Effectiveness of apremilast against Behçet's disease-associated mucocutaneous and joint involvement confirmed through switching from adalimumab

Sirs,

Apremilast is reportedly effective against oral ulcers (OU) associated with Behçet's disease (BD) (1, 2). However, evidence regarding its efficacy against lesions associated with BD other than OU remains lacking. We encountered a case wherein the effectiveness of apremilast against BD-associated mucocutaneous and joint involvement could be confirmed through switching from adalimumab (ADA).

A 34-year-old Japanese female was diagnosed with BD according to the International Study Group for BD criteria (3) at age 30 after presenting with high fever, recurrent OU, genital ulcers (GU), erythema nodosum (EN), wrist and hip joint arthritis, and positive human leukocyte antigen-B51. The patient had no ocular, gastrointestinal, or neuropsychiatric symptoms. Further, ophthalmic examinations, neck, chest, and abdominal computed tomography, and brain magnetic resonance imaging revealed no abnormalities. The administration of colchicine was initiated, but fever and elevated serum C-reactive protein (CRP) levels (1–3 mg/dl, normal ≤0.14 mg/dl) persisted. Colchicine treatment was discontinued because of persistent diarrhoea, and subsequent administration of azathioprine was discontinued due to skin rashes. The patient was then administered with ADA 40 mg/2 weeks (before apremilast was approved in Japan), which promptly led to remission and normalised serum CRP values. ADA monotherapy was observed to maintain the remission state of her BD. The patient stopped using ADA on her own volition 20 months after its commencement. Four months after discontinuing ADA treatment, her serum CRP level was elevated (3.65 mg/dL, normal ≤0.30 mg/dl), and after six months, fever, OU, pseudofolliculitis, and wrist arthritis occurred. Following the recommencement of ADA administration, the patient promptly returned to remission. ADA monotherapy was continued again for 15 months, during which remission was maintained. However, as the patient did not prefer injections, ADA was replaced with apremilast. The dosage of apremilast was reduced to 30 mg/day due to the side effect of diarrhoea caused by oral administration of apremilast 60 mg/day; however, remission was maintained without any signs of recurrence for 15 months after switching to apremilast (Fig. 1). Written informed consent for publication of this case report was obtained from the patient.

The first meta-analysis on the effectiveness of apremilast for involvement other than BD-associated OU by Iizuka *et al*. showed that apremilast significantly improved GU, EN, pseudofolliculitis, and arthritis within 12 weeks from the initiation of administration (4). The meta-analysis included studies targeting patients with mucocutaneous and joint involvement who were resistant to colchicine, systemic glucocorticoids, and immunosuppressive agents (2, 5-9). Most of the studies included patients who were refractory to treatment with tumour necrosis factor (TNF) inhibitors (up to 76.9%), with different percentages in each study (5-9). Apremilast inhibits the production of TNF and other inflammatory cytokines and promotes the production of the anti-inflammatory cytokine interleukin-10 (1, 2, 9). Hence, TNF inhibitors may not necessarily be more effective than apremilast. In our case, the remission of BD was maintained even after switching from ADA to apremilast. Since BD itself has a relapsing-remitting course, the patient may have been in the remission phase of BD regardless of the effect of apremilast. However, considering that the patient, who had maintained in remission for a long time, relapsed early after ADA discontinuation and that the patient rapidly recovered and achieved remission after ADA resumption, ADA was likely needed to maintain remission of BD in the patient, and it appears that apremilast is as effective as ADA in maintaining her remission. The LIBERATE study targeting patients with moderate to severe plaque psoriasis reported that the improvement rate of skin lesions by etanercept was maintained for nearly two years after switching from etanercept to apremilast (10). To the best of our knowledge, no reports have mentioned the effects of switching from TNF inhibitors to apremilast for treating BD.

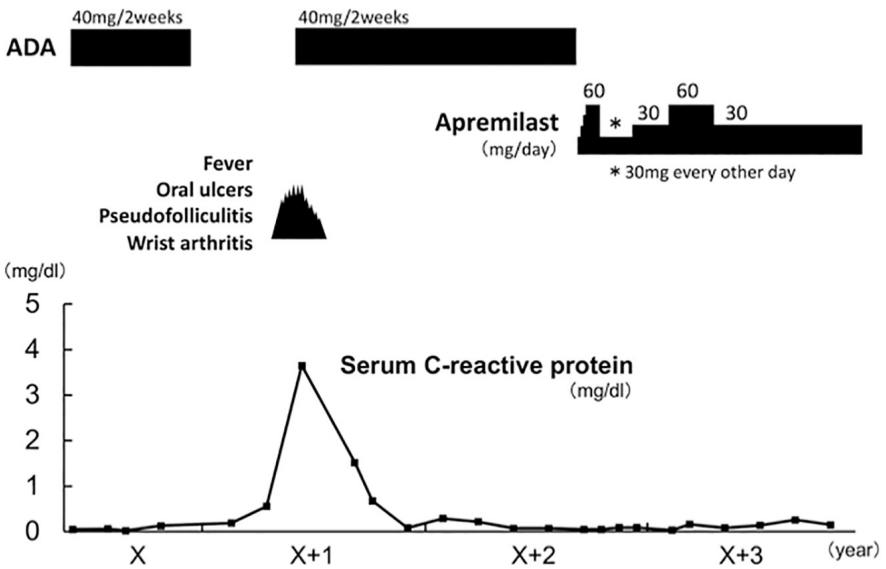

Fig. 1. Clinical course: recurrence after discontinuation of adalimumab and maintenance of remission after switching from adalimumab to apremilast.
ADA: adalimumab.

In conclusion, apremilast appears effective against the mucocutaneous and joint involvement associated with BD. Furthermore, switching to apremilast after observing improved mucocutaneous and joint involvement by TNF inhibitors, as with this case, is also considered as one of the effective options for BD treatment. Proper randomised controlled trials of apremilast for systemic manifestations associated with BD other than OU are needed in the future.

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