Drugs 2007; 67 (14): 2013-2022
0012-6667/07/0014-2013/$49.95/0

Standard and Novel Therapeutic Approaches to Behçet's Disease

Ahmet Gul

Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Contents

Abstract

Behçet's disease (BD), a systemic inflammatory disorder of unknown aetiology, is characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems. Although the treatment of BD is empirical, in recent years, it has been shown that early and effective treatment of acute inflammatory lesions and prevention of relapses can help to reduce the disease burden and improve outcome. Randomised, controlled trials are limited in BD, but those that have been conducted have documented favourable effects of colchicine, ciclosporin, azathioprine, thalidomide, dapsone, depot methylprednisolone, rebamipide, sucralfate, benzathine benzylpenicillin, interferon-α-2a and etanercept for various BD manifestations. Anti-inflammatory and/or immunosuppressive treatments should be tailored according to the disease severity and prognostic factors. More potent drugs, such as azathioprine, ciclosporin, interferon-α and infliximab, are effective in the suppression of more severe systemic features as well as mucocutaneous manifestations of BD. Although no randomised, controlled trials are yet available, results of open studies with both interferon-α and infliximab are promising for those patients with disease resistant to conventional immunosuppressive treatments. Multicentre, multi-disciplinary and long-term trials aiming to assess the efficacy of interventions in both the treatment of acute inflammatory attacks and the prevention of relapses are required in order to provide more generalisable results that can lead to better management plans.

Behçet's disease (BD), a systemic inflammatory disorder of unknown aetiology, is characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations

affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems.[1] BD has been classified among the systemic vasculitides; a vasculitis or vasculopathy with perivascular inflammatory cell infiltrates and thrombotic tendency has been documented as the main pathological finding in BD lesions. The recurrent inflammatory lesions may last a few days to several weeks and they usually heal spontaneously. However, inflammatory lesions at particular sites, such as the eyes, brain or major vessels, can result in permanent tissue damage and cause chronic manifestations or even death.[2] BD usually starts in the third or fourth decade of life. The male-to-female ratio is approximately equal in big series of patients, although BD runs a more severe course in men and in those aged <25 years at onset.[3,4]

The aetiopathogenesis of BD is currently unknown. It is generally accepted as a multifactorial disease with a strong genetic component. An enhanced and dysregulated immune response has been suggested as the cause of BD manifestations, and this can be triggered by environmental agents, including certain microorganisms, in genetically susceptible individuals.[5,6]

Since there is no pathognomonic clinical and/or laboratory finding for the diagnosis, the classification criteria (which consist of various clinical findings, including skin pathergy reaction) developed by the International Study Group are widely used for the definition of BD in clinical and basic research (table I).[7,8] However, the criteria are of limited use for the diagnosis of an individual patient.

Table I. International Study Group criteria for diagnosis ('classification') of Behçet's disease[7,8][a]

Manifestation	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by a physician or reported reliably by patient, recurrent at least three times in one 12-month period
Plus any two of the following findings:	
Recurrent genital ulceration	Recurrent genital aphthous ulceration or scarring, observed by a physician or reported reliably by patient
Eye lesions	Anterior uveitis, posterior uveitis or cells in vitreous on slit-lamp examination; or retinal vasculitis observed by qualified physician (ophthalmologist)
Skin lesions	Erythema nodosum-like lesions observed by a physician or reported reliably by patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by a physician in postadolescent patients not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by a physician at 24–48 hours, performed with oblique insertion of a 20-gauge or smaller needle under sterile conditions

a Findings are applicable if no other clinical explanation is present.

1. Goals of Management

The management of BD aims to treat inflammatory attacks and relieve the patient's symptoms, and also to prevent relapses with the use of anti-inflammatory and immunomodulatory drugs (table II).

BD is a multisystem disorder and the burden of disease differs according to the organs or systems involved. Most patients have mucocutaneous manifestations. However, long-term surveys document increased mortality due to major vessel disease and neurological involvement, as well as significant morbidity due to visual loss resulting from eye disease.[2] Male sex has been demonstrated as the strongest determinant of the severity of BD.[4] The morbidity and mortality due to BD is higher in early years of the disease, and a decrease in the frequency of mucocutaneous, articular and ocular manifestations, as well as in standardised mortality ratios, can be observed with the passage of time.[2] However, both neurological and major vascular symptoms can develop late in the course of the disease.[2,9] To date, there have been no laboratory findings that have helped to predict the BD patients with a worse prognosis.

