Behçet’s disease – a contemporary review

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ABSTRACT

Behçet’s disease (BD) is a systemic vasculitis disorder of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions and ocular lesions. It can affect other systems including vascular, gastrointestinal and neurological systems. It occurs most frequently in an area that coincides with the Old Silk Route (between latitudes 30° and 45° north in Asia and Europe). BD is slightly more frequent and has a worse clinical course in men. It is believed to be due to an auto-immune process triggered by an infectious or environmental agent in a genetically predisposed individual. HLA-B51 is the most strongly associated risk factor. The International Study Group (ISG) for Behçet’s Disease created a set of criteria for the diagnosis of BD. Available treatments include corticosteroids, azathioprine, cyclophosphamide, cyclosporine A, interferon-α, anti-tumour necrosis factor α agents, among others.

BD has a variable course characterized by relapses and remissions. Prognosis depends on the clinical involvement. Loss of visual acuity and neurological disease are major causes of morbidity and disability.

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1. Introduction

Behçet’s disease (BD) is a systemic inflammatory vasculitis of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions and other manifestations, including vascular, gastrointestinal, neurological involvement [1].

It is heterogeneous in onset, has variable organ involvement and results in considerable morbidity and increased mortality [2,3].

Recently in Turkey, country with the highest prevalence rate, a cost-analysis of BD was made, proving that it is a considerable economic burden both in direct as in indirect costs [4].

2. Historical note

First description of BD, also known as the Old Silk Route disease, has been attributed to Hippocrates in the 5th century BC, in the “Third book of endemic diseases” [5].

There are also descriptions of patients with constellation of symptoms and signs that are similar to BD since the 18th century all the way to the 20th century, namely by Neumann, Christlieb, Reis, Blüthe, Gilbert, Adamantiades, Shigeta, Pils, among others [6,7,13–15].

In 1937, Behçet, a Turkish dermatologist, identified the 3 major signs (recurrent oral aphthae, genital ulcerations, recurrent hypopyon uveitis) and grouped them on a clinical entity, publishing a report in a German journal [8] in 1937 and one in 1938 in a French journal [9]. Later in 1939 and 1940 he called it the “triple symptom complex” [10,11].

After these descriptions, many reports followed from different places. Jensen, a Danish doctor, was the first to use the eponym “Behçet” in 2 publications in 1941 (“Sur les ulcerations aphteuses de la muqueuse de la bouche et de la peau génitale combines avec les symptôms oculaires (=Syndrôme Behçet)” and “Ulcerous haemorrhagic colitis associated with Behçet’s syndrome”). Afterwards, several other authors used the eponyms “Behçet’s syndrome” and “Behçet’s disease”. In 1947, in the International Medical Congress of Geneva, in Switzerland, the disease was named “Morbus Behçet”, after Zurich Medical Faculty Professor Mischner’s proposal [6,12].

The disease is sometimes referred as Adamantiades-Behçet’s disease, however, Behçet’s disease should be preferred as suggested by International Associations and Societies of “Behçet”.

3. Epidemiology

BD occurs most frequently between latitudes 30° and 45° north in Asian and Eurasian populations in an area that coincides with the Old Silk Route, an ancient commercial route that stretched between the Mediterranean, Middle East and Far East [16].

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Estimated prevalence is between 1/1000 and 1/10,000 in the Old Silk Route (highest prevalence is in Turkey, it is 80–420 cases/100,000, depending on the geographical area; followed by Japan with low prevalence of the disease and their descendents have an intermediate risk for developing the disease, which points that environment has some role in BD [16,43,44]. However, to date, there is no information supporting the role of a single microorganism as the specific etiologic agent.

The most generally accepted theory for the role of infectious agents is that microorganism antigens have high homology with human proteins (like heat shock protein (HSP) 65, obtained from Mycobacterium, which has high homology with human protein HSP60) and that cross-reaction leads to immune response [44,45].

Retinal S antigen is located in the retina and has homology with HLA-B51 and HLA-B27; but an immune mediated response to this antigen can only occur after eye damage due to uveitis [44].

4. Pathogenesis

The cause of BD is unknown. It is believed to be due to an auto-immune process triggered by an infectious or environmental agent (possibly local to a geographic region) in a genetically predisposed individual [31,32].

4.1. Genetics and human leukocyte antigen (HLA) typing

In a Turkish study, sibling risk ratio was estimated as 11.4–52.5. Although environmental factors shared by families can influence familiar clustering they cannot account for this risk ratio, which supports a strong genetic background for BD [26].

