Apremilast in refractory orogenital ulcers and other manifestations of Behçet's disease. A national multicentre study of 51 cases in clinical practice

B. Atienza-Mateo[1], J.L. Martín-Varillas[1], J. Graña[2], G. Espinosa[3], C. Moriano[4], T. Pérez-Sandoval[4], M.D. García-Armario[5], I. Castellví[6], J.A. Román-Ivorra[7], A. Olivé[8], A. Ybáñez[9], A. Martinez-Ferrer[9], J. Narváez[10], S. Romero-Yuste[11], S. Ojeda[12], I. Ros[13], J. Loricera[1], V. Calvo-Río[1], S. Castañeda[14], M.A. Gonzalez-Gay[1], R. Blanco[1], on behalf of the Spanish Collaborative Group of Refractory Behçet's Disease

Affiliations: see page S74.

Belén Atienza-Mateo, MD
José Luis Martín-Varillas, MD
Jenaro Graña, MD, PhD
Gerard Espinosa, MD, PhD
Clara Moriano, MD
Trinidad Pérez-Sandoval, MD
María Dolores García-Armario, MD
Iván Castellví, MD, PhD
José Andrés Román-Ivorra, MD
Alejandro Olivé, MD, PhD
Amparo Ybáñez, MD
Angels Martinez-Ferrer, MD
Javier Narváez, MD, PhD
Susana Romero-Yuste, MD, PhD
Soledad Ojeda, MD
Inmaculada Ros, MD
Javier Loricera, MD, PhD
Vanesa Calvo-Río, MD, PhD
Santos Castañeda, MD, PhD
*Miguel A. Gonzalez-Gay, MD, PhD**
*Ricardo Blanco, MD, PhD**

**M.A. Gonzalez-Gay and R. Blanco shared senior authorship.*

Please address correspondence to:
Ricardo Blanco,
Rheumatology Division, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla s/n.,
39008 Santander, Spain.
E-mail: rblanco@humv.es

Received on July 5, 2020; accepted in revised form on September 21, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 127): S69-S75.

Key words: Behçet's disease, apremilast, oral ulcers, genital ulcers, multicentre study

Competing interests: see page S74.

ABSTRACT

Objective. *The objective of the present study was to assess the efficacy of apremilast (APR) in the management of refractory oral and/or genital ulcers in patients with Behçet's disease (BD).*

Methods. *National multicentre open-label observational study on BD patients with recurrent oral and/or genital ulcers. In all cases orogenital ulcers were refractory to conventional therapy. APR was given and maintained at standard dose of 30 mg twice daily. The main outcome was the achievement of oral and/or genital ulcers remission. Efficacy of APR for other clinical manifestations was also evaluated.*

Results. *We included 51 patients (35 women/16 men; mean age 44.7±13.2 years). Before APR, all patients had received several systemic conventional and/or biologic drugs. APR was initiated because of refractory oral (n=19) or genital (n=2) aphthous ulcers or both (n=30). Other manifestations found at APR onset were arthralgia/arthritis (n=16), folliculitis/pseudofolliculitis (n=14), erythema nodosum (n=3), furunculosis (n=2), paradoxical psoriasis induced by TNF-α-inhibitors (n=2), ileitis (n=2), deep venous thrombosis (n=2), leg ulcers (n=1), erythematosus and scaly skin lesions (n=1), fever (n=1), unilateral anterior uveitis (n=1) and neuro Behçet (n=1). After a mean follow-up of 8.5±6.9 months, most patients had experienced improvement of orogenital ulcers and prednisone dose had been successfully reduced or discontinued. APR also yielded improvement of some non-aphthous manifestations such as the cutaneous follicular and intestinal manifestations. However, the effect on musculoskeletal manifestations was variable.*

Conclusion. *APR yielded a rapid and maintained improvement of refractory mucocutaneous ulcers of BD, even in patients refractory to several systemic drugs including biologic therapy.*

Introduction

Behçet's disease (BD) is a chronic systemic inflammatory disorder of unknown aetiology included in the group of variable vessel vasculitis (1, 2). It is characterised by a wide range of heterogeneous clinical manifestations and the treatment depends mainly on the clinical severity and affected organs (3, 4). Major organ involvement such as ocular, neurologic, vascular and gastrointestinal disease often requires an aggressive approach, usually with immunosuppressive agents (5, 6). Although recurrent oral and/or genital ulcers are not life-threatening complications, they are one of the most characteristic features of BD. Moreover, they can be extremely painful and disabling (7, 8). Several systemic therapeutic agents such as colchicine, glucocorticoids, conventional and biologic immunosuppressive drugs have been used for orogenital aphthous ulcers with contradictory and variable results (9).

Apremilast (APR) is an orally active small molecule which inhibits phosphodiesterase-4 (PDE-4). APR modulates intracellular inflammatory pathways decreasing proinflammatory and increasing anti-inflammatory mediators (10, 11). This drug is included in the group of targeted synthetic dis-

ease-modifying antirheumatic drugs (tsDMARDs). Although combination therapy with two biological disease-modifying antirheumatic drugs (bDMARDs) is generally not recommended (12), APR may be used in monotherapy or combined with either conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or bDMARDs.

