

Case report

**Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever**

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**Running title:** Successful treatment of an FMF patient with infliximab

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**Abstract**

We report a Japanese patient with familial Mediterranean fever (FMF) who was successfully treated with the anti-tumor necrosis factor (TNF)- $\alpha$  monoclonal antibody, infliximab, and low-dose methotrexate. This patient was diagnosed as having FMF based on periodic fever with polyarthralgia typical of this disease and heterozygous mutations in the *MEFV* gene. Conventional treatment, such as colchicine and reserpine, failed to sufficiently control the FMF attacks. After starting infliximab (3 mg/kg) and low-dose methotrexate (6 mg/week), the frequency of the FMF attacks dramatically decreased and the clinical effect has remained unchanged for longer than 1 year. Combination therapy with infliximab and low-dose methotrexate may be a potent therapeutic option for FMF patients, particularly when conventional treatment is ineffective or cannot be employed because of adverse events.

**Keywords:** familial Mediterranean fever, infliximab, methotrexate, tumor necrosis factor- $\alpha$

## Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized clinically by recurrent attacks of fever, peritonitis, pleuritis and/or polyarthritis, and genetically by autosomal recessive inheritance (1). The *MEFV* gene encoding marenstrin/pyrin is responsible for this disease (2). As frequent attacks of inflammation often result in the development of renal amyloidosis with a poor prognosis, colchicine is most commonly employed for treatment of FMF (2). When this drug is ineffective or cannot be used because of adverse effects, such as diarrhea and bone marrow suppression, other pharmacotherapies are considered as the next therapeutic option (3-8). Allogeneic bone marrow transplantation has also been shown to be effective in the prevention of FMF attacks (9). Several recent reports have demonstrated that the anti-tumor necrosis factor (TNF)- $\alpha$  monoclonal antibody, infliximab, reduces the frequency of FMF attacks in Spanish and Turkish patients (10, 11).

FMF has been regarded as a very rare disease in Japan, but approximately 20 patients have been identified using gene analysis since the first case report in 2002 (12). Here, we report a Japanese FMF patient successfully treated with infliximab and low-dose methotrexate. The present patient was resistant or intolerable to conventional treatment, including colchicine, reserpine, prazosin hydrochloride and azelastine, and periodic fever with polyarthralgia ascribed to FMF disappeared in response to infliximab and low-dose methotrexate. We postulate that this combination may be a potent therapeutic option in refractory patients with FMF.

## Case report

A 20-year-old Japanese woman experienced periodic episodes of high fever, thoracoabdominal pain and polyarthralgia mainly in the shoulder and knee joints with no precipitating cause or significant family history. These attacks occurred almost every

month particularly during menstruation, and usually improved in one week with no specific therapy. She visited a neighboring hospital, but there were no abnormal findings other than positive inflammatory reactions, such as C-reactive protein, on routine laboratory data performed during febrile attacks. At age 33 the patient was referred to our hospital, and was diagnosed as having FMF based on clinical symptoms typical of this disease and a compound heterozygosity for marenostin/pyrin variant E148Q/M694I as shown in our previous report (8). To prevent FMF attacks, colchicine, reserpine, prazosin hydrochloride and diclofenac sodium were tried, but were not tolerated because of adverse events, such as diarrhea, abdominal pain, general fatigue and bone marrow suppression. After commencement of an anti-allergy drug, azelastine, the frequency of febrile attacks decreased slightly.

At age 36 excessive physical or psychic stress induced an increase in the severity and frequency of febrile attacks with thoracoabdominal pain and polyarthralgia, leading to decreased activity in daily life and general malaise. These attacks repeatedly occurred at an interval of approximately 3 days, and were uncontrollable by azelastine or other anti-inflammatory drugs (Fig. 1). The present patient refused to use interferon- $\alpha$  because of possible adverse effects, particularly depression. To improve the general status of our patient, infliximab was given at 0, 2, 6 and 14 weeks, and thereafter every 2 months at a dose of 3 mg/kg after obtaining informed consent. Oral methotrexate was coadministered at a low dose of 6 mg/week. The Local Ethical Committee approved infliximab for use in our patient. Chest X-ray and the tuberculin test were performed before commencement of infliximab, and both showed no abnormal findings suggestive of tuberculosis. The general status of our patient improved in parallel with a decrease in the severity and frequency of febrile attacks after the third administration of infliximab. Febrile attacks with thoracoabdominal pain and polyarthralgia completely disappeared even during menstruation after the fourth administration of this drug. Serum levels of TNF- $\alpha$  and interleukin (IL)-1 $\beta$  just before and 3 weeks after starting infliximab were