HLA-B51 allele located in the MHC (major histocompatibility complex) locus, on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route, with a stronger association in Turkish and Japanese patients in comparison to Caucasians [16]. In a study of tumor necrosis factor (TNF) polymorphisms, HLA-B5701 was associated with disease susceptibility in Caucasians from the United Kingdom [33].

Other genes present in the MHC locus have been studied, including MICA (MHC class I related gene) and TNF genes, however, their participation is considered to be due to linkage disequilibrium with HLA-B51 gene [34].

Several other genes, located outside the MHC region have been proposed to be involved in BD pathogenesis, namely genes of interleukin-1 (IL-1), coagulation factor V, intercellular adhesion molecule-1 (ICAM-1) and endothelial nitric oxide synthetase (eNOS) [31,35–39].

Recent studies point that Mediterranean Fever gene (MEFV) mutations are an additional genetic susceptibility factor in BD [40–42].

4.2. Environment (infectious agents, heat shock proteins) and self-antigens

Individuals from endemic areas who have immigrated to areas with low prevalence of the disease have an intermediate risk for developing the disease, which points that environment has some role in BD [1,19].

Several microorganisms have been implicated in the etiology of BD, specially herpes simplex virus-1 and Streptococcus sanguis [16,43,44]. However, to date, there is no information supporting the role of a single microorganism as the specific etiologic agent.

The most generally accepted theory for the role of infectious agents is that microorganism antigens have high homology with human proteins (like heat shock protein (HSP) 65, obtained from Mycobacterium, which has high homology with human protein HSP60) and that cross-reaction leads to immune response [44,45].

Retinal S antigen is located in the retina and has homology with HLA-B51 and HLA-B27; but an immune mediated response to this antigen can only occur after eye damage due to uveitis [44].

4.3. Cytokines and cells of the immune system

The serum levels of several cytokines including IL-1, IL-4, IL-6, IL-8, IL-10, IL-13, IL-18 and TNF-α are elevated in BD patients [32,46]. In one study IL-15 levels in the cerebral spinal fluid of patients with active BD were higher than levels of patients with BD in remission and healthy controls [47].

It has been demonstrated that a Th1-type polarization of immune response occurs in BD, its intensity being correlated with disease activity [31].

One study revealed that there is preponderance of type 1 producing cells in the CXCR3+ CD3+ T cells in BD [48].

γδ T lymphocytes have a role in the immune response to infections and in auto-immunity by recognizing bacteria-derived and autologous antigens. Patients with BD have increased numbers of γδ T cells in circulation and in mucosal lesions [49]. In one study there was an elevated number of the γ9Vδ2 subset of γδ T cells in the intraocular fluid of BD patients with uveitis [50].

γδ T lymphocytes have an activated phenotype in BD (they express activation markers, like CD 25, CD 29 and CD 69) and produce inflammatory cytokines, including IFN-γ, TNF-α and IL-8 [31].

Culture of γδ T lymphocytes from BD patients proliferates in response to mycobacterial HSP-derived peptides and in response to products from microorganisms in oral ulcers [49,51]. γδ T also proliferates in the presence of IL-12 and it has been demonstrated that serum levels of IL-12 are increased in BD, suggesting a role of IL-12 in the Th 1-type polarization in BD [52].

Antigen presenting cells (APC) produce IL-12, so it is likely that they are involved in the Th 1-type polarization in BD. They also produce IL-18 which has been shown to increase neutrophil functions [31].

Neutrophils are hyperactive in BD, with increased chemotaxis, phagocytosis, superoxide production and myeloperoxidase expression and produce several cytokines, including IL-12 [53,54]. The precise mechanism of neutrophils hyperactivity is not known, however, T cells are fundamental in their activation [31].

It is currently believed that complex interactions between T cells, neutrophils and APC are involved in the immune pathogenesis of BD (hypersensitivity of T cells to different types of antigens; cytokines produced by T cells and APC causing neutrophil hyper-activation; cytokines secreted by activated neutrophils that contribute to their own activation and also stimulate Th1 cells) [31].

5. Clinical features

BD can affect nearly every system of the body, following a course of relapses and remissions. Presentation and evolution may vary due to ethnic, geographical and individual differences.

There are 3 key features of BD: recurrent oral ulcers, genital ulcers and ocular disease.
5.1. Recurrent oral ulcers (aphthous-like)

According to the ISG criteria, recurrent oral ulcers are a sine qua non feature of BD [88].

