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Research Article

Mucocutaneous Response to New Therapeutic Strategies in Behçet's Disease: A Retrospective Cohort Study

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Mucocutaneous lesions are the most frequent symptoms of Behçet's disease (BD). Recently, new therapies are being used to treat refractory cases, but the effect of these treatments on mucocutaneous manifestations has been scarcely reported. Our objective was to describe the mucocutaneous response to the different therapies used to treat BD in routine clinical practice. We retrospectively reviewed the clinical records of all patients diagnosed with BD seen at our institution between January 2010 and January 2022. Patients with BD without mucocutaneous manifestations were excluded. We included 109 patients diagnosed with BD: 51 males (46.8%) and 58 females (53.2%). The mean age at diagnosis was 31.58 years (standard deviation (SD) 12.110) and the mean time of disease evolution was 14.94 years (SD 11.094). Oral ulcers were the most frequent symptom present in 100% of patients, followed by genital ulcers (GU) in 76.1% of patients. Twenty-four patients (22%) had severe mucocutaneous symptoms (>12 lesions/year) before treatment. We found that among patients with GU there was a higher prevalence of episodes of posterior uveitis and venous thrombosis ($p = 0.011$ and $p = 0.045$, respectively). In our series, we observed a lower complete cutaneous response to colchicine in patients with GU, pathergy or severe mucocutaneous symptoms ($p < 0.05$). Regarding the choice of a TNF-α inhibitor, we observed a lower prevalence of complete cutaneous response to adalimumab among patients with GU (53.3% complete response in patients with GU vs. 100% in patients without GU, $p = 0.022$), whereas no differences were found between clinical characteristics in the response to infliximab.

1. Introduction

Behçet's disease (BD) is a chronic, relapsing, and multisystemic inflammatory process characterized by vasculitis, hyperfunction of neutrophils, and autoinflammatory responses [1, 2]. Mucocutaneous lesions are the most frequent symptoms of BD, including oral ulcers (OU), genital ulcers (GU), and a variety of skin lesions such as acneiform eruptions and erythema nodosum. OUs are present in 97–100% of patients and significantly impair their quality of life [3]. Classically, systemic corticosteroids, colchicine, and azathioprine have been used to treat BD [2]. However, new therapies are often required to reduce the inflammatory process, improve the patient's quality of life, and prevent relapses. The effect of these treatments on mucocutaneous manifestations has been reported in randomized clinical trials and in short case series [3–5]. Nevertheless, the treatment response of dermatological manifestations has been scarcely reported in real clinical practice. Our objective was to describe the mucocutaneous response to the different therapies used to treat BD in routine clinical practice.

2. Materials and Methods

Medical records of all patients diagnosed with BD seen at the *Hospital Universitari de Bellvitge*, in Barcelona, Spain,

Table 1: Clinical manifestations presented at diagnosis and during the evolution of Behçet's disease.

	Clinical manifestations at diagnosis (n (%))	Clinical manifestation (n (%))
Mucocutaneous manifestations		
(i) Oral ulcers	73 (70.0%)	109 (100%)
(ii) Genital ulcers	60 (55.0%)	83 (76.1%)
(iii) Pathergy	0 (0%)	8 (7.3%)
(iv) Erythema nodosum	1 (0.9%)	20 (18.3%)
(v) Pseudofolliculitis	0 (0%)	49 (45%)
(vi) Acneiform nodules	0 (0%)	5 (4.6%)
(vii) Papule-pustules	0 (0%)	11 (10.5%)
Ophthalmological manifestations		
(i) Anterior uveitis	2 (1.8%)	26 (23.9%)
(ii) Posterior uveitis	2 (1.8%)	10 (9.2%)
(iii) Panuveitis	10 (9.2%)	14 (12.8%)
Venous thrombosis	5 (4.6%)	29 (26.6%)
Arterial thrombosis	1 (0.9%)	3 (2.8%)
Arthritis	8 (7.3%)	42 (38.5%)
Neurological clinic	10 (9.2%)	19 (17.4%)
Gastrointestinal symptoms	0 (0%)	3 (2.8%)
Sensorineural deafness	0 (0%)	2 (1.8%)
Orchiepididymitis	0 (0%)	3 (2.8%)
Recurrent fever	3 (2.8%)	6 (5.5%)