Randomised clinical trials (RCTs) are conducted under highly standardised design with strict inclusion criteria (13). It is possible that features of RCTs may differ from those of clinical practice (14). Two interesting randomised double-blinded phase II and III clinical trials showed efficacy and safety of APR for oral ulcers of BD (15, 16). Based on these trials, the U.S. Food and Drug Administration (FDA) has recently approved APR for the treatment of oral ulcers associated with BD (www.fda.gov) (17). However, in these trials, patients with active involvement of any major organ during the 12 months before recruitment, history of recurrent or chronic infections, latent tuberculosis or who had received biologic therapies were not included. Furthermore, patients were not allowed to receive concomitant medications indicated for the management of BD. Full information related to orogenital ulcers prior to APR onset was not available in these two trials. Moreover, follow-up was of only 28 weeks and the efficacy of APR for manifestations different from orogenital ulcers was not reported.

Taking into account all these considerations, the aim of the present study was to assess the efficacy of APR for orogenital ulcers, either combined or in monotherapy, in a National multicentre real clinical practice study of BD patients with orogenital ulcers refractory to conventional treatment. Moreover, the efficacy of APR for other clinical manifestations was also evaluated.

Materials and methods

Design and enrolment criteria

We performed a multicentre open-label observational study that encompassed 51 BD patients with refractory mucocutaneous ulcers. Besides topical treatment, oral colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and systemic glucocorticoids, patients had received at least one csDMARD and in most cases bDMARD before the onset of APR.

In a first step, BD patients undergoing treatment with APR were included in the study. Then, they were prospectively followed-up. Information on each patient was both retrospectively and prospectively assessed. For this purpose, we designed a data base file that was agreed and filled out by the investigators of each centre implicated in the study. Because of that, this was an ambispective study, partly retrospective and partly prospective. A flow chart showing the characteristics of this study is shown in the Supplementary Figure S1.

Patients were diagnosed with BD at the Rheumatology, Autoimmune Diseases or Dermatology Units of 20 referral Spanish hospitals. The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee. The indication of APR was based on the treating physician's judgment with the agreement of the patient. APR was prescribed as an off-label indication and, therefore, written informed consent was also requested and obtained from all patients.

BD diagnosis was made according to the International Study Group for BD (ISGBD) criteria reported in 1990 (18). As indicated by the Spanish National Guidelines for bDMARDs and tsDMARDs in Rheumatology (19-23), infections as well as malignancies were ruled out before starting the treatment. APR was initiated using dose escalation until reaching a maintenance dose of 30 mg twice daily.

Data collection

Data were retrospectively reviewed from the clinical records of the patients according to a specific designed protocol that included clinical and laboratory data, diagnosis, pharmacological agents used for the treatment of BD, response to APR and development of side effects. To minimise entry error, all the data were double checked.

Outcome variables, clinical definitions and laboratory data

The primary outcome variable was the efficacy of APR to achieve remission of oral and/or genital ulcers. For this purpose, we assessed remission and flares of oral and/or genital ulcers. Complete remission was considered as the disappearance of ulcers while partial remission was defined as the reduction of at least 50% in the number of ulcers and/or a reduction in the number of flares. Flare was defined as the recurrence of ulcers when complete remission was achieved for at least one month. Similar definitions (complete remission, partial remission and flare) were applied when we assessed the effect of APR on other clinical manifestations. We also assessed safety and retention rate of APR as well as the sparing glucocorticoid effect due to the use of this molecule. Serum C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), full blood cell count, liver and renal function tests were also analysed. ESR values higher than 20 or 25 mm/1st hour for men or women, respectively, and those of serum CRP greater than 0.5 mg/dL were considered raised.

Outcome variables were recorded in most patients at baseline (APR initiation) and in every visit at 1-2 weeks, 4 weeks, 3 months, 6 months, 12 months, 18 months and 24 months. These visits were performed in each individual centre following a pre-established protocol agreed by the investigators of this collaborative study. An additional subanalysis considering APR in monotherapy or combined with bDMARDs and csDMARDs was also performed. Adverse events related to APR treatment were evaluated, recorded and stored in a specific file designed for this purpose.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) for variables with a normal distribution, or as median and interquartile range (IQR) [25th-75th IQR] for those not normally distributed. The effect of APR was assessed on clinical symptoms, serum CRP and ESR values and on daily glucocorticoid dose required. Compari-

sons were performed at baseline, 1-2 weeks, 4 weeks, 3 months, 6 months, 12 months, 18 months and 24 months using the Wilcoxon's signed rank test. In addition, clinical and laboratory data of last visit were also assessed. Statistical significance was considered as a p-value ≤0.05. Statistical analysis was performed with the STATISTICA software (StatSoft, Tulsa, OK, USA).

