Terapêutica Biológica na Doença de Behçet: A Experiência de um Centro

Biologics Drugs in Behçet's Disease: A Single Centre Experience

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Resumo:

Introdução: A doença de Behçet (DB) é uma vasculite sistémica de causa indeterminada. Várias citocinas, como o TNF-α, parecem desempenhar um papel na patogénese. Desde modo, o uso de biológicos como fármacos anti- TNF-α têm aumentado, no controle das manifestações graves ou refratárias da DB.

Este estudo teve como objetivo a descrição dos resultados obtidos com biológicos na DB.

Material e Métodos: Estudo longitudinal, prospectivo, unicêntrico de doentes seguidos em consulta especializada. Recolhemos dados relativamente às manifestações, tratamentos e resultados obtidos durante o seguimento.

Resultados: A coorte inclui 243 doentes, 31% homens. Vinte doentes (8%) realizaram biológicos. Os doentes que foram submetidos a biológicos são mais novos (p = 0,030), têm menos aftose genital (p = 0,009), e mais frequentemente eritema nodoso (p = 0,009), poliartrite (p = 0,002), espondiloartrite (p = 0,024), vasculite retiniana (p = 0,011) e manifestações gastrointestinais (p = 0,024), nomeadamente úlcera gastroduodenal (p = 0,035), hemorragia digestiva (p = 0,002), e perfuração intestinal (p = 0,004). Foram usados fármacos anti-TNF-α em todos os doentes, mais frequentemente infliximab. Os biológicos foram iniciados após falência de resposta aos imunossupressores clássicos, e a maioria dos doentes entrou em remissão da doença após (93%). Três doentes desenvolveram tuberculose durante o tratamento, apesar de efetuarem testes de rastreio regulares. Foi possível parar o biológico em cinco doentes até então, sem recorrência, com um período médio de seguimento de 33 meses desde a suspensão.

Discussão: Os biológicos anti-TNF-α são altamente eficazes nas manifestações da DB refratária, embora não sejam inócuos. Pouco se sabe relativamente à duração ótima destas terapêuticas, quando e como parar. Isto é importante não só para evitar recidivas, mas também para reduzir os efeitos secundários.

Palavras-chave: Fator de Necrose Tumoral alfa/antagonistas e inibidores; Produtos Biológicos/uso terapêutico; Resultado do Tratamento; Síndrome de Behçet/tratamento farmacológico.

Abstract:

Introduction: Behçet´s disease (BD) is a systemic vasculitis of unknown cause. Several cytokines, such as tumor necrosis factor-alpha (TNF-α), appear to play a substantial role. Therefore, biologics such as anti-TNF-α agents are rising to control severe or refractory BD´s manifestations.

We aimed to describe the biological therapy´s outcomes in BD patients.

Methods: A longitudinal, prospective, unicentric cohort study with patients followed in a specialized outpatient clinic. We collected data regarding BD´s manifestations, treatments, and outcomes during follow-up.

Results: Our cohort includes 243 patients, of whom 31% were male. During follow-up, 20 patients (8%) were treated with biological drugs. Patients who received biological therapies were younger (p = 0.030), had less frequently genital aphthosis (p = 0.009), and more frequently erythema nodosum (p = 0.009), polyarthritis (p = 0.002), spondyloarthritis (p = 0.024), retinal vasculitis (p = 0.011) and gastrointestinal manifestations (p = 0.024), namely gastroduodenal ulcer (p = 0.035), digestive bleeding from ulcers (p = 0.002), and bowel perforation (p = 0.004). Anti-TNF-α agents were used in all of these patients, most frequently infliximab. Patients started biologicals after classical immunosuppressors failure, and most went into remission (93%). Three patients developed tuberculosis during treatment, regardless of regular screening tests. It was possible to stop biological therapy in five patients, so far, without recurrence, with 33 months of mean follow-up time after suspension.

Discussion: Anti-TNF-α agents are highly effective for refractory BD´s manifestations, although they are not innocuous. Little is known about the optimal duration of these therapies, regarding when and how to stop these drugs. This issue is

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essential not only to avoid relapses but also to reduce therapy side-effects.

