

## Case report

# Multi-drug resistance and side-effects in a patient with Behçet's disease

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Received on October 14, 2014; accepted  
in revised form on February 4, 2015.

Clin Exp Rheumatol 2015; 33 (Suppl. 94):  
S141-S144.

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EXPERIMENTAL RHEUMATOLOGY 2015.

**Key words:** Behçet's disease, uveitis,  
retinal vasculitis, immunosuppressive  
therapy, corticosteroids

## ABSTRACT

**Objective.** To report on the clinical course of ocular and extraocular involvement in a multidrug-resistant patient with Behçet's disease (BD).

**Methods.** A 22-year-old male with BD (bilateral panuveitis and retinal vasculitis, oral ulcers, erythema nodosum, arthralgia, epididymitis) was followed-up from 1999 to 2014. He was treated continuously with corticosteroids in combination with different immunosuppressive therapies (cyclosporine, azathioprine, methotrexate, interferon, infliximab, mycophenolate), which exerted numerous side-effects such as nephrotoxicity, nephrolithiasis, increase of liver enzymes, severe depression with suicidal ideation, severe leucopenia, pulmonary tuberculosis, pulmonary legionellosis, recurrent bronchopneumonia.

**Results.** Despite immunosuppressive and corticosteroid therapies, the patient showed multiple relapses of uveitis and systemic BD lesions and developed severe osteoporosis with multiple vertebral fractures, bilateral cataracts and steroid-associated glaucoma until 2007. Since then he has been treated with prednisone alone, currently at low dosage, remaining free from uveitis and systemic symptoms. His final visual acuity is 9/10 in the right eye and counting fingers in the left one.

**Conclusion.** BD patients are usually responsive to immunosuppressive drugs. The possibility of a multi-drug resistance as well as of multiple drug-related side effects cannot be disregarded and continuous therapy should be given in order to preserve a useful visual acuity until the disease, either spontaneously or drug-induced, runs into remission.

## Introduction

Behçet's disease (BD) is a systemic vasculitis characterised by the onset, mostly in young adults, of recurrent

oral and genital ulcers, skin lesions and uveitis (1). Ocular involvement can be found in up to 70% of patients with BD and it mainly consists of the occurrence of a posterior uveitis or panuveitis with retinal vasculitis. Uveitis might often be sight-threatening. In 1970, Mamo reported that 50% of patients with BD treated with corticosteroids alone lose visual acuity in at least one eye within two years from the onset of ocular disease (2), while an immunosuppressive therapy is usually needed to control the ocular manifestations of BD (3). Therefore, it is obvious that almost every kind of immunosuppressive therapy has been used over time in an attempt to lower the number of uveitis recurrences and to preserve visual acuity. Most consistent data are available on antimetabolites (azathioprine), alkylating agents (chlorambucil and cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus), and biologic drugs (interferon, anti-TNF-alpha agents) (4). Nevertheless, although corticosteroids are not sufficient to control the ocular manifestations of BD long term, their use is still needed to control the acute inflammatory phase for the time elapsed for "classic" immunosuppressive drugs to reach their therapeutic levels of efficacy or to gain access to the newer therapeutic options, such as interferon-alpha or anti-TNF-alpha agents, that seem to exert a very rapid effect on ocular lesions (5).

We report on the case of a patient with multiresistance to immunosuppressive treatments who also developed many immunosuppressive-related side-effects over 15 years of continuous follow-up.

## Case report

In February 1999 we examined for the first time a 22-year-old male with bilateral panuveitis, retinal vasculitis and macular oedema, recurrent oral ulcers, erythema nodosum, arthralgia and

Competing interests: none declared.

