

Ustekinumab efficacy and safety in mucocutaneous multi-refractory Behçet's disease

Sirs,

Behçet's disease (BD) is a multi-systemic inflammatory disorder characterised by recurrent oral aphthosis, genital ulcers, cutaneous lesions and relapsing uveitis. Other clinical manifestations may derive from gastrointestinal, central nervous system, and vascular involvement (1). Mucocutaneous lesions may be the earliest and the most frequent manifestations of BD, thus anticipating by many years other symptoms (2). A strong Th1 immune response, with over secretion of proinflammatory cytokines such as interleukin (IL)-12 and interferon- γ , occurs in active Behçet's disease (3). Moreover, an increase of Th17 lymphocytes in peripheral blood as well as increased serum levels of IL-17A have been observed (4). On this basis, the emergence of biological therapy targeting the IL-23/IL-17 axis might represent a viable treatment option in BD patients refractory to conventional treatments.

In this regard, we report herein a patient with BD showing mucosal and skin lesions successfully treated with ustekinumab, a monoclonal antibody targeting the p40 subunit IL-12/23.

A 36-year-old woman was referred to our Unit for a 3-year history of bipolar aphthosis and pustular skin lesions involving the chest and both the upper and lower limbs. Mucosal and skin lesions were unresponsive to topical corticosteroids. She also complained of recurrent fever episodes. Upon admission, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 70 mm/h (n.v. <25) and 14.5 mg/dL (n.v. <0.5) respectively. A full diagnostic work-up, including autoimmunity and screening for different infectious diseases, was negative. Considering that her medical history was relevant for recurrent fever attacks, the patient was also tested for mutations in the *MEFV*, *TNFRSF1A*, *NLRP3*, *PSTPIP1* and *MVK* genes responsible for the most common hereditary periodic fever syndromes. No mutations were found. The HLA-B51 allele was positive. The patient fulfilled the International Study Group Criteria and was diagnosed with BD (5). She had been successfully treated with high-dose of oral prednisone (1 mg/kg/day), but each attempt to taper corticosteroid dosage was followed by a disease relapse. Over the past years, colchicine (2 mg/day), methotrexate (up to 15 mg/week), cyclosporine (up to 5 mg/kg/day), and azathioprine (3–4 mg/kg/day) had failed to induce an adequate clinical remission. The tumour necrosis factor- inhibitors adalimumab (40 mg biweekly) and etanercept (50 mg weekly), had been also subcutaneously administered

resulting in an initial satisfying disease control, but both agents were withdrawn after a few months of treatment due to a rapid loss of efficacy over time. Therefore, the IL-1 receptor antagonist anakinra (100 mg/day) was then started, without inducing any amelioration of clinical manifestations. Anakinra was then interrupted and the patient was prescribed with ustekinumab at the induction dose of 45 mg at week 0 and 4, and then every 12 weeks, as recommended for psoriasis. A few weeks after the first injection of ustekinumab, the patient experienced the complete resolution of mucosal bipolar ulcers and of skin lesions. Acute phase reactants rapidly dropped to normal levels. Prednisone was gradually tapered to 5 mg/daily. At 9-month follow-up, the patient was symptom-free and no adverse events were observed.

The decision to treat skin and mucosal lesions in BD is usually based on the perceived severity by the doctor and the patient and their management is usually driven by codominant clinical involvements (6). In this regard, our patient showed refractory bipolar aphthosis and pustular skin lesions, which severely affected her quality of life. The evidence-based European League Against Rheumatism (EULAR) recommendations for BD management suggest that topical measures such as local corticosteroids should be the first line of treatment for isolated oral and genital ulcers and also for acne-like lesions (7). Azathioprine, thalidomide, IFN- α and in most resistant cases TNF- α antagonists should be employed only in patients with refractory skin and mucosa findings (8). Nevertheless, in the most severe cases, benefits on mucocutaneous involvement has been obtained also with biologic drugs exploiting different mechanisms (9). Indeed, Baerfeldt et al recently reported a 39-year-old woman in whom the combination of BD, psoriasis and hidradenitis suppurativa was successfully treated with ustekinumab (10). Our patient was refractory to topical measures, conventional DMARDs and even TNF- α inhibitors and treatment with ustekinumab was started. Recent studies have suggested that Th17 cells may play a relevant role in BD pathogenesis. In this regard, the upregulation of IL-17 and IL-23 by peripheral blood mononuclear cells has been observed in active BD-related uveitis (11). Nevertheless, three multicentre, randomised, phase III studies aimed to assess the efficacy of IL-17 blocker secukinumab in 118 patients with non-infectious uveitis (31 had BD) showed no significant differences in preventing uveitis *versus* placebo (12). Yet, serum IL-17 levels of patients with mucocutaneous BD have been found significantly higher than those with inactive disease, suggesting that impaired Th17 pathways may cause inflammatory attacks in BD (13, 14). IL-12 polymorphisms have

been associated with susceptibility to BD (15). Of note, IL-12 along with IL-23 is capable of inducing naive CD4+ lymphocytes to differentiate into Th1 and Th17 cells, respectively. The same cell populations are involved in the development and maintenance of other skin disorders such as psoriasis, in which the beneficial effects of ustekinumab have been extensively documented (16). A phase-2 open-label study aimed at evaluating the efficacy and safety of ustekinumab, in mucosal and eye involvement in BD is promptly to start recruiting (STELABEC 1/2) (ClinicalTrials.gov Identifier: NCT02648581). In conclusion, ustekinumab rapidly determined the complete resolution of mucosal and skin lesions in our patient and also induced a rapid and stable normalisation of acute phase reactants. The treatment was well tolerated and no adverse events occurred. However, establishing ustekinumab long-term safety and effectiveness in BD still remains a challenge and further ad hoc studies on larger cohorts of patients are needed.

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Competing interests: none declared.

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