Keywords: *Behcet Syndrome/drug therapy; Biological Products/therapeutic use; Treatment Outcome; Tumor Necrosis Factor-alpha/antagonists & inhibitors.*

Introduction

Behçet´s disease (BD) was first described in 1937, by Hulusi Behçet, as a triad of recurrent oral and genital aphthosis and uveitis.[1] BD is a systemic vasculitis of unknown cause, classified among the variable vessel vasculitis,[2] that may affect almost every organ.

Although BD has a worldwide distribution, its prevalence is higher along the ancient "´silk route" extending from the Mediterranean region to the Middle East and Far East countries.[3-6] Based on a national sample in 1997 that included 241 patients, in Portugal, a prevalence of 2.4 cases / 100 000 inhabitants was estimated.[7]

BD´s organ involvement and clinical course exhibit different phenotypes across different regions, although the factors that lead to these differences are not clear.[3-5,8] Although the BD´s pathogenesis is unclear, some studies have shown the possible contribution of the inflammatory response initiated by infectious agents or autoantigens in patients with predisposing genetic factors and perpetuated by innate and acquired immunity dysregulation.[9-12] Besides, a network of immune mediators, resulting in numerous cytokines and chemokines production, such as tumor necrosis factor--alpha (TNF-α), plays a substantial role in the inflammatory cascade, activates macrophages, and is responsible for cell-mediated immunity.[12,13]

The first reference to BD treatment with a biological drug, specifically an anti-TNFα agent (infliximab), dates back to 2001 in patients with severe panuveitis.[14] Several studies have proven biologicals effectiveness in different manifestations since then. Anti-TNFα are currently recommended in severe BD forms,[15,16] namely mucocutaneous involvement refractory to non-biological therapy, ocular involvement affecting the posterior chamber or recurrent episodes of uveitis, refractory venous thrombosis, arterial or central nervous system (CNS) involvement, severe or refractory gastrointestinal involvement and chronic or refractory joint involvement.

This study aims to describe the outcomes after biological therapy in BD patients in a single-centre cohort, as well as the complications that arose from it.

Methods

SETTING, PATIENTS AND STUDY DESIGN

We carried out a prospective, longitudinal cohort study including all patients with diagnostic criteria for BD according to the International Study Group in 1990,17 followed in the outpatient clinic of Clinical Immunology Unit, Centro Hospitalar e Universitário do Porto, between January-1981 and September-2020.

Patients were followed from the moment the diagnosis was established, and the manifestations were recorded as they arise. Hospital Ethics Committee approved the study design, and informed consent was waived due to its observational nature (study number 2020-162 (127-DEFI-129-CE)).

DATA AND DEFINITIONS

We collected data regarding demographic features and symptoms of BD: oral aphthosis (OA), genital aphthosis (GA); skin manifestations - erythema nodosum (EN), pseudofolliculitis; joint manifestations - arthralgias, monoarthritis, polyarthritis, spondyloarthritis; ocular, neurological, vascular, gastrointestinal and cardiac involvement. Ocular manifestations include uveitis, retinal vasculitis, amaurosis, papillitis, conjunctivitis, and scleritis. Neurological manifestations include hemispheric, brainstem, and spinal cord syndromes, dural sinus thrombosis, and CNS arterial occlusion. Vascular manifestations include deep vein thrombosis, thrombophlebitis, arterial aneurysms, and arterial occlusion of other than CNS vessels. Esophageal, gastroduodenal, intestinal, and perianal ulcers, digestive bleeding from ulcers, bowel perforation, and chronic inflammatory diarrhea were reported as gastrointestinal manifestations. Behçet´s Disease Current Activity Form (BDCAF) was used to score disease activity in patients receiving biologics, presented as transformed index score. We also collected data related to therapies carried out, duration of those therapies, clinical response, and complications. The presence of HLA-B*51 allele was also collected.