Results

Demographic and general data at apremilast initiation

A series of 51 patients (35 women/16 men) diagnosed with BD and treated with APR was evaluated. The mean ± SD age at APR onset was 44.7±13.2 years. HLA-B51 was positive in 20 patients (39.2%), negative in 27 (52.9%) and data were not available in another 4 cases (7.9%).

APR was initiated because severe and refractory oral (n=19), genital (n=2) aphthous ulcers or both (n=30). Other active manifestations present at APR onset were arthralgia/arthritis (n=16/ clinically evident synovitis in 5 of them), folliculitis/pseudofolliculitis (n=14), erythema nodosum (n=3), furunculosis (n=2), paradoxical psoriasis induced by TNF-α-inhibitors (TNFi) (n=2), ileitis (n=2), deep venous thrombosis (n=2), leg ulcers (n=1), erythematosus and scaly skin lesions (n=1), fever (n=1), unilateral anterior uveitis (n=1) and neuro Behçet (n=1). Elevation of acute phase reactants was observed in 24 patients (CRP in 23 and/or ESR in 11). Table I summarises the main general and clinical features at baseline and at the end of the follow-up.

Table I. Features and follow-up of 51 patients with Behçet's disease refractory mucocutaneous ulcers undergoing apremilast therapy.

Number of patients (n)	51	
Age, mean (SD) years	44.7	(13.2)
Sex, men/women, n/n	16/35	
Months from diagnosis of BD to APR onset	48	[23-120]
Main clinical symptoms for starting APR, n (%)		
Oral ulcers	19	(37.2)
Genital ulcers	2	(3.9)
Oral and genital ulcers	30	(58.9)
Other symptoms at APR onset, n	**34**	
Arthralgia/arthritis	16	
Folliculitis/pseudofolliculitis	14	
Erythema nodosum	3	
Furunculosis	2	
Paradoxical psoriasis by TNFi	2	
Deep venous thrombosis	2	
Ileitis	2	
Leg ulcers	1	
Unilateral anterior uveitis	1	
Neuro Behçet	1	
Erythematosus and scaly skin lesions	1	
Fever	1	
Systemic treatment before APR, n		
Oral glucocorticoids	47	
Colchicine	50	
NSAIDs	22	
MTX	27	
AZA	24	
Cyclosporine A	9	
Dapsone	6	
Sulfasalazine	3	
ADA	12	
IFX	10	
TCZ	5	
ETN	3	
Other treatments*	8	
Prednisone dose at APR onset, median [IQR], mg/d	10	[6-20.63]
Concomitant treatment, n		
Oral glucocorticoids	28	
Colchicine	25	
AZA	7	
MTX	5	
Hydroxychloroquine	4	
Sulfasalazine	4	
Dapsone	1	
TCZ	2	
ADA	1	
IFX	1	
Follow-up on APR therapy, mean (SD), months	**8.45**	**(6.9)**
Remission of orogenital ulcers, n (%)	45	(88.2)
Drug withdrawal, n (%)	11	(21.5)
..... inefficacy, n (%)	5	(9.8)
..... severe side-effects, n (%)	3	(5.8)
..... others, n (%)	3	(5.8)

APR: apremilast; ADA: adalimumab; AZA: azathioprine; BD: Behçet's disease; ETN: etanercept; IFX: infliximab; IQR: interquartile range; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; SD: standard deviation; TCZ: tocilizumab; TNFi: tumour necrosis factor inhibitors.
*Other treatments: cyclophosphamide (3), hydroxychloroquine (2), thalidomide (1), mycophenolate mofetil (1), golimumab (1), secukinumab (1).
Results are expressed as mean ± standard deviation (SD), median [interquartile range: IQR] or as number (percentage: %), depending on the variable analysed.

Treatment before apremilast

Previously to APR, patients had received oral colchicine (n=50, median dose [IQR] 1.5 [1–2] mg/day), oral glucocorticoids (n=47, maximum median dose [IQR] 50 [20-60] mg/day, median dose at APR onset [IQR] 10 [6.25–20] mg/day) and NSAIDs (n=22).

In addition, all patients had received csDMARDs, and in many cases bDMARDs. The decision to use a particular therapy was chosen based on clinical criteria and/or previous experience of the therapeutic success of the drug. The csDMARDs and dosages were the following: methotrexate (MTX) (n=27, median dose [IQR] 15 [15–20] mg s.c. or p.o./week), azathioprine (AZA) (n=24, median dose [IQR] 100 [100–150] mg p.o./day), cyclosporine A (n=9, median dose [IQR] 200 [175–225] mg p.o./day), dapsone (n=6, median dose [IQR] 100 [100–175] mg p.o./day), cyclophosphamide (n=3, *i.v.* pulses of 500

Table II. Evolution of main symptoms and reduction of prednisone dose during apremilast treatment.

