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Concise report

Efficacy and safety of apremilast for Behçet's syndrome: a real-life single-centre Italian experience

Giacomo De Luca[1,2,*], Adriana Cariddi[1,2,*], Corrado Campochiaro[1,2], Daniele Vanni[2], Nicola Boffini[1], Alessandro Tomelleri[1,2], Giulio Cavalli[1,2] and Lorenzo Dagna[1,2]

Abstract

Objectives. To evaluate the efficacy and safety of apremilast in treating oral ulcers (OUs), the cardinal and high-disabling feature of Behçet's disease (BD).

Methods. Twelve consecutive patients affected by BD with recurrent/relapsing OUs resistant and/or intolerant to conventional therapy were enrolled and prospectively followed. The primary endpoint was the number of OUs at week 12. Secondary endpoints were modification from baseline to week 12 in Behçet's Syndrome Activity Score (BSAS), Behçet's Disease Current Activity Form (BDCAF) score, Behçet's Disease Quality of Life (BDQOL) scale and pain of OUs, as measured by a visual analogue scale (VAS). All adverse events (AEs) were recorded during follow-up. Non-parametric tests (Wilcoxon rank test) were used and a P-value <0.05 was considered statistically significant.

Results. After 12 weeks of apremilast, there was a significant reduction in the number of OUs [0.58 (S.D. 0.67) *vs* 3.33 (S.D. 1.45) at baseline, $P = 0.02$] that was paralleled by improvement in disease activity: BSAS was 16.8 (S.D. 9.1) [from 45.9 (S.D. 19.6) at baseline] ($P = 0.02$), BDCAF score was 0.72 (S.D. 0.65) [*vs* 2.45 (S.D. 1.0) at baseline] ($P = 0.04$) and the VAS score for pain decreased to 23.3 (S.D. 13.7) [*vs* 67.9 (S.D. 17.2) at baseline] ($P = 0.02$). Consistently, an improvement of BDQOL was assessed ($P = 0.02$). Clinical improvement led to complete steroid discontinuation in six patients and a tapering of the prednisone dose in two patients ($P = 0.016$). Colchicine was discontinued in six of nine patients ($P = 0.031$). AEs related to apremilast occurred in four patients (mainly due to gastrointestinal AEs), leading to drug discontinuation in all of them.

Conclusion. Our preliminary real-world data support the use of apremilast as an effective therapeutic strategy against BD-related recurrent OUs resistant or intolerant to first-line therapy.

Key words: Behçet's disease, oral ulcers, apremilast

Rheumatology key messages

- Oral ulcers are the cardinal feature of Behçet's disease and are highly disabling.
- Effective therapeutic strategies for mucocutaneous involvement of Behçet's disease are greatly needed.
- Apremilast showed a promising efficacy against oral ulcers in a real-world scenario.

Introduction

Behçet's disease (BD) is a chronic relapsing inflammatory disorder characterized by recurrent oral (OUs) and genital ulcers (GUs), skin lesions, ocular manifestations (e.g. uveitis, conjunctivitis), arthritis and other systemic involvement as gastrointestinal, neurologic and vascular disease [1]. Mucocutaneous lesions are the hallmark of BD: multiple OUs occur in almost all patients, while GUs occur in 60–65% of cases; diverse skin lesions overall occur in 70–75% of cases and may include erythema nodosum, pseudofolliculitis, papulopustular lesions and acneiform nodules [1]. Mucocutaneous BD with recurrent OUs is highly disabling and can significantly affect patients' quality of life (QOL) [1–3].

The EULAR recommendation for the mucocutaneous lesions of BD includes colchicine and topical or systemic glucocorticoids as first-line therapy [4]. However, a substantial proportion of patients fail to respond to these

[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy and [2]Vita-Salute San Raffaele University, Milan, Italy

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*Giacomo De Luca and Adriana Cariddi contributed equally to this article.

Correspondence to: Giacomo De Luca, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Via Olgettina 60, 20132 Milano, MI, Italy. E-mail: deluca.giacomo@hsr.it

CLINICAL SCIENCE

therapies and are currently treated with various conventional or biologic immunosuppressive agents, often with unsatisfactory results [5–10]. Effective strategies for refractory OUs are needed to alleviate the burden of BD.

Apremilast is an oral phosphodiesterase-4 inhibitor approved for moderate to severe skin psoriasis and PsA [11–13]. Based on favourable results in phase II [14] and III trials [15] (ClinicalTrials.gov identifier: NCT02307513), apremilast is emerging as a promising therapeutic option for mucocutaneous BD [4]. However, the clinical effectiveness of apremilast in the real-life management of difficult-to-treat BD patients remains to be determined.