STATISTICAL ANALYSIS

Categorical variables are presented as an absolute value and relative frequency, and the numerical variables as mean + standard deviation (SD). For comparison between groups, the Pearson Chi-square test was used for categorical variables or the Fisher´s exact test; the Student t-test was used for numerical variables. BDCAF score change over time was presented in a boxplot graph and compared with a paired sample t-test. All statistical tests were 2-sided. Significance level as set to 0.05. Statistical analyses were performed using SPSS software (SPSS for Windows, version 26, Chicago, IL, USA).

Results

Our cohort includes 243 patients, of which 75 (31%) patients are male. The current age was 49.9 (+14.3) years old. The first signs and symptoms of the disease started at 28 (+12.3) years old, and patients were diagnosed as having BD at 34.7 (+12.3) years old. The HLA-B*51 allele was only accessed in 82% (n = 200) patients and positive in 54% (n = 108).

Regarding organ manifestations (Table 1), all patients had mucous manifestations, 55% skin, 43% joint, 29% ocular, 20% vascular, 19% neurological, 9% gastrointestinal and 0.4% cardiac BD involvement. Most patients have three or more organs affected by BD.

During follow-up, 20 patients (8%) were treated with biological drugs. Comparing the patients who received biological treatment with the patients who received other treatments (Table 1), we found that they were younger (p = 0.030), had less frequently GA (p = 0.009), more frequently EN (p = 0.009), polyarthritis (p = 0.002), spondyloarthritis (p = 0.024), retinal vasculitis (p = 0.011) and gastrointestinal manifestations (p = 0.024), namely gastroduodenal ulcer (p = 0.035), digestive bleeding (p = 0.002), and bowel perforation (p = 0.004). Overall, patients who received biological treatment have more organs affected (p = 0.022).

Of the 20 patients requiring biological therapy to control BD, most had only severe manifestations afflicting one organ (Table 2). One patient (patient 1) needed biological therapy twice during the follow-up period for flares in two organs, neurological and gastrointestinal, in different periods.

In this cohort, all the organ manifestations of BD are represented. The organ involvement that induced the biological therapy starting were heterogeneous (Table 2) (20 patients, n=21 organ involvement): articular (29%, n = 6), gastrointestinal (19%, n = 4), ocular (14%, n = 3), neurological (14%, n = 3), vascular (10%, n = 2), mucocutaneous (9%, n = 2) and cardiovascular (5%, n = 1). On the other hand, the proportion of patients in need of biological therapies was higher in patients exhibiting cardiac (1/1, 100%) and gastrointestinal (4/22, 18%) manifestations.

In our centre, biologicals have been used in BD since 2008. The first case was a 32-year-old man with recurrent uveitis, unresponsive to cyclosporine (patient 8) who underwent complete remission and maintained therapy (infliximab) for ten years, until loss of efficacy due to the appearance of anti-infliximab antibodies.

During the follow-up period, these 20 patients (Table 2) had 23 flares motivating therapy with 30 biological courses (Table 3). The most frequent biological agent used was infliximab. All patients started anti-TNFα agents after classical immunosuppressors failure to control BD, except for patient 18, who started infliximab in another country, and so, we do not have information regarding previous treatments attempted.

After starting the biological drug, the patients underwent complete remission in 22 cases (73%) and six into a partial remission (20%) (Table 3), with a mean BDCAF reduction of 4 points at 12 months after (Fig. 1). Eight patients underwent switch to another biological: three that presented a partial remission, two patients motivated by symptom worsening, a primary failure, and additionally, three other patients, with secondary failure: initial complete remission with disease recurrence a few months after, assumed as drug effectiveness loss (both 33 months after, in two patients with infliximab; and 61 months in one patient with etanercept).