It is usually the earliest sign of the disease (47–86% of patients) and may precede by many years the onset of other symptoms [17, 55–57, 69].

Lesions are similar to common oral aphthous ulcers, although they can be more painful and wider, with a disciform appearance with round and sharp erythematous border (punched-out), covered with grayish–white pseudo-membrane or central yellowish fibrinous base, growing rapidly from a flat ulcer to a large sore. They may occur as single ulcers or in crops and usually heal without scarring. The most commonly involved sites are gingival and buccal mucosa, tongue and lips, although ulcers can also appear in the soft and hard palate, pharinx and tonsils [58]. They can occur after local trauma or dental intervention (Fig. 1).

Oral ulcers can be classified as: [55]

- Minor (most common) – 1–5 in number, diameter < 1 cm, shallow, surrounded by an erythematous halo, moderately painful, healing without scarring in 4–14 days
- Major (less frequent) – 1–10 in number, morphologically alike, although larger (>1 cm), more painful, more persistent and may heal with scarring in 2–6 weeks
- Herpetiform (the least common) – recurrent crops of numerous small (2–3 mm) and painful ulcers which may become coalescent.

5.2. Genital ulcers

They occur in 57–93% of patients [17, 55, 56]. Ulcers are morphologically similar to oral lesions, although larger, with a more irregular border, and commonly healing with scarring (white or pigmented scars) (Figs. 2 and 3).

Scrotal lesions are the most frequent (90%) in males, epididymitis can also occur but penile lesions are infrequent; urethritis is not a feature of BD. Females have vulvar, vaginal and cervical lesions. Deep vaginal lesions can perforate the bladder originating fistulae. Perineal, perianal and groin lesions can occur in both sexes [55].

5.3. Ocular disease

Eye involvement occurs in 30–70% of cases of BD and is cause of significant morbidity. About 25% of patients with ocular disease become blind despite treatment, although prognosis is improving with the use of modern immunosuppressant therapy and of a more
aggressive treatment strategy [3,20,59–62]. It is more frequent and more severe in men [20,21].

Ocular disease is commonly bilateral and usually occurs 2–3 years after the onset of BD symptoms; it is the presenting feature in 10–20% of patients [20,59]. The typical ocular involvement is a chronic, relapsing bilateral non-granulomatous uveitis that may involve the anterior segment, the posterior segment or both (panuveitis). Recurrence and bilateral occurrence are similar in both sexes, however, men have a higher incidence of panuveitis, which carries a worse prognosis [53,59].

Anterior uveitis with hypopyon, where the inflammatory exudate forms a visible layer of cells in the anterior chamber is a characteristic sign of ocular BD, but is observed only in about one-third of patients [34].

Other ocular manifestations include iridocyclitis, keratitis, episcleritis, scleritis, vitritis, vitreous haemorrhage, retinal vasculitis, retinal vein occlusion, retinal neovascularization and optic neuritis [60,88] (Fig. 4).

Clinical symptoms and signs include blurred vision, photophobia, lacrimation, floaters, hyperemia, periorbital or global pain [3].

Recurrent attacks of inflammation lead to secondary complications namely, posterior and/or peripheral anterior synechia, iris atrophy, cataract due to inflammation and/or medication, secondary glaucoma (sometimes neovascular), atrophic retina, optic atrophy, macular oedema, macular degeneration, retinal veins occlusion, sheathed vessels, chorioretinal scars and/or proliferative vitreoretinopathy, phthisis bulbi [53,60,63].

5.4. Cutaneous lesions

Skin is involved in 38–99% of patients [17,55,56]. Papulopustular lesions (28–96%) and acne-like lesions are the most common cutaneous manifestation, and their distribution is more widespread than adolescent acne, affecting face, limbs, trunk and buttocks [17,56] (Fig. 5).

Erythema nodosum lesions are frequent (15–78% of patients), especially in females, and predominantly affect the lower limbs, although they can also appear in the face, neck and buttocks. The lesions do not ulcer and may heal leaving a residual pigmentation [17,55].

Cutaneous ulcers occur in about 3% of patients; they look like aphthous ulcers, are recurrent and commonly heal leaving a scar.
They can appear in the neck, breast, axillae, inguinal region, legs, interdigital skin in the feet [55].