Here we report the encouraging results of a prospective study evaluating the efficacy and safety of apremilast in a cohort of BD patients with recurrent/relapsing OUs that were refractory and/or intolerant to conventional therapies.

Methods

Twelve consecutive patients affected by BD with mucocutaneous involvement resistant and/or intolerant to conventional therapy (i.e. steroids and colchicine) were enrolled at our tertiary referral centre for rare diseases. All enrolled patients received oral apremilast (Otezla) at doses used for the treatment of PsA [11–13]. All patients were prospectively followed up for at least 12 weeks.

Inclusion criteria were as follows: a diagnosis of BD according to the International Study Group for Behçet's Disease criteria [16], at least 18 years of age, at least one new OU or GU within 28 days before screening and at least two OUs at the time of apremilast initiation and resistance or intolerance to conventional therapy. Patients were considered to be resistant to conventional therapy if they had experienced at least two recurrences of symptomatic OU or GU while on conventional therapy with topical corticosteroids plus systemic steroids and colchicine (at least 1 mg daily) for at least 3 consecutive months. Patients were considered to be intolerant to conventional therapy if they had contraindications to systemic steroid therapy (i.e. diabetes, hypertension, increased intra-ocular pressure, osteoporosis) and/or had experienced at least one adverse event (AE) related to colchicine (diarrhoea, 2-fold increase in liver enzymes, serum creatinine >1.5 mg/dl or 30% reduction of glomerular filtration rate, cytopenia).

Exclusion criteria were active BD-related uveitis, active BD-related gastrointestinal involvement (e.g. ulcers along the gastrointestinal tract, new onset or worsening of abdominal pain and/or diarrhoea) or major organ involvement [i.e. vascular (e.g. thrombophlebitis), pulmonary (e.g. pulmonary artery aneurysm) and central nervous systems (e.g. meningoencephalitis) manifestations] during the 12-months before enrolment, pregnancy or breastfeeding, active or chronic infections (hepatitis B or C, active or latent tuberculosis), history of a suicide attempt or any known major psychiatric illness requiring medical management within 3 years prior to enrolment and concomitant therapy with biologic agents (anti-TNF-α or cytokine blocking agents) administered within 5 half-lives of the specific drug.

Patients receiving concomitant conventional synthetic DMARDs (i.e. AZA, MTX or ciclosporin) without modifications in the dosage during the 3 months preceding the time of apremilast initiation were allowed to continue receiving these medications. Dose reduction or DMARD discontinuation after apremilast initiation was permitted.

The primary endpoint was the change in the number of OUs at week 12. Secondary endpoints were changes in the Behçet's Syndrome Activity Score (BSAS), changes in the Behçet's Disease Current Activity Form (BDCAF) score, changes in pain as measured by the visual analogue scale (VAS; with 0 representing no pain and 100 the worst pain ever experienced) and changes in the Behçet's Disease Quality of Life (BDQOL) scale at week 12. AEs were recorded every 4 weeks until week 12 for all patients and at the latest available follow-up for some patients. The study was conducted in compliance with the Declaration of Helsinki. The Institutional Review Board and Pharmacovigilance Board approved the study and all patients provided written informed consent at the time of enrolment.

Statistical analysis

Data were analysed using SPSS version 22.0 software (IBM, Armonk, NY, USA). Data are presented as mean (S.D.). Categorical data are presented as the proportion of cases or percentages. Non-parametric tests (Wilcoxon rank test) were used and a P-value <0.05 was considered statistically significant.

Results

Twelve patients [8 females, 4 males; mean age 41.5 years (S.D. 4.1); mean disease duration 64.6 months (S.D. 40.9)] diagnosed with BD were enrolled in the study. Baseline demographic and clinical characteristics are summarized in Supplementary Table S1, available at *Rheumatology* online. All patients had painful OUs, six patients (50.0%) had concomitant symptomatic GUs and eight patients (66.7%) had concomitant cutaneous involvement (pustulosis, folliculitis or erythema nodosum). A previous history of inflammatory arthritis and uveitis requiring DMARD therapy was found in two and three patients, respectively. Before apremilast initiation, eight patients (66.7%) were receiving prednisone [mean daily dose 10.3 mg (S.D. 7.1)]; nine were receiving colchicine (1 mg daily), six patients were being treated with AZA (2 mg/kg daily) and two were treated with MTX (up to 20 mg weekly). One patient each had been treated with adalimumab (40 mg every 2 weeks) and IFN-α prior to study enrolment, for arthritis and recurrent OUs and recent uveitis, respectively. At baseline, the mean number of OUs was 3.33 (S.D. 1.45), the mean number of GUs was 1.50 (S.D. 0.83), the BSAS was 45.9 (S.D. 19.6) and the BDCAF was 2.45 (S.D. 1.0) (Table 1).

