



Behçet's disease

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Behçet's disease is a systemic vasculitis characterized by recurrent oral and genital ulcers, and ocular inflammation, and which may involve the joints, skin, central nervous system and gastrointestinal tract. It is most common in those of Mediterranean and Eastern origin, although it also affects Caucasians. The aetiology of the disease remains unknown, but the most widely held hypothesis of disease pathogenesis is that of a profound inflammatory response triggered by an infectious agent in a genetically susceptible host. Supporting this is the consistent association of disease susceptibility with polymorphisms in the human leukocyte antigen complex, particularly HLA-B*51.

The diagnosis is a clinical one, and although there is no single laboratory test specific for the diagnosis of Behçet's disease, the 1990 classification criteria perform well in a clinical context. Whereas many favoured treatments for single or multisystem disease still lack a sound evidential base, cyclosporin and azathioprine perform well in clinical trials, and evidence is accumulating for the efficacy of anti-tumour necrosis factor therapy in particular clinical situations.

This review will focus on recent developments in the understanding of disease pathogenesis and clinical diagnosis, and review the evidence base for both established and new agents in the therapeutic strategy.

Key words: Behçet's disease; HLA-B*51; systemic vasculitis; immunosuppressive therapy; anti-inflammatory therapy.

Behçet's disease is a multisystem inflammatory disorder characterized by recurrent oral ulcers, genital ulcers and ocular inflammation, and which frequently involves the joints, skin, central nervous system (CNS) and gastrointestinal tract. Classified as a systemic vasculitis, it can involve both the arteries and veins of almost any organ. The aetiology of Behçet's disease remains unknown, but the most widely held hypothesis of disease pathogenesis is that a profound inflammatory response is triggered by an infectious agent in a genetically susceptible host.¹

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EPIDEMIOLOGY AND PATHOGENESIS

The geographical distribution of Behçet's disease is distinctive: it is most prevalent along the Silk Road, an ancient trading route between the Mediterranean and East Asia, where it is a major cause of morbidity.² In Turkey, the country with the highest incidence of the disease, the prevalence is estimated to be between 110 and 420 per 100 000^{2,3}, whereas that in Japan is 13–20 per 100 000, and the prevalence in the UK and USA is estimated at 1–2 per 100 000.⁴ It is unknown among Amer-Indians and has only occasionally been reported in individuals of African origin.^{5–7}

Behçet's disease usually presents in adulthood and is uncommon in children.⁸ In eastern Mediterranean populations, the disease is more common in men, who also experience more severe disease.⁹ In Asian populations, however, the sex ratio is reversed.¹⁰ Familial disease is uncommon in caucasians, but a positive family history is observed in up to 12% of non-caucasoid patients,¹¹ and a sibling risk ratio of 11.4–52.5 has been reported in a Turkish study.¹² This suggests a genetic component to the disease similar to that observed in other complex genetic disorders such as inflammatory bowel disease.

Genetic susceptibility

The genetic locus most widely studied in Behçet's disease is the human leukocyte antigen (HLA) complex on chromosome 6p21. Disease susceptibility has consistently been associated with polymorphisms in the HLA-B gene, particularly HLA-B*51.¹³ This has been confirmed in all ethnic groups, although the association is stronger in Turkish and Japanese patients than in Caucasians.¹⁴ HLA-B*51 has at least 34 allelic variants: the association has been refined to the most common molecular subtypes, HLA-B*5101 and HLA-B*5108.¹⁵ HLA-B*57 has recently also been associated with disease susceptibility in Caucasians, in whom it carried a relative risk of disease equivalent to that of HLA-B*51.¹⁶

The biological mechanism whereby specific HLA-B alleles confer disease susceptibility remains unknown. It is not clear whether these are primary associations or whether risk alleles are in linkage disequilibrium with other, causative polymorphisms. Candidates include MICA*009¹⁷ or TNF-1031C¹⁶, both of which are also present on the HLA-B*5101 haplotype.¹⁸ Furthermore, these associations are not invariable: the relative risk of disease associated with HLA-B*51 varies widely in different ethnic populations, and the disease-associated alleles are present at high frequency in some populations in whom the disease is virtually unknown.¹⁴

This indicates that other factors must also be involved in disease susceptibility, and a recent genome-wide scan has identified a second susceptibility locus on chromosome 6p.¹⁹ Polymorphisms in other candidate genes outside the HLA have also been studied, including coagulation factor V,^{20–22} endothelial nitric oxide synthase²³ and intercellular adhesion molecule-1.^{24,25} Many of these studies were, however, conducted on a limited number of patients, and positive findings have not been replicated. Thus, the contribution of other genetic variants to disease susceptibility remains unknown.