	Baseline	Week 1-2 n= 49*	Week 4 n= 45*	Month 3 n= 38	Month 6 n= 29	Month 12 n= 13	Month 18 n=5	Month 24 n=2
Outcome of oral and/or genital ulcers n, (%)								
Complete remission		19 (38.7)	32 (71.1)	32 (84.2)	21 (72.4)	6 (46.2)	3 (60)	2 (100)
Partial remission		25 (51)	10 (22.2)	2 (5.3)	7 (24.1)	7 (53.8)	2 (40)	0
No response		5 (10.3)	3 (6.7)	4 (10.5)	1 (3.5)	0	0	0
Dose of prednisone (mg/day), median [IQR]	10 [6.25-20]	10 [5-15]	10‡ [5-15]	5‡ [5-8.75]	5‡ [3.75-10]	5 [2.5-5]	4.37 [2.5-5]	NA

APR: apremilast; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; n: available data; NA: not applicable.
*All the 51 patients were assessed in week 1-2 and/or week 4. ‡$p<0.05$.
It should be noted that patient's response may change in each stage of follow-up; for example, partial remission can be moved to complete remission in the next clinic visit.

Table III. Outcome of non-aphthous symptoms with apremilast.

	1-2 Weeks	4 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Non-aphthous manifestations at APR onset (n)							
Folliculitis/pseudofolliculitis (14)	CR (6) PR (3) NC (5)	CR (10) PR (3) NC (1)	CR (10) PR (3) NC (1)	CR (6) NC (1)	CR (2)	CR (1)	
Arthralgias (11)	CR (1) NC (10)	CR (1) PR (2) NC (8)	CR (1) PR (3) NC (6)	CR (3) PR (2) NC (1) ND (1)	CR (3) PR (2) ND (2)	CR (2) PR (1)	
Arthritis (5)	PR (1) NC (4)	PR (3) NC (2)	CR (3) PR (1)	CR (3) PR (1)	PR (1)	PR (1)	
Erythema nodosum (3)	CR (2) PR (1)	CR (1) PR (1)	CR (2)	CR (1)			
Psoriasis/ erythematosus-scaly skin lesions (3)	NC (2) ND (1)	NC (2) ND (1)	PR (3) ND (1)	PR (2)	PR (2)	PR (1)	PR (1)
Ileitis (2)	CR (1) PR (1)	CR (2)	CR (2)	CR (2)	CR (1)		
Deep venous thrombosis (2)	CR (1) PR (1)	CR (1) PR (1)	CR (1) PR (1)	CR (1) PR (1)	CR (1)	CR (1)	CR (1)
Furunculosis (2)	CR (2)	CR (2)	CR (1)	CR (1)			
Leg ulcers (1)	PR	PR	CR	CR			
Unilateral anterior uveitis (1)	CR	CR					
Neuro Behçet (1)	NC	NC	NC	NC			
Fever (1)	NC	NC	NC				

APR: apremilast; CR: complete remission; IQR: interquartile range; n: number of cases; ND: no data available; NC: no changes observed; PR: partial remission.
It should be noted that patient's response may change in each stage of follow-up; for example, partial remission can be moved to complete remission in the next clinic visit.

mg every 15 days for 3 months), sulfasalazine (SSZ) (n=3, 2 g p.o./day), hydroxychloroquine (HCQ) (n=2, 200 mg p.o./day), thalidomide (n=1, 50 mg p.o./day) and mycophenolate mofetil (n=1, 3 g p.o./day). The bDMARDs and dosages were the following: adalimumab (ADA) (n=12, 40 mg s.c. every other week), infliximab (IFX) (n=10, 3-5 mg/kg i.v. at 0, 2 and 6 weeks and then every 4–8 weeks), etanercept (n=3, 50 mg s.c. every week), tocilizumab (TCZ) (n=5, 8 mg/kg *i.v.* every 4 weeks), golimumab (n=1, 50 mg s.c. every 4 weeks) and secukinumab (n=1, 300 mg s.c. every 4 weeks with previous loading dose).

Apremilast in monotherapy or in combined therapy

APR was given at standard dose of 30 mg twice daily, with the usual dose escalation performed in 5 days. Apart from glucocorticoids, colchicine or NSAIDs, APR was given in combination with conventional (n=16) or biologic (n= 2) or both conventional and biologic DMARDs (n=2) in 20 patients (Table I). An additional subanalysis comparing the efficacy of APR in monotherapy *versus* APR combined with csDMARDs and/or bDMARDs was carried out. However, there were not statistically significant differences in

