Apremilast in refractory orogenital ulcers and other manifestations of Behçet's disease. National multicenter study of 51 cases in clinical practice.

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Research article

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Abstract

Background

Oral and/or genital aphthous ulcers are the most common symptoms of Behçet´s disease (BD), and are often refractory to conventional treatment. The inhibitor of phosphodiesterase-4 apremilast (APR) has demonstrated efficacy in the treatment of this manifestations. The objective of the present study was to assess the efficacy of APR in the management of refractory oral and/or genital ulcers in patients with BD.

Methods

National multicenter 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 TNFα-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 neurobehçet (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.

Background

Behçet´s disease (BD) is a chronic systemic inflammatory disorder of unknown etiology included in the group of variable vessel vasculitis [1, 2]. It is characterized 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 disease-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.

Randomized clinical trials (RCTs) are conducted under highly standardized design with strict inclusion criteria, excluding some real-world patients and special situations to make the statistical assessment of efficacy and/or safety more efficient [13]. Because of that, features of RCTs may differ from those of clinical practice, which could influence the results of the treatment [14]. Two randomized double-blinded phase II and III clinical trials have shown 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). 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 multicenter 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.

Methods

Design and Enrollment Criteria

We performed a multicenter 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.

Patients were diagnosed with BD at the Rheumatology, Autoimmune Diseases or Dermatology Units of 20 referral Spanish hospitals. The study was approved by the Clinical Research Ethics Committee. APR was prescribed as an off-label indication and, therefore, written informed consent was also requested and obtained from all patients.

BD diagnosis was performed according to the International Study Group for BD (ISGBD) criteria reported in 1990 [17]. As indicated by the Spanish National Guidelines for bDMARDs and tsDMARDs in Rheumatology [18–22], 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 gathered 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. Data were reviewed for confirmation and stored in a computerized database. To minimize 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 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 analyzed. 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 onset) 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 center 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. Comparisons 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 onset

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%). The median [IQR] time from the diagnosis of BD to APR onset was 48 [23–120] months.

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 TNFα-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 neurobehçet (n = 1). Elevation of acute phase reactants was observed in 24 patients (CRP in 23 and/or ESR in 11). Table 1 summarizes the main general and clinical features at baseline and at the end of the follow-up.

Table 1
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 (%)	19 (37.2)
Oral ulcers	2 (3.9)
Genital ulcers	30 (58.9)
Oral and genital ulcers	
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
Neurobehçet	1
Erythematosus and scaly skin lesions	1
Fever	1

Abbreviations: APR = apremilast; ADA = adalimumab; AZA = azathioprine; BD: Behcet disease; ETN = etanercept; IFX = infliximab; IQR = interquartile range; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; TCZ = tocilizumab; TNFi = tumor 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 analyzed.

This table should appear before the text section "Treatment before apremilast". Between lines 192 and 193.

Number of patients (n)	**51**
Systemic Treatment before APR, n	47
Oral glucocorticoids	50
Colchicine	22
NSAIDs	27
MTX	24
AZA	9
Cyclosporine A	6
Dapsone	3
Sulfasalazine	12
ADA	10
IFX	5
TCZ	3
ETN	8
Other treatments*	
Prednisone dose at APR onset, median [IQR], mg/d	10 [6-20.63]

Abbreviations: APR = apremilast; ADA = adalimumab; AZA = azathioprine; BD: Behcet disease; ETN = etanercept; IFX = infliximab; IQR = interquartile range; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; TCZ = tocilizumab; TNFi = tumor 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 analyzed.

This table should appear before the text section “Treatment before apremilast”. Between lines 192 and 193.

Number of patients (n)	**51**
Concomitant treatment, n	28
Oral glucocorticoids	25
Colchicine	7
AZA	5
MTX	4
Hydroxychloroquine	4
Sulfasalazine	1
Dapsone	2
TCZ	1
ADA	1
IFX	
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)
Abbreviations: APR = apremilast; ADA = adalimumab; AZA = azathioprine; BD: Behcet disease; ETN = etanercept; IFX = infliximab; IQR = interquartile range; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; TCZ = tocilizumab; TNFi = tumor 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 analyzed.	
This table should appear before the text section “Treatment before apremilast”. Between lines 192 and 193.	

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 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 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 1**)**.

An additional subanalysis comparing the efficacy of APR in monotherapy vs APR combined with csDMARDs and/or bDMARDs was carried out. However, there were not statistically significant differences in baseline characteristics and outcome **(See Supplementary Table 1, Additional File 1)**.