Duration of therapy (months)	Immunosuppressive drug (always in combination with corticosteroids)	V.A. RE	V.A. LE	N° Uveitis Relapses (Relapse/month rate)	Extraocular Manifestations	Adverse Events
Feb. 1999 – Feb. 2000 (12 months)	Cyclosporine A alone or with Methotrexate	9/10	10/10	5 (0.4)	recurrent oral ulcers, pyodermitis, epididymitis and diffuse arthralgias	nephrotoxicity (persistent proteinuria, hematuria and increase of creatinine)
Mar. 2000 – Oct. 2000 (7 months)	Interferon – alpha and Methotrexate	9/10	10/10	2 (0.28)	recurrent oral ulcers, arthralgias and folliculitis	severe depressive state with suicidal ideation
Nov. 2000 – Jul. 2001 (8 months)	Chlorambucil	9/10	10/10	2 (0.25)	persistent arthralgias and erythema nodosum	severe leukopenia (white blood cell count 2900/ $\mu$ l)
Jul. 2001 – Jan. 2002 (6 months)	Cyclosporine A	9/10	10/10	4 (0.66)	persistent arthralgias and erythema nodosum	nephrotoxicity (proteinuria 30 mg/dl, hemoglobinuria 9 mg/dl and nephrolithiasis)
Feb. 2002 – Apr. 2002 (2 months)	Azathioprine and Methotrexate	9/10	10/10	3 (1.5)	none	-none
Apr. 2002 – Jun. 2002 (2 months)	Infliximab	8/10	8/10	0 (0)	none	pulmonary tuberculosis
Jun. 2002 – Jan. 2005 (31 months)	Corticosteroids only	8/10	CF*	14 (0.45)	recurrent oral ulcers and diffuse arthralgias	iatrogenic osteoporosis and vertebral fractures
Jan. 2005 – Sept. 2005 (8 months)	Azathioprine	8/10	CF	4 (0.5)	none	none
Oct. 2005 – Dec. 2005 (2 months)	Infliximab	9/10	CF	0 (0)	none	pulmonary legionellosis
Jan. 2006 – Mar. 2007 (14 months)	Mycophenolate	9/10	CF	5 (0.35)	recurrent oral ulcers and arthralgias	recurrent bronchopneumonia
Apr. 2007 – Oct 2014 (90 months)	Oral prednisone slowly decreased from 0.37 to 0.11 mg/kg/day	9/10	CF	0 (0)	none	none

**Fig. 1.** Behçet's disease: clinical course and adverse events during 15 years of follow-up.

VA: visual acuity; RE: right eye; LE: left eye; CF: counting fingers. \*October 2004: macular ischaemia in the left eye.

epididymitis, which had occurred in the previous year. A diagnosis of BD with severe ocular involvement was made and the patient received immediate treatment with prednisone (1 mg/kg/day) and cyclosporine A (5 mg/kg/day). Visual acuity at presentation was 9/10 in the right eye and 10/10 in the left eye. In 1999, cyclosporine A was not sufficient to control the ocular and systemic manifestations of BD, either alone or in combination with methotrexate (20 mg/week), and it was always given in combination with a continuous prednisone therapy (minimum daily dose: 0.5 mg/kg/day). In this period, the patient had five uveitis relapses, recurrent oral ulcers, pyodermitis, epididymitis and diffuse arthralgias. By February 2000, cyclosporine A was discontinued because of nephrotoxicity (persistent proteinuria, haematuria and increase of creatinine level by 30% from the baseline), and in March 2000 an interferon-alpha

therapy (9–12 M/U/week, according to the clinical response) in combination with methotrexate (15 mg/week) was undertaken, without any success: in the following seven months the patient developed two uveitis relapses, recurrent oral ulcers, arthralgias and folliculitis. Methotrexate was stopped because of the increase in liver enzymes, while interferon was definitely stopped by October 2000, due to an intervening severe depressive state with suicidal ideation. In November 2000, the incomplete control of both ocular and systemic manifestations of BD and the superimposing of a Cushing syndrome, led us to try a therapy with chlorambucil (0.1 mg/kg/day as initial dose, later increased to 0.2 mg/kg/day) along with a prednisone daily dose never lower than 0.5 mg/kg/day. In the following eight months of follow-up, the patient unfortunately showed two uveitis relapses, persistent arthralgias, a new episode of erythema

nodosum, vertebral fracture and finally a severe leukopenia (white blood cell count 2900/ $\mu$ l), requiring an immediate withdrawal from the therapy with chlorambucil. Cyclosporine (5 mg/kg/day) was reintroduced between July 2001 and January 2002, but the patient showed during this period four uveitis relapses, episodes of erythema nodosum and arthralgias and new alterations in the renal function (proteinuria 30 mg/dl, haemoglobinuria 9 mg/dl and nephrolithiasis). While waiting for the authorisation for the treatment with anti-TNF alpha agent, a combined therapy with methotrexate (15 mg/week) and azathioprine (2 mg/kg/day) was started on February 2002, but the patient showed three uveitis recurrences in the following two months. In April 2002, a therapy with infliximab was started (5 mg/kg/infusion at time 0, 14 days, then monthly for two months) and the treatment with antimetabolites discontinued.