Although their frequencies are rare, patients with sight-threatening eye involvement, arterial aneurysms, deep vein thrombosis and parenchymal neurological disease require prompt and effective treatment of inflammation to prevent irreversible tissue damage. The development of more effective treatment strategies by timely administration of

highly potent anti-inflammatory and immunosuppresive drugs have resulted in better outcomes in patients with ocular and major vessel disease.[10-12] Therefore, evaluation of prognostic factors and identification of high-risk patients at early stages of the disease is critical for tailoring treatment according to the severity of the disease and planning optimal management.

The limited number of randomised, controlled trials (RCTs) assessing the efficacy of treatments has hindered the amount of data necessary for improvements in the management of BD.[13] Some of the complex features of BD have also hampered the optimum design of clinical trials. First, BD is a multisystem disease, but drug trials frequently aim at treating only one or two of the disease manifestations as the primary outcome measure and exclude patients with systemic features or major organ involvement. The variability of disease manifestations also requires a multi-disciplinary approach and, depending on the type of clinical setting, critical differences can be observed in the composition of the study population (e.g. gender, previous treatment characteristics and severity of disease manifestations). Male patients tend to have a more severe disease, and male/female ratios may change according to the ethnicity of the patients or the type of clinic where patients are recruited such as ophthalmology, neurology or dermatology clinics.[1,9,10] For example, depending on the disease severity or as yet unknown gender-related factors, the efficacy of colchicine treatment on the recurrence of genital ulcers and erythema nodosum could not be shown if the study group had comprised only male patients with BD.[14] Differences in the definition of disease severity and resistance to treatment may result in recuitment of patients with differing drug exposure histories, which may have an effect on the response rate of the study drugs, such as in the case of infliximab trials.[15-17]

Table II. Goals of the management of Behçet's disease

Treatment of inflammatory attacks
Relieving the symptoms
Preventing or limiting tissue damage
Evaluation of prognosis
Establishment of appropriate long-term treatment
Periodic evaluation
Prevention of recurrences
Improving quality of life
Decreasing the disease burden (morbidity and mortality)

Another important feature of BD is the great variability in recurrence rates of individual exacerbations and remissions during the course of the disease. Most trials have aimed to assess the changes in the number of relapses of a particular manifestation during a short-term treatment period and, as such, they have usually been limited by the occurrence of an insufficient number of events over a time period too short for proper evaluation. Indeed, only a few RCTs have investigated the efficacy of interventions over the long term (up to 2 years).[14,18]

With the limitations of the clinical trials in BD, it is difficult to obtain generalisable and comparable data and the results should be interpreted with caution. Table III provides a list of drugs that have been investigated in RCTs in BD.

2. Treatment of Inflammatory Attacks

As stated in section 1, to date, most RCTs assessing the treatment of BD have analysed the efficacy of a drug on the recurrence rate of particular disease manifestations. On the other hand, treatment of an inflammatory attack without delay is very important, not only for relieving the symptoms, but also for preventing or limiting irreversible tissue damage, especially for lesions affecting the posterior uvea, major vessels and CNS. Table IV provides a list of agents that are commonly used in the treatment of BD.

Mucocutaneous lesions are the most frequently occurring manifestations in BD and symptomatic treatment may be satisfactory for many patients with a favourable prognosis.[32] Topical corticosteroids have frequently been used for the treatment of oral and genital aphthous ulcers; however, no trial has documented their efficacy to date. Alternatively, topical use of sucralfate suspension four times a day was shown to reduce the healing time and pain of oral and genital ulcers in a placebo-controlled trial.[28] Another trial documented the favourable

Table III. Drugs assessed in randomised controlled trials for use in Behçet's disease