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 2). As shown in the **Supplementary Table 2, Additional File 2**, 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.

Table 2
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

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 3 and Supplementary Table 3, Additional File 3**. 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.

Due to technical limitations, Table 3 is provided in the Supplementary Files sectin.

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 an 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), diarrhea (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 summarizing the features of the 51 patients with refractory orogenital ulcers on APR, including non-aphthous manifestation, combined treatment and adverse events.

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, 23, 25].

Due to the different phenotypes of the disease and the lack of consensual standards of care, BD treatment remains to be a challenge. The use of therapies is in many cases based on a few randomized clinical trials, singular case reports or small case series [26, 27]. 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 individualized therapeutic approach [9].

Several therapeutic agents have been used for orogenital aphthous ulcers with variable results [28]. 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 [29]. Colchicine remains as the first-line systemic agent used for orogenital features of BD because of its inhibition of neutrophil chemotaxis [26, 30, 31]. 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 [26, 32–35]. Kaneko et al. [36] reported that minocycline can reduce the frequency of oral ulcers, erythema nodosum and papulopustular lesions in BD patients as well as the production of pro-inflammatory cytokines by BD-peripheral blood mononuclear cells stimulated with streptococcal antigen. AZA is another drug used to avoid the development of mucocutaneous lesions of BD [37]. 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 [26, 31, 38–41], 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 relegated to the background, due to its adverse events [26, 31]. Sharquie et al. showed that dapsone was effective for the treatment of mucocutaneous lesions of BD in a double blind, placebo-controlled clinical trial [42]. With respect to TNFi, etanercept is the only drug assessed in a randomized controlled clinical trial that proved efficacy to suppress many mucocutaneous features, leading to a decrease in the frequency of appearance of oral ulcers and papulopustular lesions [4, 26]. There are also case reports of successful treatment of genital ulcers with adalimumab [26, 43]. Interferon (IFN) α has been used in mucocutaneous lesions with contradictory results and a high rate of adverse events [44–46]. A few studies suggest that anakinra, secukinumab and ustekinumab may be useful in the treatment of orogenital ulcers of BD [47–50].

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 randomized 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). However, in these trials the patients with major organ involvement of BD or comorbidities were excluded and full information on former therapies before APR was not available. Also, the time of follow-up was not very long. Moreover, to the best of our knowledge, both trials used APR in monotherapy and they did not assess the effect of APR on extra-mucocutaneous manifestations of BD [15, 16]. Thus, the strict criteria required for inclusion may constitute a limitation at the time of considering APR in real-life patients.

In our study, APR achieved a rapid and sustained response of mucocutaneous ulcers in patients refractory to several systemic drugs, including biologic therapy. Adverse events were mild and most of them well tolerated. According to our findings, APR may be combined with either with csDMARDs and/or bDMARDs with acceptable safety profile. Nevertheless, we are aware of potential limitations of our study, mainly due to its retrospective nature.

Conclusion

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

Abbreviations

APR: apremilast; BD: Behçet's disease; PDE-4: phosphodiesterase-4; tsDMARDs: targeted synthetic disease-modifying antirheumatic drugs; bDMARDs: biological disease-modifying antirheumatic drugs; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; RCTs: randomized clinical trials; FDA: Food and Drug Administration; NSAIDs: non-steroidal anti-inflammatory drugs; ISGBD: International Study Group for BD; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SD: standard deviation; IQR: interquartile range; TNFi: TNFα-inhibitors; MTX: methotrexate; AZA: azathioprine; SSZ: sulfasalazine; HCQ: hydroxychloroquine; ADA: adalimumab; IFX: infliximab; TCZ: tocilizumab; EULAR: European League Against Rheumatism; IFN: interferon.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of clinical research of Cantabria, Spain (2018.100). All patients gave their informed consent for inclusion in the study.

Consent for publication

This manuscript does not contain any individual person's data.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

BA-M received grants/research supports from Kern Pharma, AbbVie, Pfizer, Celgene and GSK.

JLM-V received grants/research supports from AbbVie, Pfizer and Celgene.

JG received grants/research supports from Abbvie, Bristol, Pfizer, Janssen, Roche, MSD, Gebro, Sanofi and Amgen.

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CM received grants/research supports from Lilly, Roche, Abbvie, Pzifer, Gebro, Novartis and Sanofi, and had consultation fees/participation in company sponsored speaker´s bureau from Bristol, Pzifer, Lilly, GSK, Celgene and Amgen.

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ED-A had nothing to disclose.