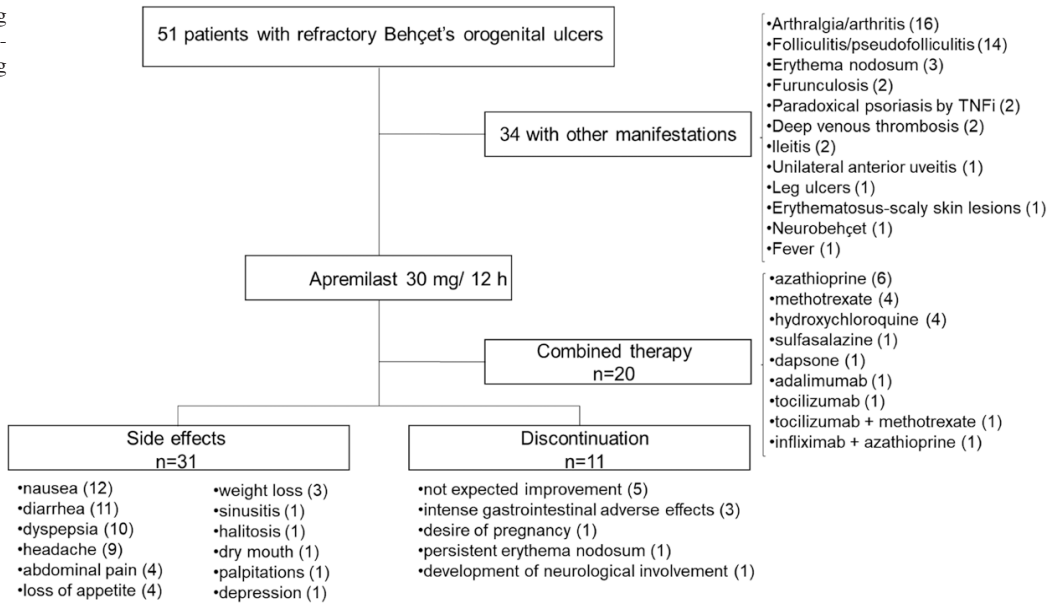

Fig. 1. Flow-chart summarising the features of 51 patients with refractory orogenital ulcers receiving apremilast therapy.

baseline characteristics and outcome (Supplementary Table S1).

Outcomes of orogenital ulcers and other clinical manifestations

Forty-four of 49 patients with available data at week 2 (89.8%) experienced a rapid improvement of the orogenital ulcers. Maintained clinical improvement of orogenital manifestations was also observed in most cases (Table II). As shown in the Supplementary Table S2, the outcome of the orogenital ulcers was similar in patients treated with APR in monotherapy to those in whom APR was used in combination with conventional or biologic DMARDs.

Following APR use, a significant reduction of prednisone dose was achieved at month 3. Consequently, the median prednisone dose was reduced from 10 [5–20.63] mg/day to 5 [5–8.75] mg/day (p=0.018).

Efficacy of APR on clinical manifestations of BD different from orogenital ulcers is shown in Table III and Supplementary Table S3. Overall, APR also yielded improvement of some non-aphthous manifestations such as the cutaneous follicular and intestinal manifestations. However, the effect on musculoskeletal manifestations was variable.

During the follow-up period, the median serum CRP fell from 0.5 [0.13–1.48] to 0.35 [0.12–0.52] mg/dL and the median ESR from 10 [4.5–20.5] to 9 [2-33.7] mm/1st hour.

Adverse events

After a mean follow-up of 8.5±6.9 months, 31 patients developed side-effects, most of them mild and within the first 3 months from the onset of APR: nausea (n=12), diarrhoea (n=11), dyspepsia (n=10), headache (n=9), abdominal pain (n=4), loss of appetite (n=4), weight loss (n=3), halitosis (n=1), dry mouth (n=1), sinusitis (n=1), palpitations (n=1) and/or depression (n=1). Due to this, 6 of them had to reduce the dose of APR to 30 mg/day.

APR was discontinued in 11 patients due to lack of effect (n=5), gastrointestinal adverse events (n=3), desire of pregnancy (n=1), persistent erythema nodosum (n=1) and development of neurological involvement (n=1). Therefore, the retention rate of APR during follow-up was 78.4%.

Figure 1 shows a flow-chart that summarises the features of the 51 patients with refractory orogenital ulcers on APR; data on non-aphthous manifestations, combined treatment and adverse events are included.

Discussion

The results from the present study indicate that in clinical practice APR yields a rapid and maintained improvement of BD's refractory orogenital manifestations. This is of potential relevance since oral and genital ulcers are the most representative manifestations of BD (8, 24, 26).

Due to the different phenotypes of the disease (27) and the lack of consensual standards of care, the use of therapies is in many cases based on a few randomised clinical trials, singular case reports or small case series (28, 29). The European League Against Rheumatism (EULAR) group has published an update of recommendations for the management of BD depending on the domain(s) affected in each patient, providing a more individualised therapeutic approach (9).

Several therapeutic agents have been used for orogenital aphthous ulcers with variable results (30). There is general agreement on the use of topical agents such as chlorhexidine, lidocaine gel and glucocorticoid preparations for oral mucosal involvement. Alpsoy *et al*. described effectiveness of sucralfate suspension for oral and genital ulcers (31). Colchicine remains as the first-line systemic agent used for orogenital features of BD (28, 32, 33). This drug has proved to be useful for the treatment of erythema nodosum, genital ulcers of women and arthritis. However, there is no full evidence on its efficacy in oral ulcers (28, 34-37). Kaneko *et al*. (38) reported that minocycline can reduce the frequency of oral ulcers, erythema nodosum and papulopustular lesions in BD patients. AZA is another drug used to avoid the development of mucocutaneous lesions of BD (39). Thalidomide has shown efficacy for the treatment of oral

