/kg per day, s.c, without

stopping colchicine. His clinical attacks decreased after anakinra treatment, but still his levels of acute phase reactants were high. Daily anakinra injection therapy was switched to monthly injection of canakinumab because of partial response to anakinra. Also canakinumab has easy implementation. After canakinumab treatment, he had no complaint or recurrence, additionally his acute phase reactants levels were normal. After 4 months of treatment with canacinumab he gave up colchicine on his own. He did not develop any symptoms.

Case Two (Siblings)

A 5-year-old girl was diagnosed FMF homozygous for M694V mutation with spinal muscular atrophy. Her attacks were characterised by fever, abdominal pain, arthritis of the ankles and headache 4 times in a month for 2-3 days. When she was admitted to our hospital, she was 8 years old. Although taking colchicine at a high dose (2 mg/day), she was suffering from severe discomfort and her acute phase reactants; ESR, CRP, fibrinogen and WBC were high. The treatment protocol was implemented like case 1. The results were succesful.

Case Three (Siblings)

He had the diagnosis of FMF for 2 years with homozygous M694V mutation, characterised by attacks of fever, abdominal and chest pain 4 times in a month lasting for 1-2 days. When he was admitted to our hospital he was 9 years old. Although he had been taking 1.5 mg dosage of colchicine for a year, the episodes were recurring. Like the other family members his acute phase reactants were high. The treatment protocol was implemented which showed successful results like other cases.

Case Four

A 15-year-old girl had been followed with FMF diagnosis homozygous for M694V mutation at our hospital for 6 years. Although taking maximum dosage of colchicine (2 mg/day) for a year, she had persistence of recurrent fever attacks 1 or 2 times in a month for 2 days, accompanied by chest pain with pleural effusion, abdominal pain, and arthritis of the knees. Her symptoms began when she was 5 years old. She was followed for a while with the diagnosis of acute rheumatic fever. She had been diagnosed with FMF and treated with colchicine at the age of 9 years. Despite the fact that her dosage of colchicine was maximum, attacks persisted and her acute phase reactants; ESR, CRP, fibrinogen and WBC were high during the attacks. The treatment protocol was implemented like other cases, with succesful results.

Discussion

Colchicine is the main treatment for patients with FMF for preventing febrile attacks and amyloidosis. The dose recommended is 1-2 mg daily. The treatment has some side effects like diarrhoea and gastrointestinal upset, but usually is well tolerated. About 5-10% patients are reported to be resistant to colchicine, however there is no established treatment for these patients as yet.[1]

MEFV gene mutations are associated with excess inflammation through increased IL-1β production in FMF. IL-1β is the proinflammatory molecule responsible for triggering the inflammatory way in the tissues. For these reasons the target in colchicine-resistant cases is the anti IL-1β agents. IL-1 receptor antagonist (anakinra) and IL-1β monoclonal antibody (canakinumab) can be used as biological agents. It has been reported that these treatments are beneficial for colchicine-resistant FMF patients.[4,5]

Anakinra is a recombinant form of human IL-1 receptor antagonist, competitively inhibits binding of IL-1a and IL-1b to IL-1 receptor type I, used as a daily s.c. injection.[5,6] Canakinumab is a human monoclonal antibody targeting IL-1β, can be preferred as it is used once per month due to the long-acting molecule. Also canakinumab is an alternative treatment if there is a problem with patient compliance from anakinra's daily injection.[4,7] Meinzer et al.[8] Ozçakar et al.[9] and Basaran et al[10] reported their case series treatment with anakinra and canakinumab in adult and paediatric patients. They reviewed the literature for FMF patients using anti-IL-1 therapies. They reported that treatment with anakinra or canakinumab were beneficial in all of theirs and the other case series in the literature. Also anti-IL-1 therapies have been reported to suppress acute phase reactants and fever attacks in colchicine-resistant patients with FMF, who have amyloidosis.[8-10]

In our report, despite the fact that the patients had maximum dosage of colchicine, they had severe and frequent attacks with high levels of acute phase reactants. Firstly, anakinra was given to all the patients in addition to colchicine and showed a rapid and dramatic effect on attacks of FMF and inflammatory findings. There were no side effects, but daily anakinra injection therapy was changed to monthly injection of canakinumab because of easy implementation.

In conclusion, we observed that anti IL-1 therapies anakinra and canakinumab are effective drugs for colchicine-resistant FMF patients to control inflammation

and symptoms. But effectiveness of anti IL-1 agents on amyloidosis is not evident. Also, the necessity of using colchicine with anti IL-1 agents was not convincing. Further studies are needed with these drugs.

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Conflict of Interest: None.

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