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Treatment of Colchicine-Resistant Familial Mediterranean Fever With Anakinra

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Introduction: Familial Mediterranean Fever (FMF) is an auto-inflammatory disease presenting with periodic fever and various clinical manifestations. Almost 10% of the patients with FMF do not respond to colchicine therapy.
Case Presentation: Herein was reported a colchicine non-responsive patient with accurate diagnosis and early treatment of FMF. She had presented with recurrent and persistent acute abdominal pain attacks and several abdominal surgeries. Addition of recombinant interleukin-1 receptor antagonist (Anakinra) to colchicine was effective to decrease the number and severity of abdominal pain in the patient.
Conclusions: This case showed the effect of additional Anakinra on children with FMF who were colchicine resistant.

Keywords: Familial Mediterranean Fever; Colchicine; Interleukin-1 Receptor Antagonist Protein

1. Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease with periodic fever and auto-inflammatory diseases. It mainly affects Turks, Armenians, Arabs, Jews and other Mediterranean populations (1-5). Ardebil and Azerbaijan provinces are the endemic geographical distribution of FMF in Iran (6, 7). Clinical diagnosis is usually confirmed with the disease locus mutations in MEFV gene on chromosome 16p13.3 (8, 9). About 95% of the patients have significant improvement in signs and symptoms of the disease with colchicine and approximately 75% of them experience a complete remission (10). Colchicine non-responder cases are a challenge in treatment which leads to a variety of drugs, including interferon alpha, thalidomide, prazosin, etanercept and anakinra (11-14). Herein we reported a colchicine non-responsive patient with accurate diagnosis and early treatment of the disease that presented with recurrent and persistent acute abdominal pain attacks and several abdominal surgeries.

2. Case Presentation

A 15-year-old girl from Tabriz, East Azerbaijan province, Iran, with the known case of Familial Mediterranean Fever (FMF), presented with complaints of severe and recurrent abdominal pain. She was admitted to Pediatric Rheumatology ward of Mofid Children's Hospital, Tehran, Iran. In the last month, leading to the hospitalization of the patient, abdominal pain worsened every evening and sometimes with non-bloody vomiting. She had been hospitalized two weeks ago with acute abdomen which led to diagnostic laparoscopy, but was not in favor of acute abdomen. The patient had been treated with colchicine 2 mg daily for her recurrent abdominal pain attacks with fever since three years ago. She had the history of ovarian cyst surgery for three times accompanied with abdominal pain and irregular menses three months ago. She also had the history of appendectomy almost four years ago. MEFV gene mutation analysis revealed component heterozygous mutation of M694V and R761H. On admission the patient had severe pain and tenderness in the right lower quadrant (RLQ) with radiation to lower extremities, neither fever nor systemic symptoms. The result of her acute phase reactants showed C-reactive protein (CRP) 47 mg/dL and erythrocyte sedimentation rate (ESR) 19 mm/h (first hour). Attacks of abdominal pain only responded to intramuscular injection of dexamethasone 0.15 mg/kg/day. After rectal biopsy to rule out amyloidosis, despite the absence of proteinuria, Anakinra began as a subcutaneous injection 1.5 mg/kg/day. She was advised to continue taking colchicine and a diet low in fat, lactose and gluten free. During the 12 month follow-up of the patient, she had only three attacks with short duration and low intensity of abdominal pain.

3. Discussion

In most of the cases, treatment with colchicine to prevent attacks of fever and systemic amyloidosis is very effective (15). In general, continuous treatment with colchicine is more effective than intermittent treatment during attacks. This way gives more subclinical inflammation control and reducing potentially amyloidosis (16). There are patients (about 5 - 10%) who do not respond to colchicine or cannot tolerate therapeutic doses (17). MEFV gene is located on the short arm of chromosome 16 that encodes a protein containing 781 amino acids, named pyrin. Normal pyrin inhibits activation of the precursor form of IL-1β to its biologically active components. Mutations in this gene result defective FMF pyrin production that leads to defective apoptosis and stimulates IL1 processing, and production of active IL-1β, which eventually leads to the uncontrolled inflammation (18). The role of IL-1β in the pathogenesis of the disease is the reason to use anakinra to treat FMF (19, 20). Anakinra is a recombinant form of interlukin-1 receptor antagonist (IL-1Ra). This receptor induced by IL-1 is an important physiological regulator. Anakinra may exert its effect with binding to the IL-1 receptor on the cell surface and preventing interaction with IL-1. Dramatic response to anakinra is observed in IL-1 origin disorders and auto-inflammatory syndromes such as systemic onset JIA, Muckle-Wells Syndrome (MWS), Deficiency of the interleukin-1 Receptor Antagonist Syndrome (DIRA) and Familial Cold Auto-inflammatory Syndrome (FCAS) (21, 22). Side effects are generally not serious. Injection site reactions, usually occur in the first four weeks and include rash, itching, erythema, and usually do not require drug discontinuation. Opportunistic and severe infections with mortality are not reported yet. For clinical monitoring purified protein derivative (PPD) test is recommended, although it is not associated with reactivation of latent Tuberculosis (TB). Complete blood count before, and monthly for three months after the start, and then four times a year to monitor laboratory data is also recommended (10). The rectal biopsy that was negative for amyloidosis, and dramatic response of the patient to daily treatment by anakinra after twenty-eight days, obliged the authors to continue anakinra only during the patient's abdominal attacks, along with taking colchicine daily.

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Authors' Contributions

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