Real-world effectiveness of apremilast in multirefractory mucosal involvement of Behçet's disease

Relapsing oral and genital ulcers (OGUs) represent the stigmata of Behçet's disease (BD) and may be very painful, affecting both quality of life and relationships. A wide number of topical and immunosuppressive drugs can be used to treat ulcers,[1] but failures are commonly reported. The efficacy of the phosphodiesterase-4 inhibitor apremilast has been proven in OGUs of BD in two randomised clinical trials (RCTs),[2 3] whereas only two case reports are available until now.[4 5] We aimed at evaluating the real-world effectiveness of apremilast in BD patients with OGUs refractory to conventional and/or biological treatments.

We retrospectively evaluated patients classified as BD, according to International Criteria for BD[6] and International Study Group[7] criteria, who underwent apremilast (30 mg two times per day) for multirefractory OGUs from November 2017 to January 2019. The number of OGUs was assessed at baseline and either at 3 and 6 months. Pain from ulcers and BD activity were evaluated via 100 mm visual analogue scale (VAS) and BD current activity form (BDCAF). We also recorded the number of OGU flares both in the 4 weeks prior to apremilast start and throughout the observation period (table 1 and online supplementary table 2). The occurrence of adverse events was also reported. Paired t-test or Wilcoxon matched-pair signed rank test were used for statistical analysis. The off-label use of apremilast was approved by the Hospital Ethics Committee in compliance with the Declaration of Helsinki. All patients provided a written informed consent.

Thirteen patients (females 9/13) with disease duration (mean±SD) of 154±167 months were analysed (table 1) (online supplementary file 1). At 3 months (data from 12/13 patients) active OGUs were significantly less (p=0.02 for both) than baseline (table 2). Three patients stopped the treatment due to diarrhoea. At 6 months, active oral ulcers and oral relapses were still lower than baseline (p=0.03 for both), whereas only a positive trend (p=0.07) for genital ulcers was seen (data from 8/13 patients) (table 2). Ulcer VAS pain was 67±16 at baseline, and a prompt amelioration was observed at 3 months (29±32, p=0.002), and confirmed at 6 months (20±19, p=0.005) (table 2). Likewise, BDCAF dropped from 4.5±2.9 of baseline to 3.2±3.4 at 3 months (p=0.01), and was persistently low up to 6 months (2.3±3.7, p=0.01) (table 2). Serious adverse events were not observed.

Table 2 Mucosal involvement, VAS pain and BDCAF assessed at baseline and throughout the observation period

	Baseline 13 patients	3 months 12 patients	P value	6 months 8 patients	P value
Number of active oral ulcers, mean (SD)	1.1 (0.6)	0.4 (0.5)	0.02	0.4 (0.5)	0.03
Number of active genital ulcers, mean (SD)	0.5 (0.5)	0.1 (0.3)	0.02	0 (0)	0.07
BDCAF, mean (SD)	4.5 (2.9)	3.2 (3.4)	0.01	2.37 (3.7)	0.01
VAS pain, mean (SD)	67.5 (16.6)	29 (32.1)	0.002	20 (19.1)	0.005

Reported p values are referred to the difference from baseline.
BDCAF, BD current activity form; VAS, visual analogue scale.

Our findings are consistent with a recent RCT on 111 BD patients,[2] which showed the efficacy of apremilast in reducing both number and pain of oral ulcers.[2] Preliminary results from another study confirm the significant decrease of total number of oral ulcers and resolution of genital ulcers over 12 weeks in the apremilast group.[3] Similarly, in our study the mean number of oral relapses during therapy was significantly lower than that in the 4 weeks prior to apremilast. Interestingly, an appreciable reduction of VAS pain and BDCAF was already seen at 3 months and persisted up to 6 months. Of note, the overall beneficial effect of apremilast also on joint symptoms should be highlighted, as emerged by the BDCAF evaluations. Apremilast was safe and no serious adverse events were observed during the time span of our study. The main limitations of our study were the small sample size and the short-term follow-up. In addition, patients had been referred to our tertiary care centres since they were difficult-to-treat or refractory to therapy, configuring a possible selection bias. Nevertheless, we provide evidence that

Table 1 Clinical and demographic characteristics of 13 patients with Behçet's disease included in our study

Demographic features		**Clinical characteristics at diagnosis, n (%)**	
Female, n (%)	9 (69.2)	Ocular involvement	4 (30.8)
Age in years, mean (SD)	44.1 (11.2)	Oral ulcers	13 (100)
HLA-B51 positivity, n (%)	6 (54.5)	Genital ulcers	9 (69.2)
Disease duration at APR baseline, months, mean (SD)	154.2 (167.8)	Other mucocutaneous involvement	7 (53.8)
Previous biological agents, n (%)		**Musculoskeletal involvement**	10 (76.9)
Tumor necrosis factor-α inhibitors	10 (76.9)	Central nervous system involvement	1 (7.7)
Anakinra	4 (30.8)	Vascular involvement	2 (15.4)
Ustekinumab	2 (15.4)	Gastrointestinal involvement	6 (46.1)
Previous immunosuppressants, n (%)		**Combination treatment at baseline, n (%)**	
Colchicine	10 (76.9)	Colchicine	4 (30.8)
Cyclosporine A	4 (30.8)	Intravenous immunoglobulins	1 (7.7)
Methotrexate	3 (23.1)	Anakinra	1 (7.7)
Azathioprine	9 (69.2)	Low dose steroids (≤10 mg prednisone /day)	10 (76.6)
Others (cyclophosphamide, thalidomide, interferon, sulfasalazine)	7 (53.9)	High dose steroids (>10 mg prednisone /day)	2 (15.4)
Flares of mucosal involvement in the 4 weeks prior to APR			
Oral ulcer flares, mean (SD)	2.2 (3.1)	Genital ulcer flares, mean (SD)	0.5 (0.7)

APR, apremilast.

apremilast may induce a meaningful and early benefit in BD patients with multirefractory OGUs also in real-life settings.

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Handling editor Josef S Smolen

Acknowledgements We would like to thank prof Giovanni Lapadula for his valuable insights.

Collaborators Marco Fornaro, Maria Grazia Giannotta, Elena Silvestri.

Contributors All authors approved the final version of the letter after being involved in drafting and revising the article for important intellectual content. As the corresponding author, GL had full access to the data and takes responsibility for the accuracy of the performed analysis and the integrity of data. GL, VV and FI were involved in the design of the study. Execution, analysis and writing of the manuscript were performed by GL and VV.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval This study was performed according to the Declaration of Helsinki and obtained the approval by the Ethics Committee in the University of Bari, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2019-215437).

GL and VV contributed equally.

To cite Lopalco G, Venerito V, Leccese P, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2019-215437

Received 27 March 2019
Revised 25 July 2019
Accepted 6 August 2019

Ann Rheum Dis 2019;**0**:1–2. doi:10.1136/annrheumdis-2019-215437

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