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Original article

Adalimumab for the treatment of Behçet's disease: experience in 19 patients

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Abstract

Objective. To describe the experience of two tertiary Spanish centres (Hospital Clínico San Cecilio, Granada and Hospital Clínic, Barcelona) with the use of adalimumab for the treatment of severe clinical manifestations in patients with Behçet's disease (BD) in whom immunosuppressive therapy had failed.

Methods. Retrospective chart review from patients with BD treated with adalimumab in two specialized Spanish centres (Hospital Clínico San Cecilio, Granada and Hospital Clínic, Barcelona).

Results. From November 2006 to February 2011, 19 patients with BD were treated with adalimumab. The reason to initiate adalimumab was refractory disease in 17 (89.5%) patients and adverse events to CSA and infliximab in two (10.5%) patients, respectively. The main clinical manifestations leading to adalimumab administration were panuveitis in eight patients, severe bipolar aphthosis in eight, retinal vasculitis in three and severe folliculitis in three. Overall, adalimumab achieved clinical improvement in 17 of the 19 patients. Of note, ocular manifestations (panuveitis and retinal vasculitis) responded rapidly in all cases. In addition to clinical improvement, treatment with adalimumab was associated with reduction in the number and dose of standard immunosuppressive agents. Of interest, seven patients had received TNF-α inhibitors before adalimumab, five infliximab and the remaining two etanercept. Adalimumab was withdrawn in only one patient due to severe infusional reaction in the form of urticaria and angioedema.

Conclusion. Adalimumab is a valid option for patients with BD and recalcitrant non-controlling manifestations with good safety profile.

Key words: Behçet's disease, adalimumab, refractory, treatment.

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystem inflammatory disorder of unknown aetiology classified among the vasculitides [1]. Clinical presentation is characterized by recurrent oral ulcers in combination with genital ulcers, ocular disease, cutaneous lesions, arthritis, and, less frequently, involvement of the gastrointestinal tract, CNS and vascular beds [1].

The aim of therapeutic strategy in BD is to prevent recurrent multisystem involvement in order to minimize potential irreversible damage [2]. Obviously treatment should be tailored according to the extent and severity of clinical manifestations [2]. One of the main problems is the lack of controlled evidence, especially for vascular, neurological and gastrointestinal involvement [3]. Nowadays, current therapeutic options include the use of topical measures for isolated oral and genital ulcers, colchicine in cases of arthritis or erythema nodosum, combination of AZA, MTX, and systemic corticosteroids (CSs) for inflammatory eye disease involving the posterior segment, with addition of CSA or infliximab if severe eye inflammation is confirmed [2, 4–6]. AZA, MTX, TNF-α inhibitors in combination with systemic CSs are effective for gastrointestinal disease [7–9]. In addition, CSs, AZA, CYC or CSA are advised for acute deep venous thrombosis and combination of CYC and steroids for pulmonary

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CLINICAL SCIENCE

and peripheral arterial aneurysms. Lastly, CNS involvement can be treated with CSs, AZA, CYC, MTX or TNF-α inhibitors [2, 4].

IFN-α is useful for ocular, articular, mucocutaneous and neurological manifestations of BD, including those resistant to standard treatment [10–18]. In particular, IFN-α is an effective option for severe ocular involvement (active panuveitis and/or retinal vasculitis) with partial or complete response documented in >90% of patients [10, 15, 17, 19, 20].

Although the introduction of these therapies has dramatically improved the prognosis of BD, a subgroup of patients developing life-threatening events, chronic resistant complications such as sight-threatening events or presenting with intolerance or side-effects to standard immunosuppressive agents exists. For these cases, TNF-α antagonism emerges as a valid option since high levels of this cytokine and its soluble receptor have been detected in the serum and aqueous humour of patients with active BD [21, 22]. Among TNF-α inhibitors, most of the experience related to off-label treatment of severe clinical manifestations of BD inadequately controlled by standard immunosuppressive regimens exist with infliximab and etanercept [23]. In fact, infliximab has been approved in Japan as an effective treatment of refractory uveoretinitis [24]. In addition, recently, adalimumab, a completely humanized IgG 1 monoclonal anti-TNF-α antibody, has been used in BD [25–31]. Data from a recent review showed that remission of BD patients treated with adalimumab ranges from 60 to 100% according to organ involvement [23]. The aim of the present study was to describe our experience with the use of adalimumab for the treatment of severe clinical manifestations in patients with BD in whom immunosuppressive therapy had failed.