Drug	Dose	Manifestation	Duration	Comparator	Result	Reference
Ciclosporin	10 mg/kg	Eye involvement	16wk	Colchicine	Favourable	19
Azathioprine	2.5 mg/kg	Eye involvement	2y	Placebo	Favourable	18
Colchicine	0.5mg tid	Oral aphthous ulcers, and others	24wk	Placebo	No efficacy	20
	1–2 mg/day	Mucocutaneous, articular	2y	Placebo	Favourable	14
Thalidomide	100 or 300 mg/day	Mucocutaneous	24wk	Placebo	Favourable	21
Dapsone	100 mg/day	Mucocutaneous	3mo	Placebo	Favourable	22
Methylprednisolone	40 mg/every 3wk	Mucocutaneous	27wk	Placebo	Favourable for erythema nodosum	23
Aciclovir	4000 mg/day for 1wk, then	Mucocutaneous	12wk	Placebo	No efficacy	24
	800 mg/day for 11wk					
Azapropazone	300mg tid	Articular	3wk	Placebo	No efficacy	25
Benzathine-benzylpenicillin plus colchicine	1.2 MIU/mo	Articular	24mo	Colchicine	Favourable	26
Rebamipide	300 mg/day	Oral aphthous ulcers	12–24wk	Placebo	Favourable	27
Sucralfate	Topical, qid	Mucocutaneous	3mo	Placebo	Favourable	28
Interferon-α-2a	2 MIU, 3/7 days	Mucocutaneous, articular	3mo	Placebo	Favourable	29
Interferon-α-2c	Topical, 10^5 U/g qid	Oral aphthous ulcers	24wk	Placebo	No efficacy	30
Etanercept	25mg, twice a week	Pathergy, skin, arthritis	4wk	Placebo	No efficacy on pathergy Favourable for oral ulcers and nodular lesions	31

bid = twice daily; **qid** = four times daily; **tid** = three times daily.

effect of the mucosa protective drug rebamipide as an adjunctive treatment for recurrent oral ulcers, by reinforcing its integrity in normal and inflammatory conditions.[27] In this study, treatment with rebamipide 300 mg/day improved the pain scores of patients with oral aphthous ulcers.[27] An improvement in the duration of and pain associated with oral aphthous ulcers was also observed in patients receiving interferon-α-2a.[29]

A double-blind, placebo-controlled trial demonstrated no effect of azapropazone for 3 weeks in the treatment of acute arthritis (≤10 days of duration) in patients with BD, as assessed by the persistence of arthritis, the development of new attacks of arthritis and the mean duration of arthritis.[23] No other NSAIDs or corticosteroids have been formally assessed for the treatment of acute arthritis in patients with BD.

Rapid resolution of intraocular inflammation is the first step to preventing permanent sequelae, including optic atrophy, maculopathy, occlusive retinopathy and diffuse atrophy and gliosis of retina, which result in partial or total loss of vision. While corticosteroids are the most frequently used drugs to control acute uveitis attacks, no RCT has been conducted to document their efficacy in BD.[33,34] Topical corticosteroids are helpful for the treatment of anterior uveitis, and periorbital injections are used for intermediate uveitis or macular oedema. Recently, favourable responses have been reported with intravitreal triamcinolone acetonide in the treatment of cystoid macular oedema secondary to BD.[35] Most patients with posterior uveal segment involvement or retinal vasculitis require systemic corticosteroids, and some even receive intravenous pulse methylprednisolone treatment, depending on the severity of ocular inflammation.[33,34]

Because of the unavoidable adverse effects of corticosteroids during long-term use and also the severity of the disease, many patients require additional immunosuppressive or immunomodulatory drugs.[33,34] However, most immunosuppressive drugs have slower onset of effect, and their use in controlling an acute attack is limited. Ciclosporin, at an unacceptably high dose of 10 mg/kg, was shown to be as effective as corticosteroids in the treatment of acute uveitis, and increased efficacy was observed when corticosteroids were combined with ciclosporin (10 mg/kg) in patients who failed to respond to either ciclosporin or prednisolone alone.[36] A rapid onset of effect was also reported for interferon-α-2a, with patients responding after 2–4 weeks of treatment.[37] However, the most rapid and effective suppression of ocular inflammation was observed in BD patients receiving infliximab. Sfikakis et al.[38] reported >50% improvement in the degree of inflammation within the first 24 hours, and complete suppression within 7 days after the infusion of infliximab 5 mg/kg in five BD patients with sight-threatening uveitis. This observation provides support for the potential role of infliximab in patients with severe uveitis, particularly because of its rapid onset of action in ocular inflammation.

Table IV. Drugs commonly used in the treatment of Behçet's disease

1. Treatment of inflammatory attack
Corticosteroids
topical: mucocutaneous lesions, anterior uveitis
systemic: mucocutaneous lesions, ocular, articular, vascular and neurological involvement (high-dose intravenous pulse treatment, depending on the disease severity)
intralesional: intraorbital, intravitreal (in selected patients with cystoid macular oedema), intra-articular
Sucralfate (topical): oral and genital ulcers
Infliximab: sight-threatening or resistant posterior or panuveitis
Interferon-α: posterior or panuveitis resistant to conventional immunosuppressive drugs
Cyclophosphamide: arterial aneurysms
2. Prevention of recurrences
Colchicine: mucocutaneous lesions and arthritis
Thalidomide or dapsone: mucocutaneous lesions (in selected patients)
rebamipide: oral ulcers
Azathioprine: ocular, mucocutaneous, articular, vascular involvement
Ciclosporin: ocular involvement and others
Infliximab: ocular involvement and others
Interferon-α: ocular involvement and others
Etanercept: mucocutaneous lesions

