Efficacy of Janus kinase inhibitor baricitinib in the treatment of refractory juvenile dermatomyositis complicated by calcinosis

Sirs,

we report the efficacy of Janus kinase inhibitor (JAKi) baricitinib in a girl affected by severe refractory juvenile dermatomyositis (JDM) complicated by calcinosis.

The patient was first evaluated at our Rheumatology Unit of Meyer Children's Hospital in Florence, Italy, at the age of 9 years complaining proximal muscle weakness, malar and heliotrope rash, Gottron's papules on the elbows and knees, periungual and gingival vasculitis and dysphagia. The manual muscle testing (MMT) and the childhood myositis assessment scale (CMAS) scores were 35/80 and 11/52, respectively. Creatine kinase value was remarkably elevated (20752 IU/L) with positive antinuclear (ANA) and anti-nuclear matrix protein 2 (anti-NXP2) antibodies. Femoral quadriceps biopsy evidenced necrosis, hypotrophic fibers and overexpression of class I major histocompatibility complex antigens. At diagnosis, the girl received 3 steroid pulses (methylprednisolone 1 g/day) followed by oral steroids and methotrexate (15 mg/m^2 once a week) subcutaneously.

Over the next five years, JDM disease course was characterised by frequent muscular and cutaneous flares complicated by calcinosis on the right lower limb, left thigh and forearm. In addition, due to long-lasting steroid therapy, the girl developed cortical cataract and osteoporosis. Considering the persistent disease activity, over time, the patient received multiple stepwise treatments: along with periodic intravenous immunoglobulins, mycophenolate mofetil, abatacept, infliximab and eventually rituximab. None of them was able to achieve an adequate control of muscular inflammatory state.

Since JDM may be considered an "acquired interferonopathy" due to the excessive expression of type 1 interferon (TI IFN)-stimulated genes (IFN signature) in muscle, blood, and skin of affected patients (1), IFN signature was performed in our patient and a remarkable upregulation of TI IFN pathway was identified. After an appropriate screening for major viral and bacterial infections, including BK and JC virus, baricitinib, in association to a low prednisone dose (0.1 mg/kg/day), was introduced as rescue targeted therapy with an escalated dose, up to 6 mg per day. After 9 weeks on JAKi treatment, she reported a significant improvement with complete recovery of skin manifestations and remarkable increase of muscular strength (MMT score 77/80). Due to the excellent disease control, oral steroids were slowly tapered until suspension after 18 weeks and no additional immunosuppressive drugs have been introduced. The whole-body magnetic resonance imaging (MRI), performed 6 months after starting baricitinib treatment, showed a considerable reduction of the muscular inflammation degree (19/84 *vs*. 48/84) and in the number of involved muscle groups (19/42 *vs*. 42/42) (Fig. 1). In addition, no progression of calcinosis lesions was observed. No adverse events and severe infections were reported. At 27-month follow-up, she is actually in good control of disease.

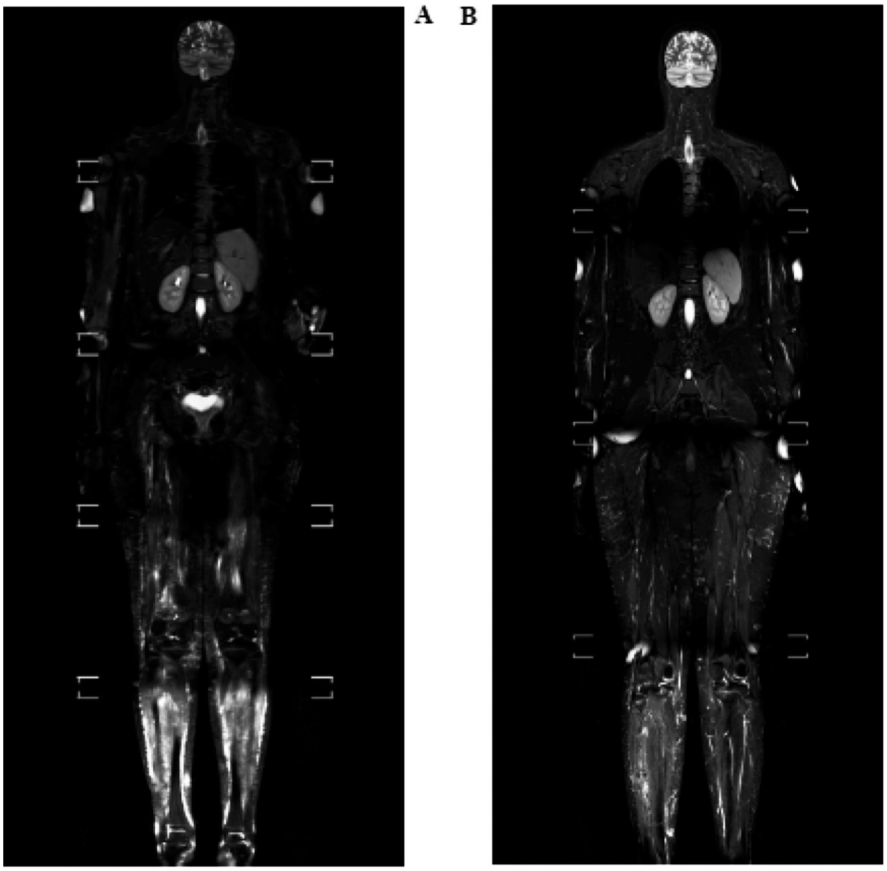

Fig. 1. Whole body magnetic resonance imaging before (**A**) and six months after (**B**) starting baricitinib treatment.

Recently, a retrospective study involving 101 JDM patients treated with JAKi, reported that 65.5% improved rash and 39.6% eliminated glucocorticoids during a median follow-up period of 19 months. Muscle strength was improved in all patients who had a previous abnormal muscle strength. No serious adverse events were reported (2). Anti-NXP2-positive patients showed higher inflammatory cytokines expression than anti-NXP2-negative patients, with a more severe disease course characterised by subcutaneous calcinosis and muscle contractures (2-5). Our patient, also anti-NXP2 positive, suffered from a severe refractory JDM and even if serum cytokine dosage was not performed, her interferon signature assay revealed a notable upregulation. The potential role of interferon signature as JDM disease activity biomarker as well as its possible correlation with JDM clinical phenotype, antibody profile and response to treatment should be evaluated in larger cohorts.

Further studies are advocated to better define the role of JAK inhibition in JDM treatment, not only in case of refractory disease, and to compare the efficacy of different molecules belonging to JAKi category for this group of patients.

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