Drugs of the Future 2009, 34(9): 749-763

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.9.1416391

CURRENT CONCEPTS IN THE TREATMENT OF ADAMANTIADES-BEHÇET'S DISEASE

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ABSTRACT

Adamantiades-Behçet's disease is a systemic vascular reaction/vasculitis of unknown etiology, which is characterized by periodically recurrent oral aphthous ulcers, genital ulcers, ocular inflammation that can be sight-threatening and various skin lesions, the most common of which are folliculitis and erythema nodosum. The disease can also affect a variety of other organs, including the central nervous system, the blood vessels and the gastrointestinal and respiratory tracts, leading to life-threatening complications. Early appropriate treatment is of major prognostic importance, should be based on both the type and the severity of lesions and focus on the most severe manifestation. This overview describes the present state of treatment regimens for Adamantiades-Behçet's disease. The number of randomized, controlled studies that have been conducted in this disease is limited. Topical sucralfate, rebamipide, colchicine, penicillin G benzathine plus colchicine, dapsone, thalidomide, azathioprine and interferon alfa have been found to be effective for orogenital ulcerations, whereas etanercept is used for oral ulcerations. Dapsone, thalidomide, interferon alfa and etanercept were shown to be effective against papulopustular lesions. Depot methylprednisolone, colchicine and penicillin G benzathine plus colchicine or dapsone were effective against erythema nodosum. Ciclosporin and azathioprine have shown a favorable effect on uveitis in randomized, controlled studies, while interferon alfa and tumor necrosis factor antagonists have revealed marked efficacy in retrospective studies or case series. Colchicine and azathioprine proved effective against arthritis. Finally, treatment options for vascular, neurological and gastrointestinal disease are based on open and observational studies or case reports. Properly designed controlled studies in Adamantiades-Behçet's disease are required in order to generate optimal treatment plans for acute/chronic management and prevention of recurrence.

INTRODUCTION

Adamantiades-Behçet's (ABD, also kown as Behçet's disease) is a systemic, chronic, relapsing vascular reaction/vasculitis (1) with recurrent oral and genital aphthous ulcers, skin lesions, uveitis and involvement of the gastrointestinal tract, central nervous system (CNS) and blood vessels (2). In 1930, Benediktos Adamantiades (1875-1962), a Greek ophthalmologist, presented for the first time the triad of ocular symptoms, oral aphthae and genital ulcers as clinical signs of a single nosological entity. Later, he added a fourth sign: vascular involvement. A Turkish dermatologist, Hulûsi Behçet (1889-1948), recognized Adamantiades' concept and dedicated his life's work to studying the disease. Both physicians agreed that the typical ocular lesion was uveitis with hypopyon, appearing at intervals and causing ocular lesions that could result in blindness (3).

The greatest prevalence of the disease worldwide is reported in Japan, the Middle East and the Mediterranean region. ABD is relatively uncommon in northern Europe and the U.S. (0.12-0.64 cases per 100,000) but is considerably more frequent in Korea, China and Japan (13.5-20 cases per 100,000) (4, 5). Turkey has the highest prevalence (80-420 cases per 100,000). The most frequent clinical manifestations in all countries are oral aphthae, genital ulcers, cutaneous and ocular manifestations, as well as arthropathy. ABD has a chronic course with unpredictable exacerbations and remissions, and often manifests itself in the third or fourth decade of life (4). Male sex, systemic onset and the presence of the B-51 HLA class I histocompatibility antigen have been reported to be associated with more severe disease (6, 7).

Diagnosis of ABD is difficult as there is no specific laboratory test; physicians often have to rule out several other conditions before

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Table I. *Criteria of the International Study Group for Adamantiades-Behçet's disease (1990).*

Mandatory symptom: recurrent oral aphthae (at least three times yearly)
Plus at least two of the following:
Genital ulcers
Ocular involvement
Skin changes (erythema nodosum, folliculitis, sterile pustules, aphthous skin ulcers)
Positive pathergy test

Table II. *Revised International Criteria for Adamantiades-Behçet's disease, traditional format (2008).*

Adamantiades-Behçet's disease: 3 or more points	Points
Recurrent oral aphthae	1
Skin manifestations (papulopustular lesions, erythema nodosum, thrombophlebitis)	1
Vessel involvement (arterial or venous thrombosis, aneurysms)	1
Positive pathergy test	1
Recurrent genital ulcers	2
Ocular involvement (hypopyon iritis, uveitis)	2

establishing the diagnosis. Delayed diagnosis and treatment of the disease can lead to increased morbidity and lethal outcome (8, 9). In 1990, the International Study Group for Behçet´s disease established diagnostic criteria, which were later only used as classification criteria, consisting of the presence of recurrent oral ulcers, relapsing at least three times in a 12-month period, plus two other signs (Table I) (10). Among several sets of diagnostic criteria, the most accurate are the recent Revised International Criteria, according to which three or more points are required for diagnosis (Table II) (2). Close monitoring and early tailored therapy are crucial in order to minimize the degree of disability and mortality in ABD.

This overview describes the present status of the treatment possibilities for ABD. Clinical sign-matched therapeutic recommendations, which are based on a comprehensive literature search for controlled studies, case reports and our own experience are provided.

THERAPEUTIC APPROACH FOR PATIENTS WITH ADAMANTIADES-BEHÇET'S DISEASE

Therapeutic management of ABD patients should be based on both the type and the severity of lesions and should focus on the most severe manifestation. Mild transient symptoms can be managed supportively. Anterior uveitis can be treated with topical corticosteroids, mydriatics or cycloplegic eye drops. Persistent or recurrent mucocutaneous lesions can be treated with topical nonsteroidal anti-inflammatory drugs and antiseptic agents, topical steroids and colchicine. It should be clear that local treatment has only local effects and the need for systemic therapy is postulated for severe mucocutaneous or systemic disease. Therapies for severe mucocutaneous and systemic ABD include systemic steroids, immunosuppressants such as ciclosporin, azathioprine, cyclophosphamide, chlorambucil and tumor necrosis factor α (TNF-α antagonists, dapsone, thalidomide and interferon alfa. Careful consideration of the risk–benefit balance is recommended for each individual patient. In younger males the disease is characterized by more severe symptoms, particularly ocular involvement and thrombosis, in addition to cardiac and pulmonary symptoms in German patients or gastrointestinal and neurological involvement in Turkish patients (4, 6, 9; data from the German Registry on Adamantiades-Behçet's Disease). The B-51 HLA class I histocompatibility antigen is associated with ocular manifestations (7). Patients exhibiting these risk factors require close monitoring and in principle more aggressive therapies. The activity spectrum of systemic agents used in ABD according to controlled studies or case reports is summarized in Table III. Favorable effects of drugs which have been assessed in randomized, controlled studies for use in ABD are shown in Table IV.

In addition to pharmacotherapy, physical therapy also helps patients with ABD to maintain strong and flexible joints. The treatment of ABD aims to reduce the frequency and intensity of flares, thus limiting morbidity and serious complications (8).