To date, no trial has been conducted assessing the treatment of BD patients with major vessel disease (arterial aneurysms, arterial occlusions or deep vein thrombosis), neurological or intestinal involvement. Corticosteroids and immunosuppressive drugs are widely used for controlling acute inflammation in these patients. Like systemic necrotising vasculitides, pulmonary artery aneurysms are usually treated with a combination of corticosteroids and cyclophosphamide,[39] with reports of improved outcomes being associated with early diagnosis and more effective treatment.[11]

There is ongoing controversy about the management of BD patients with venous thrombosis.[40] The inflammatory changes in veins and arteries of all sizes with accompanying thrombotic tendency determines the unique characteristics of vascular involvement in BD and vasculitis-related endothelial dysfunction/injury has been suggested as the main underlying pathology.[41] The thrombus observed in BD is defined as sticky to the inflamed vessel wall and, hence, pulmonary thromboembolism has been reported very rarely. The place of anticoagulants as well as the combination of corticosteroids and immunosuppressive drugs for the treatment of acute thrombotic events has long been debated by the experts; it should be kept in mind that anticoagulants may increase the risk of fatal bleeding in patients with arterial aneurysms.[11]

3. Prevention of Relapses

BD is characterised by recurrent attacks of inflammatory lesions; however, subclinical inflammatory activity can occur in involved organs, such as diffuse retinal capillary leakage even after resolution of an uveitis attack.[42] The aim of BD management should be to prevent recurrent attacks and achieve complete remission, both of which are important to improve quality of life and decrease the disease burden.

RCTs documented the favourable effects of colchicine, ciclosporin, azathioprine, thalidomide, dapsone, depot methylprednisolone, rebamipide, sucralfate, benzathine benzylpenicillin (benzathine penicillin), interferon-α-2a and etanercept for various BD manifestations (table III).

Colchicine, at doses of 1–2 mg/day adjusted to bodyweight, reduced the frequency of genital ulcers, erythema nodosum and arthritis among women, and reduced the occurrence of arthritis among men.[14] In a group of male patients with primarily mucocutaneous manifestations, thalidomide was effective in suppressing the recurrence of oral and genital ulcers, and follicular lesions in BD; a dosage of 100 mg/day was found to be as effective as 300 mg/day.[21] On the other hand, the frequency of erythema nodosum-like lesions was significantly increased and superficial thrombophlebitis lesions were observed more frequently in patients receiving thalidomide. Furthermore, polyneuropathy was detected in four patients (1 of 32 patients receiving 100 mg/day and 3 of 31 patients receiving 300 mg/day), three of whom developed it after the trial ended. With the potential teratogenic and relatively common neurological adverse effects associated with thalidomide, this treatment is advised to be reserved for patients with mucocutaneous lesions resistant to other treatments.[21] In a small study, a reduced number of oral ulcers was reported in patients receiving rebamipide 300 mg/day compared with placebo.[27] A favourable effect on the frequency of mucocutaneous lesions of BD has also been demonstrated in patients receiving dapsone 100 mg/day in a controlled trial.[22]

Corticosteroids are frequently used for controlling ongoing disease activity in the long term. To investigate the efficacy of lower doses of corticosteroids, a recent trial assessed intramuscular injections of methylprednisolone acetate 40mg or placebo every 3 weeks for 27 weeks.[23] In this study, the only beneficial effect of depot corticosteroids was observed in the recurrence of erythema nodosum lesions, mainly in women; there were no significant differences in the mean number of genital and oral ulcers or folliculitis between the corticosteroid and placebo groups.