Three patients had anti-TNFα related complications with tuberculosis (two with infliximab and one with adalimumab) (Table 3). Of these patients who developed tuberculosis, all had previous screening tests. Patient 2 have had Pott´s disease in her youth, had undergone treatment for latent tuberculosis before starting infliximab, and was being screened with an annual tuberculosis-interferon gamma release assay test (IGRA). During follow-up, the patient presented a positive IGRA and then was diagnosed with a tuberculosis abscess, despite asymptomatic. Another patient, patient 7, had sustained negative IGRA tests before and during infliximab treatment and developed disseminated tuberculosis. Albeit had unsuspected screening test, tuberculin skin test (TST), and standard chest radiography prior to infliximab, patient 16 developed pleural tuberculosis in less than six months after starting the anti-TNFα agent.

Currently, 12 patients are still in biological therapy (Table 3). Anti-TNFα therapy was stopped in seven patients (patients 1, 2, 8, 12, 13, 17, and on patient 10 twice). Two patients had BD recurrence grounding a new biological therapy course: patient 1, with a neurological flare 11 months after stopping infliximab for gastrointestinal BD; and patient 10, who had a new neurological flare 58 months after infliximab suspension. Therapy was stopped in one patient due to tuberculosis development, despite active BD gastrointestinal manifestations. Five patients remained in remission so far, with a follow-up of 33 months (DP+20) after suspension: 23 months for ocular BD (patient 8); 4 months for a neurological flare (patient 10); 24 months in a gastrointestinal BD case (patient 12); 45 months for mucocutaneous involvement (patient 13); and 63 months in articular BD (patient 17). In most cases, biological therapy weaning followed a period of dose reduction and increased intervals between administrations, together with other classic immunosuppressants (Table 3). On the other hand, in patients who experienced an adverse drug reaction or infectious complications such as tuberculosis, biological therapy has been suddenly stopped.

One patient died during the follow-up period (patient 7). Two patients were awaiting approval for a new biological drug.

Discussion

BD´s therapeutic approach should be primarily tailored to disease severity and based on the nature of organ involvement in order to identify the most appropriate treatment choice. More severe manifestations can be faced with biological drugs in order to counteract irreversible organ damage and life-threatening complications.[18] In our centre, the patients started biological due to a panoply of manifestations that include all BD,s organ damage.

Over the past few years, there has been an increase in the use of biological therapies in patients with refractory manifestations of BD. The cumulative experience is leading to a

Table 1: Demographic and clinical characteristics of patients with Behçet's disease (BD) and comparison between patients treated with biologics and patients treated with other drugs.

