



## THE MANAGEMENT OF BEHÇET'S SYNDROME

Emire Seyahi,  
Izzet Fresko,  
Melike Melikoglu,  
Hasan Yazici

Division of Rheumatology, Department of Medicine  
Cerrahpaşa Medical Faculty, University of Istanbul, Turkey

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## ABSTRACT

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Behçet syndrome (BS) is a multisystem vasculitis characterized by skin and mucosa lesions and musculoskeletal, ocular, gastrointestinal, neurological and major vessel involvement. It is seen mainly in the Mediterranean basin, Middle East and the Far East. The disease runs a more severe course among young males and the severity diminishes with age. This review describes the management of this disease, which should be individualized and varies according to site and gender.

**Keywords:** Behçet syndrome; Management.

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## RESUMO

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A síndrome de Behçet é uma vasculite multisistémica caracterizada por lesões cutâneas e mucosas e envolvimento musculoesquelético, ocular, gastrointestinal, neurológico e dos grandes vasos. É observada geralmente na bacia Mediterrânica, Médio Oriente e Extremo Oriente. É mais grave nos jovens do sexo masculino e a gravidade diminui com a idade. Esta revisão descreve o tratamento desta doença, o qual deverá ser individualizado de acordo com a localização das lesões e com o sexo do doente.

**Palavras-Chave:** Síndrome de Behçet; Tratamento.

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## THE MANAGEMENT OF BEHÇET'S SYNDROME

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### Introduction

Behçet syndrome (BS) is a multisystem vasculitis characterized by skin and mucosa lesions and musculoskeletal, ocular, gastrointestinal, neurological and major vessel involvement.<sup>1</sup> It is seen mainly in the Mediterranean basin, Middle East and the Far East.<sup>1</sup> Turkey has the highest prevalence: 8 to 42 per 10<sup>4</sup> population.<sup>2-3</sup> While the frequency is lower in western countries: 0.07 per 10<sup>4</sup> in Spain and 1 to 3 per 10<sup>4</sup> in the United States.<sup>4-5</sup> The disease runs a more severe course among young males and the severity diminishes with age.<sup>1,6</sup> Management should be individualized and varies according to site and gender. Table I summarizes the current approach.

### Mucocutaneous manifestations

The recurrent orogenital ulcerations, nodular and pustular skin lesions cause pain and affect the quality of life. These lesions, which are the hallmark of the syndrome, can recur until the syndrome abates usually slowly after the fourth decade.<sup>6</sup> Local treatment by steroid preparations or even reassurance alone can be effective in most of the cases. Colchicine, was thought to be beneficial in treating all mucocutaneous manifestations. However our double blind study showed that the drug<sup>7</sup> was not effective in oral ulcers in either sex and was only beneficial in genital ulcers and erythema nodosum among the females. Thalidomide is another alternative for oral and genital ulcerations. Another double blind placebo controlled trial by our group revealed that all mucocutaneous lesions except erythema nodosum were successfully treated by thalidomide.<sup>8</sup> However it should be reserved for severe cases due to its neurotoxicity and teratogenicity. Recently our 27-week double masked trial of

depot glucocorticoids (40 mg methylprednisolone acetate) against placebo on mucocutaneous findings showed that glucocorticoids were useful only in controlling erythema nodosum lesions among the females.<sup>9</sup> Oral azathioprine (AZA), cyclosporine A (CsA) and interferon- $\alpha$  (IFN- $\alpha$ ) may also be beneficial in resistant cases.<sup>10</sup> Trials of topical IFN<sup>11</sup> and of topical CsA<sup>12</sup> did not demonstrate any improvement in the number, size and healing time of oral ulcers. A prospective study reported favorable results with benzathine penicillin.<sup>13</sup>

Recent studies revealed that anti-tumor necrosis factor (anti-TNF) agents can be successfully used for various manifestations in BS. In a controlled trial among males, it has been shown that etanercept was effective in controlling most of the mucocutaneous manifestations of BS, whereas it did not suppress the pathergy phenomenon.<sup>14</sup>

### Joint involvement

The arthritis of BS is non destructive.<sup>15</sup> Non-steroidal anti-inflammatory drugs and local corticosteroid injections are used frequently in management. Colchicine can be effective in both males and females as shown in controlled studies.<sup>16-17</sup> IFN- $\alpha$  (5 MU/3 times a week) is highly effective in treating arthritis according to one controlled study, but caution is needed for side effects.<sup>18</sup> Azathioprine is also successful in reducing the frequency of arthritis attacks.<sup>19</sup> No controlled studies with methotrexate and sulphasalazine are reported although some authors claim that they are effective. Short courses of oral prednisolone (20-30 mg/day) may be useful in more severe cases.