Methods

Retrospective chart review from patients with BD treated with adalimumab in the Uveitis Unit of two tertiary Spanish centres (Hospital Clínico San Cecilio, Granada and Hospital Clínic, Barcelona) was performed. Ophthalmologists and internal medicine specialists work in both units. At the time of the study, the total number of patients with BD followed at two centres was 194. Retrieved data included gender, ethnicity, age at diagnosis, HLA-B51 status, initial and accumulated clinical manifestations, number and type of relapses, previous treatments and acute or chronic complications derived from disease itself or therapy. The classification criteria of the International Study Group were used for the diagnosis of BD [16]. This study was approved by the local ethics committees of Hospital San Cecilio of Granada and Hospital Clinic of Barcelona, and was conducted in compliance with the protocol Good Clinical Practices and Declaration of Helsinski principles. Patients signed informed consent giving authorization to use their individual information in our databases and in our retrospective studies. Before starting TNF-α inhibitors, patients had a baseline laboratory evaluation in the form of complete blood cell count, liver function test, blood urea nitrogen, serum creatinine level, chest X-ray, and tuberculin skin sensitivity test (purified protein derivative). If a patient had a strong positive skin test, an abnormal chest X-ray or any risk factors, such as a family history of tuberculosis, we gave isoniazid with the anti-TNF-α agent. Adalimumab was administered on a compassionate-use basis after obtaining informed consent from the patients.

The response of clinical manifestations to adalimumab administration was considered the main end-point. Secondary outcome measures recorded were the number and dosage of immunosuppressive drugs used by each patient before and after adalimumab treatment. Given the lack of validated BD Current Activity Form (BDCAF) for Spanish patients and the absence of uniform criteria to define refractory and relapsing BD, we used the following definitions for mucocutaneous, gastrointestinal and neurological manifestations: (i) complete response was considered if there was disappearance of signs or symptoms and partial response if improvement or stabilization of clinical parameters was recorded; (ii) progressive disease unresponsive to steroids and a combination of standard immunosuppressive agents was labelled as refractory; and (iii) relapses were documented when re-appearance or worsening of previous manifestations were detected.

In addition, ocular involvement severity and response to treatment was evaluated according to the Standardization of Uveitis Nomenclature (SUN) Workgroup criteria and changes in best-corrected visual acuity (BCVA) score expressed in a decimal scale. Complete response was considered to be achieved with the presence of <0.5+ cellular reaction in the anterior chamber and vitreous humour (scale 0–4) and remission of vasculitis was evaluated by a score from 0 to 3 at fundus examination and fluorescein angiography test (0 = absence of vasculitis, 1 = vasculitis of peripheral retinal vessels, 2 = posterior pole vasculitis, 3 = vasculitis with evidence of white patches of retinitis) [32]. Relapse was considered when there was an increase of at least 50% of inflammation and retinal vasculitis scores.

Results from continuous variables are presented as median [interquartile range (IQR)] and categorical data as percentages. Comparison between pre- and post-adalimumab-selected covariates was analysed using Mann–Whitney U-test for quantitative variables and Fisher's exact test for categorical data. Statistical significance was defined as $P < 0.05$. Calculations were performed with the statistical package PAWS version 18 (SPSS, Inc. 2009, Chicago, IL, USA).

Results

General characteristics

From November 2006 to February 2011, 19 of 194 patients with BD were treated with adalimumab, 11 of 64 from Hospital Clínico San Cecilio, Granada and 8 of 130 from Hospital Clínic, Barcelona. Two patients from Hospital Clínic and five patients from Hospital San Cecilio have been previously published [33, 34].

Seventeen (89.5%) of 19 patients fulfilled the 1990 International Study Group Criteria for BD. The other two patients, with the incomplete form of the disease presented with oral ulcers, retinal vasculitis and positive analysis for HLA-B51. Twelve (63%) patients were female and the median age at diagnosis was 34 years (15, range 14–60) (Table 1). All patients were Caucasian.

Clinical characteristics

Median age at the beginning of adalimumab was 40 (15) (range 26–63) years, with a median interval time between diagnosis and start of treatment of 4 (3) (range 1–14) years. The main demographic characteristics and clinical manifestations leading to adalimumab administration are depicted in Table 1.

The reason to initiate adalimumab was refractory disease in 17 (89.5%) patients and adverse events to CSA and infliximab in two (10.5%) patients, respectively. All patients were treated with a dose of 40 mg scheduled every 2 weeks subcutaneously, except one who received the drug every 3 weeks. Median follow-up under adalimumab treatment was 25 (22) (range 3–49) months.