The results of these trials suggest that differences in the response rates between men and women for various disease manifestations probably reflect the variability in the disease severity. Anti-inflammatory and/or immunosuppressive treatments are generally helpful for the suppression of BD manifestations, but it is necessary to tailor the degree of suppression according to the disease severity and prognostic factors. More potent drugs, such as ciclosporin, azathioprine, interferon-α and anti-tumour necrosis factor (TNF) agents, are effective in the suppression of more severe systemic features as well as mucocutaneous manifestations of BD.[15,16,18,19,37] In a double-blind study, ciclosporin was effective in treating not only uveitis, but also oral and genital ulcers and skin manifestations during a 16-week period, although the ciclosporin dosage was unacceptably high.[19] Similarly, azathioprine at a dose of 2.5 mg/kg was effective in controlling the progression of eye disease, and these patients also had less frequent oral ulcers, genital ulcers and arthritis.[18] Compared with placebo, azathioprine was associated with a reduction in the development of new eye disease in BD patients who showed no signs of eye disease prior to treatment. Moreover, BD patients with eye disease experienced fewer episodes of severe uveitis attacks with hypopyon.[18] A long-term analysis (an average of 8 years) of the patients in this study revealed that the emergence of blindness and a 2-line drop in visual acuity were observed more frequently in the placebo group.[12] In addition, a trend towards more frequent occurrence of extraocular disease manifestations was noted in the placebo group.[12] Similarly, azathioprine at a dose of 2.5 mg/day was more effective in patients with a shorter disease duration (<2 years) at the beginning of the trial, which supports the importance of starting effective therapy as early as possible.[12] Uncontrolled studies have provided evidence for the efficacy of chlorambucil[43,44] and tacrolimus (FK506)[45] in the treatment of ocular inflammation in BD.

None of these drugs are universally effective and there is always a group of patients unresponsive to these immunosuppresive treatments.[34] In a series of 880 BD patients with uveitis who were treated with conventional immunosuppressive agents, the risk of losing vision at 7-year follow-up was 21%.[10] There may be a rationale for using a combination of immunosuppressive drugs affecting different pathogenic mechanisms for the treatment of patients with resistant disease, similar to in patients with inflammatory rheumatic disorders; however, to date, no RCTs have been performed to evaluate the efficacy of combined immunosuppressive therapy in BD uveitis.

Although no RCTs are currently available, results of open studies with interferon-α or infliximab are promising for those patients with disease resistant to conventional immunosuppressive treatments.[15,16,37,46] Recombinant human interferon-α-2a treatment, starting at a dose of 6 MIU/day and with a dose reduction according to a decision tree until discontinuation, provided a response rate of 92% in 50 BD patients with sight-threatening uveitis or retinal vasculitis; remission of ocular inflammation was achieved at week 24.[37] Infliximab was also associated with a rapid onset of action of in the treatment of ocular inflammation,[38] and was also effective in the suppression of recurrent uveitis attacks and had a corticosteroid-sparing effect in BD patients who were resistant to conventional immunosuppressive drugs.[15,16,47]

Ohno and colleagues[16] evaluated the efficacy of infliximab 5 or 10 mg/kg (given at weeks 0, 2, 6 and 10) in 13 BD patients with uveoretinitis resistant to ciclosporin. They reported that the mean number of ocular attacks (reported as a frequency over 14 weeks) decreased from 3.96 to 0.98 for those in the 5 mg/kg group and from 3.79 to 0.16 for those in the 10 mg/kg group during the infusion period.[16] In another group of 13 patients who had ≥2 attacks of posterior/panuveitis or retinal vasculitis despite the combination of azathioprine, ciclosporin and corticosteroids in the preceding 6 months, infliximab infusion was given at a dose of 5 mg/kg at weeks 0, 2, 6 and 14; in this study, weeks 0–22 were defined as the infusion period and weeks 23–54 were defined as the observation period.[15] Infliximab provided an attack-free remission in 31% of patients during the infusion period. In the remaining 69% of patients, uveitis attacks were less frequent and less severe during the infusion period compared with the 6-month previous-treatment period and the observation period.[15] A sustained remission (with four infusions of infliximab) for up to 54 weeks, could be obtained in only 1 of 13 patients, which indicated that the treatment should be continued in order to maintain the beneficial effects in most patients. Also, 77% of the uveitis attacks that were observed during the infliximab infusion period occurred at the end of the 8-week period that followed the last infliximab infusion (i.e. at either 14 or 22 weeks) and, as such, the authors suggested that the remission rate may have been higher with shorter infusion intervals.[15] The decision of whether to use interferon-α or infliximab for BD patients with serious ocular inflammation currently depends on personal experiences and health insurance policies; RCTs comparing the efficacy of both drugs in the treatment of acute ocular inflammation and prevention of relapses would be very informative.[17]