### Eye Disease

Eye involvement is the most serious manifestation of BS and affects about 50 % of the patients.<sup>1,6</sup> It de-

\*Division of Rheumatology, Department of Medicine  
Cerrahpaşa Medical Faculty, University of Istanbul, Turkey

Table I. Treatment of Behçet's syndrome

Lesions	Suggested treatment
<b>Orogenital ulcers, skin lesions</b>	
Mild	Topical treatment Colchicine 1.5 mg/day
Severe	Azathioprine 2.5 mg/kg/day Prednisolone up to 20 mg/day Thalidomide 100 mg/day Etanercept 25 mg, 2 times a week
<b>Arthritis</b>	
Mild	Nonsteroidal antiinflammatory drugs Colchicine 1.5 mg/day
Severe	Azathioprine 2.5 mg/kg/day Interferon- $\alpha$ 5 MU/3 times a week Prednisolone up to 20 mg/day
<b>Eye disease</b>	
Mild	Local treatment with mydriatics and steroids under tight control
Severe	Cyclosporine A 5 mg/kg/day Azathioprine 2.5 mg/kg/day Interferon- $\alpha$ up to 3-5 MU/day (see text) Infliximab 5 mg/kg/dose Prednisolone 40-60 mg/day for 1-2 months, then tapered (reserved for acute attacks)
<b>Deep vein thrombosis</b>	Azathioprine 2.5 mg/kg/day Aspirin Anti-coagulation?
<b>Arterial disease</b>	Prednisolone 1 mg/kg/day for 1-2 months, then tapered for the maintenance Cyclophosphamide monthly 1 g boluses Surgery (for abdominal and peripheral aneurysms)
<b>Neurological disease</b>	Boluses of prednisolone 1 g/day (5-7 consecutive days) Cyclophosphamide monthly 1 g boluses Azathioprine 2.5 mg/kg/day
<b>Gastrointestinal involvement</b>	Prednisolone 30-60 mg/day Sulphasalazine 3-6 mg/day Azathioprine 2.5 mg/kg/day Thalidomide 50-200 mg/day Surgical resection

velops within the first few years of the disease onset and runs its most severe course during these years.<sup>1,6</sup> It can be defined as a combination of recurrent attacks of non-granulomatous uveitis and retinal vasculitis.<sup>1</sup> This eventually results in cataract, glaucoma and phthisis bulbi. Eye disease is treated with immunosuppressives. AZA (2.5 mg/kg/day) was found to be effective in preventing visual attacks in a double blind controlled study.<sup>19</sup> We reassessed the results of the 8-year follow-up of these patients who had initially been treated with

AZA for 2 years.<sup>20</sup> The patients who had initially been treated with AZA in the double blind study had again less blindness, visual impairment and extra-ocular complications compared to placebo. Another immunosuppressive drug that has found wide spread use is CsA. It was found to be superior to monthly pulses of cyclophosphamide in a single blinded study conducted in a limited number of patients.<sup>21</sup> It induces a very rapid anti-inflammatory effect in doses of 2-5 mg/kg/day but care is required to monitor its toxic effects such as rises in

serum creatinine, hypertension, occasional episodes of neuropathy and hearing loss. Based on evidence from transplantation studies and a retrospective study in BS, its use is not recommended in central nervous system (CNS) disease.<sup>22</sup> Our group currently uses the combination of AZA and CsA in severe uveitis. The effect of this combination was assessed in 141 patients with severe uveitis refractory to AZA. The combination improved actual visual acuity but did not affect baseline visual acuity, which is the amount of vision after an attack has subsided.<sup>23</sup>

IFN- $\alpha$  offers promising results and seems to be another alternative in the management of uveitis in BS.<sup>24</sup> The drug was even beneficial in refractory posterior uveitis of BS to conventional medications.<sup>25</sup> Side effects of IFN- $\alpha$  include flu-like symptoms, liver enzyme elevations, cytopenias and severe mood changes.<sup>24-25</sup> Nowadays, there is great interest in TNF- $\alpha$  blockage in the management of eye disease.<sup>26-28</sup> Anti-TNF agents (especially infliximab at 5 mg/kg) show successful results in controlling severe and resistant uveitis.<sup>26-28</sup> However, relapses are frequent after withdrawal.