MUCOCUTANEOUS DISEASE

Recurrent, painful oral aphthous and genital ulcers together with cutaneous lesions are considered key features of ABD. Recurrent oral aphthous ulcers precede other manifestations in approximately 70% of the patients (8). It is important to exclude other possible causes or associated conditions, such as anemia, cyclic neutropenia, folic acid or iron deficiency, ulcus vulvae acutum, aphthous-like ulcerations in HIV-positive patients and gastrointestinal diseases such as Crohn's disease and ulcerative colitis.

Skin manifestations predominantly include papules and pustules, typically appearing with raised erythema and a dome-shaped pustule in the center, erythema nodosum-type lesions, pyoderma, skin ulcers and superficial thrombophlebitis. Severe complications of relapsing oral and genital ulcers include pharyngeal stenosis, scarring of deep vaginal ulcers, labial destruction, bladder or urethral fistulae, as well as vasculitic lesions, Sweet-like lesions, necrotizing vasculitis and pyoderma gangrenosum, causing severe morbidity (11).

In mucocutaneous disease, topical regimens acting symptomatically are essential but fail to prolong the disease-free intervals. Therefore, they should accompany systemic therapy in order to increase effectiveness.

Colchicine should be regarded as the first choice for the treatment of oral and genital aphthous ulcers and erythema nodosum-type lesions. Colchicine may be combined with pentoxifylline, penicillin G benzathine for resistant mucous lesions or short-term prednisolone in acute mucocutaneous exacerbation. Rebamipide is effective against oral aphthous ulcers only 3 months after the initiation of treatment. Dapsone and thalidomide are restricted to particularly resistant cases due to potential side effects. Azathioprine, ciclosporin, dapsone and interferon alfa have been proven to control mucocutaneous manifestations in controlled and open trials (Table IV) (12-15) and should be used in severe or refractory disease.

Table III. *Targeted sites of selected systemic agents used in ABD.*

	Oral aphthae	Genital ulcers	Skin manifestations	Ocular	Neurological	Vascular	Articular	Gastrointestinal
Corticosteroids	+	+	+**	+	+	+	+	+
Colchicine	+*	+*	+**	–	–	–	+*	–
Dapsone	+*	+*	+*	–	–	–	–	–
Ciclosporin	+	+	+	+*	–	+	–	–
Interferon alfa	+*	+*	+*°	+	+	+	+	–
Cyclophosphamide	+	+	+	+	+	+	–	–
Chlorambucil	+	+	+	+	+	+	–	–
Azathioprine	+*	+*	–	+	–	–	+*	+
Methotrexate	+	+	+	–	+	–	+	–
Infliximab	+	+	+	+	+	+	+	+
Etanercept	+	?‡	+	+	?‡	?‡	+	?‡

*Favorable effects assessed in randomized, placebo-controlled studies (**only erythema nodosum, *°only papulopustular lesions); ‡evaluation not conclusive given lacking studies.

Table IV. *Drugs with favorable effects assessed in randomized, placebo-controlled studies in ABD.*

Drug	Dose	Manifestation (favorable effect)	Comparison	Patients	Duration	Ref.
Sucralfate	3 times daily, topical	Oral and genital ulcers	Placebo	40	3 months	30
Methylprednisolone	40 mg/3 weeks i.m.	Erythema nodosum	Placebo	85 (50% women)	27 weeks	40
Colchicine	1-2 mg/day p.o.	Women: oral and genital ulcers, erythema nodosum Men: arthritis	Placebo	50 (48% women)	24 weeks	42
Penicillin G benzathine plus colchicine	Penicillin G benzathine 1.2 mL IU/month i.m. plus colchicine 1-1.5 mg/day p.o.	Oral and genital ulcers, erythema nodosum	Colchicine	154	24 months	46
Rebamipide	300 mg/day p.o.	Oral ulcers	Placebo	35	12-24 weeks	48
Dapsone	100 mg/day p.o.	Oral and genital ulcers, papulopustular lesions, erythema nodosum	Placebo	20	3 months	41
Thalidomide	100 or 300 mg/day p.o.	Oral and genital ulcers, papulopustular lesions	Placebo	96 (only men)	24 weeks	53
Azathioprine	2.5 mg/kg/day p.o.	Eye involvement, oral and genital ulcers, arthritis	Placebo	73 (only men)	2 years	56
Ciclosporin	10 mg/kg/day p.o.	Eye involvement	Colchicine	96	16 weeks	60
Interferon alfa	6 mL IU 3 times weekly s.c.	Oral and genital ulcers, papulopustular lesions	Placebo	50 (38% women)	3 months	65
Etanercept	25 mg 2 times weekly s.c.	Oral ulcers, papulopustular and nodular lesions	Placebo	40 (only men)	4 weeks	70

Administration of anti-TNF-α agents is not recommended in new mucocutaneous manifestations, but only as adjunct treatment in patients with vision-threatening inflammation, including patients with retinal vasculitis, in whom these agents often have a fast-onset therapeutic effect (15). Moreover, anti-TNF-α agents can be administered to patients with a poor quality of life or intolerance to adequate doses of other agents, such as azathioprine, colchicine or thalidomide, or to patients who require long-term prednisolone over a threshold dose that induces cushingoid status (7.5 mg/day).

Topical treatment of mucocutaneous manifestations

Most experiences in the local treatment of oral aphthosis are based on studies in recurrent aphthous stomatitis (RAS). Several studies were performed with significant results. As a rule, topical measures should be the first-line treatment for isolated oral and genital ulcers. Application should depend on the patient's personal experience and preference. The combination of a steroid paste at night, an anesthetic gel and an antiseptic mouth rinse repeatedly during the day, accompanied by general measures, is commonly recommended. For acne-like lesions, folliculitis and perifolliculitis in ABD, several topical treatments have proven suitable according to clinical experience, although they have not been tested in controlled studies: 1) clindamycin 1%/benzoyl peroxide 1% gel for acne vulgaris; 2) a cream formulation of a mild steroid and an antiseptic such as hydrocortisone 1%/chlorhexidine 1% for inflammatory lesions on the face; and 3) flumethasone 0.02%/clioquinol 3% for lesions on the body (12, 16). Erythema nodosum-type lesions are locally treated like erythema nodosum of other etiology and often require additional systemic therapy in case of multilocular and recurrent lesions.

Dietary and general measures

Triggering of new aphthae eruption and persistence of lesions can be prevented by avoiding hard, acidic, salty or spicy foods, as well as nuts, nut chocolate, citrus fruits, alcoholic and carbonated beverages or hard toothbrushes (individual cases without validation in controlled studies) (17). In a single-blind, crossover trial, as well as in open studies, the number and frequency of aphthae were reduced by using a lauryl sulfate-free toothpaste (18, 19). Protective bioadhesives with formulations of 2-octylcyanoacrylate reduced pain and healing time of recurrent oral aphthous ulcers in a controlled, randomized, single-blind study. The significant pain relief that tissue adhesives provide should be taken into account. They are available as nonprescription over-the-counter devices (20).

Local anesthetics

Topical analgesics such as lidocaine hydrochloride 2% gel (Dynexan® mouth gel, Gelicaine® 2% gel, Xylocaine® 2% gel) or spray (Xylocaine® pump spray), polidocanol adhesive dental paste (Solcoseryl™) or benzocaine lozenges (Anaesthesin® or Dolo-Dobendan® lozenges) can attenuate pain clinically, but data from clinical trials of these agents are very limited. A variety of other local anesthetics are available, including combination sprays of tetracaine hydrochloride and polidocanol, or benzocaine and cetylpyridinium chloride in mouthwashes. Lidocaine 2% viscous solution can be carefully applied directly on the lesions and reduces acute pain, but its analgesic effect diminishes over a few hours (21). This short and weak effect can be explained by the solution's short time of contact and its basic pH, which does not allow lidocaine to dissociate into its active form in the inflamed tissue.