between January 2010 and January 2022 were retrospectively reviewed. International Criteria for Behçet's Disease (specificity 90.5% and sensitivity 94.8%) were used for diagnosis [6]. Patients with BD without mucocutaneous manifestations were excluded.

Demographic data, disease characteristics, treatments used, and mucocutaneous and overall responses to treatments were recorded. A complete response was defined as no disease flares, and a partial response as a significant decrease in disease flares compared to no treatment. In general, duration of 6 months on treatment was considered to assess inefficacy; however, in patients with a more aggressive course, this time could be shortened at the practitioner's decision. Response was assessed in patients with concomitant treatments when the drug was used in monotherapy. As this is a retrospective study in a real clinical practice setting, no washout periods between treatments were performed.

The data obtained were analyzed with SPSS 17.0. Categorical variables were compared using the Fisher's exact test. Comparison between two continuous variables, after confirmation of data normal distribution, was performed using the Student's t-test. Otherwise, the Mann–Whitney U test was used. Statistical significance was established at a value of $p < 0.05$.

3. Results

One hundred nine patients diagnosed with BD were included: 51 males (46.8%) and 58 females (53.2%). The percentage of Caucasian in our study was 80.7%, followed by patients from Morocco (17.4%) and Hispanics (1.8%). The genetic study performed in 59 patients shows that 35.6% and 5.1% were HLA-B51 and HLA-B27 positive, respectively. The mean age at diagnosis was 31.58 years (standard deviation (SD) 12.110) and the mean time of disease evolution was 14.94 years (SD 11.094). The clinical manifestations presented at the time of diagnosis and during evolution, as well as the characteristics of each affected organ, are shown in Table 1. Twenty-four patients (22%) presented severe mucocutaneous symptoms (>12 lesions/year) prior to treatment.

We found that among the patients with GU there was a higher prevalence of episodes of posterior uveitis and venous thrombosis ($p = 0.011$ and $p = 0.045$; respectively). Moreover, GU was more frequent in males than females (87.9% vs. 62.7%; $p = 0.02$). The presence of erythema nodosum was higher in patients who were HLA-B51 positive (50% vs. 6%; $p = 0.021$) and in Caucasian patients (18% of Caucasians vs. 10.5% of Moroccans; $p = 0.02$).

The main reason for treatment indication was skin manifestations in 50 patients (38.8%), followed by ophthalmologic lesions in 20 patients (18.3%). The used treatments, cutaneous severity, discontinuation reason, and cutaneous and overall response are reported in Table 2. Comparison between the skin response and the response on the main extracutaneous organs to different therapies used for the treatment in our cohort is shown in Table 3.

In our series, severe mucocutaneous symptoms were associated with poor response to different conventional treatments (oral corticosteroids, colchicine, and azathioprine; $p < 0.05$). In addition, the presence of GU, pathergy or severe mucocutaneous symptoms were associated with a lower complete cutaneous response to colchicine (complete cutaneous responses: 27.5% in patients with GU vs. 44.4% without GU, $p = 0.021$; 0% with pathergy vs. 33.8% without pathergy, $p = 0.037$; 0% with severe mucocutaneous symptoms vs. 42.1% without severe mucocutaneous symptoms, $p = 0.002$). We also observed a lower prevalence of complete cutaneous response to adalimumab among patients who presented GU (53.3% complete response in

Table 2: Cutaneous and overall response to the different therapies used for the treatment of Behçet's disease in our cohort.

