

Interleukin-6 targeting therapy in familial Mediterranean fever

Sirs,

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterised by recurrent fever, serositis and synovitis attack (1). Colchicine is the established first-line therapy for disease control (2). However, this is not effective in some patients, so IL-1 inhibitors are used as a successful alternative (3). Unfortunately IL-1 blockers have not yet been approved and registered in Japan. Herein, we present a patient with FMF who was successfully managed with tocilizumab therapy.

In September 2011, a 19-year-old Japanese female was referred to our clinic with fever, a sore throat, polyarthralgia and fever-associated skin rashes lasting a couple of days (Fig. 1). Laboratory data revealed elevated levels of C-reactive protein (1.14 mg/dL), liver enzymes (aspartate aminotransferase: 786 IU/ml, alanine aminotransferase: 879 IU/ml) and ferritin (1,341 ng/ml). Endotoxin, enterotoxin, and infectious causes (hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus and parvovirus B19) were ruled out, and a diagnosis of adult-onset Still's disease (AOSD) was suspected because of the negativity of specific antibodies such as anti-nuclear antibody, rheumatoid factor, the presence of a fever-associated skin rash and fulfilling the diagnostic criteria for AOSD (4). Treatment with 1 mg/kg/day prednisolone and 8 mg/week methotrexate (MTX) was started; however, the symptoms of periodic fever and polyarthralgia remained.

As a result of concerns about the transition to chronic articular type of AOSD, 8 mg/kg tocilizumab treatment was combined with the steroid and MTX therapy. The patient's symptoms, including skin rash, disappeared promptly, so prednisolone and MTX treatment were tapered and then stopped, while 8 mg/kg tocilizumab treatment at 4-week intervals was continued. Her medical history revealed recurrent episodes of fever lasting two or three days without arthralgia or abnormal pain every 2 months interval since the age of 7 years. Genetic analysis of the *MEFV* gene, which causes FMF when mutated, was performed with informed consent and revealed M694I/ heterozygous mutation (Fig. 2). The elevation of ferritin could be rarely observed in FMF patients (5), and elevated levels of serum ferritin were transient in the present case. Therefore, the original diagnosis of AOSD was questioned, and we concluded that the patient had developed FMF-related erysipelas-like skin lesions and synovitis in the context of pre-existing untreated FMF. Tocilizumab treatment was stopped, and colchicine treatment was scheduled. However, after the cessation of tocilizumab treatment, the patient did not present with febrile attack and sustained drug-free remission state



Fig. 1. Fever-associated erythematous skin rash (erysipelas-like skin lesions) on the thigh in this patient.

was continued for 4 months. However, she relapsed with febrile attack, which was successfully managed by colchicine treatment (0.5mg/day).

To our knowledge, this is the first case of a patient with FMF treated with tocilizumab. Recent studies indicate that IL-1 inhibition is a promising treatment for patients with colchicine-resistant FMF (6). IL-6 is also considered to be a main mediator of the host reaction to tissue damage in autoinflammatory diseases (7). However, the role

of IL-6 in the pathogenesis of FMF is not well established. Theoretically, IL-6 blockers may have therapeutic effects in an IL-1-mediated disease since IL-1 induces IL-6 transcript and a significant increase in serum IL-6 levels observed in FMF patients (8). Indeed, tocilizumab has proved effective in systemic-onset juvenile idiopathic arthritis (SoJIA) in which a unique IL-1 β signature has been identified (9). However, therapeutic effect of tocilizumab was not confirmed in patients with chronic infantile neurological cutaneous articular (CINCA) syndrome a typical IL-1-mediated disease (10). It is established that cryopyrin mutations in CINCA leading to caspase-1 activation linking to accelerated secretion of activated IL-1 β (10). FMF is caused by inherited mutations in the *MEFV* gene, which encodes pyrin (1). Pyrin regulates caspase-1 activation and consequently IL-1 β production (11). In addition to its role in activating caspase-1, pyrin also modulates a transcriptional factor, NF- κ B, that induces other proinflammatory cytokines (12). These observations suggest a more complex picture of inflammatory cascades in FMF. A link between *MEFV* mutation and IL-1 β production in FMF may be less evident compared to those in CINCA. It is therefore possible that tocilizumab can control proinflammatory clinical manifestations seen in FMF by effectively blocking these proinflammatory cytokine cascades. Nevertheless, long-term follow-up is essential to ensure that the beneficial effects of tocilizumab therapy do not remit over time. The mainstay of treatment for FMF is still colchicine (13), which prevents AA amyloidosis. Tocilizumab also shows promising effects against AA amyloidosis by eradicat-