Antiseptic and anti-inflammatory therapies

Patients with recurrent aphthous ulcerations may benefit from triclosan, chlorhexidine or chamomile mouth rinses. Available examples are triclosan in Breeze™ mouthwash, chlorhexidine in mouthwashes like Corsodyl™ solution, chlorhexamide fluid or chamomile extract in Kamillosan® solution. Triclosan is an antibacterial agent with antiseptic, anti-inflammatory and analgesic effects. In a double-blind, crossover study 30 patients with a history of RAS were treated with mouth rinses containing triclosan 0.15% twice daily for 30 s (22). These patients experienced a significant decrease in the number of new lesions and pain relief. Patients using chlorhexidine gluconate 0.2% mouthwash three times daily had significantly longer ulcer-free periods than patients receiving placebo (23). Chamomile extract solution (Kamillosan®) as a mouth rinse mildly inhibits inflammation. A recent study investigated the analgesic effect of *Chamomilla recutita* in RAS patients; its analgesic effect was excellent in 82% and good in 18% of patients (24). After the application of diclofenac sodium 3% in hyaluronan 2.5%, a significant reduction in pain lasting up to 8 h was reported in a randomized, double-blind study (21).

Topical steroids

Although controlled studies are not available, topical steroids such as triamcinolone acetonide 0.1% in Orabase® (Kenalog® in Orabase®) and prednisolone acetate 0.5% in mouth ulcer-healing paste (Dontisolon® D) twice daily are the most commonly used therapeutic regimens with a satisfactory effect. Additionally, a therapeutic benefit can be obtained from a mouthwash containing betamethasone 0.05% (Celestamine® N 0.5 liquid). Physicians should always keep in mind the fact that long-term steroid use may predispose to local *Candida* infections. For satisfactory results, combination treatment with a topical anesthetic during the day and a steroid paste at night is appropriate according to our clinical experience. For the treatment of genital and extragenital ulcers in ABD, experience has shown that a combination of fluorinated steroids and antiseptics formulated in a cream base is effective (e.g., dexamethasone 0.1% + chlorhexidine hydrochloride 1% or flumethasone 0.02% + clioquinol 3%). An intralesional injection of triamcinolone acetonide 10 mg/mL (Volon® A 10) is indicated only in painful, deep, single oral or genital aphthous ulcers (0.1-0.5 mL per lesion) (17).

Antibiotics

Tetracyclines not only exhibit antibacterial properties but also inhibit matrix metalloproteinases (MMP), which contribute to the inflammatory process by promoting the breakdown of tissues and were shown to exhibit increased activity in recurrent aphthous ulcers. As a consequence, tetracyclines could stimulate the growth of mucosal cells and rapid healing of ulcers. Localized therapy with tetracycline solution effectively reduced pain, size and duration of oral aphthae by 5% in a single-blind, randomized study (25). Tetracycline

hydrochloride may either be dissolved as a powder (250 mg) in 5 mL of water immediately before application, or a chemically stabilized standard formula can be prescribed. In a double-blind, crossover study in RAS, the pain-relieving and duration-shortening effect of a mouth rinse containing chlortetracycline (Aureomycin®) was reported (26). Topical minocycline hydrochloride 2% in aqueous solution as a mouthwash four times daily for 1 min appeared to be superior to tetracycline hydrochloride 2.5% in aqueous solution for the treatment of pain and the duration of RAS in a small single-blind, crossover study (27). Finally, doxycycline, the most potent inhibitor of MMP-2 and MMP-9 among tetracyclines, was tested in a 1.5% hydrogel formulation four times daily in a randomized, double-blind, placebo-controlled trial involving 49 patients with RAS. Treatment with doxycycline resulted in healing of 65% of ulcers within 3 days, whereas only 25% of these lesions were cured in the placebo group (28). Therapy with tetracyclines is contraindicated in pregnancy due to teratogenic effects and in children up to 8 years of age due to their effect on teeth appearance.

Sucralfate

Sucralfate is an antacid commonly used to treat peptic ulcers. It exerts a soothing effect on lesions by adhering to mucous membrane tissues and forming a protective barrier on the affected site. Rattan et al. showed significant therapeutic value for sucralfate solution, applied four times daily, with regards to healing time and pain in RAS patients in a prospective, double-blind, placebo-controlled, crossover trial with a follow-up of 2 years (29). Alpsoy et al. showed a reduction in mean frequency, healing time and pain of oral ulceration, as well as healing time and pain of genital ulcerations, in ABD patients (30). For the treatment of ulcerations in the throat or pharynx, sucralfate can be swallowed. Sucralfate use should be limited in cases of renal insufficiency.

Local cauterization with a 1-2% silver nitrate solution or a silver nitrate caustic stick reduced the pain of solitary aphthae in a randomized, single-blind, placebo-controlled trial and several case reports (31). As a complication of this classical therapeutic method, long-term extensive application of silver nitrate may result in argyrosis, with blue–grey discoloration of the skin and mucous membranes (32).

Other alternative methods involve the application of 5-aminosalicylic acid 5% cream three times daily, which significantly reduced pain and healing time in a small, double-blind, placebo-controlled study (33). A significant decrease in the number of new aphthous ulcers and pain was also observed in a Swedish double-blind, crossover study testing the effect of a mouth rinse containing amyloglucosidase and glucose oxidase in children. The solution was freshly prepared (0.5 g of a powder containing amyloglucosidase 4%, glucose oxidase 0.16% and lactoperoxidase in 10 mL water) and the mouth was rinsed twice daily for 1 min (34). Nonetheless, in a study of Zendium® toothpaste, which also contains the enzymes amyloglucosidase and glucose oxidase, no statistically significant improvement could be detected (26). Low-concentration prostaglandin E_2 (PGE_2) 0.6% gel applied twice daily in amounts of 0.5 g on the lesions significantly prevented new aphthae and consequently may have a prophylactic effect, whereas reduction of pain and healing time did not reach statistical significance in a short, 10-day, single-phase, double-blind, placebo-controlled trial (35).

According to several patients' experience, application of raw egg whites may at least partially relieve oral pain. An interesting finding in patients with recurrent oral ulceration is that they mention a reduction of oral aphthae during periods of smoking compared to phases of abstinence. In laboratory tests, biochanin A alone and in combination with nicotine resulted in decreased secretion of interleukins IL-8 and IL-6 and vascular endothelial growth factor (VEGF) by human keratinocytes and dermal microvascular endothelial cells, supporting an anti-inflammatory effect. For this reason, biochanin A alone or in combination with nicotine could play a significant role in the topical management of aphthae in the future. Moreover, the possible development of topical nicotinic acetylcholine receptor subtype-specific agonists could be an alternative for the treatment of skin and mucosal lesions that avoids systemic adverse effects (36, 37). Last but not least, a study conducted in three patients showed remission of aphthosis during therapy with chewable nicotine tablets (38).