Evidence for involvement of environmental agents in disease pathogenesis

Although it is clear that there is a significant genetic component to susceptibility to Behçet's disease, environmental factors also play a role. The study of migrant

populations has yielded interesting epidemiological findings: Turkish individuals who have emigrated to Germany have a significantly lower risk of disease than individuals of Turkish origin living in Turkey, although their risk remains higher than that of the native German population.²⁶ Similarly, the disease is virtually unknown in Japanese immigrants to Hawaii, mainland USA or South America²⁷ despite a high prevalence in Japan.

The most plausible environmental trigger is an infectious agent, and evidence of ongoing or previous infection with a variety of viral agents has been sought. These include herpes simplex virus I,^{28–30} the hepatitis viruses^{31,32} and parvovirus B19.³³ Potential bacterial triggers including mycobacteria,³⁴ *Borrelia burgdorferi*³⁵, *Helicobacter pylori*³⁶ and a variety of streptococcal antigens.^{34,37–40} Most recently, antibodies to *Saccharomyces cerevisiae* have been proposed as a serological marker of disease^{41,42}, but the clinical relevance of this finding is uncertain.

Evidence for an autoimmune basis of Behçet's disease

Alternatively, Behçet's disease may be primarily autoimmune in origin. This does not exclude an infective trigger, which could operate through molecular mimicry⁴³ or some other mechanism, but implies that the disease is perpetuated by an abnormal immune response to an autoantigen in the absence of ongoing infection.⁴⁴ A number of factors mitigate against a classic autoimmune origin, including the lack of association with other autoimmune diseases, the lack of association with the autoimmune HLA haplotype (HLA-A1-B8-DR3), the lack of a female preponderance and the absence of organ non-specific autoantibodies such as anti-nuclear antibodies.⁴⁵

There is, however, no doubt that an inflammatory response to several autoantigens is found in Behçet's disease. Anti-endothelial antibodies, for example, are a frequent but non-specific finding.^{46,47} The retinal S antigen is an interesting candidate autoantigen found mainly in the retina. Other putative autoantigens include heat shock proteins^{34,48}, killer immunoglobulin-like receptors⁴⁹, tropomyosin⁵⁰, co-stimulatory molecules⁵¹, oxidized low-density lipoprotein⁵² and the retinal S antigen.^{53,54} However, whether any of these autoantigens are truly pathogenic or whether the immune response directed towards them results from the profound inflammatory reaction associated with disease activation remains unknown.

There is also strong evidence for generalized aberrant T-cell responses in Behçet's disease. When compared with healthy controls, patients with Behçet's disease have an increased number of circulating $\gamma\delta$ T-cells.⁵⁵ These cells exhibit early activation markers and produce inflammatory cytokines⁵⁵, although their target antigen is unclear. An increased production of interferon gamma (IFN- γ) by $\alpha\beta$ T-cells has also been demonstrated in active Behçet's disease⁵⁶, and circulating T-cells are predominantly of the T-helper 1 (Th1) phenotype.⁵⁷ The mechanism by which these abnormalities contribute to disease pathogenesis is, however, uncertain: some authors have suggested that the primary abnormality is a defect in T-cell signal transduction, which results in a lowered threshold for activation to multiple antigens.⁵⁸ Alternatively, an increased production of interleukin-12 (IL-12) by antigen-presenting cells may bias the T-cell response towards a Th1 phenotype⁵⁵ and result in enhanced non-specific inflammation.

PATHOLOGY

The common histopathological lesion underlying the clinical manifestations of Behçet's disease is vasculitis, involving particularly the venules. Lesions are characterized by

perivascular lymphocytic and monocytic cellular infiltration, with or without fibrin deposition in the vessel wall and surrounding tissue necrosis.⁵⁹ Significant neutrophil infiltration is also seen, particularly in early lesions including those of the pathergy reaction.⁶⁰

Active systemic disease is associated with many non-specific features of systemic inflammation, including an elevation in the level of circulating pro-inflammatory cytokines⁶¹, increased C-reactive protein⁶² and increased β_2 -microglobulin.⁶³ Levels of myeloperoxidase, generated by activated neutrophils, are also raised⁶⁴, although it is unclear whether the neutrophil hyperreactivity seen in Behçet's disease reflects genetic influences or persistent activation by external agents.⁶⁵

CLINICAL FEATURES

Recurrent aphthous ulceration

Recurrent aphthous ulceration is the sine qua non of Behçet's disease. Oral ulcers are usually the earliest sign of disease and may precede the onset of systemic symptoms by many years. Oral ulcers are similar to common mouth ulcers in appearance and localization, although they may be more extensive and painful, evolving quickly from a flat ulcer to a large sore. Lesions may occur singly or in crops, and subside without scarring. The most common sites of oral ulceration are the tongue, lips and gingival and buccal mucosa, although involvement of the palate, pharynx and tonsil can also occur. Oral ulcers may be classified into *minor ulcers* (diameter < 10 mm, shallow, surrounded by an erythematous halo and healing without scarring), *major ulcers* (morphologically similar but larger, more painful and more persistent, and which may leave a scar on healing) and *herpetiform ulcers* (recurrent crops of hundreds of small and painful ulcers that may become confluent).