Histologically, skin lesions are characterized by vasculitis and thrombosis. Early lesions show a leukocytoclastic vasculitis or a neutrophilic vascular reaction, older lesions have a lymphocytic vasculitis [55,64,65].

5.5. Neurological disease

Neurological involvement, first described in 1941, occurs in 5–10% of patients and is associated with high morbidity [1,66]. It usually happens within 5 years after the onset of the disease and is more frequent in men. Central nervous system (CNS) is more frequently involved than the peripheral nervous system [66,67].

Parenchymal brain disease (Neuro-Behçet) is more common (approximately 80%), particularly affecting the brainstem and/or basal ganglia, and is associated with worse prognosis. Non-parenchymal disease includes dural sinus thrombosis, arterial vasculitis and aseptic meningitis [66].

Clinical symptoms include bilateral pyramidal signs, extrapyramidal signs, hemiparesis, behavioural changes, sphincter disturbance, cranial nerve palsies, headache [66,68].

Cerebral spinal fluid is frequently normal, but can have increased pressure, increased number or neutrophils and/or lymphocytes and increased protein content [66].

On magnetic resonance imaging (MRI) basal ganglia, brainstem or deep white matter region lesions are frequently visible [1,66].

5.6. Vascular disease

BD is a systemic vasculitis that affects both arteries and veins of all sizes. Vascular involvement was first described in 1946 [1,70]. Cardiovascular manifestations have been described in 7–49% of patients, 3–16 years after BD onset, being more frequent in males [21,70–72].

Veins are more frequently affected, resulting in both superficial thrombophlebitis and deep venous thrombosis which occur in 30–40% of patients [34,73].

Thromboses of the superior and inferior vena cava (occur 0.2–9% of cases), of dural sinuses and of supra-hepatic veins (Budd–Chiari syndrome – in 2–3% of patients), and pulmonary arterial aneurysms (1%) can occur and are associated with a poor prognosis [73–75,141].

The pathogenesis of thrombosis in BD is still not known [73].

5.7. Cardiac disease

Cardiac involvement includes pericarditis, myocarditis, endocarditis, mitral valve prolapse, valve lesions, intracardiac thrombosis, endomyocardial fibrosis, myocardopathy, coronary artery lesions [70,76].

5.8. Gastrointestinal disease

Gastrointestinal involvement is variable in different populations (3–26%), being much more frequent in Japan than in the Middle East and Mediterranean [1,77,78].

Clinical features include anorexia, vomiting, dyspepsia, diarrhea, abdominal pain. Mucosal inflammation and ulcers can occur throughout the gastrointestinal tract, more frequently in the ileocecal region, less frequently in the colon and sparing the rectum [77,78] (Fig. 6).

5.9. Articular involvement

It affects between 45 and 60% of patients and may be the first manifestation of the disease in about 16.5% of them. Inflammatory arthralgia, arthritis and synovitis may occur. The most frequent manifestation is a non-erosive, non-deforming oligoarthralgia that typically involves the knees, ankles and wrists [79].

5.10. Pathergy

It is the non-specific hyperreactivity of the skin following minor trauma, which is specific to the disease.

The pathergy test consists of the intradermal puncture of the skin with a 20-gauge or smaller needle 5 mm obliquely into the patient’s flexor aspect of the avascular forearm skin under sterile conditions and without injecting saline. It is considered positive when an indurated erythematous small papule or pustule forms within 48 h. Positivity of the test varies with geographical location, being positive in more than 60% of Middle Eastern patients, in 15% of Korean patients and in about 5% of Caucasian, which considerably reduces its diagnostic values in populations with low positivity [3,34].

A study demonstrated that surgical cleansing of the skin before the puncture reduced the test positivity [80].

Clinical spectrum of BD in children (<16 years) is similar to adult disease, yet they have more frequently perianal aphthosis and arthralgia and less frequently genital ulcers and vascular involvement. Oral ulcerations are the presenting symptom in the majority of patients. Frequency reports of eye disease vary among studies, however, the course of uveitis is generally more severe in children [27,28].

Pregnancy has a variable influence on BD among patients and even between different pregnancies in the same patient with relapses, worsening of symptoms or remission. When exacerbation occurs it is more frequent in the first trimester [29,30].

Fig. 6. Esophageal ulcer.
6. Diagnostic criteria

As there are no pathognomonic clinical or laboratorial findings of BD, several diagnostic criteria have been developed during the years, all having in common the 3 major features of oral ulceration, genital ulceration and eye lesions.