Systemic treatment of mucocutaneous manifestations

Systemic corticosteroids

Although systemic corticosteroids are used very successfully as anti-inflammatory agents in several ABD manifestations, such as mucocutaneous, ocular, arthritic, neurological, neuropsychiatric, gastrointestinal, pulmonary or renal symptoms, controlled studies are lacking and the long-term use of these agents is limited due to their side effects. Despite the short-term rescue value of high-dose systemic steroids, they apparently neither prevent the occurrence of new lesions nor improve the long-term prognosis of ABD. Consequently, gradual tapering according to clinical and laboratory inflammation parameters is advisable and finally discontinuation should be attempted. In most cases, however, systemic steroids are used in combination with other immunosuppressants. Steroids are some of the few systemically administered drugs that can be used during pregnancy. In cases of exacerbation of orogenital ulcerations, prednisolone 10-30 mg/day or its equivalent for up to 1 month may be administered to patients who have responded inadequately to therapy with colchicine and pentoxifylline. Based on our experience, i.v. pulse therapy with 100 mg/day for 3 days results in rapid improvement in severe cases of oral aphthous ulcers without the side effects associated with long-term prednisolone use (39). The only reported long-term double-blind study detected a reduction of erythema nodosum lesions in the corticosteroid group receiving i.m. depot methylprednisolone 40 mg every 3 weeks (40).

Colchicine and dapsone

Both substances inhibit neutrophil chemotaxis. Colchicine 1.0-2.0 mg/day and dapsone 100-150 mg/day (intermittent administration of ascorbic acid and reduction of smoking are useful in preventing hematological side effects) can be used for oral and genital aphthae and erythema nodosum, whereas colchicine can be used for arthritis in ABD. Moreover, dapsone significantly decreased papulopustular lesions in a randomized, controlled, double-blind study (41), whereas colchicine did not (42). However, no effect of dapsone on arthritis was shown in comparison with colchicine. A favorable effect on pyoderma gangrenosum-like lesions was also reported for dapsone (43).

Treatment with colchicine reduced the number and duration of lesions in up to 63% of RAS patients in an open trial and smaller studies also confirmed its efficacy (44). Therapy with a colchicine-containing suspension (1-2 mg/day) over at least 4-6 weeks and subsequent long-term therapy, eventually over years depending on treatment tolerability and effectiveness, is recommended. Relapses of aphthous ulcers after withdrawal of colchicine are common and a reinitiation of colchicine treatment does not guarantee a similar success. Contraception should be used by women for 3 months and by men for up to 6 months after cessation of colchicine therapy. From our experience, a combination therapy of colchicine and pentoxifylline, penicillin G benzathine or interferon alfa is possible and could support the effect on mucocutaneous and aphthous lesions. However, colchicine may induce serious side effects, such as acute leukopenia in patients concurrently treated with azathioprine or methotrexate (45). The combination of colchicine (1-1.5 mg/day p.o.) and penicillin G benzathine (1.2 million IU i.m. every 3 weeks or monthly) was tested in open and controlled studies. The effect of the combined therapy was significantly stronger on genital ulcers and erythema nodosum, but both colchicine and penicillin G benzathine also reduced the manifestation index when used alone (46, 47). According to the recommendations of the New European League Against Rheumatism (EULAR), colchicine should be preferred when the dominant lesion is erythema nodosum (16).

Rebamipide

Rebamipide, an amino acid derivative of 2(1*H*)-quinolinone, is used for gastroduodenal ulcers and for the treatment of gastritis. It works by enhancing mucosal defense, scavenging free radicals and temporarily activating the gene encoding cyclooxygenase-2. In a double-blind, placebo-controlled study in ABD patients, the number of oral aphthae and pain were significantly decreased in the rebamipide group after 3 months of treatment (300 mg/day) (48), and rebamipide was well tolerated.

Pentoxifylline

Pentoxifylline has a suppressive effect on $CD8^+$ T cells and inhibits the production of various proinflammatory cytokines, such as TNF-α. Pentoxifylline (400 mg 2-3 times daily) showed satisfactory efficacy, improving orogenital symptoms of ABD, in an uncontrolled open-label study and several case reports (49, 50), but did not cause statistically significant improvement of RAS in a randomized, double-blind, placebo-controlled study, except for a reduction in the median ulcer size (51). Although its benefit is limited, pentoxifylline could be considered as a therapy with few side effects, e.g., in children or resistant cases with orogenital symptoms.

Thalidomide

Thalidomide is effective against orogenital and intestinal ulcerations. In a recent study it was well tolerated and effective in eight RAS patients who were administered 100 mg/day for a mean time of 4.8 months (52). In the only randomized, double-blind, placebo-controlled trial of the agent conducted in ABD patients, thalidomide decreased orogenital aphthosis and follicular lesions, while the number of erythema nodosum lesions increased (53). However, in older open and retrospective studies, initial doses of 100-300 mg/day were finally reduced to 50 mg/day or discontinued after 3 months in order to avoid sensory neuropathy. Re-treatment with 50-100 mg/day for a week in the event of a relapse is possible (54, 55). Due to the compound's teratogenicity, it is absolutely contraindicated in pregnancy. In our opinion, thalidomide should only be used in exceptional cases.

Antimetabolites (azathioprine and methotrexate)

Favorable effects have been described on severe oral and genital aphthosis (reduction of frequency and extent) with azathioprine at a dose of 2.5 mg/kg/day, as well as improvement of arthritis and long-term prognosis of eye involvement in ABD patients in a randomized, placebo-controlled trial (56, 57). Azathioprine could not improve papulopustular lesions. The product is contraindicated in pregnancy and breastfeeding and it is not recommended for use in pediatric patients.

Methotrexate (7.5-20 mg/week) has been reported to be effective on orogenital aphthosis and also on cutaneous pustular vasculitis in case series only (45, 58). Due to its spectrum of activity and according to our clinical experience, methotrexate is effective against arthritis. Folic acid should be administered concurrent with methotrexate treatment, and blood cell counts and liver function should be monitored during therapy with azathioprine or methotrexate.

Calcineurin inhibitors (ciclosporin)

The primary effect of ciclosporin is inhibition of T-lymphocyte activation and recruitment. The compound resulted in partial or complete remission of mucocutaneous symptoms in 120 of 142 (85%) ABD patients in several trials conducted since 1983, either as monotherapy or in combination with steroids to increase its anti-inflammatory effect (14). Positive results are reported on aphthous ulcers in about 70% of patients and on cutaneous symptoms in about 40% of subjects in randomized, double-blind studies using different doses (3-6 mg/kg). Initially, doses of up to 10 mg/kg/day were used and a low maintenance dose of 2 mg/kg/day could suppress mucocutaneous symptoms (59, 60). Rapid dose reduction or abrupt withdrawal can lead to rebound phenomena. Its use is absolutely contraindicated in breastfeeding women, and pregnancy and renal insufficiency are considered relative contraindications.