After 12 weeks of apremilast, there was a significant reduction in the number of OUs [0.58 (S.D. 0.67), $P=0.02$] (Table 1) as well as GUs [0.17 (S.D. 0.41)]

Table 1 Results at 12 weeks after apremilast therapy

Characteristics	Baseline	Week 12	*P*-value
Number of OUs, mean (S.D.)	3.33 (1.45)	0.58 (0.67)	0.02
Patients on systemic steroids, *n* (%)	8 (66.7)	2 (16.7)	0.016
Steroid daily dose, mean (S.D.)	9.17 (11.69)	0.83 (1.95)	0.017
Patients on colchicine, *n* (%)	9 (75.0)	3 (25.0)	0.03
BSAS, mean (S.D.)	45.9 (19.6)	16.8 (9.1)	0.02
BDCAF, mean (S.D.)	2.45 (1.0)	0.72 (0.65)	0.04
VAS pain of OUs, mean (S.D.)	67.9 (17.2)	23.3 (13.7)	0.02
BDQOL, mean (S.D.)	14.07 (4.13)	10.15 (4.11)	0.018
Patients with cutaneous disease, *n* (%)	8 (66.7)	0 (0)	0.01

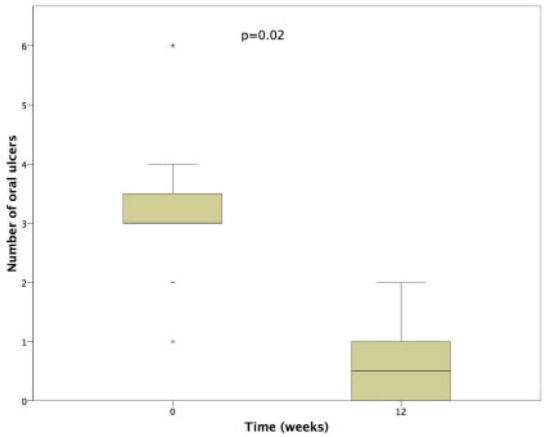
(Fig. 1), even though this latest did not reach statistical significance due to the small number of patients with active GUs at baseline (P = ns). Of the eight patients with cutaneous involvement, none had residual pustulosis or folliculitis at the end of the follow-up ($P = 0.01$) (Table 1); only one patient presented a recurrence of erythema nodosum, successfully treated with a 4-week course of ibuprofen.

The clinical improvement of BD-related mucocutaneous manifestations was paralleled by a significant reduction in disease activity and patient-reported scores, as well as by global improvements in QOL. Specifically, the BSAS decreased from 45.9 (S.D. 19.6) at baseline to 16.8 (S.D. 9.1) at week 12 ($P = 0.02$) and the BDCAF score decreased from 2.45 (S.D. 1.0) to 0.72 (0.65) ($P = 0.04$). Of note, a marked improvement in the pain VAS for OUs was also observed [from 67.9 (S.D. 17.2) at baseline to 23.3 (13.7) at week 12; $P = 0.02$]. Consistently an improvement of overall QOL was achieved [BDQOL 14.1 (S.D. 4.13) at baseline *vs* 10.15 (4.11) at week 12; $P = 0.02$] (Table 1).

Clinical improvement led to complete corticosteroid discontinuation in six patients and to a significant corticosteroid dose reduction in the remaining two patients ($P = 0.016$). Specifically, the mean daily prednisone equivalent dose decreased from 9.17 mg (S.D. 11.69) at baseline to 0.83 mg (S.D. 1.95) at week 12 ($P = 0.017$). Clinical response also allowed discontinuing colchicine in six of nine patients ($P = 0.031$) (Table 1). In addition, four of four patients receiving AZA solely for mucocutaneous involvement were able to discontinue this drug. MTX was continued in the two patients with inflammatory arthritis. In these patients, remission of arthritis had been achieved with MTX prior to apremilast initiation and no further modifications were observed during the 12-week study period. The patient previously treated with adalimumab before study enrolment was successfully treated with apremilast for recurrent OUs (Supplementary Table S2, available at *Rheumatology* online).

AEs related to apremilast occurred in four patients. Diarrhoea was the most common drug-related AE, recorded in three cases. It occurred at week 4 in two patients and at week 8 in one patient. One patient presented with suicidal ideation 4 weeks after apremilast initiation. In all four cases, AEs led to complete drug discontinuation.

Fig. 1 Changes from baseline in the number of OUs at 12 weeks



The number of OUs decreased from 3.33 (S.D. 1.45) at baseline to 0.58 (S.D. 0.67) at week 12. The reduction in the mean number of OUs after apremilast therapy was statistically significant ($P = 0.02$).