and genital ulcers and papulopustular lesions in patients with BD. Nevertheless, maintenance treatment is frequently required to prevent the development of recurrences (28, 33, 40-43), which together with the possibility of the appearance of nodular lesions and worsening of erythema nodosum, as well as the serious adverse events that this drug can cause, limit its use. Cyclosporin is another agent not frequently used, due to its adverse events (28, 33). Sharquie *et al*. showed that dapsone was effective for the treatment of mucocutaneous lesions of BD (44). With respect to TNFi, etanercept is the only drug assessed in a randomised controlled clinical trial that proved efficacy to control many mucocutaneous features (4, 28). There are also case reports of successful treatment of genital ulcers with adalimumab (28, 45). Interferon (IFN) α has been used in mucocutaneous lesions with contradictory results and a high rate of adverse events (46-48). A few studies suggest that anakinra, secukinumab and ustekinumab may be useful in the treatment of orogenital ulcers of BD (49-52).

APR is an oral small molecule which inhibits PDE-4 and increases the levels of intracellular cyclic AMP, modulating several inflammatory pathways (10, 11). A randomised phase II trial that included 111 patients with BD showed that patients treated with APR had a significant reduction in the number of oral ulcers at 12 weeks (15). However, this trial did not provide enough information on previous therapies and extra-mucocutaneous manifestations. A recent phase III trial has shown significant improvement of pain and number of oral ulcers in 104 patients treated with APR, resolution maintained over 12 weeks and in many cases also resolution of genital ulcers (16). Because of that, the U.S. FDA has recently approved APR for BD ulcers (www.fda.gov) (17).

The design of our study constitutes a potential limitation of our study. Nevertheless, we observed that APR yielded a rapid and sustained response of mucocutaneous ulcers. Adverse events were mild and, in most cases, well tolerated. These findings support the information reported on APR in RCTs.

In conclusion, we report real life data showing that APR therapy is effective in highly refractory BD orogenital ulcers.

Acknowledgements

The authors acknowledge all the members of the participating hospitals.

Affiliations

[1]Dept. of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander; [2]Dept. of Rheumatology, Complejo Hospitalario Universitario A Coruña; [3]Dept. of Autoimmune Diseases, Hospital Clinic, Barcelona; [4]Dept. of Rheumatology, Complejo Asistencial Universitario de León; [5]Dept. of Rheumatology, Hospital Lluís Alcanyís, Xàtiva; [6]Dept. of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona; [7]Dept. of Rheumatology, Hospital La Fe, Valencia; [8]Dept. of Rheumatology, Hospital Universitario Germans Trias i Pujol, Badalona; [9]Dept. of Rheumatology, Hospital Universitario Doctor Peset, Valencia; [10]Dept. of Rheumatology, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat; [11]Dept. of Rheumatology, Complejo Hospitalario Universitario de Pontevedra; [12]Dept. of Rheumatology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas; [13]Dept. of Rheumatology, Hospital Son Llàtzer, Mallorca; [14]Dept. of Rheumatology, Hospital Universitario de La Princesa, IIS-Princesa, Madrid, Spain.

Members of the Spanish Collaborative Group of Refractory Behçet's Disease

Manuel Martín-Martínez, Elvira Díez-Álvarez (Complejo Asistencial Universitario de León); Esperanza Martínez (Hospital Lluís Alcanyís, Xàtiva); Francisca Sivera (Hospital General Universitario de Elda); Jaime Calvo-Alen (Hospital Universitario Araba, Vitoria); Isabel de la Morena (Hospital General Universitario de Valencia); Francisco Ortiz-Sanjuán (Hospital La Fe, Valencia); Ana Pérez-Gómez (Hospital Príncipe de Asturias, Alcalá de Henares); Sergi Heredia, Águeda Prior-Español (Hospital Universitario Germans Trias i Pujol, Badalona); Carolina Díez (Hospital del Bierzo, Ponferrada); Juan José Alegre (Hospital Universitario Doctor Peset, Valencia); Ignasi Figueras (Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat); Ana Isabel Turrión (Hospital Universitario de Salamanca); Pilar Trénor (Hospital Clínico Universitario de Valencia); Carmen González-Vela, José L. Hernández (Hospital Universitario Marqués de Valdecilla, Santander).