Alkylating agents (chlorambucil and cyclophosphamide)

An alternative compound with efficacy in ABD patients with neurological, vascular and ocular symptoms is chlorambucil (5-12 mg/day p.o. and 2 mg/day as maintenance dose) (61). It is a slow-acting alkylating agent, interferes with DNA replication by cross-linking and causes decreased B- and T-cell function. The efficacy of chlorambucil against orogenital aphthae and skin manifestations was only demonstrated in case series (62). Physicians should be aware of its cumulative toxicity and possible dyscrasia. Cyclophosphamide, a fast-acting alkylating agent, also caused marked improvement in orogenital aphthae in severe cases of ABD (63). However, dose-dependent adverse effects such as pulmonary fibrosis and hemorrhagic cystitis limit its use.

Interferon alfa-2a and -b

In numerous open, prospective studies and case series, summarized in several review articles, a significant recovery or complete remis-

sion of oral and genital ulcers, as well as skin symptoms (papulopustular lesions, erythema nodosum), was reported with interferon alfa therapy, with satisfactory improvement observed within 1-4 months (13, 64). Interferon alfa-2a (6 mL IU s.c. 3 times weekly) significantly decreased pain, the duration of oral aphthous ulcers and the frequency of genital ulcers and papulopustular lesions in a randomized, placebo-controlled, double-blind study in BD patients (65). Interferon alfa-2b (3 mL IU s.c. every other day) plus colchicine (1.5 mg/day p.o.) was more effective than colchicine plus penicillin G benzathine (1.2 mL IU i.m. every 3 weeks) in a randomized trial (66). Interferon alfa also represents an effective treatment in BD patients with arthritis and vascular involvement. Our recommended dose is 6-9 mL IU interferon alfa-2a or -b three times weekly for 6 months followed by 3 mL IU s.c. three times weekly for long-term treatment. In patients with ocular manifestations, better results are expected with interferon alfa-2a treatment (17, 67).

Biologic agents (infliximab, etanercept and adalimumab)

Apart from its role in ocular involvement, infliximab, a chimeric anti-TNF-α monoclonal antibody, was rapidly effective in oral and genital ulcers and/or arthritis in the majority of BD patients in self-controlled studies and many case reports. Rapid improvement of severe uveitis, gastrointestinal manifestations, severe mucocutaneous symptoms and cerebral vasculitis has been reported in cases refractory to conventional immunosuppressants. A few days following the first dose a rapid response can be observed, even in patients with refractory recurrent disease with both oral and genital manifestations, without evidence of recurrence for 6-8 weeks (68, 69).

Etanercept (25 mg s.c. twice weekly), a dimeric fusion protein of the human p80 TNF-α receptor and the Fc portion of human immunoglobulin gamma, appeared to be highly effective against oral aphthae, papulopustular and nodular skin lesions but did not show statistically significant efficacy on genital aphthae or arthritis in a 4-week, randomized, double-blind, placebo-controlled trial in BD and in case reports with RAS (70, 71). These effects were described at the end of the first week. Improvement of mucocutaneous symptoms with infliximab after failure of treatment with etanercept was mentioned in a single case report.

Infliximab and etanercept are recommended by experts for mucocutaneous manifestations in patients with poor quality of life, resistance or intolerance to adequate doses of azathioprine, colchicine or thalidomide and requiring prednisolone at a dose > 7.5 mg/day for up to 2 years or as add-on therapy. Infliximab infusions (5 mg/kg) initially at weeks 0, 2 and 4 and maintenance therapy every 6-8 weeks or etanercept 25 mg twice weekly are possible (15).

Finally, adalimumab, a fully human monoclonal anti-TNF-α antibody, induced complete remission in two resistant cases of RAS already after the first injection (40 mg s.c. every other week) (72, 73). Due to a lack of larger studies of the long-term course and adverse effects (e.g., infections, autoimmune reactions, delayed hypersensitivity reactions, neurological and cardiac symptoms), the use of anti-TNF-α agents is limited.

OCULAR INVOLVEMENT

Relapsing ocular involvement is one of the major manifestations in BD and can be seen in 60-80% of patients (74, 75). It is characterized by iritis, uveitis, occlusive retinal vasculitis and optic nerve neuropathy, all of which lead to blindness in up to 50% of patients within 5 years if left untreated (76, 77). Ocular involvement occurred in 79 of 140 patients (56%) in Berlin (78). Thus, ocular involvement in Berlin is comparable to that found elsewhere and is within the range reported in other publications (79, 80). In our studies, ocular involvement was bilateral in 58 patients (73.4%) and unilateral in 21 (26.6%), comparable to the results of other studies, which showed 78-95% bilateral involvement. The mean age at the onset of ocular involvement is 29.8 years in Germany (78), which is comparable to the mean onset age of 28 years reported in Turkey by Tugal-Tutkun et al. (80). The rate of ocular involvement as the first manifestation ranges from 0.5% to 18% and was 8.6% in patients from Berlin (78). Evidence demonstrates that all ocular structures are involved at the onset of the disease. Hypopyon is not pathognomonic for BD and was very rare in the series from Turkey (80) and Germany (78, 81) with an incidence of < 1%. Ocular involvement of BD is a vasculitis involving the posterior more than the anterior part of the eye. One explanation for the low incidence of hypopyon nowadays might be early diagnosis and prompt treatment.

Visual prognosis is important in long-term follow-up and various studies still consider BD to be a severe risk factor for blindness. The natural course of the disease is characterized by a poor long-term visual prognosis and a loss of useful vision (i.e., visual acuity of < 0.1) in most eyes. A visual acuity of < 0.1 was reported in 21-53% of study patients in Spain (82), Turkey (80), Taiwan (83) and Japan (84). In our series of 136 involved eyes, 21% had a final visual acuity of < 0.1 at the end of the follow-up (78). Our data showed that the overall male-to-female ratio was 1:0.82 and there was no statistically significant difference among the different nations.

Treatment

Mild attacks of anterior uveitis are treated with topical ophthalmic drops and ointments of corticosteroid agents 3-6 times a day. In severe cases, administration should initially be more frequent. After several days, the frequency of instillation is reduced. Nonsteroidal anti-inflammatory drugs allow reduction of the corticosteroid dose and are useful in cases where corticosteroids are contraindicated.

Ciclosporin combined with systemic corticosteroids is the treatment of choice for ocular BD, but this can cause severe side effects, such as Cushing's syndrome, osteoporosis or renal failure. In Germany, ciclosporin is officially approved for prescription and paid by public health insurance for the treatment of uveitis. Other drugs such as azathioprine, cyclophosphamide or chlorambucil are also used but often do not act rapidly enough or have not yet been studied in detail. Nevertheless, according to the EULAR recommendations, azathioprine, initially in combination with corticosteroids, has been suggested for ocular involvement and has also been discussed as a long-term therapy to avoid ocular recurrences. In severe or refractory cases, ciclosporin or infliximab in combination with azathioprine and corticosteroids, or alternatively interferon alfa with or without corticosteroids, has been recommended (16). Colchicine is much less effective for posterior uveitis.

Corticosteroids

Topically applied eye drops reach the posterior segment poorly and therefore do not achieve therapeutic concentrations in the posterior

segment of the eye. Periocular injections of steroids are useful in cases of acute attacks of mild posterior uveitis, intermediate uveitis, vitritis and cytoid macular edema, especially in unilateral cases.

