Tofacitinib suppresses disease activity and febrile attacks in a patient with coexisting rheumatoid arthritis and familial Mediterranean fever

Gök K[1], Cengiz G[1], Erol K[1], Ozgocmen S[1]

ACTA REUMATOL PORT. 2017;42:88-90

ABSTRACT

Familial Mediterranean fever (FMF) is the most common hereditary auto-inflammatory (periodic fever) syndrome, and usually successfully treated with colchicine. However, nearly 5-10% of FMF cases are resistant or intolerant to colchicine and treatment options are highly restricted in these cases. Biologics including anakinra, canakinumab, rilonacept, etanercept, infliximab, interferon-alpha, and tocilizumab are shown to have efficacy to control FMF attacks. Tofacitinib, a Janus kinase (JAK) inhibitor, is an orally administered non-biologic disease modifying anti-rheumatic drug for the treatment of rheumatoid arthritis (RA). Herein we report a female patient with coexisting RA and colchicine resistant FMF whose FMF attacks and disease activity were completely controlled after treatment with tofacitinib, a small-molecule JAK3 inhibitor.

Keywords: Familial mediterranean fever; Treatment; Biological agents.

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common hereditary auto-inflammatory (periodic fever) syndrome characterized by recurrent febrile attacks, serosal inflammation and synovitis[1,2]. Mediterranean fever (MEFV) is the gene responsible for FMF and patients who are homozygote for M694V may have more severe disease[2]. In recent years, an association between *MEFV* mutations and rheumatic diseases, like rheumatoid arthritis (RA) and ankylosing spondylitis has been suggested[3,4].

1. Division of Rheumatology, Dept PMR, ERU Gevher Nesibe Hospital, Kayseri

Here we describe a female patient with coexisting RA and colchicine resistant FMF, whose FMF attacks and RA activity were completely controlled after treatment with tofacitinib. The informed consent of the patient for this publication was taken.

CASE REPORT

A twenty-seven years old Turkish women attended our outpatient clinic with complaints of pain and swelling in multiple joints and morning stiffness lasting more than two hours. These symptoms had persisted for two months. She had a history of appendectomy and febrile periodic abdominal attacks beginning in childhood. Five years ago, she was diagnosed with FMF and her frequent abdominal attacks (more than 6 times per month) reduced with colchicine treatment 1.5 mg daily. However, her complaints worsened two years ago, when she was pregnant and the frequency of febrile abdominal attacks increased after delivery, despite 2 mg daily colchicine intake.

On admission, her physical examination revealed swollen and tender hand, wrist, foot, knee and ankle joints. Spine, sacroiliac joints and neurological examination were normal. Laboratory analysis revealed C-reactive protein (CRP) 79.9 mg/L, erythrocyte sedimentation rate (ESR) 65 mm/hour, hemoglobin 10.8 g/dL, fibrinogen 450 mg/dL and normal white blood cell and platelet counts. Rheumatoid factor, anti-CCP and anti-cyclic citrullinated peptide (CCP) and human leukocyte antigen (HLA) B27 were negative. She was homozygote for *M694V* and *R202Q* mutations. Hand/wrist radiographs showed erosive changes in two metacarpophalangeal joints. Ultrasonography revealed synovitis with increased Doppler flow signals in multiple joints and confirmed erosions in hand joints. Disease activity score (DAS28) was 6.9. Patient was start-

TABLE I. PATIENT'S BASELINE AND FOLLOW UP DATA UNDER TREATMENT WITH TOFACITINIB

	Baseline (SSZ-HCQ-P)	Tofacitinib 1st month	Tofacitinib 2nd month	Tofacitinib 3rd month	Tofacitinib 6th month	Tofacitinib 12th month
ESR (mm/h)	47	24	19	12	8	5
CRP (mg/L)	29.1	31.4	16.9	3.35	3.27	3.17
Hb (g/dL)	9.9	10.5	10.4	10.8	11.5	10.7
MCV (fl)	75.7	78.9	82.3	81.6	81.6	78.9
WBC, X10E3/uL	9.53	7.92	9.50	6.69	6.81	6.57
Platelets, X10E3/uL	414	301	279	266	296	261
Triglyceride (mg/dL)	90.6	NA	71	62.4	73	70
Cholesterol (mg/dL)	115.1	NA	116	134.6	134	128
HDL-C (mg/dL)	40.1	NA	42	41.6	41	40
LDL-C (mg/dL)	56.88	NA	59.8	80.52	78.4	74
Creatinin (mg/dL)	0.52	0.47	0.54	0.54	0.66	0.63
Fibrinogen(mg/dL)	354	413	–	278	287	–
Tender joint count (44 joints)	17	4	1	1	0	0
Swollen joint count (44 joints)	7	2	1	0	0	0
DAS-28 (CRP)	6.49	4.29	2.91	2.12	1.48	1.47
VAS-pain (mm)	90	40	5	5	0	0
Frequency of FMF attacks in a month	2-3	0	0	0	0	0

