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Case report

Efficacy of adalimumab in Behçet's disease. Description of 6 cases

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ABSTRACT

Behçet's disease (BD) is a systemic vasculitis, with a more aggressive course in young males. Orogenital ulcers, uveitis and cutaneous lesions are the most frequent manifestations.

We analyzed the effects of adalimumab on six patients with BD pretreated with inmunosupressive therapy, two of whom had received infliximab. We observed a good clinical response in all patients. To date, after a mean follow-up of 26.8 months, patients continue receiving adalimumab, with good clinical control, no adverse effects have been reported with adalimumab.

Eficacia del adalimumab en la enfermedad de Behçet: descripción de 6 casos

Palabras clave:
Enfermedad de Behçet
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RESUMEN

La enfermedad de Behçet (EB) es una vasculitis sistémica, y afecta con mayor agresividad a varones jóvenes. Sus manifestaciones más frecuentes son las aftas orogenitales, la uveítis y las lesiones cutáneas.

Analizamos 6 pacientes con EB, que recibieron adalimumab para controlar la enfermedad. Todos habían recibido terapia inmunosupresora, además 2 de ellos recibieron infliximab. Observamos una buena respuesta clínica al fármaco. Actualmente, con un seguimiento medio de 26,8 meses, los pacientes siguen en tratamiento con adalimumab, con buen control clínico y sin que se hayan detectado efectos adversos relacionados con el anti-TNF.

Introduction

Behçet disease (BD) is a systemic vasculitis. Its most common manifestations are oral-genital ulcers, polyarthritis, ocular involvement (uveitis) and skin involvement (erythema nodosum, folliculitis and pathergy).[1,2] The use of antagonists of tumor necrosis factor alpha (anti-TNF) biological agents as part of a therapeutic strategy for the management of systemic vasculitis is increasingly frequent.[3]

Adalimumab (Humira®) is a human anti- TNF-alpha that, in most cases, is self-administered subcutaneously every 14 days.

The medical literature there are some described cases of BDtreated with adalimumab, with a good clinical response.[4-12] We present our experience with 6 BD patients treated with adalimumab.

Clinical observation

6 Spanish patients (Caucasian), meeting international criteria for BD[13] are described, 4 being women. The mean age was 42.5± 2.8 years (range 38-46). Average time of disease 14.1±6.5 years (range 5-22). All patients had involvement of mucous membranes (mouth ulcers and / or genitals). Five patients had ocular involvement, 3 skin lesions and one woman had neurological disease (inflammatory leukoencephalopathy) (Table 1). All patients had negative autoantibodies and normal complement levels (C3, C4, factor B).

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Table 1
Patient characteristics

Gender Age, years	BD Motive	BD duration, for use of Adalimumab[a]	Prior years	Concomitant treatment	Evolution medication	Adverse effects	Adalimumab Follow up, months
Female (38)	Bipolar ulcers[a] Erythema nodosum Pseudofolliculitis Knee arthritis Joint pain HLA B5 (−)	22	Aza, Ste Colchi, Cyclo	None	Asymptomatic	No	40
Female (41)	Uveítis[a] Oral Ulcers Inflammatory leukoencephalopathy	5	Cyclo, Ste Infli	Colchi, Para	Improvement (Oral Ulcers Back pain)	No	23
Female (42)	Uveítis[a] Oral ulcers Erythema nodosum Skin lesions HLA B5 (+) Pathergy (−)	10	Aza, Ste Cyclo	Aza	Asymptomatic	No	30
Female (44)	Bilateral panuveitis[a] Repeat oral ulcers	11	Cyclo, Ste Infli	Ste	Asymtomatic	No	41
Male (46)	Uveítis[a] Repeat oral ulcers	17	Aza, Ste Cyclo	Ste, NSAID	Asymptomatic	No	12
Male (44)	Uveítis[a] Pseudofolliculitis Oral ulcers Sacroilitis	20	Aza, Ste Colchi, Cyclo	Ste, NSAID Para	Improvement (Oral ulcers Heel pain/low back pain)	No	15

Aza indicates azathioprine; BD, Behçet's disease; Colchi, colchicine; Cyclo, cyclosporin; Infli, infliximab; NSAID, non steroidal anti-inflammatory drugs; Para: paracetamol; Ste, steroids.
[a]Motive for use of adalimumab.