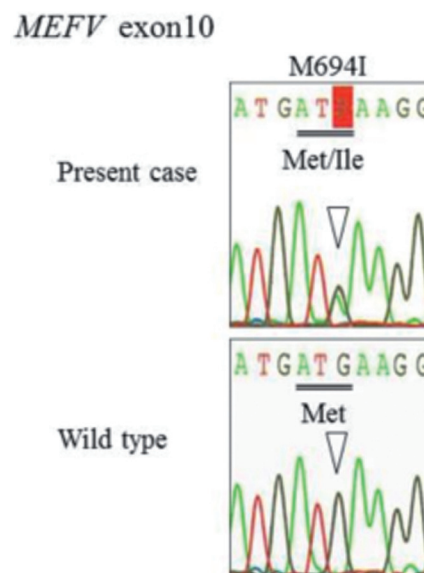


Fig. 2. DNA sequence electropherograms demonstrating the M694I mutation.

DNA sequencing demonstrates a heterozygous missense mutation (G to A) transition in codon 694 of *MEFV* gene (exon 10) converting a Methionine (Met) to Isoleucine (Ile).

ing the acute-phase reactant, serum amyloid A (14). Therefore, tocilizumab could be an alternative therapeutic option for FMF patients with established AA amyloidosis. In conclusion, anti-IL-6 directed therapy may be beneficial in the treatment of FMF, based on the proinflammatory cascades seen in this disorder. Further studies of a large number of patients would be necessary to confirm this.

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References

1. EL-SHANTI H, MAJEED HA, EL-KHATEEB M: Familial mediterranean fever in Arabs. *Lancet* 2006; 367: 1016-24.
2. BEN-ZVI I, LIVNEH A: Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. *Nat Rev Rheumatol* 2011; 7: 105-12.
3. SORIANO A, VERECCHIA E, AFELTRA A, LANDOLFI R, MANNA R: IL-1 β Biological Treatment of Familial Mediterranean Fever. *Clin Rev Allergy Immunol* 2013 Jan 16.
4. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al.*: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424-30.
5. KORKMAZ C, OZDOGAN H, KASAPÇOPUR O, YAZICI H: Acute phase response in familial Mediterranean fever. *Ann Rheum Dis* 2002; 61: 79-81.
6. BERKUN Y, EISENSTEIN E, BEN-CHETRIT E: FMF – clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S90-5.
7. VAITLA PM, RADFORD PM, TIGHE PJ *et al.*: Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the anti-interleukin-6 receptor monoclonal antibody tocilizumab. *Arthritis Rheum* 2011; 63: 1151-5.
8. BAGCI S, TOY B, TUZUN A *et al.*: Continuity of cytokine activation in patients with familial Mediterranean fever. *Clin Rheumatol* 2004; 23: 333-7.
9. SANDBORG C, MELLINS ED: A new era in the treatment of systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2439-40.
10. SNEGIREVA LS, KOSTIK MM, CAROLI F, CECCHERINI I, GATTORNO M, CHASNYSK VG: Failure of tocilizumab treatment in a CINCA patient: clinical and pathogenic implications. *Rheumatology* 2013 Mar 12. [Epub ahead of print]
11. CHAE JJ, AKSENTIJEVICH I, KASTNER DL: Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. *Br J Haematol* 2009; 146: 467-78.
12. CHAE JJ, WOOD G, RICHARD K *et al.*: The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment. *Blood* 2008; 112: 1794-803.
13. OZTURK MA, KANBAY M, KASAPOGLU B *et al.*: Therapeutic approach to familial Mediterranean fever: a review update. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S77-86.
14. OKUDA Y, TAKASUGI K: Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. *Arthritis Rheum* 2006; 54: 2997-3000.