Of note, among the three patients with diarrhoea, two were concomitantly treated with colchicine and one of these patients had a history of BD-related gastrointestinal involvement (previous ulcers in the colon), which was inactive at the time of study enrolment.

In patients remaining on apremilast therapy, a longer follow-up (ranging from 24 to 60 weeks) revealed no further AEs. One additional patient had a recurrence of erythema nodosum and a flare of inflammatory arthritis while on apremilast therapy associated with MTX; however, it was successfully managed with a brief cycle of ibuprofen. None of the patients presented with possible drug-related laboratory abnormalities (Supplementary Table S2, available at *Rheumatology* online).

Discussion

The presence of painful and recurrent OUs is the hallmark of BD, being the first and the most common manifestation

of BD, and occurs in almost all patients. Mucocutaneous BD with recurrent/relapsing OUs is highly disabling: the size, duration, ulcer-free period and pain related to OUs all have a significant influence on both disease activity and patients' QOL[1–3].

The EULAR recommendations suggest colchicine and topical or systemic glucocorticoids as first-line therapy for mucocutaneous BD [4]. However, the efficacy of colchicine is not universal [5–7]; in addition, a substantial proportion of patients experience recurrent, relapsing or resistant mucocutaneous manifestations. For lesions that are resistant to colchicine, AZA, IFN-α, thalidomide, TNF-α and cytokine blocking agents are prescribed in clinical practice, often with mixed or dissatisfying results [8–10]. Of note, a recent study revealed that physicians are often recalcitrant, using conventional immunosuppressive agents for the management of OUs despite these being the main clinical manifestation of active BD [17]. In addition, most BD patients receiving immunosuppressive therapies continue to have low to moderate disease activity due to refractory OUs. Given this clinical reality, effective therapeutic strategies for OUs are eagerly awaited.

Apremilast is an oral phosphodiesterase-4 inhibitor approved for use in moderate to severe psoriasis and PsA [11–13]. Efficacy and safety of apremilast for BD-related OUs has emerged in a phase II trial: the mean number of OUs per patient at week 12 was significantly lower in the apremilast group, and this improvement was paralleled by a greater decline in pain for OUs from baseline to week 12 with apremilast than with placebo [14]. The promising results of the phase II trial paved the way for a phase III trial (ClinicalTrials.gov identifier: NCT02307513) on 208 patients with BD. Preliminary results from this trial are likely to propose apremilast as a feasible and effective therapy to treat OUs, as apremilast effectively reduced the number and pain of OUs at week 12, improved time to OUs resolution and maintained the resolution of OUs during a 52-week follow-up [15]. Favourable treatment effects were also observed for GU resolution. The safety profile was consistent with the known safety profile of apremilast for PsA [11–13, 15]. However, the efficacy and safety of apremilast in a real-world scenario are yet to be elucidated.

Here we conducted a prospective study to evaluate the 12-week efficacy and safety of apremilast in a cohort of BD patients with recurrent/relapsing OUs resistant and/or intolerant to conventional therapy. Our results are in keeping with those from clinical trials and support the use of apremilast, either as monotherapy or combined with DMARDs, to treat this cardinal clinical feature of BD. In this study, a significant reduction in the number of OUs was obtained after 12 weeks and was paralleled by a dramatic improvement in disease activity and pain scores, as well as QOL. Consistently, apremilast had a robust steroid-sparing effect, leading to discontinuation or at least substantial tapering in the majority of patients. Similarly, colchicine therapy was discontinued in a substantial percentage of patients due to optimal control of OUs with apremilast. Conversely, ongoing MTX therapy was maintained in the two patients with inflammatory arthritis, already in clinical remission, thus limiting information that can be drawn on the efficacy of apremilast on BD-related arthritis patients. Analysis of safety data, however, showed a considerable rate of drug discontinuation due to diarrhoea in the first 4 weeks. This complication occurred in two of three patients while on concomitant colchicine therapy. Furthermore, one of them had had BD-related gastrointestinal involvement. It is thus plausible that concomitant treatment or underlying pathophysiology contributed to apremilast-induced diarrhoea in these patients. In addition, the long disease duration and the presence of multisystemic disease in the majority of our patients probably accounts for the higher rate of AEs observed in our real-world setting compared with that reported in clinical trials: in the phase III trial, patients with both gastrointestinal involvement and uveitis requiring immunosuppressants were excluded.

Our study has some limitations. The small number of patients enrolled, although in line with the rarity of the condition, is a major one, the 'real-life setting', which influences the clinical diversity of patients enrolled and the concomitant use of DMARDs or colchicine in the majority of them (even though at a stable dose) and the lack of a placebo arm all limit the drawing of firm conclusions. However, the same real-world setting represents a strength of our study, which could be proposed as the starting point for larger multicentre studies with longer follow-ups.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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