



Treatment of Behcet's disease

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Review Article

Abstract

Behcet's disease is a systemic disease classified among vasculitides. Major manifestations are mucous membrane lesions (oral aphthosis and genital aphthosis), skin manifestations (pseudofolliculitis, erythema nodosum), ocular manifestations (uveitis, retinal vasculitis), joint manifestations, vascular lesions (small to large vessel thrombosis, aneurysm), gastrointestinal manifestations, orchiepididymitis, and some rare manifestations like cardiac, pulmonary, and renal impairment. Diagnosis is mainly clinical. The International Diagnosis Criteria for Behcet's Disease may be of help. The gold standard of treatment for mucocutaneous lesions is colchicine. In refractory cases, levamisole, thalidomide, and dapsona may be of help. For major organ involvement like the eyes and the brain, immunosuppressive drugs and prednisolone are the gold standard. In refractory cases, biological agents are the last resort. For gastrointestinal manifestations, sulfasalazine and prednisolone are the first-line treatment. For vascular involvement, the first line treatment was anticoagulation, but recently it was shown that immunosuppressive drugs and prednisolone were confirmed to be the best. In all refractory cases and for all different organs, the last resort is biological agents.

KEYWORDS: Behcet's Disease, Treatment, Manifestation, Diagnosis

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Introduction

Behcet's disease (BD) is a multisystemic disease classified among vasculitides.¹⁻³ The main pathologic feature is leukocytoclastic vasculitis. The disease is mainly seen along the historical Silk Road, but can be seen nowadays all over the world with a prevalence going from 0.64 (Yorkshire) to 300 (Turkey) per 100,000 inhabitants.⁴⁻¹¹ The prevalence in Iran was

estimated from 16 to 80 patients per 100,000 inhabitants.¹²⁻¹⁴

The men to women ratios are from 0.38 in the US¹⁵ and 0.63 to 1.00 in Korea¹⁶ to 3.40 in Saudi Arabia¹⁷ and 1.00 to 4.90 in Kuwait.¹⁸

BD is a disease of the youth but can be seen at any age.^{3,10} The mean age goes from 40 years (Brazil) to 20.8 years (Ireland), but the majority of countries are between 25 and 30 years. In Iran, the mean age is 26 years with a standard deviation of 11.3. At the onset of the disease, the youngest was 1 year old and the oldest 70 years.¹⁹

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Clinical manifestations of the BD are dominated by mucous-membrane manifestations [oral aphthosis (OA), genital aphthosis (GA)], skin manifestations [pseudofolliculitis (PF), erythema nodosum (EN), skin aphthosis], and ocular manifestations [anterior uveitis (AU), posterior uveitis (PU), retinal vasculitis (RV)]. In Iran, OA was seen in 97.3% of patients with 95% confidence interval (95%CI) of 96.9-97.7%. GA was seen in 64.6% (95%CI: 63.4-64.7), PF in 54.5% (95%CI: 53.3-55.7), skin manifestations in 64.9% (95%CI: 63.7-66.1), ocular manifestations in 56.8% (95%CI: 55.6-58), EN in 22.5% (95%CI: 21.5-23.5), skin aphthosis in 7% (95%CI: 6.4-7.6), AU in 41.2% (95%CI:40-42.4), joint manifestations in 37.4% (95%CI: 36.2-38.6), cataract in 19.6% (95%CI: 18.6-20.6), mono-arthritis in 7.6% (95%CI: 7-8.2), PU in 44.9% (95%CI: 43.7-46.1), RV in 32.1% (95%CI: 31-33.2), arthralgia in 17.2% (95%CI: 16.3-18.1), oligo-arthritis in 16.8% (95%CI: 15.9-17.7), ankylosing spondylitis in 2% (95%CI: 1.7-2.3), neurological manifestations in 3.7% (95%CI: 3.2-4.2), peripheral lesions in 0.3% (95%CI: 0.2-0.4), central manifestations in 3.5% (95%CI: 3.1-3.9), isolated headache in 7.9% (95%CI: 7.2-8.6), gastrointestinal manifestations in 7.4% (95%CI: 6.8-8), gastroduodenitis in 2.4% (95%CI: 2-2.8), peptic ulcer in 1.3% (95%CI: 1-1.6), chronic diarrhea in 2.2% (95%CI: 1.8-2.6), rectorrhagia in 1% (95%CI: 0.8-1.2), abdominal pain and nausea in 1.9 (95%CI: 1.6-2.2), vascular involvement in 8.3% (95%CI: 7.6-9), phlebitis in 5.7% (95%CI: 5.1-6.3), large vessel involvement in 1.7% (95%CI: 1.4-2), superficial phlebitis in 2.2% (95%CI: 1.8-2.6), cardiac manifestations in 0.6% (95%CI: 0.4-0.8), pulmonary manifestations in 0.9% (95%CI: 0.7-1.1), and epididymitis in 4.7% (95%CI: 4.2-5.2).¹⁹