Identification of the underlying pathogenetic mechanisms in BD should eventually help develop better therapeutic modalities. Various environmental factors are considered as triggers of BD manifestations in genetically susceptible individuals.[5] Antigen-specific immune responses have been demonstrated against four peptides from microbial heat shock protein (HSP)-65 and the homologous human-HSP60 in BD.[48,49] Following promising results in a rat uveitis model,[50] a recent phase I/II trial was performed to assess the efficacy of oral tolerisation with BD-specific HSP60 peptide (336–351) linked to recombinant cholera toxin B (CTB) subunit administered three times weekly.[51] No adverse effect was observed with oral administration of 336–351-CTB, and five of eight BD patients with ocular involvement were able to withdraw their immunosuppressive drugs gradually over a period of 6–9 weeks without relapse of uveitis. Also, three of five responding patients remained free of relapsing

uveitis for 10–18 months after tolerisation was discontinued.[51]

HSP65 is found in a variety of micro-organisms, including *Streptococcus oralis*, which has been frequently implicated as an aetiological factor in BD.[1,5] A randomised, prospective trial was conducted to evaluate the effectiveness of benzathine benzylpenicillin combined with colchicine in the prophylaxis of recurrent arthritis in BD patients.[26] Significantly lower numbers of arthritis episodes and longer episode-free periods were observed in patients receiving colchicine plus benzathine benzylpenicillin for 24 months compared with patients receiving only colchicine, but the duration, severity and pattern of arthritis episodes were found to be similar in both groups.[26] The prophylactic efficacy of benzathine benzylpenicillin in BD manifestations other than arthritis has not been confirmed by randomised trials.

4. Disease-Specific Adverse Effects

In most of the controlled clinical trials, no adverse event specific to patients with BD was reported. On the other hand, observation of some adverse events in BD patients have indicated the need to assess these events in larger series of patients. For example, some BD patients receiving ciclosporin developed neurotoxicity.[52] However, the issue of whether the risk of neurotoxicity or precipitation of neurological involvement is increased in BD patients compared with other conditions where ciclosporin neurotoxicity was observed has not yet been resolved.[53]

Increased frequencies of erythema nodosum-like lesions in BD patients using thalidomide may be an example of disease-specific adverse effects.[21] However, an increase in the number of superficial thrombophlebitis was also noted in BD patients in the thalidomide trial.[21] Frequent use of thalidomide in multiple myeloma patients revealed an association between thalidomide and deep vein thrombosis. It may be difficult to differentiate erythema nodosum-like lesions from superficial thrombophlebitis in BD patients with nodular skin lesions, and the thalidomide-induced risk of superficial or deep vein thrombosis in BD patients with systemic manifestations should be investigated carefully.

No BD-specific adverse event was reported in patients receiving infliximab infusions, but the possibility of inducing thrombotic tendency and neurologic manifestations with TNF inhibition indicates the need for careful evaluation and follow-up.[17]

5. Conclusions

Although the treatment of BD is empirical, in recent years, it has been shown that early and effective treatment of acute inflammatory lesions and prevention of relapses can help to reduce the disease burden and improve outcome. RCTs are limited in BD, but they have documented the favourable effects of colchicine, ciclosporin, azathioprine, thalidomide, dapsone, depot methylprednisolone, rebamipide, sucralfate, benzathine benzylpenicillin, interferon-α-2a and etanercept for various BD manifestations. Anti-inflammatory and/or immunosuppressive treatments should be tailored according to the disease severity and prognostic factors. More potent drugs, such as azathioprine, ciclosporin, interferon-α and infliximab, are effective in the suppression of more severe systemic features as well as mucocutaneous manifestations of BD. Although no RCTs are yet available, results of open studies with both interferon-α and infliximab are promising for those patients with disease resistant to conventional immunosuppressive treatments. Multicentre, multidisciplinary and long-term trials aiming to assess the efficacy of interventions in both the treatment of acute inflammatory attacks and the prevention of relapses are required in order to provide more generalisable results, which can lead to better management plans.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Gul has received speaker's honoraria from Schering-Plough, Wyeth and Abbott; travel grants from Schering-Plough, Novartis, Wyeth and Abbott; and investigator-initiated drug trial support from Schering-Plough.