Mason and Barnes (1969) considered Behçet’s diagnosis when 3 major criteria or 2 major and 2 minor criteria were present. Major criteria were: Oral ulceration, Genital Ulceration, Eye lesions (Uveitis, Corneal ulceration, Retrobulbar neuritis) and Skin lesions (Pustules, Ulceration, Erythema nodosum, Erythema multiforme). Minor criteria: Gastrointestinal lesions, Thrombophlebitis, Cardiovascular lesions, Arthritis, Central nervous system lesions and Family history [81].

Behçet’s Disease Research Committee of Japan also defined diagnostic criteria in 1972, which were revised in 1987 and 2003, that consider Complete disease when 4 major criteria are present; Incomplete disease when there are 3 major features, 2 major and 2 minor or typical recurrent ocular symptom plus 1 major or 2 minor features; Suspected disease when patients have 1 or 2 major symptoms. Major criteria are: Recurrent aphthous ulceration of the oral mucous membrane, Skin lesions (Subcutaneous thrombophlebitis, Foliculitis, Acne-like lesions, Cutaneous hypersensitivity), Eye lesions (Iridocyclitis, Chorioretinitis, Retino-uveitis, Definite history of chorioretinitis or retino-uveitis), Genital ulcers. Minor features: Arthritis without deformity or ankylosis, Gastrointestinal lesions characterized by ileocaecal ulcers, Epididymitis, Vascular lesions, Central nervous system symptoms [82,83].

O’Duffy in 1974 considered diagnostic oral or genital ulceration and 2 other features and vasculitis on biopsy specimen supported the diagnosis. Major criteria: Oral ulceration, Genital ulceration, Uveitis, Dermal vasculitis (erythema nodosum). Minor: Arthritis, Central nervous system involvement, Colitis, Phlebitis, Large vessel arteritis [84].

In 1980, Zhang considered Complete disease when 3 major or 2 major plus 2 minor criteria were present and Incomplete disease when there were 2 major features or 1 major and 2 minor. Major criteria: Oral ulceration, Genital ulceration, Uveitis. Minor criteria: Skin (Erythema nodosum, Erythema multiforme, Pathergy), Arthritis, Vasculitis (Thrombophlebitis, Arteritis, Aneurysm), Pulmonary (Haemoptysis, Lung infiltration, Interstitial fibrosis), Gastrointestinal lesions (Ulceraion, Bleeding, Perforation), Renal (Renal damage, Ulceration of bladder, Haematuria, Epididymitis), Neurological features [86].

Dilsen et al (1986) also defined a set of criteria emphasizing the pathergy test [87].

In 1985 during the Fourth International Conference on Behçet’s Disease, in London, an International Study Group (ISG) for Behçet’s Disease was created, in order to create a set of criteria for the diagnosis of Behçet’s disease that could be used in the future. These ISG criteria were published in 1990, considering diagnosis of Behçet’s disease when Recurrent oral ulcers plus 2 other features are present, in the absence of other clinical explanations. Criteria: Recurrent oral ulceration (Minor aphthous, Major aphthous, Herpetiform ulceration), Recurrent genital ulceration (Aphthous ulceration or scarring), Eye lesions (Anterior uveitis, Posterior uveitis, Cells in vitreous on slit lamp examination, Retinal vasculitis observed by ophthalmologist), Skin lesions (Erythema nodosum, Pseudofolliculitis, Papulopustular lesions, Acneiform nodules), Positive pathergy test (read at 24–48 h) [88] (Table 1).

7. Clinical activity

There are several assessment forms for measuring clinical activity, including the Iranian Behçet’s Disease Dynamic Activity Measure, the European Behçet’s Disease Current Activity Form and the one proposed by the Behçet’s Disease Research Committee of Japan [83,86].

8. Laboratory studies

There are no laboratory findings specific for BD. There may be an increase in inflammatory parameters, such as C-reactive protein, erythrocyte sedimentation rate, peripheral leucocytes and platelet counts during the active phase of the disease. Serum levels of several cytokines, including TNF-α, IFN-γ, IL-1β, IL-6 and IL-8, can also be elevated. Moderate anaemia of chronic disease can be present. Autoantibodies, such as the antinuclear antibodies and rheumatoid factor, are usually absent [3,34,89].

9. Differential diagnosis

It is of the utmost importance to collect a detailed clinical history as it can help exclude other conditions. A variety of diagnosis should be excluded, depending on the clinical presentation (Table 2).