In our practice we use glucocorticoids in the management of acute attacks. We try to use as briefly as possible and taper them as soon as the attack subsides. During attacks local steroid eye drops and mydriatics are also used to prevent synechiae and alleviate pain. Vitrectomy and cataract surgery are occasionally performed but their effects on visual acuity are not clear.<sup>10</sup>

## Major Vessel Disease

Major vessel disease develops in 5-40 % of the patients<sup>1,6</sup> and has a male preponderance. Behçet's syndrome is one of the few vasculitides that can involve both sides of the circulatory system<sup>1</sup>. Venous involvement is more prominent than arterial disease. Lower extremity deep vein thrombosis is the most frequent manifestation. This may progress to vena cava thrombosis. Acute venous thrombosis causes pain, erythema and swelling, whereas chronic vein thrombosis can cause postphlebitic syndrome with skin ulcers and hyperpigmentation. Post-mortem examinations revealed that the thrombus is tightly adhered to the vessel wall.<sup>1</sup> This may account for the rare occurrence of thrombophlebitis in BS. Therefore, the role of anticoagulation in deep vein thrombosis is controversial. Our

group uses AZA and low dose aspirin for venous thrombosis. AZA has been shown to prevent superficial and deep vein thrombotic events, albeit in a small number of patients.<sup>1</sup> Fibrinolytic therapy has been disappointing. Arterial aneurysms, especially pulmonary arterial aneurysms carry a more severe prognosis than venous thrombosis. They can rupture or fistulate into the bronchi causing massive hemoptysis and even death in about 23-50 % of the cases.<sup>29-30</sup> Aneurysms of the peripheral arteries should be corrected surgically although there is a recurrence rate of about 30%.<sup>31</sup> We suggest monthly pulses of cyclophosphamide combined with 1mg/kg of prednisolone and tapering the prednisolone dose to <10 mg/day after three months. The medical management of pulmonary arterial aneurysms should consist of the same regimen. Anti-coagulation is contraindicated because of the risk of bleeding. Our experience with intra-arterial embolisation is limited.<sup>32-33</sup> Surgical resection is also not successful.<sup>34</sup>

## Central Nervous System Disease

The frequency of neurological involvement is about 5-6 % in cross-sectional studies.<sup>1,35</sup> This rate can double when BS patients are followed for long time.<sup>2</sup> There are two types of neurological involvement in BS.

1) Parenchymal CNS disease (75 %) is a late manifestation, developing after 5-10 years of the disease onset.<sup>6,35</sup> The disease causes severe cognitive, pyramidal and cerebellar disturbance and leads to disability and increased mortality.<sup>35</sup> Although there are no controlled studies on the management of CNS disease in BS, the disease is usually treated with high doses of corticosteroids and cyclophosphamide or AZA. Sporadic cases treated with infliximab and IFN- $\alpha$  have also been reported<sup>36</sup>

2) Thrombosis of the dural sinuses and increased intracranial pressure develop rather early in the disease course (25 %). It causes headaches with or without bilateral papilledema. Dural sinuses thrombi were found to be strongly associated with peripheral major vessel disease<sup>37</sup> and have a rather good prognosis compared to that of the parenchymal type.<sup>6,35</sup> This form is also empirically treated with corticosteroids and AZA. In severe cases with visual impairment, lumboperitoneal shunting should be considered.<sup>38</sup>

## Gastrointestinal Disease

Gastrointestinal involvement is relatively rare among the patients from the Mediterranean countries.<sup>39</sup> The frequency is higher among patients from Far East.<sup>40</sup> It is characterized mainly by aphthous ulcerations, found especially in terminal ileum and caecum. These ulcerations can cause ileo-cecal perforation. Thalidomide again has been shown to be effective alone<sup>41</sup> or combined with AZA.<sup>42</sup> There are few case reports suggesting that anti-TNF agents could be beneficial in intestinal disease.<sup>43</sup> In severe refractory cases, surgical resections are required.<sup>44</sup>

## Conclusions

We believe that medical management should be aggressive in the young and male patient with BS.

The treatment and management of eye disease of BS have become more effective in the last 20 years. However the management of CNS disease and vascular lesions are less satisfactory.

### Corresponding author:

Hasan Yazici, MD

Safa sok. 17 / 7, Kadikoy/ Istanbul 81310 Turkey

Telephone: + 902 124 143 220

E-mail: hyazici@attglobal.net

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