Laboratory findings in Iran¹⁹ were as: normal erythrocyte sedimentation rate (ESR < 20) in 46.5% (95%CI: 45.3-47.7), ESR between 20 and 50 in 32.6% (95%CI: 31.5-33.8), ESR between 51 and 100 in 13.8% (95%CI: 13-14.6), and ESR superior to 100 in 1.3% (95%CI: 1-1.6). Abnormal urine sediment was seen in 12.2% (95%CI: 11.4-13.0) of patients. Proteinuria was detected in 2.2%

(95%CI: 1.8-2.6), cast in 0.2% (95%CI: 0.1-0.3), and hematuria in 6.3% (95%CI: 5.7-6.9). Like most of BD symptoms, abnormal urine sediments were transient. Renal biopsy was done in 18 patients for persistent proteinuria (WHO type II: 3 cases, type III: 7 cases, type IV: 5 cases, type V: 2 cases, and amyloidosis: 2 cases). Pathergy test was positive in 52.5% of patients (95%CI: 51.3-53.7). HLA-B5 was checked in 6261 patients and was positive in 53.3% of them (95%CI: 52.1-52.1). HLA-B51 was checked in 1534 patients, it was detected in 47.9% of them (95%CI: 45.2-50.4). HLA-B27 was checked in 5933 patients, it was detected in 8.6% of them (95%CI: 7.9-9.3).

Disease Classification: 98.3% of the patients in Iran were classified by the International Criteria for Behcet's Disease.¹⁹ Looking at previous criteria for Behcet's disease, the rate of classification (sensitivity) was 97.2% with the Iran Classification Tree, 86.3% with the Korean criteria, 86.1% with the Japanese revised criteria, 81.0% with Dilsen revised criteria, and 78.0% with the International Study Group (ISG) criteria.¹⁹

BD progresses by repeated cycles of attacks and remissions. After the attack, the healing process starts and lasts for several days to several months. Then the remission occurs. However, it is not a definitive remission. A new attack will occur after several days of remission to several months, or even years, and everything starts all over again. For short attacks, the healing is complete and the tissue or the involved organ returns to its pre-attack state without any sequel. If the healing process takes long, sequels may appear. Longer the healing process, more chance to get sequels. Sometimes, before the healing process completes, a new attack occurs, aggravating the precedent attack. This is what usually happens with ocular lesions, where from one attack to another, lesions accumulate and progress toward severe loss of vision or blindness. In the past, the majority of BD patients with ocular lesions became blind in few years. Benezra and Cohen said in the past that after 10 years 74% of ocular

involvement of BD lead to the loss of useful vision, no matter what treatment was used.²⁰ However, this is no more the case.²¹

Treatment

The aim of the treatment in BD is to accelerate the healing process and to prevent from sequels. If possible, it has to maintain the remission by preventing from new attacks. There are two categories of lesions.

The first category comprises those manifestations that produce some burden without serious complications (e.g. mucocutaneous or many types of joint manifestations). These lesions do not require aggressive treatment, because complete healing is not indispensable and usually a shorter healing time with longer remission period will suffice. Not all patients in this group need treatment, especially those with very mild manifestations of short duration and long remission. In this group, colchicine is the first line, followed by levamisole, thalidomide, dapsone, and non-steroidal anti-inflammatory drugs (NSAID) are the mainstay.