10. Treatment

Main goals of treatment are relieving symptoms, achieving a rapid resolution of inflammation, preventing or limiting tissue damage, reducing frequency and severity of attacks, and avoiding complications [90].

The treatment used is determined by which organ(s) is (are) affected and the extension and severity of the involvement.
10.1. Corticosteroids

Corticosteroids are used in the treatment of ocular BD, gastrointestinal, neurological, cardiovascular involvements and mucocutaneous disease (topical treatment) [91]. Treatment is started with a high dose with subsequent tapering over several weeks as fast as clinical manifestations permit.

They can be used as topical therapy (ocular and mucocutaneous disease), periocular corticosteroids injections (ocular disease) and/or as systemic therapy (oral prednisolone (1 mg/kg/day)) or intravenous methylprednisolone pulses (1 g/day for 3 days) [3].

Despite successfully decreasing acute inflammation, corticosteroids alone often fail to prevent relapses, so they are frequently used in combination with other medications. Combined treatment is also used in order to diminish corticosteroid dose [3].

Side effects include elevated intraocular pressure, cataract, gastrointestinal ulceration, hypertension, diabetes mellitus, electrolyte abnormalities, osteoporosis, reduced resistance to infections and Cushingoid appearance [92,93].

In a recent double-blind study of low-dose depot corticosteroids vs placebo, low-dose depot corticosteroids (40 mg of methylprednisolone acetate administered as intramuscular injection, every 3 weeks) were not successful in the treatment of genital ulcers, oral lesions and folliculitis and arthritis; however, they were helpful in controlling erythema nodosum lesions, especially in female patients [94].

10.2. Colchicine

Colchicine is an anti-inflammatory plant alkaloid that inhibits neutrophil migration by interfering with microtubule formation [3]. It is effective in controlling cutaneous and articular involvement and is usually well tolerated in the dose of 1.0–2.0 mg/day [95].

Most common side effects are gastrointestinal (nausea, vomiting, diarrhea, abdominal pain). It can cause alopecia and bone marrow suppression, so blood count should be monitored in patients taking colchicine [96].

10.3. Alkylating agents (chlorambucil and cyclophosphamide)

Alkylating agents interfere with DNA replication, impairing lymphocytes proliferative response and functions. They have been used in combination with corticosteroids in the treatment of refractory eye disease and CNS involvement [3]. However, because of their dose-dependent side effects they should be reserved for cases refractory to other treatments [92].

A retrospective study of BD patients with refractory uveitis treated with short-term chlorambucil improved ocular involvement in 2/3 of cases and reduced the number of attacks [97].

Side effects include bone marrow suppression, hepatotoxicity, secondary malignancies, and infertility [34].

Current recommendations propose the use of cyclophosphamide when there is neurological or cardiovascular involvement [91].

10.4. Methotrexate

Methotrexate, a folate analogue, has been reported to be helpful in the treatment of CNS involvement, severe mucocutaneous disease and anterior uveitis [3,98].

They are effective in the treatment of most of BD features, especially refractory eye disease, although cyclosporine A is the most frequently used. Cyclosporine A used in combination with corticosteroid has a corticosteroid sparing effect, permitting the use of lower dosages [3].

Nevertheless, as they are cytostatic agents, disease may relapse as they are tapered or stopped.

Side effects include neurotoxicity, hepatotoxicity, nephrotoxicity, hypertension, hirsutism, paraesthesia, gastrointestinal manifestations, gingival hyperplasia [3].

10.5. Calcineurin inhibitors (cyclosporine A, tacrolimus)

Calcineurin inhibitors interfere with the activation and recruitment of T lymphocytes.

They are effective in the treatment of most of BD features, especially refractory eye disease, although cyclosporine A is the most frequently used. Cyclosporine A used in combination with corticosteroid has a corticosteroid sparing effect, permitting the use of lower dosages [3].

Nevertheless, as they are cytostatic agents, disease may relapse as they are tapered or stopped.

Side effects include neurotoxicity, hepatotoxicity, nephrotoxicity, hypertension, hirsutism, paraesthesia, gastrointestinal manifestations, gingival hyperplasia [3].

10.6. Azathioprine

Azathioprine is a pro-drug that is converted to 6-mercaptopurine which, in turn, is converted to 6-thioguanine (6-TG) nucleotides and inhibit purine ring synthesis and, consequently, DNA and RNA synthesis. It also inhibits the proliferation of T and B lymphocytes [99].