Competing interests

B. Atienza-Mateo received grants/research support from AbbVie, Pfizer and Lilly. J.L. Martín-Varillas is a member of speaker's bureau and received grants/research support from AbbVie, Pfizer, Celgene, Lilly, Janssen, Roche and Nordic Pharma. J. Graña received grants/research support from AbbVie, Bristol, Pfizer, Roche, MSD, Gebro, Sanofi and Amgen. G. Espinosa received grants/research support from Actelion, Janssen, GSK, Boehringer and Amgen. C. Moriano received grants/research support from Lilly, Roche, AbbVie, Pfizer, Gebro, Novartis and Sanofi, and had consultation fees/participation in company sponsored speaker's bureau from Bristol, Pfizer, Lilly, GSK, Celgene and Amgen. A. Olivé had consultation fees/participation in company sponsored speaker's bureau from Celgene. S. Ojeda had consultation fees/participation in company sponsored speaker's bureau from Celgene. I. Ros received grants/research support from Celgene as principal investigator of PREVAIL study on apremilast in psoriatic arthritis. J. Loricera attended conferences (less than $ 10,000 per year per entity) with Novartis, AbbVie, Roche, MSD, Bristol-Myers Squibb, Lilly, Pfizer and Celgene, and participated in courses and lectures sponsored by Novartis, MSD, AbbVie, Celgene and Gebro Pharma. V. Calvo-Río had consultation fees/participation (less than $ 10,000 per year per entity) in company sponsored speaker's bureau from AbbVie, Lilly, MSD, UCB Pharma and Celgene. M.A. Gonzalez-Gay received grants/research support from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche and MSD. R. Blanco received grants/research support from Abbott, MSD and Roche, and had consuòtation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche, Bristol-Myers Squibb, Janssen and MSD.

References

1. MCGONAGLE D, MCDERMOTT MF: A proposed classification of the immunological diseases. *PLoS Med* 2006; 3: e297.
2. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. HATEMI G, SILMAN A, BANG D *et al*.: EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-62.
4. HATEMI G, SILMAN A, BANG D *et al*.: Management of Behçet disease: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for the management of Behçet's