MDG-A had nothing to disclose.

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AMF had nothing to disclose.

JN had nothing to disclose.

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JL attended conferences 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.

VC-R had consultation fees/participation in company sponsored speaker’s bureau from Abbvie, Lilly, MSD, UCB Pharma and Celgene.

CG-V had nothing to disclose.

SC had nothing to disclose.

JLH had nothing to disclose.

MAG-G received grants/research supports from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker´s bureau from Abbott, Pfizer, Roche and MSD.

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Authors' contributions

BA-M, JL-MV, JL and RB have made substantial contributions to the conception and design of the work. All authors have contributed to the acquisition, analysis and interpretation of the data and have drafted the work. JL, SC, MAG-G and RB have substantively revised the work. All authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature. Submitted version of the manuscript has been approved by all authors.

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Figures

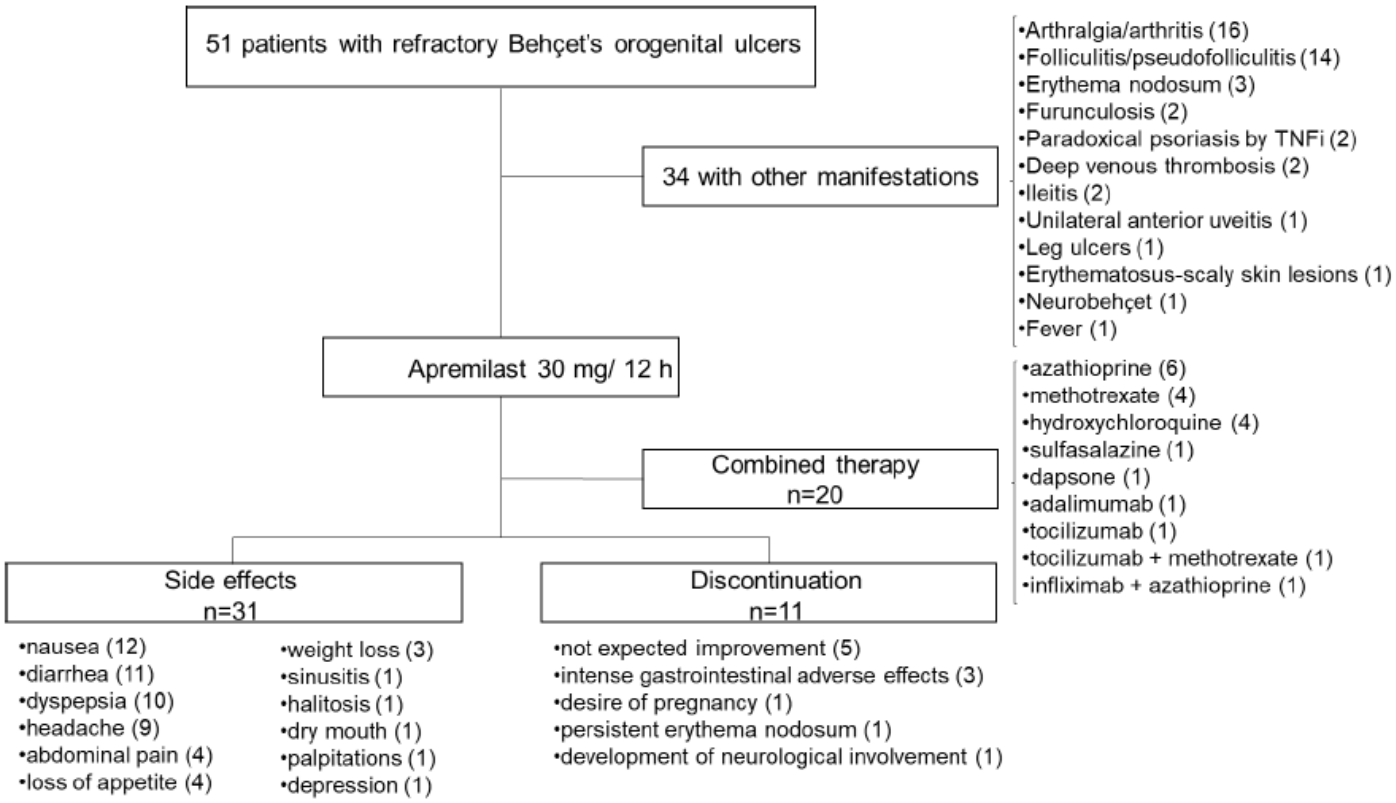

Figure 1

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

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