References

1. Sakane T, Takeno M, Suzuki N, et al. Behçet's disease. N Engl J Med 1999 Oct 21; 341 (17): 1284-91
2. Kural-Seyahi E, Fresko I, Seyahi N, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 2003 Jan; 82 (1): 60-76
3. Yazici H, Tuzun Y, Pazarli H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis 1984 Dec; 43 (6): 783-9
4. Gul A, Uyar FA, Inanc M, et al. Lack of association of HLA-B*51 with a severe disease course in Behçet's disease. Rheumatology (Oxford) 2001 Jun; 40 (6): 668-72
5. Gul A. Behçet's disease: an update on the pathogenesis. Clin Exp Rheumatol 2001 Sep-Oct; 19 (5 Suppl. 24): S6-12
6. Gul A. Behçet's disease as an autoinflammatory disorder. Curr Drug Targets Inflamm Allergy 2005 Feb; 4 (1): 81-3
7. International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. Lancet 1990 May 5; 335 (8697): 1078-80
8. The International Study Group for Behçet's disease. Evaluation of diagnostic ('classification') criteria in Behçet's disease: towards internationally agreed criteria. Br J Rheumatol 1992 May; 31 (5): 299-308
9. Akman-Demir G, Baykan-Kurt B, Serdaroglu P, et al. Seven-year follow-up of neurologic involvement in Behçet syndrome. Arch Neurol 1996 Jul; 53 (7): 691-4
10. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, et al. Uveitis in Behçet disease: an analysis of 880 patients. Am J Ophthalmol 2004 Sep; 138 (3): 373-80
11. Hamuryudan V, Er T, Seyahi E, et al. Pulmonary artery aneurysms in Behçet syndrome. Am J Med 2004 Dec 1; 117 (11): 867-70
12. Hamuryudan V, Ozyazgan Y, Hizli N, et al. Azathioprine in Behçet's syndrome: effects on long-term prognosis. Arthritis Rheum 1997 Apr; 40 (4): 769-74
13. Saenz A, Ausejo M, Shea B, et al. Pharmacotherapy for Behçet's syndrome. Cochrane Database Syst Rev 2000; (2): CD001084
14. Yurdakul S, Mat C, Tuzun Y, et al. A double-blind trial of colchicine in Behçet's syndrome. Arthritis Rheum 2001 Nov; 44 (11): 2686-92
15. Tugal-Tutkun I, Mudun A, Urgancioglu M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. Arthritis Rheum 2005 Aug; 52 (8): 2478-84
16. Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behcet's disease with refractory uveoretinitis. J Rheumatol 2004 Jul; 31 (7): 1362-8
17. Rosenbaum JT. Blind insight: eyeing anti-tumor necrosis factor treatment in uveitis associated with Behçet's disease. J Rheumatol 2004 Jul; 31 (7): 1241-3
18. Yazici H, Pazarli H, Barnes CG, et al. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990 Feb 1; 322 (5): 281-5
19. Masuda K, Nakajima A, Urayama A, et al. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. Lancet 1989 May 20; I (8647): 1093-6
20. Aktulga E, Altac M, Muftuoglu A, et al. A double blind study of colchicine in Behçet's disease. Haematologica 1980 Jun; 65 (3): 399-402
21. Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998 Mar 15; 128 (6): 443-50
22. Sharquie KE, Najim RA, Abu-Raghif AR. Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study. J Dermatol 2002 May; 29 (5): 267-79
23. Mat C, Yurdakul S, Uysal S, et al. A double-blind trial of depot corticosteroids in Behçet's syndrome. Rheumatology (Oxford) 2006 Mar; 45 (3): 348-52
24. Davies UM, Palmer RG, Denman AM. Treatment with acyclovir does not affect orogenital ulcers in Behçet's syndrome: a randomized double-blind trial. Br J Rheumatol 1988 Aug; 27 (4): 300-2
25. Moral F, Hamuryudan V, Yurdakul S, et al. Inefficacy of azapropazone in the acute arthritis of Behçet's syndrome: a randomized, double blind, placebo controlled study. Clin Exp Rheumatol 1995 Jul-Aug; 13 (4): 493-5
26. Calguneri M, Kiraz S, Ertenli I, et al. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease: a randomized clinical trial. Arthritis Rheum 1996 Dec; 39 (12): 2062-5
27. Matsuda T, Ohno S, Hirohata S, et al. Efficacy of rebamipide as adjunctive therapy in the treatment of recurrent oral aphthous ulcers in patients with Behçet's disease: a randomised, double-blind, placebo-controlled study. Drugs R D 2003; 4 (1): 19-28
28. Alpsoy E, Er H, Durusoy C, et al. The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. Arch Dermatol 1999 May; 135 (5): 529-32
29. Alpsoy E, Durusoy C, Yilmaz E, et al. Interferon alfa-2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. Arch Dermatol 2002 Apr; 138 (4): 467-71
30. Hamuryudan V, Yurdakul S, Rosenkaimer F, et al. Inefficacy of topical alpha interferon in the treatment of oral ulcers of Behçet's syndrome: a randomized, double blind trial. Br J Rheumatol 1991 Oct; 30 (5): 395-6
31. Melikoglu M, Fresko I, Mat C, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. J Rheumatol 2005 Jan; 32 (1): 98-105
32. Barnes CG. Treatment of Behçet's syndrome. Rheumatology (Oxford) 2006 Mar; 45 (3): 245-7
33. Kim EC, Foster CS. Immunomodulatory therapy for the treatment of ocular inflammatory disease: evidence-based medicine recommendations for use. Int Ophthalmol Clin 2006; 46 (2): 141-64
34. Jabs DA, Rosenbaum JT. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 2001 May; 131 (5): 679
35. Karacorlu M, Mudun B, Ozdemir H, et al. Intravitreal triamcinolone acetonide for the treatment of cystoid macular edema secondary to Behçet disease. Am J Ophthalmol 2004 Aug; 138 (2): 289-91
36. Nussenblatt RB, Palestine AG, Chan CC, et al. Randomized, double-masked study of cyclosporine compared to prednisolone in the treatment of endogenous uveitis. Am J Ophthalmol 1991 Aug 15; 112 (2): 138-46