During the two subsequent months, neither ocular relapses nor systemic symptoms were detected. Visual acuity was 8/10 in both eyes with a bilateral initial subcapsular cataract. By June 2002, the patient started complaining of fever, night sweats and productive cough. Clinical and radiologic findings revealed the onset of a pulmonary tuberculosis (PPD and chest x-ray negative before infliximab initiation) and infliximab therapy was abruptly stopped. The patient successfully benefited from a standard antitubercular therapy (isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1500 mg and ethambutol 1200 mg daily for two months, then isoniazid 300 mg and rifampicin 600 mg daily for 4 months) with complete clinical and radiologic remission of the pulmonary lesions. Between June 2002 and January 2005, the patient was treated with corticosteroids only (intravenous methylprednisolone, oral prednisone and peribulbar triamcinolone injections), and, although the minimum prednisone daily dose was 30 mg, the ocular and the systemic manifestations of BD were poorly controlled. Multiple selective apheresis procedures were also tried, but during this period the patient displayed fourteen severe uveitis relapses, diffuse arthralgias, ureterolithiasis requiring two surgical procedures and a progressive iatrogenic osteoporosis with two vertebral fractures. In October 2004, a macular ischaemia was diagnosed in the left eye during a uveitis recurrence, which did not respond to an aggressive therapy with corticosteroids and aspirin: the visual acuity dropped to counting fingers and did not recover later on. In January 2005, the poor control of the ocular disease and the severity of the side-effects related to the corticosteroid therapy, required to start an immunosuppressive therapy again. The patient was therefore given azathioprine 0.17 mg/kg/day (100 mg) with the addition of an antitubercular prophylaxis (isoniazid 300 mg/day), always in combination with oral corticosteroids. In the following eight months, the patient developed a steroid-induced glaucoma, requiring a combined topical (timolol, dorzolamide and bromonidine eye drops) and systemic therapy (ac-

etazolamide despite the previous renal lesions), four uveitis relapses, additional vertebral fractures and systemic hypertension, treated with amlodipine. By October 2005, the patient finished a nine-month course of antitubercular prophylaxis and was started again on infliximab with the standard protocol. A pulmonary legionellosis ensued after three infusions (6) and the therapy with anti-TNF alpha agent was definitely discontinued.

Between January 2006 and March 2007, a trial with mycophenolate 2–3 gr/day was carried out with no success (five uveitis relapses, subsequent oral ulcers and arthralgias) and finally stopped because of recurrent bronchopneumonia. During this period, the patient also underwent cataract extraction with intraocular lens implantation and was continued on a mean daily dose of 25 mg of prednisone. Two further ocular relapses occurred at one and two months after the discontinuation of mycophenolate. It is of note that, between February 1999 to May 2007, the patient received, apart from the systemic therapy, a total of 35 peribulbar injections in the right eye and 53 in the left eye of triamcinolone 40 mg, in order to control the uveitis relapses.

BD has been inactive and the patient has been free from ocular and systemic symptoms since May 2007. This resulted in a very slow progressive reduction of the daily dose of prednisone from 25 mg/day (0.37 mg/kg/day) to 7.5 mg/day (0.11 mg/kg/day). Nevertheless, by March 2013, despite being on antihypertensive therapy with amlodipine since 2005 and receiving aspirin since 2004, he complained of recurrent episodes of angina caused by stenosis of the proximal left anterior coronary artery and underwent angioplasty with stent placement.

Figure 1 summarises the immunosuppressive therapy used in our patient, visual acuity in both eyes at the beginning of each period in inactive phase, number of ocular relapses during each specific therapy, relapse per month rate, extraocular manifestations and side-effects.

Visual acuity at the last examination was 9/10 in the right eye and counting

fingers in the left one, with no signs of active ocular lesions in both eyes, and a normal intraocular pressure without specific therapy.

### Discussion

Ocular manifestations of BD are among the few ocular diseases requiring immunosuppressive therapy as the first line treatment. It is generally believed that the immunosuppressive drugs used to control the eye involvement are usually also helpful in suppressing the onset of other extraocular manifestations of the disease (4). The widespread use of standard or "classic" immunosuppressive drugs, such as chlorambucil, azathioprine, cyclosporine A and interferon alpha have proven effective in the management of the ocular manifestations of BD and in preserving a satisfactory visual acuity (3, 4, 7, 8). Nevertheless, an eventual unresponsiveness to these treatments or the onset of side-effects require a reduction of the dosage or a withdrawal from the treatment in selected cases. Nowadays, biologic agents such as infliximab and adalimumab, both anti-TNF alpha monoclonal antibodies, have proven effective in the treatment of refractory uveitis in BD (9–12).