Mouth ulcers frequently occur at sites of dental intervention or other local trauma. A negative association between smoking and recurrent aphthous ulcers without systemic disease is well established^{66,67}, and in Behçet's disease, smokers often experience a relapse of mouth ulcers after quitting.⁶⁸ An interesting case report suggested that nicotine replacement patches may be useful in Behçet's disease.⁶⁹

Genital ulcers occur in 72–94% of cases^{4,70} and are morphologically similar to oral ulcers but frequently heal by scarring. In males, they most commonly occur on the scrotum, and penile lesions are uncommon. Epididymitis is also common, but urethritis is not a feature of Behçet's disease, which may be useful in distinguishing it from Reiter's syndrome. In females, ulcers occur on the vulva, vagina and cervix, and may cause dyspareunia. Groin, perianal and perineal ulcers occur in both sexes.

Eye disease

Ocular involvement is reported in 30–70% of patients with Behçet's disease^{4,9,70} and is both more common and more severe in men than in women.^{9,70} Ocular disease is usually bilateral and characteristically occurs within 2–3 years of disease onset.⁷⁰ Indeed, it is the presenting feature in 10–20% of patients.

Chronic, relapsing bilateral uveitis involving both the anterior and posterior uveal tracts is a significant cause of morbidity. Anterior uveitis with hypopyon, in which the inflammatory exudate forms a visible layer of cells in the anterior chamber, is a characteristic sign of ocular Behçet's disease but is only observed in one-third of

patients. Together with posterior uveitis and retinal vasculitis, this may cause visual loss in up to 25% of patients, although prognosis is improving with the use of modern immunosuppressants.⁷¹ Other ocular lesions include iridocyclitis, scleritis, keratitis, vitreous haemorrhage, optic neuritis, retinal vein occlusion and retinal neovascularization.⁷² Interestingly, conjunctivitis is rare, and it has been suggested that the paradoxical sparing of the conjunctiva and complete absence of respiratory mucosal lesions may indicate a primary role of gastrointestinal pathogens in the initiation and perpetuation of disease.⁷²

Skin disease

Skin disease occurs in about 80% of patients with Behçet's disease, and lesions often occur in combination.⁴ Erythema nodosum is common, particularly in females.⁹ It usually affects the lower limbs and may resolve leaving hyperpigmented areas. Superficial thrombophlebitis is also common and may be confused with erythema nodosum. Papulopustular lesions and acneiform nodules also occur. These are morphologically identical to adolescent acne, although their distribution may be more widespread, affecting the arms as well as the face, torso and buttocks. An association between acne and oligoarthritis has recently been identified⁷³, as in reactive arthritis.

Pathergy

Pathergy is the name given to non-specific hyperreactivity of the skin following minor trauma, which is specific to Behçet's disease. The formal pathergy test involves the intradermal injection of the skin with a 20-gauge needle under sterile conditions and without injecting saline. It is considered positive if an erythematous sterile papule develops within 48 hours. Histological examination reveals the rapid infiltration of neutrophils, usually accompanied by lymphocytes⁶⁰ and with variable degrees of vascular infiltration.⁷⁴ The suppression of the reaction after surgical cleaning of the skin provides further evidence for a role of bacterial flora in disease pathogenesis.⁷⁵ Pathergy is the only specific feature of Behçet's disease and is positive in more than 60% of Middle Eastern patients.⁷⁶ However, it occurs in only 15% of Korean patients⁷⁷ and 5% of Caucasians⁷⁸, reducing its diagnostic value in these groups.

Articular disease

Joint manifestations are very common in Behçet's disease, occurring in almost two-thirds of patients.^{4,79} Synovitis, arthritis and/or arthralgia may occur, occasionally preceding other symptoms. The most frequent manifestation is a non-erosive, non-deforming oligoarthralgia, typically involving the knees, ankles and wrists.⁷⁹ Histological examination of the synovial fluid may reveal neutrophils and mononuclear cells, associated with small vessel vasculitis. Destructive lesions rarely occur, and sacroiliitis and spinal joint involvement are not features of Behçet's disease.