	Patients (*n* (%))	Cutaneous severity (>12 lesions/year) (*n* (%))	Concomitant treatment (*n* (%)) *	Duration on monotherapy, mean (range), months	Stop due to loss/lack of efficacy (*n* (%))	Stop due to lack of activity (*n* (%))	Complete overall response** (*n* (%))	Complete cutaneous response (*n* (%))	Incomplete cutaneous response (*n* (%))
Oral corticosteroids	77 (70.6%)	20 (26.0%)	***	***	6 (7.8%)	33 (42.9%)	27 (35.5%)	50 (65.8%)	26 (34.2%)
Colchicine	88 (80.7%)	19 (21.6%)	47 (53.4%)	115.0 (0–498)	13 (14.7%)	11 (12.5%)	27 (31.8%)	39 (47.0%)	44 (53.0%)
Azathioprine	36 (35.8%)	12 (33.3%)	27 (75%)	20.6 (0–156)	5 (13.9%)	9 (25%)	14 (38.9%)	18 (50.0%)	18 (50.0%)
Methotrexate	23 (21%)	12 (52.2%)	20 (86.9%)	8.3 (0–63)	6 (26.1%)	4 (17.4%)	8 (34.8%)	12 (52.2%)	11 (47.8%)
Cyclosporine A	15 (13.8%)	6 (40%)	13 (86.7%)	13.3 (0–67)	4 (26.7%)	2 (13.3%)	3 (21.4%)	6 (42.9%)	8 (57.1%)
Apremilast	6 (5.5%)	5 (83.3%)	2 (33.3%)	18.6 (0–80)	0 (0%)	0 (0%)	3 (50%)	4 (66.7%)	2 (33.3%)
Adalimumab	24 (22.0%)	12 (50%)	20 (83.3%)	13.1 (0–99)	7 (29.2%)	2 (8.3%)	9 (37.5%)	17 (70.8%)	7 (29.2%)
Infliximab	8 (7.3%)	2 (25%)	6 (75%)	36.4 (0–162)	1 (12.5%)	0 (0%)	3 (42.9%)	7 (100%)	0 (0%)
Tocilizumab	3 (2.8%)	1 (33.3%)	2 (66.7%)	3.0 (0–9)	1 (33.3%)	0 (0%)	3 (100%)	3 (100%)	0 (0%)

*Concomitant treatment is considered the use of more than one drug at any time during follow-up. **Overall response was considered as cutaneous and extracutaneous manifestations response. ***Concomitant treatment with oral corticosteroids and duration on monotherapy with oral corticosteroids were not assessable because in a large proportion of patients corticosteroids were used during outbreaks (intermittent therapy or therapy added to baseline treatment) or as initial treatment at diagnosis until they were switched for another immunomodulator.

Table 3: Comparison between the skin response and the response on the main extracutaneous organs affected to the different therapies used for the treatment of Behçet's disease in our cohort.

	Complete overall response* (*n* (%))	Complete cutaneous response (*n* (%))	Complete ophthalmological response (*n* (%))	Complete articular response (*n* (%))	Complete response of venous thrombosis episodes (*n* (%))	Complete neurological response (*n* (%))
Oral corticosteroids	27 (35.5%)	50 (65.8%)	12 (36.7%)	11 (35.5%)	10 (52.6%)	6 (40.0%)
Colchicine	27 (31.8%)	39 (47.0%)	11 (33.3%)	8 (33.3%)	9 (47.4%)	6 (50.0%)
Azathioprine	14 (38.9%)	18 (50.0%)	5 (41.7%)	5 (34.7%)	6 (54.5%)	3 (30.0%)
Methotrexate	8 (34.8%)	12 (52.2%)	4 (30.1%)	6 (42.9%)	1 (100%)	1 (33.3%)
Cyclosporine A	3 (21.4%)	6 (42.9%)	2 (14.3%)	1 (33.3%)	3 (75.0%)	1 (33.3%)
Apremilast	3 (50%)	4 (66.7%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Adalimumab	9 (37.5%)	17 (70.8%)	11 (64.7%)	4 (44.4%)	5 (100%)	0 (0%)
Infliximab	3 (42.9%)	7 (100%)	2 (50%)	2 (50.0%)	1 (100%)	0 (0%)
Tocilizumab	3 (100%)	3 (100%)	1 (33.3%)	1 (100%)	1 (100%)	—