Particularly, in an open-label trial, infliximab was proven effective in reducing the number of uveitis recurrences, in exerting a corticosteroid-sparing effect and in providing a better visual prognosis in patients with BD resistant to different classic immunosuppressive treatments (azathioprine, cyclosporine and corticosteroids) (13). However, increased risk of serious infections (tuberculosis and other opportunistic infections) has been reported in many studies (14).

More recently new different therapeutic approaches have been proposed for the treatment of recalcitrant BD and its ophthalmic involvement. These are based on the inhibition of pro-inflammatory cytokines and their receptors that are thought to be involved in BD pathogenesis (15, 16). Although small case series only have been published on this topic, anti IL1 (anakinra and canakinumab), anti IL6 (tocilizumab) and anti IL1 $\beta$  (gevokizumab) agents seem to be promising alternative for the treatment of BD (15, 16).



The severity of the ocular involvement of the patient reported above compelled us to begin immediately with the administration of immunosuppressive drugs in combination with high dose corticosteroids. Nevertheless, all the selected therapeutic regimens were largely ineffective in controlling both ocular and systemic manifestations of BD, and they were additionally associated with the occurrence of very severe side-effects over time (nephrotoxicity and nephrolithiasis by cyclosporine A; hepatotoxicity by methotrexate and azathioprine; severe leukopenia by chlorambucil; severe depression with suicidal ideation by interferon alpha; broncopneumonia by mycophenolate). During the two short periods of treatment with infliximab, the patient was free of ocular relapses, but the development of pulmonary tuberculosis first and a legionellosis then has nullified its potential effect. It is of note that PPD and chest x-ray were both negative before the first administration of infliximab. Theoretically, this might be due to the immunosuppressive therapy assumed by the patient at the time of PPD screening, which might have altered the response. This finding arises an important question on the most appropriate tuberculosis screening for these patients. Another possible option to get control of eye lesions in BD is to prefer the local therapy to achieve uveitis remission, especially if the patient does not present concomitantly any other systemic manifestations. In our patient we have used peribulbar triamcinolone injections in combination with systemic therapy when uveitis reactivated, and throughout the follow-up we have administered a total of eighty-eight peribulbar injections in both eyes. Another possible way of delivering local corticosteroids are intravitreal injections of triamcinolone, or the use of an intravitreal implant of fluocinolone acetonide, which release the drug over a period of three years (16). However, those effective routes of administration of corticosteroids in BD patients might carry significant local adverse events, such as intraocular pressure raise or onset of a secondary glaucoma, both needing medical or surgical therapy in up to 71% of the cases (16).

In our patient we have chosen to add peribulbar triamcinolone injections to systemic therapy to treat uveitis recurrence in the early period of follow-up: this is because using this route the frequency of intraocular pressure increase is lower compared to intravitreal injections or implant, and the withdrawal of the drug cause reversible effect. In the last few years, this route of corticosteroids administration has also been discontinued because of the increase of intraocular pressure. This was probably related to the chronic systemic corticosteroids therapy, because we have obtained a return to normal intraocular pressure once the daily dose of systemic corticosteroids was reduced.

Clinical experience seems to state for a long period of BD activity ranging between 8 and 10 years, during which uveitis relapses are more common (17). Our patient experienced nine years of continuing ocular and extraocular manifestations of the disease, followed by seven years of complete remission, despite being on what is generally considered an accepted low dose of corticosteroids (prednisone 0.11 mg/kg/day). It is impossible to ascertain whether after such a longstanding active disease, the disease itself is to be considered self-extinguished or if the remission resulted from the different immunosuppressive therapies given to the patient. Our case clearly demonstrates that the management of patients affected by Behçet's disease is a very difficult challenge in some cases. A multi-drug resistance as well as multiple drug-related side-effects might be encountered. Beside the efficacy of the single adopted therapy, that is very difficult to assess in BD patients due to the typical relapsing-remitting course of the disease, a careful attention should be paid to the side-effects related to either the "classic" or the "new" therapies available: in fact, in some instances, as in our patient, they might strongly affect the final therapeutic result.

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