In controlled trials, it has been shown to decrease incidence, frequency and severity of eye disease, to have a positive effect on arthritis and mucocutaneous lesions and to improve the long-term prognosis of BD [100,101].

Side effects include gastrointestinal intolerance with anorexia, nausea and vomiting, bone marrow suppression, and infection [102].

10.7. Thalidomide

Thalidomide is a cyclic derivative of glutamic acid that has immunomodulatory properties, including diminished TNF production and activity and decreased neutrophil migration [103].

It is effective in oral and genital ulcers, papulopustular skin lesions, neurological and gastrointestinal involvement [3,103,104]. Due to its side effects it is not a first line therapy.

Side effects include teratogenicity, peripheral neuropathy, sedation, dizziness, headache, nausea, weight gain [105].

10.8. Sulfasalazine

Sulfasalazine has anti-inflammatory and immunosuppressive properties including inhibition of prostaglandin and leukotriene synthesis, free radical scavenging, immunosuppressive activity, impairment of white cell adhesion and function and inhibition of cytokine synthesis [106].

It has been used in patients with gastrointestinal involvement [34].

10.9. Dapsone

Dapsone is an anti-infective drug that also has anti-inflammatory properties and that, in a double-blind placebo-controlled study has shown to improve oral, genital and cutaneous lesions [3,107].

10.10. Pentoxyfilline

Pentoxyfilline inhibits the synthesis of several cytokines, including TNF-α and has been used in the treatment of oral and genital ulcers [108].

10.11. Interferon-α (IFN-α)

IFN-α is a naturally occurring cytokine that has immunomodulatory properties. It has been shown to reduce the number of circulating γδ-T cells, to increase human leukocyte antigen (HLA) 1
expression on peripheral monocytes from patients with BD and to inhibit T cell adhesion to endothelial cells in vitro [3,109].

It was first used in the treatment of BD due to its antiviral activity against herpes simplex virus type 1 [110].

Several studies have revealed high rates of response of ocular lesions. Frequency of arthritis, genital and papulopustular lesions and duration of oral ulcers are also diminished. There has also been improvement/resolution of neurological and vascular involvement [3,111–113]. Recently it was published a retrospective report of IFN-α use in 7 children with corticoid-dependent uveitis with clinical improvement, allowing corticosteroid dose reduction/suspension in 5 patients [28].

The doses of IFN-α used have ranged from 3 to 9 × 10^6 units 3 times a week; nevertheless, the optimum dosage and duration of interferon in the treatment of BD still needs to be determined.

Side effects include a flu-like illness at the start of the treatment, leucopenia, thrombocytopenia, alopecia, pruritus and depression. Autoantibodies production can also occur. Even so, IFN-α is usually well tolerated and side effects improve/disappear with dose tapering [112,113].

10.12. Anti-TNF-α therapies (infliximab, etanercept, adalimumab)

TNF-α is a fundamental cytokine in the establishment and maintenance of the inflammatory response. It is considered to be involved in BD pathogenesis based on several findings: higher levels of TNF-α have been found in the aqueous humour and serum of BD patients with uveitis; the number of TNF-α producing cells is increased in the active phases of the disease; TNF-α has been involved in experimental animal models of uveitis [110,112].

At present, there are 3 TNF-α inhibitors available: infliximab, a recombinant chimeric monoclonal antibody; adalimumab, a humanized monoclonal antibody; and the fusion protein human p75 TNF-α receptor IgG1 etanercept [110].

Infliximab reduces the frequency of uveitis attacks, is successful treating refractory macular oedema and improving visual acuity, especially in cases resistant to combination therapy with azathioprine, cyclosporine and corticosteroids and has a corticosteroid-sparing effect [114–119]. There are reports of its efficacy in refractory cases of mucocutaneous, gastrointestinal and CNS involvement, arthritis and one case of pulmonary aneurysms with life-threatening haemoptisis [78,130–139]. It has been administered as intravenous infusions of 5–10 mg/kg at weeks 0, 2, 6, 10 and afterwards every 6–8 weeks [78,130–139]. More studies are necessary to determine the optimal therapeutic scheme and combined use with other medications.

Etanercept has revealed a decrease of mucocutaneous features in a randomized, double-blind, controlled trial using 25 mg subcutaneously twice a week during 4 weeks vs placebo. There are reports of rapid improvement of mucocutaneous lesions and arthritis. Two children with BD uveitis were treated with etanercept, one with a favourable response and the other without. Estrach et al reported the case of a patient that failed to improve with etanercept but responded to infliximab [142–145].