Vascular disease

Behçet's disease is a systemic vasculitis, affecting both arteries and veins. Small-vessel vasculitis accounts for much of the pathological process of disease, and clinically manifest large-vessel involvement occurs in between 7 and 49% of patients.^{4,70}

Venous involvement is more common and may result in both superficial thrombophlebitis and deep venous thrombosis.⁸⁰ Thromboses of the superior and inferior vena cava, dural sinuses and Budd-Chiari syndrome also occur and are associated with a poor prognosis. Arterial aneurysms and occlusions are associated with the presence of venous thromboses.⁸¹ Pulmonary arterial aneurysms are an important cause of mortality and have been reported in 1% of a large Turkish cohort.⁸¹ In this group, haemoptysis was the presenting complaint in all but one of the 24 cases. Cardiac involvement is rare, but pericarditis, coronary valve lesions, intracardiac thrombosis, endomyocardial fibrosis and coronary artery involvement have all been described.

No specific defect in the coagulation cascade has been identified in Behçet's disease. Thrombophilic factors known to induce intravascular clotting, such as anti-cardiolipin antibodies, are increased in the overall population but are not specifically associated with thrombo-embolic complications^{82,83} and probably result from endovascular disruption rather than a primary thrombophilic process.

Gastrointestinal disease

The involvement of the gastrointestinal tract is very variable in different populations, being very much more common in Japan than in Turkey.^{4,84} The spectrum of clinical symptoms is wide and includes anorexia, vomiting, dyspepsia, diarrhoea and abdominal pain. Indeed, Behçet's disease shares many of the features of the inflammatory bowel diseases, and the gastrointestinal inflammation is typically similar to that of Crohn's disease, with segmental mucosal inflammation and punched-out, fissuring or aphthoid ulcers, most frequently localized to the ileocaecal region.⁸⁵ Although strictures are unusual, transmural inflammation and fistulae are frequently observed.⁸⁶ Granulomata, the hallmark of Crohn's disease, have occasionally been described, and Behçet's disease is an important differential in the diagnosis of inflammatory bowel disease.

CNS involvement

Involvement of the CNS occurs in 5–10% of patients.⁴ Neurological manifestations usually occur within 5 years of disease onset and are most common in men. Parenchymal brain involvement is most common (80%) and particularly affects the brainstem.⁸⁷ Non-parenchymal disease, including dural sinus thrombosis, aseptic meningitis and arterial vasculitis, may also occur. Clinical presentation are variable, but the most common are bilateral pyramidal signs, hemiparesis, behavioural changes, headaches and sphincter disturbance.⁸⁷ The cerebrospinal fluid is often normal but may also show an increased number of neutrophils with or without lymphocytes, increased protein concentration and increased pressure. Neurological disease carries a high morbidity⁸⁸, and the mortality is usually estimated at 5–10%.^{87,88}

Constitutional symptoms

In addition to specific organ involvement, many patients experience significant non-specific symptoms, particularly fatigue and generalized malaise, with or without fever and weight loss.

SPECIAL SITUATIONS

Pregnancy

Pregnancy is often stated to be associated with disease remission, but its influence is variable, and in 20% of patients pregnancy is associated with disease exacerbation.⁸⁹ No increase in the complications of pregnancy have been observed.⁹⁰ Transient neonatal Behçet's disease in the infants of affected mothers has, however, been described, suggesting that disease may be mediated by a placental transfer of maternal antibody.^{174,175}

Children

Behçet's disease is uncommon in children. It affects both sexes equally, and a family history of disease is more common than in adults. The clinical manifestations are very similar to that of adult-onset disease, although uveitis is generally less frequent.^{91,92} Recurrent episodic fever is a particularly prominent feature of Behçet's disease in children.

DIAGNOSIS AND DISEASE MONITORING

Disease definition

There is no specific test for Behçet's disease, and the diagnosis is based upon clinical criteria. A number of classifications have been formulated, each with its own list of clinical features.^{93–96} In 1990, these were amalgamated into the International Study Group Classification criteria (Table 1).⁹⁷ These have now been widely adopted, and although intended for the definition of patients participating in research programmes rather than for the diagnosis of individual patients, they also perform well in a clinical context.^{98,99}

Differential diagnosis

Although the diagnosis of Behçet's disease may be straightforward once the possibility has been recognized, incomplete disease or unusual presentations often represent

Table 1. International study group criteria for the diagnosis of Behçet's disease.⁹⁷

Recurrent oral ulceration	Minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which have recurred at least three times in a 12-month period
<i>And two of the following</i>	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in post-adolescent patients not on corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 hours
The findings are applicable only in the absence of other clinical explanations.	

a diagnostic challenge. A detailed clinical history is essential to exclude other conditions and reveal subtle features of this complex disease.

Reiter's syndrome may be associated with oral and genital ulcers, although the arthritis is generally erosive. Urethritis and sacroileitis are not features of Behçet's disease.

Sarcoidosis can also present with erythema nodosum, uveitis and arthralgia, but genital ulcers are not a feature. Chest radiography may be helpful.

Stevens-Johnson syndrome also presents with mucocutaneous involvement and conjunctivitis but is not associated with thrombophlebitis, uveitis or arterial disease.