Table 1 Demographic and main clinical characteristics of 19 patients with BD treated with adalimumab

	n or *n* (%)
Sex, male/female	7/12 (37/63)
Age at diagnosis, years, median (IQR)	34 (15)
HLA-B5 positivity	6 (31.6)
Clinical manifestations at the start of adalimumab[a]	
Ocular involvement	10 (50.6)
Panuveitis	8
Retinal vasculitis	3
Recurrent scleritis	1
Scleritis with recurrent anterior uveitis	1
Mucocutaneous involvement	9 (47.4)
Severe aphthosis	8
Severe folliculitis	3
Cutaneous vasculitis	2
Erythema nodosum	1
Gastrointestinal	2 (10.5)
Anal fistula	2
Peripheral nervous system	1 (5.3)
Number of immunosuppressive and immunomodulatory drugs used before adalimumab,[b] median (IQR)	2 (1)
Colchicine	13
Prednisone	16
MTX	8
AZA	5
CSA	3
CYC	1
TNF-α inhibitor	7
Infliximab	5
Etanercept	2

All data presented as *n* or *n* (%) unless indicated otherwise. [a]Several patients presented with more than one clinical manifestation. [b]Several patients required more than one drug.

Response to treatment

Ocular involvement

Overall, 18 eyes from 10 BD patients showed ocular involvement. Four eyes corresponding to two patients presented with recurrent scleritis and scleritis with recurrent anterior uveitis, respectively, and they showed a complete resolution of inflammatory signs. The remaining 14 eyes with posterior involvement in the form of retinal vasculitis and panuveitis presented with complete response; they had <0.5+ cellular reaction in anterior chamber and vitreous and disappearance of signs of vasculitis at fundus examination and on fluorescein angiography at the last visit. Complete resolution of inflammation was noted after an average period of 2.9 (range 1–4) weeks. Four eyes had improvement in visual acuity by at least three lines of vision measured as BCVA score. Two eyes improved by one and two lines each, respectively. Three additional eyes maintained unchanged BCVA, whereas two eyes decreased two lines and one eye one line of vision at last visit. The remaining two eyes decreased BCVA significantly due to a macular hole and a vitreous haemorrhage that required pars plana vitrectomy in both cases (Table 2). Patients with posterior ocular involvement presented an initial and final right eye BCVA [median (IQR)] of 0.7 (1) and 0.85 (0.84), respectively. In contrast, initial and final BCVA in the left eye was 0.45 (0.69) and 0.35 (0.87), respectively. The difference between initial and final BCVA score for each eye did not reach statistical significance (data not show).

During adalimumab treatment, three (15.8%) patients suffered from relapse of BD in the form of uveitis. Interestingly, one of these patients experienced the ocular recurrence 4 months after adalimumab was withdrawn due to the absence of ocular inflammation during 14 months of treatment, and improved with its reintroduction. In the remaining two cases, a complete response was achieved after increasing the dose of CSs. We did not find any statistical difference in age, gender, clinical manifestations or number of immunosuppressive drugs used by those patients who presented recurrences during adalimumab treatment and those who remain relapse-free (data not shown).

Other organ involvement

Regarding severe aphthous disease, complete response was documented in five (62.5%) patients, whereas the remaining three cases responded only partially (Table 3). The accompanying folliculitis and erythema nodosum observed in four patients showed a partial response to adalimumab. There were two patients with cutaneous vasculitis diagnosed by biopsy of the legs with painful nodules. One of these patients also presented with symptoms and electrophysiological evidence of peripheral neuropathy. This last patient showed a complete clinical response in addition to improvement in EMG/nerve

TABLE 2 Individual characteristics of patients with posterior ocular involvement

Patient	Age, years	Sex	Type of eye involvement	Eye	Initial BCVA	Final BCVA	Previous treatment	Final treatment	Response/time to response (weeks)	Time on adalimumab, months	Relapse
1	28	F	Panuveitis	R	0.4	0.7	PDN/AZA/colchicine	MTX	Complete (2)	5	No
				L	0.8	1.2					
2	40	F	Panuveitis	R	1.2	1	PDN/MTX/etanercept	MTX	Complete (4)	24	No
				L	0.15	0.05					
3	60	M	Panuveitis	R	1.2	0	CSA/colchicine	Colchicine	Complete (4)	12	No
				L	0.05	0.05					
4	26	M	Panuveitis	R	0.1	1	PDN/MTX/ infliximab	PDN/AZA	Complete (2)	29	Yes
				L	0.1	0.7					
5	26	M	Panuveitis + retinal vasculitis	R	0.15	0.15	PDN/CSA/infliximab/colchicine	PDN	Complete (4)	23	Yes
				L	1	0.1					
6	24	M	Panuveitis	R	0.15	0.2	PDN/infliximab	PDN	Complete (4)	27	Yes
				L	0.5	0.5					
7[a]	41	M	Panuveitis + retinal vasculitis	R	1	1	PDN/infliximab/colchicine	—	Complete (2)	10	No
				L	0.8	1					
8[a]	24	F	Panuveitis + retinal vasculitis	R	1	1	PDN/infliximab	PDN	Complete (4)	27	No
				L	0.4	0.2					