37. Kotter I, Zierhut M, Eckstein AK, et al. Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. Br J Ophthalmol 2003 Apr; 87 (4): 423-31
38. Sfikakis PP, Theodossiadis PG, Katsiari CG, et al. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 2001 Jul 28; 358 (9278): 295-6
39. Erkan F, Gul A, Tasali E. Pulmonary manifestations of Behçet's disease. Thorax 2001 Jul; 56 (7): 572-8
40. Yazici H, Yurdakul S, Hamuryudan V. The management of Behçet's syndrome: how are we doing? Clin Exp Rheumatol 1999 Mar-Apr; 17 (2): 145-7
41. Zierhut M, Mizuki N, Ohno S, et al. Immunology and functional genomics of Behçet's disease. Cell Mol Life Sci 2003 Sep; 60 (9): 1903-22
42. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, et al. Neovascularization of the optic disc in Behçet's disease. Jpn J Ophthalmol 2006 May-Jun; 50 (3): 256-65
43. Mudun BA, Ergen A, Ipcioglu SU, et al. Short-term chlorambucil for refractory uveitis in Behçet's disease. Ocul Immunol Inflamm 2001 Dec; 9 (4): 219-29
44. Mamo JG. Treatment of Behçet disease with chlorambucil: a follow-up report. Arch Ophthalmol 1976 Apr; 94 (4): 580-3
45. Mochizuki M, Masuda K, Sakane T, et al. A multicenter clinical open trial of FK 506 in refractory uveitis, including Behçet's disease: Japanese FK 506 Study Group on Refractory Uveitis. Transplant Proc 1991 Dec; 23 (6): 3343-6
46. Tugal-Tutkun I, Guney-Tefekli E, Urgancioglu M. Results of interferon-alfa therapy in patients with Behçet uveitis. Graefes Arch Clin Exp Ophthalmol. Epub 2006 May 4
47. Sfikakis PP, Kaklamanis PH, Elezoglou A, et al. Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet disease. Ann Intern Med 2004 Mar 2; 140 (5): 404-6
48. Pervin K, Childerstone A, Shinnick T, et al. T cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behçet's disease. J Immunol 1993 Aug 15; 151 (4): 2273-82
49. Hasan A, Fortune F, Wilson A, et al. Role of gamma delta T cells in pathogenesis and diagnosis of Behçet's disease. Lancet 1996 Mar 23; 347 (9004): 789-94
50. Phipps PA, Stanford MR, Sun J-B, et al. Prevention of mucosally induced uveitis with a HSP60-derived peptide linked to cholera toxin B subunit. Eur J Immunol 2003; 33: 224-32
51. Stanford M, Whittall T, Bergmeier LA, et al. Oral tolerization with peptide 336-351 linked to cholera toxin B subunit in preventing relapses of uveitis in Behçet's disease. Clin Exp Immunol 2004 Jul; 137 (1): 201-8
52. Kotake S, Higashi K, Yoshikawa K, et al. Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. Ophthalmology 1999 Mar; 106 (3): 586-9
53. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol 1999 May; 246 (5): 339-46

Correspondence: Professor *Ahmet Gul*, Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Capa 34390, Istanbul, Turkey.
E-mail: agul@istanbul.edu.tr