Acute and severe inflammation in anterior, posterior or panuveitis, as well as retinal vasculitis, should be treated with higher doses of systemic steroids because of the rapid response and this is the treatment of choice in the acute phase of the disease. Oral prednisolone (1-2 mg/kg/day) or i.v. methylprednisolone pulse therapy (1 g/day) is preferred in cases with posterior involvement or in bilateral cases, in addition to calcineurin inhibitors or other immunosuppressants for steroid-sparing purposes. After remission of the disease has been obtained, the dose is gradually tapered to the maintenance dose of 15-20 mg/day. Although oral corticosteroid monotherapy has a palliative effect on ocular attacks, long-term treatment should be avoided because of the side effects (85, 86).

Ciclosporin

Ciclosporin 2-10 mg/kg/day in two divided doses is the treatment of choice (14, 59). It was shown to be effective in about 70-80% of cases with severe uveitis resistant to conservative therapy with colchicine, corticosteroids and azathioprine. Ciclosporin and steroids are the most rapidly-acting agents for acute uveitis. The long-term use of ciclosporin is limited by the development of neurological side effects, hirsutism, gingival hyperplasia, gastrointestinal disturbances and hypertension. Ciclosporin-related nephrotoxicity occurs in about 75% of cases, representing a very serious complication. Therefore, blood levels have to be maintained between 50 and 150 ng/mL. During treatment with ciclosporin, renal function and blood pressure should be monitored carefully (75, 87).

Azathioprine

Azathioprine (2.5 mg/kg/day p.o.) reduced the incidence, frequency and severity of ocular disease when compared with placebo in a large, randomized, placebo-controlled trial (56, 88).

Alkylating agents (chlorambucil and cyclophosphamide)

Chlorambucil is gradually increased to a total dose of 5-12 mg/day (or 0.1-0.2 mg/kg/day) if there is no idiosyncratic reaction. It is used in combination with corticosteroids, improving the long-term visual prognosis (89, 90).

Cyclophosphamide is more toxic than chlorambucil and should be reserved for very refractory sight-threatening cases. At a dose of 2 mg/kg/day or as a pulsed i.v. injection (200 mg/week) combined with prednisolone (10-15 mg/day) cyclophosphamide may be used to treat retinal vasculitis in ocular ABD. This medication has not yet been studied in detail and has severe side effects, such as pulmonary fibrosis, renal toxicity and hemorrhagic cystitis (91).

Interferon alfa

Interferon alfa therapy has been used to treat mucocutaneous ABD for over 10 years (13, 65). Although patients with ocular involvement were initially excluded, high response rates have been reported in case series and noncontrolled studies (13). Recent reports suggest that interferon alfa is also effective in ocular ABD and our data confirm this impressive effect (13, 67, 92-97).

In 2004, Deuter et al. (95) published the results of a 5-year follow-up study. A visual acuity of < 0.1 was seen in 40% of all eyes at the initiation of treatment and in only 13.3% after a mean treatment duration of 40.6 months. During a 5-year follow-up, visual acuity remained stable in 33% (n = 5) of the eyes and improved in 66.6% (n = 10). In a series published by Kötter et al. (92), only 12% of the patients had recurrences under therapy and visual acuity showed a mean 2-line improvement after a treatment duration of 24 months. Visual acuity remained stable in 22% of the eyes, improved in 75% and deteriorated in 2.7%. In a study by Krause et al. (67) three eyes had anacrusis at the beginning and seven (7%) still had a visual acuity of 0.1. In a study conducted in Turkey, more than 90% of the treated eyes showed improved visual acuity and additional steroid therapy could be stopped in 46% of them (96). Bodaghi et al. (97) reported that in a series of 23 patients receiving interferon alfa for ocular ABD, 76.3% had stable or improved visual acuity. The mean steroid dose could be tapered from 20.8 mg/day to 9.7 mg/day. In 52.6% of the patients reported by Krause et al. (67) interferon alfa treatment could be discontinued, whereas 40% of these patients developed recurrences. These encouraging results with interferon alfa in ABD led to the use of this treatment modality in other forms of chronic uveitis, but with less efficacy.

In the study by Krause et al. (67), 92% of all eyes showed stable or improved visual acuity in the long-term follow-up. A visual acuity of < 0.1 was found in 28% of all eyes at the beginning but in only 19.7% at the end of therapy. Visual acuity remained stable in 61% of eyes, improved in 30% and deteriorated by > 2 lines in only 9% of all eyes. While an improvement in visual acuity was achieved in one-third of the affected eyes in that study, Deuter et al. (95) reported improvement in 66% of the affected eyes and Tugal-Tutkun et al. (96) in 95% of eyes. This may be partly due to the fact that Krause et al. started treatment early and found an initial visual acuity of < 0.1 in only 28% of all eyes as opposed to the 40% reported by Deuter et al. Most of the patients had stable visual acuity in the long-term follow-up (67).

In contrast to reports on the natural disease course or on other treatment regimens that show a poor long-term visual prognosis and a loss of useful vision (i.e., visual acuity < 0.1) in most eyes, the results with interferon alfa demonstrate remarkable efficacy in ocular ABD. A visual acuity of < 0.1 was reported for 24% (n = 4) of the patients in a study conducted in Spain by Torres et al. (82), for about 41% (n = 647) of the evaluated eyes in a trial conducted in Turkey by Tugal-Tutkun et al. (80), for about 53% (n = 103) of patients in a study conducted in Taiwan by Chung et al. (83) and for 21-49% (n = 128) of the patients in a study conducted in Japan by Yoshida et al. (84). In a long-term follow-up of 15 eyes, Deuter et al. (95) found that about 13.3% of their patients had a final visual acuity of < 0.1 with interferon alfa therapy. Krause et al. (67) reported that only 9% of the affected eyes had deteriorated visual acuity, whereas 19% had a final visual acuity of < 0.1. Thus, 81% of all affected eyes had useful vision (visual acuity > 0.1) at the end of follow-up.

In contrast to all other immunosuppressants used to treat ocular ABD, interferon alfa has tolerable and reversible side effects, especially when compared with those of TNF-α antagonists. The development of autoimmune phenomena should be particularly monitored. Special considerations have to be taken into account in patients with depression and psychosis. These patients should not

be given interferon alfa or must be treated under psychiatric cotherapy and supervision due to the risk of suicide. Side effects such as infections or secondary malignancies are rare.

The major advantage of interferon alfa compared to all other drugs is the possibility of discontinuing treatment without a high rate of recurrences. Another very important fact is that in nearly all cases steroid treatment can be reduced or stopped (67). This was also shown in the studies by Kötter et al. (92) and Deuter et al. (95).

Biologic agents

Several patients with ocular ABD described in the literature have been treated with TNF-α antagonists. Infliximab is an effective and fast-acting medication for the treatment of ocular ABD, but it is only recommended for use in selected patients with severe disease, balancing the efficacy and the possible side effects (15, 98, 99). In particular, patients with recurrent posterior uveitis, active CNS disease, intestinal inflammation, arthritic or mucocutaneous manifestations with reduced quality of life are eligible for treatment with TNF-α antagonists. In addition, these agents may be administered as add-on therapy in patients refractory to traditional treatment. It is also possible to use the impressive fast-acting effect as a single shot with a single infusion of infliximab for acute posterior uveitis (15) and for long-term therapy in those patients with uncontrolled recurrences despite treatment with ciclosporin or azathioprine at an infliximab dose of 5 mg/kg every 6-8 weeks for a duration of 2 years.

