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Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever

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ABSTRACT

Familial Mediterranean fever (FMF) patients may present with different joint complaints, one being the 'protracted attack' that lasts for weeks. We present a 15 year-old boy with polyarthritis (right wrist, knee, shoulder, and both ankles) while on colchicine treatment for FMF. His polyarthritis was resistant to treatment with prednisolone and methotrexate, and etanercept was instituted (0.8 mg/kg/week). He responded dramatically to etanercept and remained in full remission, although the drug was stopped at 4 months due to social and financial causes. We suggest that anti-TNF drugs may be an alternative for resistant attacks. However the timing and dosage, as well as efficacy, need to be further studied.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessively inherited disorder typically manifested by fever and polyserositis. The articular disease occurs in 70-75% of the patients. Three unique types of arthritis have been described (1). Acute arthritis attacks represent 95% of the reported cases, and are characterized by short duration, self-limited episodes. Large joints of the lower extremities are most frequently involved. Rarely, there is a polyarticular involvement, which resembles juvenile idiopathic arthritis (JIA). The second type, protracted arthritis, lasts more than a month, accounts for 5% of the cases and recovers without any sequels. The third type is the abortive attack with arthralgia as the only manifestation (2). On the other hand, FMF patients have an increased rate of certain rheumatic diseases (Henoch-Schönlein purpura, polyarteritis nodosa, rheumatoid arthritis, juvenile idiopathic arthritis), it has been suggested that this might be because of the increased inflammatory milieu (3, 4). Indeed, FMF patients have been reported to have high levels of acute phase proteins, even during attack free period (5).

We describe a case with FMF who developed prolonged arthritis, which could finally be controlled by a TNF-α receptor inhibitor, etanercept.

Case report

The patient presented at the age of 10, suffering from daily peaks of fever, arthritis of the ankle, a rheumatic rash during fever, with an ESR of 127 mm/h and a CRP elevated to 30 mg /dl (normal < 0.8 mg/dl). He had no conjunctivitis. He had had two short attacks of fever and arthritis/arthralgia within the last 9 months. The family history was negative. He was diagnosed as systemic juvenile idiopathic arthritis (JIA), and prednisolone and methotrexate were commenced. Although the typical features of systemic JIA disappeared, his acute-phase reactants (APRs) remained high. On follow-up, he was observed to experience attacks of fever, abdominal pain and arthralgia accompanied by a raise in APRs. Colchicine was added to the treatment regimen with a possible diagnosis of FMF. His attacks subsided and APRs returned to normal. MEFV mutation analysis revealed that he was homozygous for the E148Q mutation.

At the age of 15, he was admitted with the complaints of fever, arthralgia, swelling of wrists and ankles, and abdominal pain. On physical examination he had a normal blood pressure, and an elevated body temperature (38.8°C); diffuse myalgia; swelling, warmth, and decreased range of motion in his right wrist, knee, shoulder, and both ankles. Attacks of the patient were characterized by fever and incapacitating myalgia, and arthritis. Although the fever subsided in a few days, the arthritis persisted for months, and did not respond to NSAIDs. He was unable to attend school with three-month absences, and bound to bed.

The laboratory investigations showed a normal urinalysis; normal hemoglobin level and platelet count, with leukocytosis (23500/mm^3); normal renal and liver function tests. APRs were high (ESR 99 mm/h; fibrinogen 660 mg/dl, CRP 12.1 mg/dl); ASO and RF levels were within normal ranges; ANA was negative. Serological tests for viral hepatitis (A-E), TORCH, EBV, HIV, salmonella, and brucella were all negative. The cultures were negative. Chest radiogram and echocardiography were normal. Ig D level was normal. The

patient was subsequently screened for TNFRSF1A mutation, for TNF-α receptor associated periodic fever syndrome (TRAPS), no mutation was detected.

Intravenous bolus methyl prednisolone (500 mg/m^2) was instituted, in addition to colchicine, due to incapacitating and long lasting arthritis. Although the temperature returned to normal in two days, the arthritis persisted. Despite ongoing oral prednisolone (1mg/kg/-day), methotrexate (oral then s.c. 12.5 mg/m^2/week, for about 3 months) and NSAIDs, his joint complaints continued, and his APRs remained high. Etanercept was instituted (0.8 mg/kg/-week). After the second dose of etanercept, the arthritis dramatically improved, and his APRs returned normal. No adverse event was observed during the treatment period (four months). The drug was stopped at the end of the 4th month due to social and financial causes. He is in excellent condition six months after the cessation of treatment and only receives colchicine.