The second group of lesions comprises those producing major morbidities. Among them are ocular lesions, as seen before, neurological manifestations, major vascular lesions (large vessel thrombosis, aneurysm), and the rare cardiopulmonary lesions. This group needs aggressive and early treatment. For them, immunosuppressive drugs, whether in mono therapy or combination therapy, associated to corticosteroids, is the first line treatment. In resistant cases biologic agents will be of help.

Both groups may benefit of symptomatic or local treatments.

Colchicine

Colchicine is the first line treatment for mucocutaneous lesions of BD. It was first used in 1977 by Mizushima²² and Haim and Friedman-Birnbaum.²³ Its efficacy raised some polemics, especially after the surveys of Aktulga et al.²⁴ and Yurdakul et al.²⁵ despite several case reports attesting its efficacy.²⁶⁻³¹ A double blind

control study of colchicine versus placebo, by Davatchi et al. showed its efficacy for mucocutaneous lesions and mild forms of joint involvement.³² The starting dose is 1 mg daily, taken at night. In some resistant cases it may be raised to 1.5 to 2 mg daily. Side effects are rare, mainly in the form of diarrhea especially in those taking more than 1 mg daily. In very rare cases, abnormality of liver function tests (LFT) as elevation of hepatic enzymes can be seen, necessitating the discontinuation of colchicine if the abnormal LFT persists. However, in the study of Davatchi et al., side effects were the same in the colchicine and the placebo group, with no statistically significant difference between them.³²

Colchicine has to be continued for longtime. Its discontinuation will result in the return of attacks to their original state (rate of recurrence and duration).

Levamisole

It is an immunomodulatory drug first used by Hamza and Ben in Tunisia.³³ It was followed by de Merieux et al.³⁴ who used it in 11 patients. More reports came later by Hamza et al.,³⁵ and Davatchi et al.³⁶ The indication is like colchicine, but for patients not responding to it.³⁷ Side effect is classically agranulocytosis. Therefore, regular CBC has to be done to discover it. We never observe it.³⁶ The same was for de Merieux et al.³⁴ The classic dose is 150 mg daily, 3 consecutive days per week. Upon good results, the dose may be decreased to two or one day per week.

Levamisole was rather forgotten in the past decades; but a new report from Sun et al. opened new insight into the mechanism of the drug and its benefits in concomitant use with colchicine. They observed a significant decrease of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF- α) in 64 patients with mucocutaneous lesions.³⁸

Thalidomide

It is an experimental drug used in resistant cases of BD.¹ It is not for daily or routine use.² It was used for all kinds of manifestations.³⁹ The main indication is mucocutaneous manifestations

resistant to other treatments.⁴⁰ The treatment starts with 200 mg daily. As soon as possible, upon the remission of symptoms, the dose is decreased to 100 mg daily, and if possible to 50 mg as the maintenance dose.³⁹ The safe dose, without side effects, would be 50 mg taken at night, 3 nights per week.⁴⁰ Side effects are mainly peripheral neuropathy and drowsiness. In difficult cases, the classical dose still can be used monitoring closely the neuropsychological manifestations.⁴¹ Later, a double-blind, controlled study demonstrated the effectiveness of thalidomide in the treatment of mucocutaneous lesions of BD.⁴² Sayarlioglu *et al.* used it successfully in a case of intestinal perforation not responding to immunosuppressive drugs.⁴³ Thalidomide has been lately shown to be not only an anti-inflammatory drug, but also an immunoregulatory drug by decreasing the TNF- α receptor levels, cluster of differentiation 8 (CD8)/CD11b⁺ and CD16/CD56⁺ cells. On the other hand CD4⁺CD45RO⁺ T cells and gammadelta⁺ T cells increased after treatment.⁴⁴

Dapson

It is an anti-leprotics agent used in resistant cases of mucocutaneous lesions successfully.⁴⁵ Not all authors agree with its efficacy in all resistant cases.⁴⁶ It is used as 50-100 mg daily. Side effects are hemolysis, liver toxicity, and hypersensitivity syndrome. It has recently been successfully used by Joshi and Mamta in pyoderma gangrenosum.⁴⁷

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are mainly used for joint manifestations of BD.^{2,37,48} As they are transient and follow the general scheme of attack and remission, and also as they go to remission without joint destruction (no sequels), no aggressive treatment is needed. NSAIDs have to be started at full dose and then tapered to a moderate dose until arthritis subsides. Usually, this will not take more than a few weeks. In case of resistant cases, especially in the rare chronic polyarthritis forms, disease-modifying antirheumatic drugs (DMARDs) will be necessary. The best choice will be methotrexate with low dose prednisolone.