Intraocular surgery

ABD still remains a risk factor for blindness. The risk of losing useful vision (i.e., visual acuity < 0.1) was 20% in the study by Krause et al. (67) and differs worldwide, ranging to up to 75%. Retinal detachment and secondary glaucoma are severe complications of occlusive retinal vasculitis. More than half of the eyes will develop complications in follow-up due to the chronic and recurrent course of the disease. As in other types of intraocular inflammation, cataract formation is the most frequent complication in about 37% of eyes. Another major cause of deteriorated vision is chorioretinal inflammation and scar formation in 36% of eyes. Retinal vessel occlusion can be detected in 29%, maculopathy in 27% and opticopathy is found in about 23% of eyes. Secondary glaucoma varies widely over the range of 1-43% in the literature (77, 81, 100, 101).

Recurrent uveitis with occlusive vasculitis can cause tractional retinal detachment and/or painful secondary glaucoma, conditions which often result in phthisis bulbi or even enucleation. Some advanced cases with retinal detachment and secondary cataracts or glaucoma require surgery. However, surgical manipulation of the eyes of patients with ABD often involves relapsed inflammation (93, 102, 103). A favorable outcome of ocular surgery in cases of severe eye involvement can be achieved as described previously (103). Other case series describe posterior or anterior synechia in 26% of eyes (104). Kadayifcilar et al. (105) reported fibrinous reactions in 13%, pupillary membranes in 6% and posterior synechia in 18% of eyes. Matsuo et al. (106) reported uveitis attacks in 25% of cases following surgery and Barker et al. (107) found severe inflammation following surgery in 13% of eyes and posterior synechia in 18%.

NEUROLOGICAL INVOLVEMENT

The systemic vasculitis of ABD attacks several parts of the peripheral nervous system and more often the CNS. First described by Kummer in 1930 (3), in many studies and case reports the overall frequency of neurological ABD ranges from 2% to 50% (4, 74, 108, 109). About 11% of patients with neurological ABD have been reported to the German Registry on Adamantiades-Behçet's disease (4, 110). Neurological involvement usually manifests 4-6 years after the onset of ABD, but rarely as a first clinical sign (25, 111, 112).

Neurological involvement can be divided into parenchymal and non-parenchymal involvement. The main parenchymal inflammatory lesions are localized in the brainstem, the basal ganglia, the paraventricular hemispheres and the spinal cord. The distribution of these lesions leads to neurological signs such as cranial nerve palsy, ocular motor dysfunction, loss of sensory and motor tract function, incontinence, nystagmus, ataxia, speech impairment, movement disorders and other signs (108, 109, 111, 114). Headache, a reduced level of consciousness and seizures are the predominant symptoms of aseptic meningoencephalitis, another important presentation of neurological ABD (111).

Nonparenchymal involvement includes dural sinus thrombosis, intracranial hypertension, arterial occlusion, dissection or aneurysms, hemorrhage and, less frequently, neuropathy and myopathy (113-116). Nevertheless, the role of psychopathological presentations in neurological ABD is underestimated (114).

The course of ABD may be monophasic, relapsing–remitting, chronic progressive or entail silent involvement (108). Poor prognostic factors are multifocal and spinal manifestations, more than two attacks per year, progressive course and pathological findings in the cerebrospinal fluid (CSF).

Diagnostic methods include magnetic resonance imaging with arteriovenography using coronary computed tomography angiography or magnetic resonance angiogram. The most commonly affected regions are the mesodiencephalic junction (46%), the pontobulbar region (40%) and the hypothalamic–thalamic region (23%) (115). Examination of the CSF regularly shows pleocytosis (109, 111), elevated protein content and inconstant positive oligoclonal bands (111, 113). This summarizes a few fine differences to distinguish between ABD and other chronic or specific infectious diseases.

Treatment

Treatment of neurological ABD is based on experience with immunosuppressant and immunomodulating substances in other organ involvement in ABD because there are little controlled data (16). Corticosteroids are recommended for any acute attack in neurological ABD. An i.v. pulse therapy with high-dose methylprednisolone 1000 mg/day for 5 days (up to 7 days) and subsequent switch to oral single-dose prednisolone 1 mg/kg/day, tapered in conjunction with one of the other immunosuppressants, is the suggested therapy (4, 16). Tapering should be started when a therapeutic effect is achieved. Oral azathioprine (1-2.5 mg/kg/day) can be used for neurological ABD, although the evidence to support its use in this indication is weak (113, 114). Oral methotrexate (5-25 mg/week) is an alternative to achieve remission in neurological ABD, but toxicity to the CNS limits its use (108, 116). For severe cases with

a higher risk an i.v. pulse therapy with cyclophosphamide at a dose of 500-1000 mg/m^2 body surface area monthly is widely accepted (109, 114).

Among the second-line treatments, chlorambucil 0.1-0.2 mg/kg/day has been used successfully in a few cases, as has interferon alfa (3-9 million IU 3 times weekly) (116-118). Interferons should be avoided in case of depression with a risk of suicide. According to the EULAR recommendations, chlorambucil is regarded as a second-line drug due to a high risk for myelotoxicity and increased malignancies (16).

TNF-α-blocking drugs (infliximab or etanercept) are recommended by experts for patients in whom treatment with cyclophosphamide and prednisolone was unsuccessful (15). Infliximab 5 mg/kg is administered i.v. and etanercept is given s.c. at a dose of 50 mg once weekly or 25 mg twice weekly (119). However, very limited published evidence is available in support of the use of these compounds in neurological ABD.

Because of several reports of toxicity to the CNS, ciclosporin should be avoided in the treatment of neurological ABD (109, 111). According to the EULAR recommendations it can be used in patients with ocular involvement who cannot tolerate other agents (16).

Further investigations are necessary to show whether sinus thrombosis is a primary rather than a secondary inflammatory phenomenon. Until there are more neuropathological and clinical insights into sinus thrombosis, anticoagulation together with immunosuppressive therapy appears to be necessary. Anticoagulation may stop the further evolution of thrombosis and could prevent venous congestion and infarction. According to neurological recommendations, initial i.v. heparin therapy for about 2 weeks should be followed by treatment with phenprocoumon or warfarin sodium for at least a 6-month period. In case of a coagulation disturbance, the anticoagulation therapy should be continued throughout life.

Neurological symptoms such as headache or depression require a specific drug therapy or a psychotherapeutic approach. Headache may originate from different etiologies, for example, encephalitis, pseudotumor cerebri (120) or sinus thrombosis, but it may also be influenced by the psychological or physical state of the patient (121). Adverse effects should be kept in mind when choosing the optimal medication in any individual patient.

For exact recommendations in the future, more and larger randomized and controlled clinical trials are needed. Moreover, targeted therapies with antibodies against T-lymphocyte antigens or IL-6 receptor proteins may play a more outstanding role in neurological ABD (116). Stem cell transplantation has also been performed in an effort to prevent disease progression (122).

MAJOR VESSEL INVOLVEMENT AND THROMBOPHLEBITIS

One of the main causes of mortality and morbidity in patients with ABD is vascular involvement, seen in 7-38% of all ABD patients (4, 123-126). The mechanism of venous thrombosis in ABD is not fully understood, but is believed to be a result of an existing vasculitis or a hypercoagulable state. Due to the fatal consequences of vascular involvement and deep venous thrombosis (DVT), one of the most common manifestations encountered in vascular ABD, accurate diagnosis and appropriate treatment are very important.