There is a considerable clinical overlap between *Crohn's disease* and *ulcerative colitis* with extragastrointestinal involvement, and Behçet's disease with predominantly gastrointestinal involvement.

Other causes of periodic fevers, such as *familial Mediterranean fever*, *hyper IgD syndrome* or periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, should be considered in children as recurrent febrile episodes may characterize the onset of Behçet's disease.

Patients with significant neurological involvement may occasionally be misdiagnosed as having *multiple sclerosis*.

Other chronic systemic diseases associated with recurrent aphthous ulceration include *systemic lupus erythematosus* and *celiac disease*.

Recurrent orogenital ulceration may also be associated with *bullous skin disorders* and *erythema multiforme*.

Laboratory investigations

Laboratory findings are non-specific in Behçet's disease. Moderate anaemia of chronic disease is common, and a neutrophil leukocytosis is seen in 15% of patients. Serum immunoglobulins may be non-specifically elevated. Autoantibodies such as rheumatoid factor, anti-nuclear antibody and anti-neutrophil cytoplasmic antibody are usually negative. Importantly, non-specific markers of inflammation such as C-reactive protein level and erythrocyte sedimentation rate can be normal despite active orogenital, ocular or CNS disease.⁶² HLA typing is generally not useful in a diagnostic context because of the lack of sensitivity of the association with HLA-B*51.

Disease activity index

In the absence of any specific marker of disease activity, monitoring of the disease is primarily clinical. This has been recently facilitated by the publication of a disease activity index: the Behçet's Disease Current Activity Form is a convenient and logical tool, and can easily be administered during the course of a routine consultation to provide a standard for comparison.^{100,101}

TREATMENT

Although the number of randomized controlled trials in Behçet's disease is increasing, treatment remains predominantly empirical, and considerable differences exist in practical approaches to treatment. The primary goals of management are symptom control, early suppression of inflammation and prevention of end-organ damage, the treatment options being anti-inflammatory agents and immunosuppressants. Drugs are

frequently used in combination in order to maximize efficacy while minimizing side effects. The spectrum of clinical manifestations requires close multidisciplinary co-operation for optimal care.

TOPICAL TREATMENT

Oral ulceration can often be treated by the topical application of corticosteroids, using creams or mouthwashes (5 mg prednisolone in 20 ml water, four times daily¹⁰²), or by direct application through a conventional corticosteroid inhaler. Similarly, genital ulceration often responds to topical corticosteroid therapy, although long-term use may be complicated by skin atrophy. Topical sucralfate suspension is an alternative topical therapy for aphthous ulceration.¹⁰³ Topical mydriatic agents and corticosteroid eye drops may be useful for mild ocular disease.

Systemic corticosteroids

Intravenous systemic corticosteroids are frequently used in the management of acute disease exacerbations, including acute uveitis and neurological disease.¹⁰⁴ They may be usually used in combination with calcineurin inhibitors or other immunosuppressants^{102,105}, and a synergistic action with cyclosporin in ocular disease has been described.¹⁰⁶ The long-term use of oral corticosteroids is to be avoided if possible because of the significant adverse effects.

Calcineurin inhibitors (cyclosporin and tacrolimus)

Cyclosporin is the mainstay of treatment of severe Behçet's disease.¹⁰⁷ In ocular disease, it has been shown to decrease the frequency and severity of acute uveitis^{104,108,109} and, in a controlled study, was more effective than cyclophosphamide in the initial phase of the disease.¹¹⁰ It has also been reported to have a favourable effect on mucocutaneous disease, hearing loss, thrombophebitis and systemic symptoms.^{104,109} The long-term use of cyclosporin is limited by the development of side effects, particularly hypertension and renal impairment. In Behçet's disease, an important issue is the incidence of neurological side effects of cyclosporin: in a Japanese retrospective cohort study, the incidence of neurological disease was significantly higher in patients on cyclosporin than on other treatments¹¹¹, and cyclosporin-associated side effects could not be distinguished from CNS involvement by disease. Indeed, cyclosporin may accelerate the development of neurological involvement in Behçet's disease¹¹¹ and should be avoided in patients with CNS involvement.¹⁰⁷

Tacrolimus acts through a similar mechanism to cyclosporin and has also used to treat refractory posterior uveitis in Behçet's disease.¹¹² Importantly, tacrolimus and cyclosporin have different side effect profiles, which may be an important issue in the choice of immunosuppressive therapy.¹¹³ Both tacrolimus and cyclosporin are associated with nephrotoxicity, hypertension and neurotoxicity. Tacrolimus is, however, less frequently associated with hyperlipidaemia, and cyclosporin is less associated with diabetes mellitus. In contrast to cyclosporin, tacrolimus does not induce hypertrichosis, gingival hypertrophy or coarsening of the features, which may improve patient compliance.