Discussion

The protracted arthritis of FMF is characterized by a long duration (6). Although colchicine is the unique drug effective in FMF, arthritis may be less responsive than fever and serositis (7).

The gene responsible for FMF, MEFV, is expressed in the cells of myelomonocytic lineage, notably granulocytes. The expression of MEFV is stimulated by pro-inflammatory mediators such as IL-1, tumour necrosis factor-alpha (TNF-α), and interferon-γ, which induce the eventual inflammatory steps (8). Etanercept (Enbrel®, Wyeth), is a recombinant human protein with anti-inflammatory properties. It inhibits TNF-α activity by competitively binding to it and preventing interactions with its cell surface receptors. It is approved by the FDA for the treatment of rheumatoid arthritis (9), and juvenile idiopathic arthritis (10). Beneficial effects of TNF-inhibitors have also been reported for the treatment of TRAPS (11), chronic infantile neurological cutaneous articular (CINCA) syndrome (12), hyperimmunoglobulinemia D syndrome (13), ankylosing spondylitis (14), and inflammatory bowel disease (15). Most common adverse events with etanercept are infections, especially upper respiratory tract infections (16).

The presented patient was accepted to have FMF because of his typical sign and symptoms that responded to colchicine treatment. We have previously reported that we believed E148Q to be a disease causing mutation, albeit a mild form, since an important percentage of our E148Q homozygote patients had typical features of FMF such as this patient (17, 18).

Ozgocmen *et al.* reported a 35-year-old woman with FMF associated with spondylitis and bilateral protracted arthritis (19). The patient was resistant to colchicine, sulfasalazine and methotrexate; and was put on infliximab treatment (3 mg/kg) at weeks 0, 2, and 6 and repeat infusions every six weeks. She started to feel better after the 14th week of treatment, and yielded complete remission of the febrile episodes. Spondylitis responded well, but her hip mobility remained limited.

This is the first use of etanercept in a child for a feature or association of FMF. This patient had initially presented with features of systemic JIA and had responded to methotrexate and corticosteroids (17). Subsequently he was noted to have typical attacks of FMF with fever and arthritis subsiding in 3-4 days. Following the diagnosis of FMF and the colchicine treatment his attacks were under quite good control. However, his last attack was a prolonged and disabling polyarthritis, without features of ankylosing spondylitis, in contrast to the case reported by Ozgocmen *et al.* (19).

A patient is classified as JIA if an objective joint symptom lasts for longer than 6 weeks. However, this patient also had FMF, which may be regarded as an exclusion factor from JIA. On the other hand during his first attack the fever was also prolonged and there was a rash during fever, which was highly suggestive of a systemic form of JIA. It is interesting that some authors suggest systemic JIA to be included among the auto-inflammatory syndromes.

During his last attack his fever disappeared quickly as in FMF, which made the differential diagnosis more difficult. He was put on etanercept without a clear differentiation between an associated JIA and prolonged arthritis of FMF and responded dramatically. When etanercept was discontinued at the end of the 4th month because of social reasons, he remained normal. This fact may favor the diagnosis of a protracted attack of FMF arthritis, since JIA is expected to require more prolonged treatment. Other expensive treatments, such as interferon, have been used for resistant cases of FMF (20).

In 1991, Schattner *et al*. measured TNF-alpha levels in the plasma, in supernatants of peripheral blood mononuclear cells incubated alone or with an inducer. No TNF-alpha was found in plasma. Induced TNF-alpha production was markedly decreased in patients with acute FMF (during attack, 4 U/ml), increased in asymptomatic FMF patients (25 U/ml), compared to control subjects (14 U/ml). They concluded that a marked decrease in this response in acute FMF patients is suggestive of exhaustion of cells that are already highly activated to produce TNF and the possible participation of TNF in the pathogenesis of FMF (21). In 1999, Gang *et al.* have showed increased levels of soluble TNF receptors fusion protein p55 (sTNFr p55) and p75 (sTNFr p75) during attacks (22). In 2002, Notarnicola *et al*. measured the transcript abundance of TNF-alpha, and showed that this was more elevated in attack free FMF patients than in the controls (23).

Anti-TNF drugs seem to be a logical choice in FMF because of the known heightened inflammation and activated inflammatory pathway in patients with mutated pyrin molecule. Future studies may enlighten whether anti-TNF drugs can be instituted for even shorter periods for incapacitating myalgia or prolonged arthritis in resistant cases of FMF.

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