[a]These two patients presented with unilateral ocular involvement. F: female; M: male; L: left eye; R: right eye; PDN: prednisone.

conduction studies, whereas adalimumab was ineffective in the other patient with nodular cutaneous vasculitis.

Two patients suffered from gastrointestinal BD in the form of perianal fistulas. One of these patients responded to treatment with healing of the fistula and is actually asymptomatic, but the other one presented with recurrent fistulas and developed urticaria and angioedema with adalimumab administration, leading to discontinuation of medication, and finally required partial colectomy.

Previous and final treatments

Previous to adalimumab treatment, all patients received at least one immunosuppressive conventional drug, with a median of 2 (1) (Table 1). Sixteen (84.2%) patients were under CS treatment with oral prednisone at a median dose of 10 (10) (range 2.5–60) mg/day. MTX was used in eight (42.1%) patients at a median dose of 17.5 (5) (range 10–20) mg/week, AZA in five (26.3%), CSA in three (15.8%), thalidomide in two (10.5%) and i.v. CYC in one (5.3%). Of note, seven (36.8%) patients had received TNF-α inhibitors before adalimumab, five of them with infliximab and the remaining two with etanercept. In four patients, infliximab became ineffective after a median of 13.5 months. In the remaining patient, infliximab was withdrawn due to severe anaphylactic reaction. Regarding patients previously treated with etanercept, in one of them it was ineffective and, in the remaining case, etanercept was replaced because this drug seems to be less effective than infliximab or adalimumab on various manifestations of BD and a more favourable administration schedule of adalimumab (every 2 weeks instead once or twice weekly s.c. injection of etanercept). Finally, 13 (68.4%) patients were treated with colchicine (supplementary data Table S1, available at *Rheumatology* Online).

At the last visit, nine patients were under CS therapy, with a median dose of 5 (5.7) (range 2.5–10) mg/day, four patients were receiving MTX at a median dose of 7.5 (range 5–7.5) mg/week and only two patients were under treatment with AZA. In addition, seven patients were receiving colchicine. Therefore, in addition to improvement in clinical manifestations, a significant number of patients achieved a reduction in the dose and number of standard immunosuppressive drugs, although these differences did not reach statistical significance (Table 2 and supplementary Table S2, available at *Rheumatology* Online). All the patients except four continued on adalimumab injections until the last follow-up. Adalimumab was withdrawn in three patients due to maintenance of complete remission of eye inflammatory disease after 5, 12 and 18 months of continuous adalimumab administration. In the remaining patient, drug was discontinued after 3 months due to severe adverse effects (see below).

Safety

Adverse effects were documented in two patients: the first presented malaise and fever that were transitory and disappeared with paracetamol, and the second experienced a severe infusion reaction in the form of urticaria

TABLE 3 Response of clinical manifestations other than eye disease to adalimumab treatment

Manifestation	*n*	Complete response, *n* (%)	Partial response, *n* (%)	Global response, *n* (%)
Severe aphthosis	8	5 (62.5)	3 (37.5)	8 (100)
Severe folliculitis	3	–	3 (100)	3 (100)
Cutaneous vasculitis	2	1 (50)	–	1 (50)
Erythema nodosum	1	–	1 (100)	1 (100)
Anal fistula	2	1 (50)	–	1 (50)
Peripheral neuropathy	1	1 (50)	–	1 (50)
Total	17	8 (47)	7 (41.2)	15 (88.2)

and angioedema that forced the withdrawal of adalimumab.

Discussion

We described the clinical response of the largest case series of patients with BD treated with adalimumab. Overall, 17 of the 19 patients improved completely or partially with adalimumab administration. Regarding ocular involvement, all patients showed complete resolution of inflammatory ocular involvement and 64% of eyes with posterior involvement had improved or maintained BCVA at last visit. In addition, adalimumab was well tolerated.

During recent years there has been increasing off-label use of this agent for treatment of several refractory manifestations of BD, and improvement of clinical features was achieved in 60–100% of patients [23]. These percentages seem to be similar with the other TNF-α inhibitors (infliximab and etanercept) [23] and IFN-α, with partial or complete response documented in 70–90% of patients [10, 15, 17, 19, 20].