The patients had received conventional treatment: steroids, azathioprine, cyclosporine, anti-inflammatory drugs, colchicine and 2 received infliximab (Table 1).

We decided to start treatment with adalimumab (40 mg/ 14 days sc) due to the lack of response in the control of symptoms (one patient had recurrent oral and genital ulcers) and ocular involvement (5 patients with uveitis of repetition and visual deterioration), Two patients with uveitis (one of which also presented inflammatory leukoencephalopathy), received infliximab for 6 and 12 months respectively, due to a poor clinical response to previous immunosuppressants.

Improvement of symptoms was observed after the second dose of adalimumab in 4 patients, remaining asymptomatic until the time of publication.

A male patient (case No. 6) currently has episodes of oral ulcers, heel pain and hip pain, as well as a woman (case No. 2) who has oral ulcers and pain. In both patients the discomfort due to the underlying disease is less intense than when it led to the therapeutic change, and is manageable with symptomatic treatment.

The current mean time of treatment with adalimumab is 26.8± 12.3 months (range 12-41), with good tolerance and no sequelae due to medication.

Discussion

The indication of anti-TNF drugs as part of a therapeutic strategy for the management of systemic vasculitis is increasingly frequent.[3] As BD is a vasculitis with a chronic course and relapses, where further treatment options are limited and not without side effects, the use of anti-TNF is a possibility in order to control symptoms in these patients.

We have presented 6 patients who received adalimumab for BD, observing a good clinical response and tolerance (mean follow up of 26.8 months).

We conducted a review of the literature,[4-12] identifying 9 items, a total of EB 20 patients who received adalimumab (Table 2). The mean age of patients was 39.5 (range 21-55) years, 9 were women, and the median time since the onset of disease (n=8 patients) was 6.75 (range 1-10) years.

The most frequent indications for receiving adalimumab were: ocular involvement (uveitis and retinal vasculitis)[4,5,10,12] in 9 patients, of whom 6[4,10,12] had previously received infliximab to control the symptoms. 5 patients for skin involvement (oral-genital ulcers and cutaneous vasculitis)[5,7,11,12] were treated with adalimumab, of whom 2 had previously received infliximab.[11,12]

Less frequently, 3 patients with neurological involvement,[6,12] 2 with gastrointestinal involvement,[9,12] all had received infliximab as well as one patient[8] who had symptoms of pulmonary hemorrhage with aneurysm and pulmonary artery thrombosis who had received pulse cyclophosphamide and subsequently adalimumab.

In total 13 patients in the medical literature[4,6,9-12] received infliximab for a time ranging from 1 to 30 months and one[11] also received etanercept (sc) for cutaneous involvement. The reason for changing the biological therapy was an allergic reaction in one patient,[10] patient preference in 4 cases[4,9] and relapse of the disease in others.[6,11,12]

The reason for relapse of disease despite immunosuppressive and / or biological therapy[4,6,9-12] is unknown, which seems to point to different drug mechanisms action in BD that remain to be identified. Maybe the situation is similar to the treatment of rheumatoid arthritis with anti-TNF, where failure to one of them does not preclude the patient from responding to another anti-TNF with different structure, antigenicity and even mechanism action.[14]

In the pathogenesis of BD there is altered T cell function, an increase of TNF alpha that induces inflammatory symptoms.[15-17] Therefore immunosuppressive therapy and anti-TNF would play an important role in the pathogenesis of BD. There are many publications (mainly open studies) with these drugs that showed their effectiveness in controlling the symptoms.[18]

Table 2
Review of the literature: cases of Behcet's disease treated with adalimumab