Cyclophosphamide

Pulsed intravenous cyclophosphamide may be used in the treatment of uveitis in Behçet's disease, but dose-dependent adverse effects particularly infertility, haematological dyscrasias and malignancy, limit its use. Previously a mainstay of the management of severe disease, it is generally being replaced by calcineurin inhibitors and anti-tumour necrosis factor (TNF) agents where these are available.

Azathioprine

Azathioprine, alone or in combination with other immunosuppressive drugs, is an important disease-modifying agent. In a large randomized, placebo-controlled trial, azathioprine 2.5 mg/kg/day reduced the incidence, frequency and severity of eye disease, and had a favourable effect on arthritis and oral and genital ulceration when compared with placebo in patients also taking corticosteroids.¹¹⁴ Early treatment with azathioprine also improves the long-term prognosis in Behçet's disease when compared with placebo.^{115,116}

Infliximab and etanercept

The use of infliximab in Behçet's disease was first described in 2001¹¹⁷, since which a number of case series and single reports have been published (Table 2). Initial indications for treatment were sight-threatening uveitis and severe inflammatory gastrointestinal disease. Infliximab has subsequently been used for severe orogenital

Table 2. Case studies reporting the use of biological anti-tumour necrosis factor agents in Behçet's disease.

Reference number	Number of patients	Organ involvement	Outcome	Agent	Year
117	5	Uveitis	Favourable 5/5	Infliximab	2001
163	1	Gastrointestinal	Favourable	Infliximab	2001
164	2	Gastrointestinal	Favourable	Infliximab	2001
165	1	Uveitis	Favourable	Infliximab	2001
166	1	Orogenital ulceration	Favourable	Infliximab	2001
167	1	Orogenital ulceration, retinal vasculitis	Favourable	Infliximab	2001
168	1	Orogenital ulceration with rheumatoid arthritis	Favourable	Infliximab	2002
169	1	Uveitis, orogenital ulceration, erythema nodosum	Favorable	Infliximab	2002
118	1	Orogenital ulceration, erythema nodosum	No response	Etanercept	2002
170	1	Cerebral vasculitis	Favourable	Infliximab	2003
171	1	Orogenital ulceration, arthritis, retinal vasculitis	Favourable	Infliximab	2003
172	1	Gastrointestinal	Favourable	Infliximab	2003
173	3	Resistant posterior uveitis	Favourable 3/3	Infliximab	2003

ulceration and for cerebral vasculitis. These anecdotal case studies have generally reported an immediate and dramatic resolution of both organ-specific and systemic symptoms, often in patients refractory to conventional immunosuppression, although the long-term outcome is unknown.

There are fewer published reports of the use of the fusion protein etanercept in Behçet's disease, although the results of a number of studies are awaited. Interestingly, the unsuccessful use of etanercept has been reported in one patient subsequently responsive to infliximab.¹¹⁸ Infliximab is generally superior to etanercept in Crohn's disease, possibly because of differences in their mode of action, but it remains to be shown whether this is also true in Behçet's disease.¹¹⁹

The dramatic response of many patients with Behçet's disease to anti-TNF biological agents has resulted in the wide use of these agents in severe or intractable disease exacerbations. At the 10th International Conference on Behçet's disease in June 2002, 38% of physicians had direct experience of anti-TNF antibodies in Behçet's disease.¹²⁰ The use of infliximab for Behçet's disease is, however, currently limited by both a lack of efficacy data and cost, and a number of clinical trials are now underway to provide more information. It is hoped that these will demonstrate whether anti-TNF agents are truly superior to conventional immunosuppressive therapy.

Interferon alpha

IFN- α is another biological agent that has been used in Behçet's disease. Initial case reports appeared to demonstrate a significant benefit in patients with mucocutaneous disease, ocular disease and articular manifestations (reviewed in refs. 121,104). A number of small open studies of IFN- α at doses ranging from 3×10^6 to 9×10^6 IU three times weekly showed considerable promise¹²²⁻¹²⁶, although relapses were frequent after cessation of therapy. Although a paper describing the results of a controlled trial were retracted because of concerns about scientific impropriety¹²⁷⁻¹²⁹, the usefulness of IFN- α has recently been confirmed in a placebo-controlled trial¹³⁰ that demonstrated a significant decrease in aphthous ulceration and the number of papulopustular lesions. The cost and invariable side effect of 'flu-like symptoms may, however, limit the long-term use of IFN- α in mild or moderate disease, and the effect on the outcome of ocular disease remains unknown.