SSZ: sulfasalazine; HCQ: hydroxychloroquine; P: prednisolone; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin; MCV: Mean corpuscular volume; WBC: White blood cell counts; HDL-C: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; DAS 28: disease activity score; VAS: visual analogue scale; NA: not available

ed on sulfasalazine 2 g daily, hydroxychloroquine 400 mg daily, methotrexate 10 mg weekly and prednisolone 15 mg daily. Colchicine was maintained 1.5 mg daily dose, increased to 2 mg daily if attacks occurred. After three weeks MTX was ceased because of intolerance. Despite 3-months of combined treatment with sulfasalazine, hydroxychloroquine and tapered dose of prednisolone, the patient continued to have frequent abdominal attacks (2-3 times per month) and RA high disease activity. Biological treatments were decided to be used, however the patient refused parenteral medications. Tofacitinib, an orally administered Janus kinase (JAK) inhibitor, was started 5 mg twice daily. Sulfasalazine, hydroxychloroquine and prednisolone were tapered and ceased after 1-month and the patient continued on tofacitinib monotherapy and 1.5 mg daily colchicine. The patient was followed for 12-months under treatment with tofacitinib and colchicine. She was completely attack free and no adverse events occurred. Patient's baseline and 12--months follow up data is showed in Table I.

To the best of our knowledge this is the first case reporting good control of FMF attacks and disease activity with tofacitinib and colchicine treatment in a patient with concomitant RA and colchicine resistant FMF.

Nearly 5-10% of FMF cases are resistant or intolerant to colchicine[5]. Anakinra, canakinumab, rilonacept, etanercept, infliximab, thalidomide, interferon-alpha, tocilizumab, herbal dietary supplements and non-steroidal anti-inflammatory drugs have been suggested as alternative treatments in colchicine irresponsive/resistant or intolerant patients with FMF[6-8].

Tofacitinib is a non-biologic DMARD approved by the FDA for the treatment of adults with moderately to severely active RA. This potent effect of tofacitinib warrants further research to elucidate the underlying mechanism in the prevention of FMF attacks.

In conclusion, frequent FMF attacks and high disease activity were successfully controlled by tofacitinib, which was well tolerated in combination with colchicine in our patient.

CORRESPONDENCE TO
Salih Ozgocmen
ERU Gevher Nesibe Hospital, Talas Blv, 38030, Kayseri, Turkey
E-mail: sozgocmen@hotmail.com

REFERENCES

1. Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. Arthritis Rheum 2009;61:1447-1453.
2. Dewalle M, Domingo C, Rozenbaum M, et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). Eur J Hum Genet 1998;6:95-97.
3. Akkoc N, Sari I, Akar S, et al. Increased prevalence of M694V in patients with ankylosing spondylitis: additional evidence for a link with familial mediterranean fever. Arthritis Rheum 2010;62:3059-3063.
4. Kalyoncu M, Acar BC, Cakar N, et al. Are carriers for MEFV mutations "healthy"? Clin Exp Rheumatol 2006;24:S120-122.
5. Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum 1991;21:143-155.
6. Akgul O, Kilic E, Kilic G, Ozgocmen S. Efficacy and safety of biologic treatments in Familial Mediterranean Fever. Am J Med Sci 2013;346:137-141.
7. Ozgocmen S, Akgul O. Anti-TNF agents in familial Mediterranean fever: report of three cases and review of the literature. Mod Rheumatol 2011;21:684-690.
8. Wu B, Xu T, Li Y, Yin X. Interventions for reducing inflammation in familial Mediterranean fever. Cochrane Database Syst Rev 2015:CD010893.