	Total (n=243)	Patients treated with biologics (n=20)	Patients with other treatments (n=223)	*p*
Male gender, n (%)	75 (30.9%)	5 (25%)	70 (31.4%)	0.624
Age at onset, mean (+ SD)	28.1(+ 12.3)	25.1(+ 12.8)	28.3 (+ 13.3)	0.297
Age at diagnosis, mean (+ SD)	34.7(+ 12.3)	33.5(+ 12.4)	34.8 (+ 12.3)	0.650
Age (current), mean (+ SD)	49.9(+ 14.3)	43.3(+ 14.1)	50.5 (+ 14.9)	0.030
Manifestations, by organ, n (%)				
Mucosal	243 (100%)	20 (100%)	223 (100%)	-
Oral aphthosis	243 (100%)	20 (100%)	223 (100%)	-
Genital aphthosis	181 (74.5%)	10 (50.0%)	171 (76.7%)	0.009
Skin	133 (54.7%)	14 (70.0%)	119 (53.4%)	0.168
Erythema nodosum	72 (29.6%)	11(55.0%)	61 (27.4%)	0.009
Pseudofoliculitis	96 (39.5%)	6 (30.0%)	90 (40.4%)	0.476
Joint	104 (42.8%)	12 (60.0%)	92 (41.3%)	0.155
Monoarthritis	6 (2.5%)	1 (5.0%)	5 (2.2%)	0.406
Polyarthritis	32 (13.2%)	8 (40.0%)	24 (10.8%)	0.002
Spondyloarthritis	22 (9.1%)	5 (25.0%)	17 (7.6%)	0.024
Arthralgias	80 (32.9%)	8 (40.0%)	72 (32.3%)	0.620
Ocular	71 (29.2%)	9 (45.0%)	62 (27.8%)	0.125
Uveitis	63 (25.9%)	8 (40.0%)	55 (24.7%)	0.180
Retinal vasculitidis	12 (4.9%)	4 (20.0%)	8 (3.6%)	0.011
Papilitis	2 (0.8%)	0	2 (0.9%)	1.000
Conjunctivitis	4 (1.6%)	0	4 (1.8%)	1.000
Scleritis	5 (2.1%)	1 (5.0%)	4 (1.8%)	0.352
Amaurosis	8 (11.4%)	1 (12.5%)	7 (11.3%)	1.000
Vascular	48 (19.8%)	5 (25.0%)	43 (19.3%)	0.357
Deep vein thrombosis	28 (11.5%)	4 (20.0%)	24 (10.8%)	0.262
Thrombophebitis	28 (11.5%)	2 (10.0%)	26 (11.7%)	1.000
Arterial aneurysms	8 (3.3%)	2 (10.0%)	6 (2.7%)	0.134
Arterial occlusion	3 (1.2%)	1 (5.0%)	2 (0.9%)	0.228
Neurological	47 (19.3%)	6 (30.0%)	41 (18.4%)	0.236
Neuro-Behçet	36 (14.8%)	5 (25.0%)	31 (13.9%)	0.190
Brainstem syndrome	14 (5.8%)	0	14 (6.3%)	0.645
Spinal cord syndrome	12 (4.9%)	2 (10.0%)	10 (4.5%)	0.258
Arterial occlusion CNS	5 (2.1%)	0	5 (2.2%)	1.000
Chronic headache	20 (8.2%)	1 (5.0%)	19 (8.5%)	0.712
Gastrointestinal	22 (9.1%)	5 (25.0%)	17 (7.6%)	0.024
Esophageal ulcer	4 (1.6%)	0	4 (1.8%)	1.000
Gastroduodenal ulcer	4 (1.6%)	2 (10.0%)	2 (0.9%)	0.035
Perianal ulcer	5 (2.1%)	0	5 (2.2%)	1.000
Digestive bleeding from ulcer	4 (1.6%)	3 (15.0%)	1 (0.4%)	0.002
Bowel perforation	5 (2.1%)	3 (15.0%)	2 (0.9%)	0.004
Chronic inflammatory diarrhea	16 (6.6%)	2 (10.0%)	14 (6.3%)	0.628
Cardiac	1 (0.4%)	1 (5.0%)	0 (0%)	0.082
Number of organs affected, n (%)				
1	41 (16.9%)	1 (5.0%)	40 (17.9%)	
2	73 (30.0%)	4 (20.0%)	69 (30.9%)	
3	59 (24.3%)	3 (15.0%)	56 (25.1%)	
4	46 (18.9%)	6 (30.0%)	40 (17.9%)	
5	23 (9.5%)	6 (30.0%)	17 (7.6%)	
6	1 (0.4%)	0	1 (0.4%)	
HLA acessed, n (%)	200 (82.3%)	18 (90.0%)	182 (81.6%)	0.393
HLA-B*51 positive, n (%)	108/200 (54.0%)	7/18 (38.9%)	101/182 (55.5%)	0.218

Table 2: Clinical characteristics of Behçet's disease (BD) patients treated with biological therapies.