Author Gender-Age	BD Motive for use of adalimumab	Duration of BD, years	Prior treatment	Evolution	Adverse events	Adalimumab follow up, months
Ariyachaipanich 2009 Female (30)	BD+intestinal ulcers	ND	Ste, Aza, Infli	Good	No	22
Takase 2009 Female (42)	BD+uveitis Allergic to infliximab	7	Infli, Cyclo	Good	No	6
Yildiz 2009 Male (44)	BD+SpA	1	NSAID, SSz, Colchi	Good for both diseases	No	16
Olivieri 2009 Male (47)	BD+ refractory genital ulcers	6	Colchi, Tali, Cyclo, Aza, Ste infli	Good	No	20
Lee 2009 Male (43)	BD+ aneurisms of pulmonary artery+ thrombosis	6	Ste, Cyclo	Good	No	12
Callejas 2008	BD	ND	Ste, Colchi	Good	1 allergic reaction-angioedema	18
	Vasculitis (n=1)		MTX, Cyclo	(except one patient)		1 (AE)
Female (34)	Oral ulcers (n=1)					6
Female (36)	Panuveitis (n=3)					10
Male (38)						26
Male (53)						
Female (55)						
Belzunegui 2008 Male (36)	BD Neuro-Behçet	10	Ste, Cyclo, Infli Aza	Good	No	24
Mushtaq 2007	BD	8	Ste, Cyclo	Good	No	24
	Panuveítis (n=3)	6	MTX, Cyclop			36
Female (41)		10	Aza, Myco, Infli			36
Male (28)			Fotocoagulación con láser			
Female (21)						
Van Laar 2007	EB	ND	Colchi, Cyclo, Thali, Aza, Ste	Good	3 patients with lichenoid skin lesions	11
	Uveítis (n=2)		MTX, Pento, Infli			19
Male (43)	CNS (n=2)					13
Male (40)	Colitis (n=1)					13
Female (41)	Oral ulcers+ arthritis (n=1)					6
Male (36)						22
Female (43)						
Male (34)						

AE indicates adverse events; Aza, azathioprine; BD, Behçet's disease; Ciclop, cyclophosfamide; CNS, Central Nervous System; Colchi, colchicine; Cyclo, cyclosporin; Infli, infliximab; MTX, methotrexate; Myco, mycophenolate; ND, no data; NSAID, non steroidal anti-inflammatory drugs; Pento, pentoxifillin; SpA, ankylosing spondylitis; SSz, sulphasalacine; Ste, steroids; Thali, thalidomide.

In the recommendations by EULAR,[19,20] the authors confirmed the lack of solid evidence (randomized, double-blind trials) on the efficacy of drugs in BD, but recommended, given the systemic involvement of disease, the use of immunosuppressants (cyclosporin A, azathioprine, interferon alpha and anti-TNF).

All reported cases responded to this drug, showing a good safety profile: there were only 4 adverse events described (one allergy[5] and 3 lichenoid skin lesions at the site of injection[12]). The mean follow-up time with adalimumab was 17 months (range 1-36).

Compared with our patients we observed that the most common indication was ocular involvement, as well as a patient with inflammatory leukoencephalopathy. Two had received infliximab with relapse of symptoms (eye inflammation and neurological disease). Our patients showed no adverse events at the time of publication.

Adalimumab appears to be a useful treatment for BD. Although published evidence to date is limited and is based exclusively on small case seriesshowing good efficacy and tolerability in patients with this type of vasculitis, resistant to other immunosuppressive agents, although further studies are needed to determine the dose and optimal and safe treatment regimens with anti-TNF for the management of BD.

Conclusions

According to our study and prior published data in the medical literature, we believe that anti-TNF therapy, especially adalimumab, is a good option for patients with BD who are resistant to conventional therapy. We found no adverse effects in patients treated with adalimumab, which coincides with the few cases reported in the reviewed literature.

Conflict of interest

The authors have no conflict of interest.

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