Systemic immunosuppressants are used to reduce inflammation in major vessel disease, but there are no randomized, controlled studies and no firm evidence for the treatment of DVT and peripheral arterial aneurysms in ABD. Of major interest is the fact that patients who experienced thrombosis showed elevated acute-phase reactant levels at recurrence and the majority of the study subjects showed increased acute-phase reactants at DVT diagnosis. In periods when acute-phase reactants were suppressed by high-dose corticosteroids and immunosuppressants, no progression of venous thrombosis was observed in patients with thrombosis recurrence, suggesting the possible role of systemic inflammation in venous thrombosis in ABD and supporting the need for anti-inflammatory agents and immunosuppressants in the treatment of vascular ABD (124).

A trend for larger vessel involvement with placebo compared to azathioprine was observed in a controlled study (123). According to the EULAR recommendations, systemic immunosuppressants such as azathioprine 2.5 mg/kg/day may be prescribed for DVT of the extremities (16). In former recommendations, heparin infusions, fibrinolytics (i.v. streptokinase) plus high-dose corticosteroids (100-250 mg/day i.v. and/or p.o.) in acute phase, as well as maintenance treatment with coumarinics or warfarin plus immunosuppressants (chlorambucil 0.1 mg/kg p.o. or cyclophosphamide pulse therapy 500 mg i.v. once weekly plus mesna or ciclosporin 3-5 mg/kg/day) initially in combination with corticosteroids (prednisolone 30 mg/day p.o.) were proposed. Alternatively, interferon alfa (3-9 million IU s.c. 3-5 times weekly) in combination with corticosteroids was suggested as maintenance therapy for DVT (61). However, anticoagulants, antiplatelet or antifibrinolytic agents cannot generally be recommended and remain controversial, because pulmonary embolisms are rare despite the high rate of DVT. A reason to avoid these agents is that a possible coexisting pulmonary arterial aneurysm could result in fatal bleeding (16).

Monthly pulses of cyclophosphamide may be preferred for thrombosis of the superior vena cava or for Budd-Chiari syndrome. Early use of cyclophosphamide (alternatively chlorambucil) and high-dose steroids was able to improve the prognosis of patients with pulmonary arterial aneurysms in case reports (127-129). According to the EULAR recommendations, treatment with cyclophosphamide for at least 2 years followed by azathioprine is recommended. Surgery is associated with a high risk of mortality (16).

GASTROINTESTINAL INVOLVEMENT

Gastrointestinal tract involvement is experienced by 3-16% of ABD patients and the ileocecal area is typically affected (129, 130). Abdominal pain, diarrhea and bleeding are the most common gastrointestinal symptoms. Severe bleeding and perforation in ABD are often seen as complications of pre-existing or coexisting deep ulcers (131).

The aim of a recent study by three groups of Japanese gastroenterology specialists was the development of consensus-based guidelines for the diagnosis and management of intestinal ABD based on a modified Delphi approach (130). As a standard treatment for intestinal ABD, mesalazine 2.25-3 g/day or sulfasalazine 3-4 g/day is preferred. With severe systemic symptoms, corticosteroids are indicated (prednisolone 0.5-1 mg/kg/day for 1-2 weeks, tapered by 5 mg every week). When patients are corticosteroid-dependent or

-resistant, immunosuppressive agents are indicated (azathioprine 50-100 mg/day). In patients who are refractory to pharmacological therapy or have severe intestinal disease, enteral nutrition is usually indicated. When severe intestinal complications persist, surgical treatment and resection is advisable.

With intolerance to enteral nutrition and when intestinal symptoms persist despite treatment with corticosteroids or immunosuppressive agents, infliximab therapy must be considered as an alternative treatment. In ABD patients with corticosteroid dependence or resistance, leukapheresis may be used. A consensus could not be reached regarding experimental therapies for intestinal ulceration, including thalidomide, antibiotics and endoscopic ethanol spray (130). According to the EULAR recommendations, sulfasalazine, corticosteroids, azathioprine, TNF antagonists and thalidomide should be tried first before surgery, except in emergencies (16).

ADAMANTIADES-BEHÇET'S DISEASE IN CHILDHOOD

A particularly sensitive group of ABD patients are children. In recent years, the number of reports of childhood ABD has increased (132-136).

Prompt remission of the disease can be obtained with high doses of corticosteroids. Long-term treatment can lead to corticosteroid dependence and also to a variety of side effects. Other medication options include the adult regimens of azathioprine, ciclosporin, methotrexate or cyclophosphamide (137).

Available literature on alternative approaches such as interferon is limited. Ocular manifestations remain a key feature of the disease, with a frequency of 30% in the pediatric population compared to 60-80% in adult patients (80, 110, 135, 138). In a recent, long-term, retrospective analysis, seven children with corticosteroid-dependent uveitis were treated with interferon alfa (1.5-3 million IU s.c. weekly) with encouraging results. All patients had received antiplatelet doses of salicylates prior to the treatment and colchicine, which was not discontinued. Five of seven patients achieved remission relatively fast, two of whom could discontinue corticosteroids while corticosteroids were reduced in the other three (139).

Infliximab use is only documented in the form of case reports. Ugras et al. (140) described the case of a 12-year-old female patient with painful oral ulcers, abdominal pain, recurrent mucous diarrhea, genital ulcers and arthritic episodes resistant to all other commonly used drugs, who achieved a dramatic remission with infliximab.

Another 15-year-old girl with recurrent painful oral ulcers and extensive genital ulcers who required bladder catheterization was treated with infliximab with satisfying results. The patient had responded poorly to corticosteroids, colchicine and pentoxifylline (141).

Thalidomide can be an effective medication for children with ABD, especially with intestinal involvement. Seven children with intestinal involvement were treated with thalidomide (2 mg/kg/day, increased to 3 mg/kg if necessary) with positive results. Neurotoxicity under thalidomide must always be kept in mind (142).

As mentioned above, pentoxifylline can be considered one of the best therapies for the pediatric population in resistant cases, due to minimal side effects.

CONCLUSIONS

ABD has a worldwide prevalence and early diagnosis and treatment are of major importance for the patient's quality of life. The diagnosis of the disease remains challenging, as there are no specific laboratory tests. Making the decision for appropriate treatment can also be difficult because the onset and symptomatology are different for individual patients. Therapy aims to reduce the number of exacerbations and minimize mortality, providing a symptom-free period. The therapeutic strategy should be planned focusing individually on the most severe manifestations. The physician has a broad spectrum of available medications, including systemic steroids and immunosuppressants, but should always take into consideration the risk–benefit ratio of each regimen.

The most recent results from trials in ABD could be characterized as promising, but larger studies for the long-term course and adverse effects of medications are needed, especially in the pediatric population. Meta-analyses of individual trials could be the best alternative, providing invaluable outcomes for the future treatment of the disease.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Nikolaos A. Trikalinos of MetroWest Medical Center, Framingham, Massachusetts, for editing the manuscript.

DISCLOSURE

The authors state no potential conflicts of interest.

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