Patient number	Gender	Age at onset	Age at diagnosis	Manifestations (all)	HLA-B*51 status	Reason to start biologics
1	F	13	18	OA, EN, uveitis, NeuroBehçet, spinal cord syndrome, inflammatory recto-colitis	+	Neurological and gastrointestinal
2	F	39	57	OA, GA, monoarthritis, spondyloarthritis, GI ulcer with perforation and digestive bleeding, inflammatory colitis; GI stenosis	+	Gastrointestinal
3	F	25	26	OA, GA, EN, uveitis, polyarthritis, arthralgias,	-	Articular
4	F	27	40	OA, GA, pseudofolliculitis, arthralgias, colitis, GI ulcer with perforation and digestive bleeding	-	Gastrointestinal
5	M	31	35	OA, GA, chronic headache, DVT, thrombophlebitis, arterial aneurysms, spondyloarthritis	-	Vascular
6	M	33	36	OA, EN, arterial aneurysms and arterial occlusion	-	Vascular
7	F	43	46	OA, EN, pseudofolliculitis, uveitis, retinal vasculitis, arthralgias, (Tako-Tsubo syndrome)	+	Ocular
8	M	18	19	OA, GA, pseudofolliculitis, uveitis, retinal vasculitis, polyarthritis, arthralgias, and NeuroBehçet	+	Ocular
9	F	10	10	OA, GA, arthralgias, spondyloarthritis	+	Articular
10	F	34	35	OA, EN, pseudofoliculitis, retinal vasculitidis, NeuroBehçet, DVT	+	Neurological
11	F	35	40	OA, cutaneous vasculitis, EN, polyarthritis	-	Mucocutaneous
12	F	48	48	OA, EN, uveitis, DVT, GI ulcer with perforation and digestive bleeding, spondyloarthritis	NA	Gastrointestinal
13	F	10	37	OA, GA, EN, skin ulcer, uveitis, polyarthritis	-	Mucocutaneous
14	F	8	37	OA, GA, polyarthritis, DVT and pulmonary embolism, miscarriage, recurrent myopericarditis	+	Cardiovascular
15	M	8	36	OA, GA, pseudofolliculitis, EN, uveitis, retinal vasculitis, NeuroBehçet, spinal cord syndrome	NA	Neurological
16	F	20	43	OA, arthralgias, polyarthritis	+	Articular
17	F	17	17	OA, GA, pseudofoliculitis, arthralgias	-	Articular
18	M	45	47	OA, pseudofoliculitis, EN, arthralgias, uveitis, NeuroBehçet	-	Ocular
19	F	19	20	OA, EN, polyarthritis, spondyloarthritis	-	Articular
20	F	21	24	OA, polyarthritis, arthralgias, thrombophlebitis	-	Articular

DVT - deep vein thrombosis; EN - erythema nodosum; F – female; GA - genital aphthosis; GI - gastrointestinal; M – male; NA – not accessed OA - Oral aphthosis.

transition from the old classic therapies considered until now as the gold standard to newer drugs.[18] Among these, anti-TNF-α agents have been increasingly employed showing to be effective in all severe BD manifestations resistant to conventional therapy.[16,18,19] In our centre, all patients who underwent biological treatment had received an anti-TNF-α agent, and biological therapy followed classical immunosuppressors failure. Most of our patients went into BD remission (93%) after starting biological drugs, with significant symptoms decrease, bearing witness to these therapies effectiveness.

Some authors describe cases of BD recurrence with life-threatening manifestations after biologicals are withdrawn.[20,21] In our centre, we have tried to suspend the biological therapy in seven patients, in which, five of them successfully so far. Two patients had BD recurrence after suspension, both with a neuro-Behçet syndrome, requiring a new biological course. Therefore, frequent monitoring of these patients is necessary after anti-TNF-α cessation in order to an earlier detection of relapses. Also, it will be important to also extend the time of surveillance in clinical

Table 3: Biological therapies used during follow-up in patients with Behçet's disease and clinical outcomes. Each line represents a biological therapy course.