Thalidomide

Thalidomide has a variety of immunomodulatory properties, one of which is the downregulation of TNF production across a broad range of cell types.¹³¹ In controlled trials, thalidomide has been shown to be effective in the management of recurrent aphthous ulceration¹³², and there is experience of its use in the management of erythema nodosum leprosum, human immunodeficiency virus-associated aphthous ulceration, chronic graft-versus-host disease and haematological malignancies. It is considered by many to be the most effective treatment of orogenital ulceration in Behçet's disease¹⁰⁷, although limited response rates were achieved in the only published placebo controlled trial in Behçet's disease.¹³³

The use of thalidomide is limited by its well-documented teratogenicity, and it should be recommended only in the absence of safer therapeutic options.^{134,135} Guidelines are available on the clinical use and dispensing of thalidomide, emphasizing the need for patient information, informed consent and adequate contraception.¹³⁶ Stringent requirements are in place in the USA to control and monitor access to thalidomide.¹³⁷

The other major side effect of thalidomide is the development of peripheral neuropathy. Electrophysiological evidence of decreased sensory nerve action potentials is common and associated with a cumulative dose. Indeed, clinical or subclinical peripheral neuropathy eventually limits treatment in many patients. Close monitoring of sensory nerve action potentials, including baseline monitoring¹³⁸, is vital in order to predict the onset of peripheral neuropathy. The UK guidelines recommend baseline nerve conduction studies on at least three peripheral nerves, with follow-up testing after every 10 g cumulative dose or every 6 months. It is suggested that a fall from baseline of over 40% should lead to a discontinuation of treatment, whereas falls of 30–40% should precipitate a review of therapy. If symptoms develop between tests, patients should discontinue the drug immediately and seek advice.¹³⁶ Preventing neuropathic disease is essential as this may be irreversible.

Pentoxifylline

Pentoxifylline is another agent with anti-TNF activity that has been used for the management of orogenital ulceration in Behçet's disease. Licensed for use in peripheral vascular disease, the major pharmacological effect of pentoxifylline is inhibition of the production of various pro-inflammatory cytokines, in particular TNF.^{139,140} It also has a direct suppressive effect on CD8 + T-lymphocytes, probably through the inhibition of perforin.¹⁴¹ Furthermore, it suppresses the production of free radicals and reduces neutrophil-induced tissue damage.¹⁴² Although no controlled trials have been published, anecdotal reports have indicated that it may be a useful treatment option in Behçet's disease, particularly in the management of orogenital ulceration.^{143,144}

Dapsone

Dapsone is an anti-infective agent with significant anti-inflammatory properties. Although its mechanism of action is incompletely understood, dapsone appears to modify neutrophil chemotaxis and function, reversibly inhibits myeloperoxidase activity, inhibits neutrophil lysosomal activity and acts as an anti-oxidant.¹⁴⁵ It is licensed for the treatment of leprosy and dermatitis herpetiformis but is also used in the management of a variety of inflammatory, autoimmune and bullous diseases.¹⁴⁵ Dapsone is a useful drug, particularly for the management of the mucocutaneous symptoms of Behçet's disease. In a double-blind, placebo-controlled, cross-over clinical trial, dapsone 100 mg daily was associated with a significant improvement in oral and genital ulceration, as well as in cutaneous disease.¹⁴⁶ Side effects include haemolysis, methaemoglobinemia and agranulocytosis; regular monitoring for possible adverse events is required.

Colchicine

The anti-inflammatory action of colchicine is thought to be the result of an inhibition of neutrophil migration.¹⁴⁷ In one controlled trial in Behçet's disease, colchicine was effective in the management of erythema nodosum and arthralgia but not eye disease, orogenital ulceration or synovitis.¹⁴⁸ However, a more recent, larger study showed colchicine to be associated with improved mucocutaneous and joint symptoms when compared with placebo, particularly in women.¹⁴⁹ As it is generally well tolerated when

used at a dose of 1.0–2.0 mg/day, colchicine therefore has an important niche in the management of mild to moderate disease.¹⁴⁹

Other therapies

The correction of haematinic deficiency (iron, vitamin B₁₂ or folate) is an important non-specific intervention as this condition may aggravate recurrent aphthous ulceration.¹⁵⁰

Thrombotic disease is treated with *warfarin*, although the degree and duration of anti-coagulation is debated. Patients may develop new thromboses despite anti-coagulation, presumably related to the underlying vascular inflammation.¹⁰² Superficial thrombophlebitis may respond to oral aspirin.⁴ No data on the use of prophylactic anti-platelet agents are available.

Both *penicillin* and *minocycline*³⁹ have been used in the treatment of Behçet's disease, the rationale being that there may be a bacterial involvement in disease pathogenesis. In a controlled trial, the combination of penicillin and colchicine was more effective in the prevention of joint symptoms¹⁵¹ and in the control of mucocutaneous disease¹⁵² than colchicine alone.