In our series, ocular disease was the most frequent manifestation refractory to treatment. To prevent permanent visual loss, it is crucial to achieve the recovery of ocular lesions in the shortest time possible. Complete resolution of ocular inflammation was noted in our series after an average period of 2.9 weeks. This is in accordance with other studies performed in patients with BD using adalimumab [35] or other TNF-α inhibitors [23]. In front of standard immunosuppressive treatments used alone or in combination, the faster action of anti-TNF therapy may be one of the key points to choose them to treat patients with BD and severe ocular involvement [36].

Other clinical manifestations also responded well to adalimumab. Good response in mucocutaneous manifestations was documented in all our patients and in 73–100% in other series [23]. Although folliculitis in BD rarely requires biologics [37], three of our patients presented with severe and extended folliculitis that was unresponsive to several immunosupressive drugs such as colchicine, MTX, AZA or infliximab in combination with prednisone. In addition, two of these patients had severe bipolar aphthosis and the remaining patient had panuveitis.

Only two patients did not respond to adalimumab. One of them had perianal fistula and the other nodular cutaneous vasculitis. Literature about treatment of gastrointestinal BD with TNF-α inhibitors is scarce [7, 8, 38–40]. In these patients with refractory disease, infliximab showed to be effective in clinical and imaging grounds with good long-term efficacy. Recently two cases of steroid-dependent gastrointestinal BD treated with adalimumab have been reported [41]. We do not know the reason for the absence of response in one of our patients with anal fistula, but we hypothesize more severe disease or insufficient dosage of adalimumab.

In addition to clinical improvement, treatment with adalimumab was associated with reduction in the number and dose of standard immunosuppressive agents. Furthermore, it exhibited a relevant CS-sparing effect and, interestingly, CSs were discontinued in 7 (43.8%) patients. It has been reported that 95% of patients who responded to some TNF-α inhibitor can taper their glucocorticoid dosage and that 57% of those are able to discontinue it [23]. Until now, there is no standard protocol for the use of TNF-α inhibitors in BD. Unsolved issues include the dosage schedule, time of administration and concomitant administration of other immunosuppressive medication. Data to strongly support the use of any of these medications over the others is lacking, although some combinations are of interest. For example, the addition of AZA and CSA or CSA and MTX to infliximab seems to be superior to monotherapy for sustained ocular remission in a series of 369 patients [42]. In agreement, the European League Against Rheumatism expert committee [2] recommended that infliximab should be used in combination with AZA and CSs if the patient has severe eye disease.

In our series, seven (36.8%) patients had received infliximab or etanercept before adalimumab. In five of them, the reason to switch was that these TNF-α inhibitor agents became ineffective and, interestingly, adalimumab was able to achieve a clinical response.

This observation is in accordance with several previous reports from other autoimmune diseases, such as RA or psoriasis, in which failure of treatment with a particular TNF-α inhibitor did not preclude a good response with another anti-TNF-α antagonist. A recent article has been published about 17 BD patients with predominant mucocutaneous lesions who were successfully treated

switching from infliximab to adalimumab [43]. Therefore patients failing infliximab may successfully be treated with adalimumab. In addition, s.c. administration by the patient itself without need of in-hospital i.v. administration represents an advantage. These facts may open the door to the use of adalimumab as a first line of treatment in selected patients with BD with severe clinical manifestations.

Safety is always an issue in anti-TNF therapy [44]. The use of adalimumab in patients with BD showed an acceptable safety profile comparable to that observed in patients with chronic inflammatory arthritis and Crohn's disease [45]. In our study, two patients developed adverse effects, but only one discontinued treatment because of the severity of the infusional reaction (urticaria and angioedema).

There are several limitations in our report due to its retrospective nature. The evaluation of clinical manifestations and treatment decisions were dependent on the medical staff, making direct comparisons difficult. The clinical features leading to the use of adalimumab in the current series of patients with BD were heterogeneous and the number of patients included was limited. These facts make it difficult to draw firm conclusions. In spite of these limitations, our study represents a real picture of patients with refractory BD in whom adalimumab may be a valuable option. Whether this anti-TNF-α inhibitor can be used as first-line therapy deserves further investigation and should be evaluated in properly designed randomized clinical trials that include its comparison against the commonly used standard immunosuppressive drugs.

Rheumatology key messages

- New therapy options are needed for treating patients with refractory/relapsing BD.
- The addition of adalimumab improves recalcitrant non-controlling manifestations of BD.
- TNF-α inhibitors seem to have a good safety profile in cases of refractory BD.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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