Patient number	Age at flare	Manifes-tations	Previous treatments	Reason to switch	Biologics (drugs)	Biologics (time)	Outcome	Biologics (weaning)	Reason to stop biologics	Current status
1	15	Inflammatory colitis	CCS, mesalazine, AZA	No response	Infliximab	Aug./2014 to Sept./2017	Complete remission	Dose reduction + CCS and AZA	Clinical stability	Asymptomatic
1	18	NeuroBehçet	CCS	New flare after CCS weaning	Infliximab	Aug./2018 and so on	Complete remission	-	-	-
2	57	Inflammatory colitis	CCS, AZA	No response	Infliximab	Sept./2012 to Dec./2013	Partial remission (clinical improvement but sustained endoscopic colitis)	-	Switch to another biological	Ileocecal recurrence with perforation and GI bleeding requiring segmental enterectomy; awaiting approval for another drug
2	58	Inflammatory colitis	Infliximab	Partial remission	Adalimumab	May/2014 to Feb./2017	Complete remission	Sudden stop	Tuberculosis abscess in the psoas muscle	
3	28	Severe polyarthritis	CCS, MTX	No response	Adalimumab	Dec/2017 and so on	Partial remission	-	-	Keeps morning stiffness and arthralgias
4	52	Ileitis, severe erosions, ulcers	CCS	New flare after CCS weaning	Infliximab	Aug./2018 and so on	Complete remission	-	-	Sequelae of multiple abdominal fistulas and ileocolectomy; recurrent subocclusive symptoms.
4	53	Sustained enterocuta-neous fistulas	Infliximab	Partial remission	Infliximab	Aug./2018 and so on	Complete remission	-	-	
5	35	Arterial aneurysms	CCS, cyclophosphamide	No response	Infliximab	Nov./2016 and so on	Complete remission	-	-	Asymptomatic
6	36	Arterial aneurysms and occlusion	CCS, cyclophosphamide	No response	Infliximab	Jan./2018 and so on	Complete remission	-	-	Asymptomatic
7	46	Recurrent uveitis	CSA	No response	Infliximab	Feb./2010 to Jan./2013	Complete remission	Sudden stop	Tuberculosis (pulmonary, pleural and peritoneal)	Deceased - cardiogenic shock due to stress cardiomyopathy (Tako-Tsubo syndrome)
8	32	Recurrent uveitis	CSA	No response	Infliximab	Feb./2008 to Oct./2018	Complete remission	Sudden stop (reaction after infliximab administration)	Loss of efectiveness due to anti-infliximab antibodies	Asymptomatic
9	16	Severe polyarthritis	CCS, MTX	No response	Infliximab	Jan./2013 to Sept./2013	Partial remission	-	Switch to another biological	Asymptomatic
9	16	Severe polyarthritis	Infliximab	Partial remission	Etanercept	Nov./2013 to Dec./2018	Complete remission	-	Switch to another biological	-
9	22	Severe polyarthritis	Etanercept	Loss of effecti-veness after initial remission	Adalimumab	Dec./2018 and so on	Complete remission	-	-	-
10	35	NeuroBehçet	CCS	No response	Infliximab	July/2011 to July/2013	Complete remission	Dose reduction and increase interval between administrations +CCS and colquichine	Pregnancy	Asymptomatic
10	41	NeuroBehçet	CCS, c olquichine	New flare	Infliximab	Apr./2018 to May/2020	Complete remission	Dose reduction and increase interval between administrations + CCS, AZA and colquichine	Clinical stability	-

Table 3 (cont.): Biological therapies used during follow-up in patients with Behçet's disease and clinical outcomes. Each line represents a biological therapy course.