*Overall response was considered as cutaneous and extracutaneous manifestations response.

patients with GU vs. 100% complete response in patients without GU, $p = 0.022$), whereas, no differences were found between clinical characteristics in response to infliximab.

4. Discussion

Mucocutaneous lesions are the most frequent symptoms in BD, both in the early and advanced stages of the disease, and in a significant proportion of patients can be the only manifestation of de disease [7]. Recently, different clustering and association studies have revealed that BD patients can be classified into multiple phenotypes [8, 9]. Regarding GU, in our series, their presence was significantly more frequent among men, in contrast to what has previously been published [9]. GU may also be associated with a higher prevalence of episodes of posterior uveitis and venous thrombosis. An organ-specific phenotypic classification has been proposed [5], but in our study, we report multiple organ involvement in the same patient, so it would be difficult to apply this classification in these cases.

The use of intensive immunosuppressive treatments in BD is usually reserved for manifestations inducing high morbidity and mortality (ocular, central nervous system, gastrointestinal, and vascular involvement) or for the treatment of recurrent cutaneous and articular manifestations producing a significant negative impact on the quality of life of the patients [1, 2]. The literature on the benefits of these treatments from the cutaneous point of view is scarce, as most of these drugs are prescribed to control the overall disease and not primarily the cutaneous manifestations. In our series, 22% of patients were treated with adalimumab, 7.3% with infliximab, and 5.5% with apremilast, achieving complete cutaneous responses in 70.8%, 100%, and 66.7%, respectively. Therefore, these treatments can be an effective alternative for the management of BD's cutaneous involvement that is refractory to conventional treatments. Good mucocutaneous responses to infliximab and adalimumab have been described [2, 4], with no differences between the two treatments [10]. Although recent guidelines consider these drugs to be the treatment of choice in patients with clinical manifestations refractory to conventional immunosuppressants [4, 5], there is no consensus on which is more adequate. In our series, patients who presented with GU showed a lower rate of complete cutaneous response to adalimumab. There were no different responses to infliximab depending on the type of cutaneous lesion. In our cohort, no specific concomitant treatment regimen showed superiority over others, and there is no statistical difference compared to monotherapy.

The limitations of this study are that it is a retrospective descriptive review of data from a single institution and the limited number of patients treated with some of the new drugs. In addition, this is a study in real clinical practice in which occasionally treatments are combined if the response is incomplete or corticosteroids are used for the treatment of the outbreak.

5. Conclusions

Although mucocutaneous manifestations are the most frequent symptoms in BD and constitute almost all the diagnostic criteria, little data are available on cutaneous response to the different immunosuppressive treatments recently introduced for the treatment of BD. We report data in routine clinical practice of 109 patients with BD in whom complete cutaneous response rates were higher with tumor necrosis factor-alpha (TNF-α) inhibitors and apremilast than with classic immunomodulatory treatments, which remain as a step prior to the use of the new treatments. We highlight the poor cutaneous response to colchicine in cases of GU, pathergy, or severe cutaneous manifestations. Regarding the choice of a TNF-α inhibitor, there is no algorithm that allows prioritizing one over another in the approach to mucocutaneous manifestations. However, in our series, we observed that the presence of GU is associated with a lower rate of complete cutaneous response in patients treated with adalimumab. Further randomized controlled trials are needed to compare the safety and effectiveness of the new available treatments.

Data Availability

The data supporting the conclusions of this study are available upon request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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