within normal limits (<5 pg/ml). Methotrexate was stopped approximately 9 months after commencement because of gastrointestinal symptoms, but the patient has since remained in good general condition with no FMF attacks for 6 months under infusion of infliximab alone at 2-month intervals (Fig. 1). There were no adverse events ascribable to infliximab.

## Discussion

It has been proposed that pro-inflammatory stimuli, such as inflammatory cytokines, the autonomic nervous system, hormones or some types of stress, are normally balanced by marenostriin/pyrin expressed on mature neutrophils (1, 2). Disruption of this balance by mutations in the *MEFV* gene could easily cause microtubular activation and migration of neutrophils, resulting in FMF attacks (2). According to a recent report mutations at position 694 of the *MEFV* gene have a crucial role in development of FMF but also in showing a severe phenotype (13). The present patient showed a heterozygous mutation of M694I, and additional effects of E148Q may have caused clinical symptoms typical of FMF (8).

Colchicine is widely used for treatment of FMF with regard to its ability to strongly inhibit neutrophil chemotaxis (2). In the present patient, however, colchicine and other anti-inflammatory drugs were ineffective or could not be used because of adverse effects, while the combination therapy with infliximab and low-dose methotrexate completely controlled FMF attacks. There were two reasons for using low-dose methotrexate in our patient. One is that she showed polyarthralgia uncontrollable by non-steroidal anti-inflammatory drugs during FMF attacks. Methotrexate is a key drug for rheumatoid arthritis, but may be effective also for polyarthralgia in FMF attacks (11). The other is that infliximab is a chimeric drug of human and mouse origin. To avoid the production of neutralizing antibodies to infliximab, low-dose methotrexate has to be coadministered in Japan based on clinical

experience in rheumatoid arthritis (14). Methotrexate was stopped 9 months after commencement because of adverse effects in our patient, but no FMF attacks with polyarthralgia have since occurred for 6 months with infliximab therapy alone. These findings suggest that infliximab may play a central role in suppressing FMF attacks as shown in a recent report (11). Etanercept, which is another TNF antagonist available in Japan, has also been shown to suppress FMF attacks (15, 16), but our patient refused this drug due to the necessity of subcutaneous injections at a frequency of twice a week.

It remains unclear how TNF- $\alpha$  is involved in the pathogenesis of FMF, although serum levels of this cytokine are often elevated in febrile attacks (17). A recent report hypothesized that marenostriin/pyrin on neutrophils can adequately regulate the activity of caspase-1, which increases the production of IL-1 $\beta$  in response to proinflammatory cytokines, such as TNF- $\alpha$  (18). IL-1 $\beta$  is a potent cytokine inducing inflammatory reactions, including high fever. This regulatory function of marenostriin/pyrin may be impaired by mutations in the *MEFV* gene as seen in FMF, clinically resulting in febrile attacks through excessive production of inflammatory cytokines. The present patient showed no increase in serum levels of either TNF- $\alpha$  or IL-1 $\beta$  before commencement of infliximab, but these results might be due to the low disease activity of FMF at sampling between febrile attacks.

In conclusion, a combination therapy of infliximab and low-dose methotrexate may be effective in the prevention of FMF attacks. Even if an increase in serum levels of TNF- $\alpha$  is unconfirmed, infliximab should be considered as a potent therapeutic option for refractory patients with FMF.