Patient number	Age at flare	Manifes-tations	Previous treatments	Reason to switch	Biologics (drugs)	Biologics (time)	Outcome	Biologics (weaning)	Reason to stop biologics	Current status
11	42	Refractory skin ulcers	Colchicine, MTX, CSA	No response	Infliximab	Oct./2016 and so on	Complete remission	-	-	Asymptomatic
12	59	Inflammatory ileocolitis	CCS, CSA, SLZ	No response	Infliximab	July/2011 to May/2012	No response and increase GA	-	Switch to another biological Clinical stability	Asymptomatic
12	64	Inflammatory ileo-colitis	Infliximab	No response	Adalimumab	Apr./2013 to Sept./2018	Complete remission	Increase interval between administrations + CCS and AZA		
13	44	Refractory skin ulcers	CSA, AZA, CCS	No response	Infliximab	May/2010 to Feb./2013	Complete remission	-	Switch to another biological Clinical stability	Asymptomatic
13	47	Refractory skin ulcers	Infliximab	Loss of effectiveness after initial remission	Adalimumab	May/2013 to Dec./2016	Complete remission	Sudden stop (reaction after adalimunab administration with lip edema and oral aphtosis) + CCS and thalidomide		
14	37	Recurrent myopericarditis	CCS, cyclophosphamide	No response	Infliximab	Sept./2015 and so on	Complete remission	-	-	Asymptomatic
15	44	NeuroBehçet	Colchicine, CCS, CSA	No response	Infliximab	Sept./2017 and so on	Complete remission	-	-	Asymptomatic
16	47	Severe polyarthritis	Colchicine, CCS, MTX, plaquinol, AZA, SLZ	No response	Infliximab	Mar./2016 to Sept./2016	Complete remission	Sudden stop	Pleural tuberculosis	Asymptomatic
16	48	Severe polyarthritis	Infliximab	New flare and previous pleural tuberculosis	Adalimumab	Nov./2018 and so on	Complete remission	-	-	-
17	18	Severe polyarthritis	Colchicine, MTX	No response	Etanercept	Oct./2014 to July/2015	Complete remission	Increase interval between administrations + CCS and AZA	Clinical stability	Asymptomatic
18	55	Recurrent uveitis	CCS (previous follow-up in another country)	No response	Infliximab	Mar./2016 to Dec./2018	Complete remission	-	Switch to another biological	Keeps morning stiffness
18	57	Recurrent uveitis	Infliximab	Loss of effectiveness after initial remission	Adalimumab	Feb./2019 and so on	Partial remission	-	-	-
19	20	Severe polyarthritis	Colchicine, plaquinol, CCS	No response	Adalimumab	Nov./2019 (single dose)	No response and increase OA	-	-	Keeps OA, severe polyarthritis; awaiting approval for another drug
20	23	Severe polyarthritis	Colchicine, SLZ	No response	Adalimumab	Feb./2020 and so on	Partial remission	-	-	Keeps morning stiffness

AZA – azathioprine; CSA – ciclosporin; CCS – corticosteroid; MTX - methotrexate; SLZ – salazopyrine

trials with anti-TNFα agents as most studies only address treatment outcomes within a few weeks after biologics introduction. On the other hand, bearing in mind that these therapies are not innocuous, very little is known regarding optimal biological therapy duration after achieving a long-standing complete remission, when and how to stop therapy in order to avoid relapses.

Despite a regular latent tuberculosis screening, before and during the biological therapies well established in our centre, three patients developed tuberculosis during treatment. The risk is higher in anti-TNF-α agents,[22] given the role of this cytokine in the pathogens of mycobacterial infections. TNF-α is required for the granuloma formation and inhibition of the reactivation of dormant bacilli.[23] Along with these therapies, it is essential to emphasize the need for a regular screening test without despising a high clinical suspicion. On the other hand, both screening tests evaluate cell-mediated immunity and can give false-negative results in immunosuppressed patients. Nowadays is recommended to use both screening tests in these patients (TST and IGRA)

together with clinical assessment.[24] Of notice, in one case, the diagnosis was made in an asymptomatic patient who presented a positive screening test, and in another patient who presented an extensive disease despite negative screening tests.

Our study´s main strengths lie in the fact that we have considered all BD´s organ manifestations refractory to conventional therapies, not limited to a specific organ. Also relevant is the high number of BD patients followed at our centre, and the experience with biological therapies for over ten years. The main weaknesses of this study are due to its observational nature with its inherent limitations and with the fact that these patients represent only 8% of our sample.

Conclusion

BD is a systemic inflammatory disorder in which several cytokines appear to play a substantial role. Biological targeted therapies are highly effective in controlling refractory BD´s manifestations, although they are not innocuous. Currently, little is known about the optimal duration of these therapies after the achievement of long-standing complete remission, regarding when and how to stop these drugs. This is important not only to avoid relapses that can sometimes be life-threatening but also to reduce the deleterious therapy side-effects.

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PREVIOUS PRESENTATIONS

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