Adalimumab has maintained disease remission in 3 patients with uveitis with no recurrence and stable visual acuities during the follow-up after being switched from infliximab to adalimumab [146]. In another report, 6 patients with refractory disease (2 with uveitis, 2 with CNS involvement, 1 with colitis and 1 with severe oral lesions and arthritis) were treated with adalimumab (with or without other immunosuppressive therapy) with clinical improvement [147].

The most common side effects are upper respiratory tract infection and headache. Autoantibody production, infusion reaction, rash, eczema, contact dermatitis and pruritus can also occur [148].

11. EULAR (European League Against Rheumatism) recommendations for treatment of BD 2008

Eye disease [91]
- Azathioprine and local and systemic corticosteroids

Refractory eye involvement
- Cyclosporine A or infliximab in combination with azathioprine and corticosteroids
- IFN-α alone or with corticosteroids

Major vessel disease
- Acute deep vein thrombosis: corticosteroids, azathioprine, cyclophosphamide or cyclosporine A
- Thrombosis of the vena cava and Budd–Chiari syndrome: cyclophosphamide
- Pulmonary and peripheral arterial aneurysms: cyclophosphamide and corticosteroids; surgery
- Anticoagulants, antiplatelet and antifibrinolytic agents are not recommended (pulmonary embolism is rare and there is the risk of major bleeding in case there are concomitant pulmonary aneurysms)

Gastrointestinal involvement
- Sulfasalazine, corticosteroids, azathioprine, TNF-α antagonists or thalidomide; surgery

Articular involvement
- Colchicine; IFN-α, azathioprine, TNF-α antagonists in resistant cases

Neurological involvement
- Parenchymal disease: corticosteroids, IFN-α, azathioprine, cyclophosphamide, methotrexate, TNF-α antagonists
- Dural sinus thrombosis: corticosteroids
- Cyclosporine should be avoided in case of neurological involvement due to neurotoxicity

Mucocutaneous involvement (oral, genital and skin lesions)
- Topical measures: corticosteroids preparations, lidocaine gel, chlorhexidine, sucralfate suspension
- Erythema nodosum: colchicine
- In resistant cases: azathioprine, IFN-α, TNF-α antagonists

12. Prognosis

BD has a variable course characterized by relapses and remissions. Prognosis depends on the clinical involvement. Loss of visual acuity and neurological disease are major causes of morbidity and disability.

Prognosis of BD improved in the last decade due to the use of modern immunosuppressant therapy and of a more aggressive treatment strategy [60–62].

The disease usually is more severe in males and in the Eastern and Mediterranean regions. The mortality rate in adult cases varies with series, the highest was reported in Turkey (9.8%) and is related to large vessel vasculitis causing sudden-death by aneurysm rupture or thrombosis [27,72].

Disease course usually gets better with the passage of time with decrease in mortality rate [3].
13. Future

Further investigation is needed on the various aspects of the etiopathogenesis of BD. Recently it was reported a case of a female patient with severe mucocutaneous BD and arthritis refractory to conventional therapy (corticosteroids, cyclosporine, azathioprine, methotrexate, colchicine) and infliximab that improved with anakinra, a IL-1 blocker [149]. So this biological agent may be an option in the future for treatment of refractory patients.

There is the need of further studies to determine efficacy of different therapeutic options in BD.

As mentioned in the pathogenesis, it has been hypothesized that cross-reactivity between microbial HSP65 and human HSP60 can trigger the disease in predisposed hosts by stimulating T cells and causing TNF-α production by various cell types. In an animal model (Lewis rats) uveitis induced by the human HSP60, could be inhibited with the HSP60 peptide linked to recombinant cholera toxin B (CTB) subunit [150]. After the promising results in this experimental study, the same strategy was used in a Phase I/II clinical trial by oral administration of HPS60 peptide (336–351)–CTB, 3 times weekly, followed by gradual withdrawal of all immunosuppressive drugs used to control the disease in 8 patients with BD. It was possible to withdraw immunosuppressive therapy in 5 of the patients without relapse of uveitis; 3 of these patients remained free of recurrence for 10–18 months after oral tolerization therapy stopped [151]. Efficacy of this therapy still needs to be confirmed in Phase III trials and randomized controlled studies, however, tolerization therapy seems to be promising in the management of BD [90].

14. Conflict of interest statement

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