Tofacitinib for familial Mediterranean fever: a new alternative therapy?

**Rheumatology key message**

- Tofacitinib could be an alternative therapy for FMF patients resistant/intolerant to conventional therapy.

Sex, FMF is the most common hereditary autoinflammatory disease worldwide. It is a monogenic, autosomal recessive disease caused by mutations in Mediterranean Fever (MEFV) gene on chromosome 16, which encodes the protein pyrin, also called marnenostin, an important regulator of inflammasome complex formation [1]. FMF is characterized by recurrent fever associated with serositis and elevation of acute-phase reactants caused by an exaggerated release of IL-1β secondary to inflammasome activation. Several therapies have been used to treat FMF; the standard treatment protocol involves colchicine, which greatly reduces pathogenesis but also mediated by IL-1β.

Here, we describe a patient with FMF who underwent several treatments before beginning a regimen of tofacitinib and reaching full disease remission. In 2015, a 16-year-old male patient with a history (since childhood) of recurrent fevers, cutaneous rash and recurrent abdominal pain with diarrhea that had been relieved with NSAIDs or high-dose glucocorticoids was re-evaluated as an outpatient owing to worsening symptoms. Tests for different autoimmune disorders, neoplastic conditions and immunodeficiencies were negative. Still’s disease was diagnosed, and conventional treatment was initiated. Clinicians used multiple treatments, starting with steroids and methotrexate; however, after several adverse side effects, etanercept was initiated, with no clinical or laboratory response. Tocilizumab was administered but was effective for only a few months, after which the patient’s clinical response progressively diminished. During this period, genome-sequencing was performed wherein a heterozygous MEFV mutation, known as the Glu148Gln (G442C) single nucleotide polymorphism, was revealed. The patient met two major clinical criteria for FMF diagnosis: typical attacks with generalized peritonitis and typical attacks with monoarthritis [5]. Because the patient was colchicine-resistant, canakinumab was administered with marked clinical improvement; however, the effects lasted only 1 week and not for the expected 4 weeks. Because the patient’s condition continued to worsen, tofacitinib (5 mg twice/day) was administered with subsequent remission of clinical symptoms and permanent reversal of acute-phase reactants to normal values during the 2-month treatment period. The patient is now fully functional, with complete recovery of physical and mental activities. Anakinra, another IL-1β antagonist, was not available in Colombia during this period.

Tofacitinib is a small-molecule drug that targets the Janus kinases (JAK) family of tyrosine kinases; it is specifically selective for JAK3. Tofacitinib allows blockade of the entire JAK–STAT pathway, provoking important downregulation in the expression of some cytokines, such as IL-2, IL-4, IL-6 and IL-7, and subsequently exerting important immunosuppressive effects. Furthermore, it has been used to treat RA, inflammatory bowel disease and alopecia areata. A study on a Turkish patient with concomitant RA and colchicine-resistant FMF treated with tofacitinib reported complete clinical and laboratory remission [6]. Our patient would be the first to use tofacitinib for FMF alone. Our results provide motivation to determine the molecular mechanisms through which tofacitinib induces remission in FMF patients. One possible mechanism is inhibition of STAT3 activation, which would indirectly block the pathway in which IL-1β plays a key role. This theory can be substantiated by a case report that demonstrated adequate response to tofacitinib in a patient with synovitis, acne, pustulosis, hyperostosis and osteitis syndrome, a disease with multifactorial pathogenesis but also mediated by IL-1β [7].

**Funding:** No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

**Disclosure statement:** The authors declare no conflicts of interest.

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Accepted 1 November 2018

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Letters to the Editor

Since 2010, she presented diffuse, painful, sometimes tender, non-tender, and dysplasia with chromosome 20 deletion and low risk myelodysplastic syndrome subtype was multilineage cytopenias (29 patients with skin lesions similar to those with KFD but without any systemic feature, which they called Kikuchi disease (KFD)). We report a case of a 67-year-old European woman had a diagnosis of low-risk myelodysplastic syndrome in 2009. The myelodysplastic syndrome subtype was multilineage cytopenias and dysplasia with chromosome 20 deletion and low risk on the Revised International Prognostic Scoring System. Since 2010, she presented diffuse, painful, sometimes erosive erythematous and violaceous papulonodular skin lesions that initially affected extremities (Fig. 1A), then extended to hands, thighs, arms, breasts, ears and nose (Fig. 1B).

Six months of hydroxychloroquine was not effective, nor were topical corticosteroids. Prednisone 1 mg/kg/day was initiated, with clinical improvement, but with recurrence when the dose was tapered. Laboratory exams showed 2470/mm³ neutrophil count, 10 g/dl haemoglobin level, 177 000/mm³ thrombocyte count and normal C-reactive protein level. The patient was positive for antinuclear antibodies, at 1/320e, in a speckled pattern, without specific anti-extractable nuclear antigens (ENA) and mildly increased anti-DNA antibodies, 15 Ui/ml (n < 7). Complement levels were normal and testing for antiphospholipid antibodies was negative. Histology of skin biopsies revealed typical features of CLE, including vascular alteration of basal keratinocytes, deep perivascular infiltrate of lymphocytes and abundant mucin deposits in the reticular dermis. Dermal inflammatory infiltrates consisted mainly of regular mononuclear cells without dysplasia, nuclear debris or neutrophils (Fig. 1C).

Mononuclear-cell staining revealed CD163+ macrophages, some positive for myeloperoxidase, associated with granulocyte B+ cytotoxic CD8+ lymphocytes and CD123+ plasmacytoid dendritic cells (Fig. 1D and E).

This pathological pattern strongly suggested a KLIP associated with CLE, rather than cutaneous involvement of myelodysplastic syndrome. To discriminate between the two entities, screening for clonal myeloid mutations revealed a DNA (cytosine-5)-methyltransferase 3A (DNMT3A) mutation in blood but not skin, which argued against clonal skin involvement, so-called leukaemia cutis.

Given the severity of the cutaneous involvement and the inefficacy of hydroxychloroquine, treatment with lenalidomide 5 mg/day was proposed, but declined by the patient.

Myelodysplastic syndromes are frequently associated with autoimmune and inflammatory disorders such as vasculitis, inflammatory arthritis and neutrophilic dermatosis [2–4]. Only a few cases of CLE in the subset of myelodysplastic syndromes have been reported. Among 123 patients with myelodysplastic syndrome-related immune diseases, we described eight (with systemic lupus erythematosus) with mainly cutaneous and joint involvement [4]. KFD is a rare clinicopathological disease characterized by fever and cervical lymphadenopathies, accompanied by chills and leukopenia. The disease can precede the occurrence of systemic lupus erythematosus (30%), present simultaneously (47%) or present after its onset [5, 6]. Recently, Thai et al. [1] described 29 patients with skin lesions similar to those with KFD but without any systemic feature, which they called Kikuchi disease-like inflammatory pattern, or KLIP. The 24 patients with KLIP had dermatomyositis, Behçet’s disease, haematological disease (angioimmunoblastic T cell lymphoma, cutaneous T cell and acute myeloid leukaemia), DRESS syndrome, atopic dermatitis and acute viral infection; the most frequent was CLE (n = 16 patients). The authors suggested that KLIP may be considered a new histopathological inflammatory pattern, strongly associated with an autoimmune disease, especially lupus erythematosus.