Low-dose weekly *methotrexate* may be effective in the management of neurological manifestations of Behçet's disease¹⁵³ and ocular disease.¹⁵⁴

Sulfasalazine has been used in the treatment of gastrointestinal disease.^{155,156}

Mycophenolate mofetil is a specific inhibitor of B- and T-lymphocytes, and is widely used in transplantation. It is often used as a steroid-sparing agent in a manner analogous to azathioprine and has increasingly been used with tacrolimus or cyclosporin in steroid-free regimens. In Behçet's disease, an open trial of mycophenolate in combination with prednisolone showed no benefit.¹⁵⁷ However, its efficacy as an immunosuppressant in other systemic autoimmune diseases suggests that it may nonetheless have a role.¹⁵⁸

Non-steroidal anti-inflammatory agents are generally considered to be of little benefit in the arthritis of Behçet's disease.^{104,159}

Acyclovir is not effective in the treatment of orogenital ulceration.¹⁶⁰

The use of the anti-CD52 monoclonal antibody *CAMPATH-1H* in active Behçet's disease has recently been reported.¹⁶¹ *CAMPATH-1H* recognizes CD52, a cell surface protein of unknown function present on all lymphocytes and monocytes. It has been used in a variety of autoimmune diseases and haematological malignancies, as well as in transplantation. In this open study of 18 patients, remission was achieved in 72%, and although treatment was well tolerated, all patients experienced prolonged lymphopenia.

No controlled trials of *chlorambucil* in Behçet's disease have been published, even though this was a mainstay of treatment for many years.¹⁶² Since the introduction of cyclosporin, however, many investigators have discarded it because of significant, cumulative toxicity and risk of malignancy.

PROGNOSIS

Behçet's disease is characterized by relapses and remission, and its clinical course is highly variable. Overall, the disease is more severe in Mediterranean and Eastern cohorts than in Western populations, and it is generally more severe in males than

females. A recently published, 20-year outcome study of 387 Turkish patients revealed an overall mortality of 9.8% in Behçet's disease.⁷⁰ This is higher than previously reported⁷⁶ and probably reflects the long duration of follow-up and the severity of disease in this population. As with previous studies, both morbidity and mortality were highest in young males. Interestingly, overall mortality decreased with the passage of time, consistent with the observation that the prognosis of Behçet's disease is generally good after the initial years. Blindness and neurological disease are the major cause of permanent disability.

Practice points

- although developed for research and clinical trials purposes, the 1990 International Study Group Classification Criteria (see Table 1 above) perform well in a clinical context and may be helpful in establishing a diagnosis
- the course of the disease is generally more severe in those of Mediterranean and Eastern origin and in males. It is rare, albeit reported, in African populations and absent in Amer-Indians
- recurrent aphthous ulceration of the oral mucosa is the sine qua non of Behçet's disease. Genital ulcers occur in 72-94% of cases
- ocular disease is the presenting feature in 10–20% of patients and is usually chronic, relapsing and bilateral. The classical clinical sign of anterior uveitism—hypopyon—is only observed in one-third of those with eye disease. Eye involvement is a cause of significant long-term morbidity with visual loss in up to 25% of patients
- pathergy is the only specific feature of Behçet's disease. Its diagnostic value is dependent on ethnicity as it occurs in over 60% of Middle Eastern but only 5% of caucasoid patients
- CNS involvement occurs in 5–10% of patients and carries a 5–10% mortality. There are reports that it may be accelerated by cyclosporin therapy/toxicity, which should therefore be avoided in those with CNS disease
- cyclosporin remains the bedrock of therapy for severe Behçet's disease, with definite benefit in ocular disease and reported benefit for other manifestations. Its use is limited by its well-established toxicity profile, including that on the CNS (see above)
- early treatment with azathioprine has been shown to improve long-term prognosis versus placebo in two randomized controlled trials
- targeting the cytokine TNF α via infliximab/etanercept in reverse disease has been associated with prompt and dramatic remission, although no clinical trials have been published to date
- many experienced clinicians consider thalidomide to be the most effective treatment of orogenital ulceration despite a limited response rate in the only published placebo-controlled randomized controlled trial in Behçet's disease. Guidelines for the safe use and monitoring of this drug are available in the UK and USA, and must be stringently adhered to by the prescribing physician
- recent epidemiological data suggest that the prognosis of the disease is generally good after the initial years, underscoring the importance of prompt recognition and appropriate treatment

Research agenda

- although the association of Behçet's disease with HLA-B*51 has been known for more than 25 years, the mechanism by which it operates remains uncertain
- the geographic distribution of disease and the wide variation in relative risk of HLA-B51 support the involvement of other, environmental, risk factors in disease pathogenesis
- the use of biological anti-TNF agents offers significant promise for the treatment of severe Behçet's disease, although the results of clinical trials are awaited.

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