disease. *Ann Rheum Dis* 2009; 68: 1528-34.
5. OZGULER Y, HATEMI G, YAZICI H: Management of Behçet's syndrome. *Curr Opin Rheumatol* 2014; 26: 285-91.
6. ALIBAZ-ONER F, SAWALHA AH, DIRESKENELI H: Management of Behçet's disease. *Curr Opin Rheumatol* 2018; 30: 238-42.
7. YAZICI H, SEYAHI E, HATEMI G, YAZICI Y: Behçet syndrome: a contemporary view. *Nat Rev Rheumatol* 2018; 14: 107-19.
8. MELIKOGLU M, MELIKOGLU MA: What affects the quality of life in patients with Behçet's disease? *Acta Reumatol Port* 2014; 39: 46-53.
9. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome, *Ann Rheum Dis* 2018; 77: 808-18.
10. MAN HW, SCHAFER P, WONG LM *et al*.: Discovery of (S)-N-[2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl] acetamide (apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-alpha inhibitor. *J Med Chem* 2009; 52: 1522-4.
11. SCHAFER PH, PARTON A, CAPONE L *et al*.: Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal* 2014; 26: 2016-29.
12. BOLETO G, KANAGARATNAM L, DRAMÉ M, SALMON JH: Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2019; 49: 35-42.
13. MARTIN K, BÉGAUD B, ATRY P, MIREMONT-SALAMÉ G, FOURRIER A, MOORE N: Differences between Clinical trials and postmarketing use. *Br J Clin Pharmacol* 2004; 57: 86-92.
14. STUART EA, COLE SR, BRADSHAW CP, LEAF PJ: The use of propensity scores to assess the generalizability of results from randomized trials. *J R Stat Soc Ser A Stat Soc* 2001; 174: 369-86.
15. HATEMI G, MELIKOGLU M, TUNC R *et al*.: Apremilast for Behçet's syndrome - a phase 2, placebo-controlled study. *N Engl J Med* 2015; 372: 1510-8.
16. HATEMI G, MAHR A, ISHIGATSUBO Y *et al*.: Trial of apremilast for oral ulcers in Behçet's syndrome. *N Engl J Med* 2019; 381: 1918-28.
17. HATEMI G, SEYAHI E, FRESKO I *et al*.: One year in review 2019: Behçet's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S3-17.
18. Criteria for diagnosis of Behçet's disease International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
19. RIANCHO-ZARRABEITIA L, CALVO-RÍO V, BLANCO R *et al*.: Anti-TNF-α therapy in refractory uveitis associated with sarcoidosis: Multicenter study of 17 patients. *Semin Arthritis Rheum* 2015; 45: 361-8.
20. CALVO-RÍO V, DE LA HERA D, BELTRÁN-CATALÁN E *et al*.: Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S54-7.
21. FERNÁNDEZ-DÍAZ C, LORICERA J, CASTAÑEDA S *et al*.: Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicentre study of 63 patients. *Semin Arthritis Rheum* 2018; 48: 22-7.
22. ATIENZA-MATEO B, MARTÍN-VARILLAS JL, CALVO-RÍO V *et al*.: Comparative study of infliximab versus adalimumab in refractory uveitis due to Behçet's disease. National multicenter study of 177 cases. *Arthritis Rheumatol* 2019; 71: 2081-9.
23. CALDERÓN-GOERCKE M, LORICERA J, ALDASORO V *et al*.: Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. *Semin Arthritis Rheum* 2019; 49: 126-35.
24. ZEIDAN MJ, SAADUOUN D, GARRIDO M, KLATZMANN D, SIX A, CACCOUB P: Behçet's disease physiopathology: a contemporary review. *Auto Immun Highlights* 2016; 7: 4.
25. MENDES D, CORREIA M, BARBEDO M *et al*.: Behçet's disease- a contemporary review. *J Autoimmun* 2009; 32: 178-88.
26. KRAUSE I, ROSEN Y, KAPLAN I *et al*.: Recurrent aphthous stomatitis in Behçet's disease: clinical features and correlation with systemic disease expression and severity. *J Oral Pathol Med* 1999; 28: 193-6.
27. HATEMI G, SEYAHI E, FRESKO I *et al*.: One year in review 2018: Behçet's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 115): S13-27.
28. SALEH Z, ARAYSSI T: Update on the therapy of Behçet disease. *Ther Adv Chronic Dis* 2014; 5: 112-34.
29. ESATOGLU SN, HATEMI G: Update on the treatment of Behçet's syndrome. *Intern Emerg Med* 2019; 14: 661-75.
30. VITALE A, RIGANTE D, LOPALCO G *et al*.: New therapeutic solutions for Behçet's syndrome. *Expert Opin Investig Drugs* 2016; 25: 827-40.
31. ALPSOY E, ER H, DURUSOY C, YILMAZ E: The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999; 135: 529-32.
32. ALPSOY E: Behçet's disease: A comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. *J Dermatol* 2016; 43: 620-32.
33. LIN P, LIANG G: Behçet disease: recommendation for clinical management of mucocutaneous lesions. *J Clin Rheumatol* 2006; 12: 282-6.
34. AKTULGA E, ALTAC M, MUFTUOGLU A *et al*.: A double-blind study of colchicine in Behçet's disease. *Haematologica* 1980; 65: 399-402.
35. YURDAKUL S, MAT C, TÜZÜN Y *et al*.: A double-blind trial of colchicine in Behçet's syndrome. *Arthritis Rheum* 2001; 44: 2686-92.
36. CALGUNERI M, KIRAZ S, ERTENLI I, BENEKLI M, KARAARSLAN Y, CELIK I: The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease. A randomized clinical trial. *Arthritis Rheum* 1996; 39: 2062-5.
37. MAZZOCCOLI G, MATARANGOLO A, RUBINO R, INGLESE M, DE CATA A: Behçet syndrome: from pathogenesis to novel therapies. *Clin Exp Med* 2016; 16: 1-12.
38. KANEKO F, OYAMA N, NISHIBU A: Streptococcal infection in the pathogenesis of Behçet's disease and clinical effects of minocycline on the disease symptoms. *Yonsei Med J* 1997; 38: 444-54.
39. YAZICI H, PAZARLI H, BARNES CG *et al*.: A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; 322: 281-5.
40. HAMURYUDAN V, MAT C, SAIP S *et al*.: Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; 128: 443-50.
41. GARDNER-MEDWIN JM, SMITH NJ, POWEL RJ: Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behçet's disease: use of neurophysiological studies to detect thalidomide neuropathy. *Ann Rheum Dis* 1994; 53: 828-32.
42. SAYLAN T, SALTIK I: Thalidomide in the treatment of Behçet's syndrome. *Arch Dermatol* 1982; 118: 536.
43. HAMZA MH: Treatment of Behçet's disease with thalidomide. *Clin Rheumatol* 1986; 5: 365-71.
44. SHARQUIE KE, NAJIM RA, ABU-RAGHIF AR: Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study. *J Dermatol* 2002; 29: 267-79.
45. VITALE A, EMMI G, LOPALCO G *et al*.: Adalimumab effectiveness in Behçet's disease: short and long-term data from a multicenter retrospective observational study. *Clin Rheumatol* 2017; 36: 451-5.
46. BOYVAT A, SISMAN-SOLAK C, GURLER A: Long-term effects of interferon α2a treatment in Behçet's disease. *Dermatology* 2000; 201: 40-3.
47. ALPSOY E, DURUSOY C, YILMAZ E *et al*.: Interferon α-2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. *Arch Dermato*. 2002; 138: 467-71.
48. KESKIN Y, SEYAHI E, POYRAZ C, UGURLU S, OZYAZGAN Y, YAZICI H: Interferon alfa-associated depression in patients with Behçet's syndrome: a prospective controlled study. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S175.
49. GRAYSON PC, YAZICI Y, MERIDETH M *et al*.: Treatment of mucocutaneous manifestations in Behçet's disease with anakinra: a pilot open-label study. *Arthritis Res Ther* 2017; 19: 69.
50. LOPALCO G, FABIANI C, VENERITO V, LAPADULA G, IANNONE F, CANTARINI L: Ustekinumab efficacy and safety in mucocutaneous multi-refractory Behçet's disease. *Clin Exp Rheumatol* 2017; 35: 130-1.
51. MIROUSE A, BARETE S, MONFORT JB *et al*.: Ustekinumab for Behçet's disease. *J Autoimmun* 2017; 82: 41-6.
52. DI SCALA G, BETTIOL A, COJAN RD, FINOCCHI M, SILVESTRI E, EMMI G: Efficacy of the anti-IL 17 secukinumab in refractory Behçet's syndrome: A preliminary study. *J Autoimmun* 2019; 97: 108-13.