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## Figure legend

Figure 1: Clinical course of the patient. The frequency of febrile attacks with thoracoabdominal pain and polyarthralgia dramatically decreased after starting infliximab and low-dose methotrexate. CRP: C-reactive protein

Infliximab (3 mg/kg)

Methotrexate

Azelastine

Colchicine

Diclofenac sodium

Menstruation

Serositis

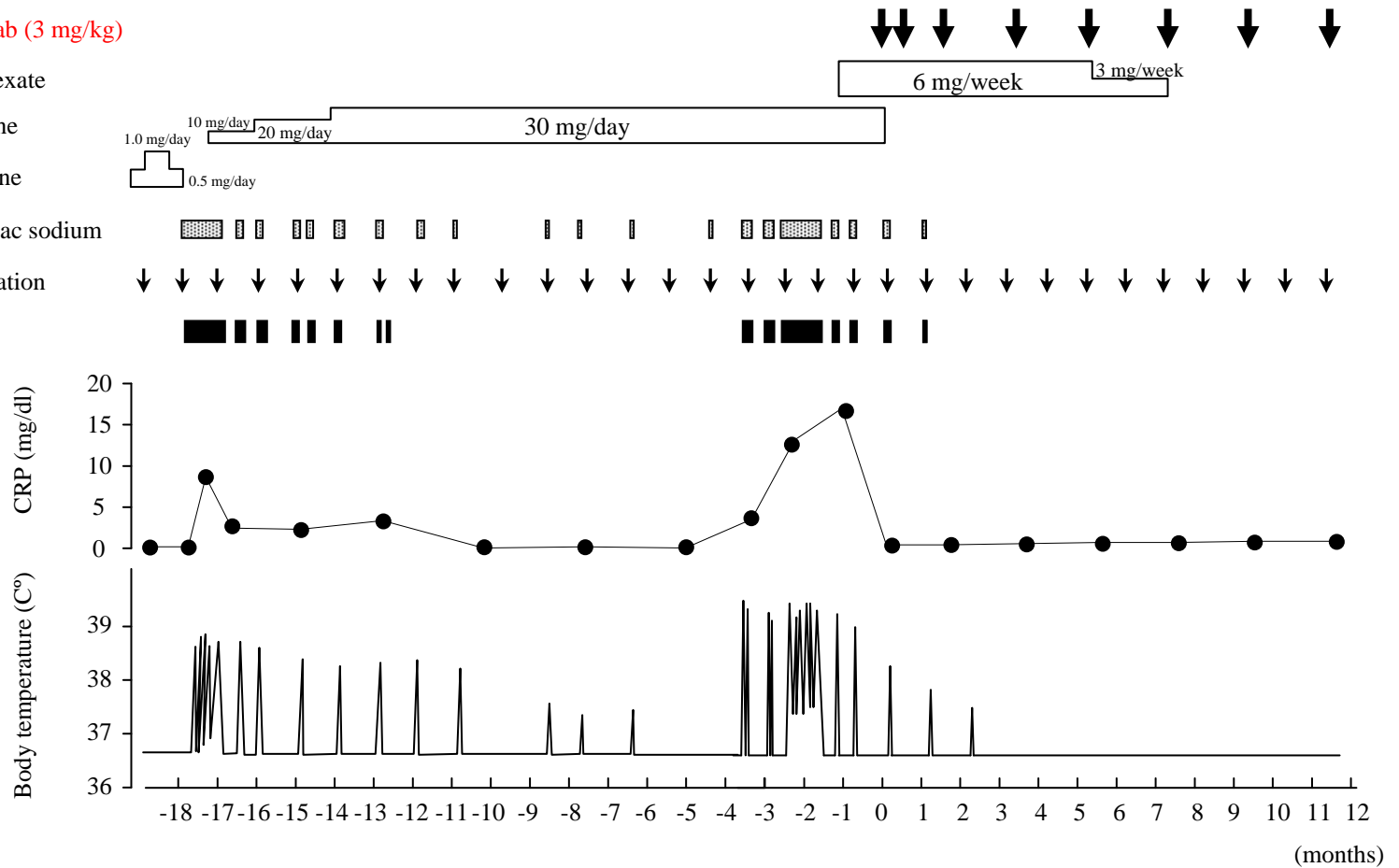


Figure 1