Another indication of NSAIDs is EN, with or without joint manifestations, starting with a high dose and then adjusting to the need.

For superficial phlebitis and mild forms of deep-vein thrombosis, DMARDs can be used, always starting with a high dose and then adjusting.

Local treatment

Steroids are indicated in different situations. For mild oral aphthosis with few attacks per year (less than one attack per month), systemic medication is not necessary. Triamcinolone in Orabase, an ointment that stick to the mucosa, is indicated if an aphthous lesion is too painful. It is to used in local application up to 4 times a day. For resistant genital aphthosis, local (in situ) injection of triamcinolone acetonide may help, but is not always efficient.^{2,37}

Benzoyl peroxide is an antiseptic used locally for genital aphthosis to accelerate the healing process.

Immunosuppressive and immunomodulatory drugs

They are used for lesions of high morbidity like ocular, central nervous system (CNS), vascular, gastrointestinal, and all other resistant manifestations of the disease. The main products used in BD are cyclophosphamide, chlorambucil, azathioprine, methotrexate, and cyclosporine. They are all to be used in association with prednisolone.

In the past, cyclophosphamide for BD was used as oral tablets with the dose of 2-3 mg/kg daily. It was used in combination with prednisolone.⁴⁹ The results in ocular manifestations were very interesting.⁴⁸ It is now used in pulse therapy.⁵⁰⁻⁵⁶ Pulse cyclophosphamide (PCP) dose is usually 750 mg per square meter of body surface (around 1000 mg), in perfusion, once monthly. It is combined with daily prednisolone (0.5 mg/kg). Once a good response is obtained, prednisolone is gradually tapered to the minimum dose maintaining the good result. After 6 monthly doses, pulses are given as bimonthly, then once every 3 months, and finally as needed (*pro re nata* or PRN). PCP is an effective treatment.

Good results are not due to the combined steroids but to PCP itself, as shown in a double blind control study of PCP versus placebo, receiving both equal doses of prednisolone.⁵⁷ Results are interesting.^{58,59}

Chlorambucil was one of the first cytotoxic drugs to be used for the treatment of ophthalmologic manifestations of BD.⁶⁰ It is used as 0.2 to 0.3 mg/kg body weight. Prednisolone is associated as 0.5 mg/kg body weight daily. Upon obtaining good results, prednisolone is tapered gradually. In a longitudinal study on 89 patients with a mean follow-up duration of 26.2 ± 2.6 months, all parameters of the eyes [mean VA, inflammatory index of the AU, PU, RV, and the total adjusted disease activity index (TADAI)] improved significantly.⁶¹

Azathioprine (AZA) was used early in the treatment of BD.^{62,63} Results were not satisfactory because used at low dose (2 mg/kg daily).⁶⁴ A controlled study in 1990 showed its effectiveness in BD.⁶⁵ A more recent work, on 2000, showed its efficacy in ocular lesions of BD, in 32 patients. The result of the disease activity index of AU, PU, the TADAI, and the mean VA improved significantly, but not the mean retinal vasculitis.⁶⁶ A recent work from 2010 showed also good response with azathioprine, but less in those having retinal vasculitis.⁶⁷

Methotrexate (MTX) was first used in ocular manifestations of BD at a low dose of 7.5 mg weekly in the 1990⁶⁸ and 1998.⁶⁹ Higher dose (15 mg weekly) at the beginning of the treatment were used later, in 2003.⁷⁰ In resistant cases, doses up to 25 mg weekly may be used. It is mainly indicated in PU (mainly particularly posterior uveitis). It is less efficient in RV. A longitudinal study of 15 years follow-up on 597 patients with BD (4462 eyes in the years of follow-up) showed an improvement of 47% of VA, an improvement of 89% of PU, and an improvement of 55% of RV.⁷¹ MTX can be used for other manifestations of BD, mainly for mucocutaneous and joint manifestations when resistant to other treatments.

Cyclosporine A is an immunomodulator

acting principally on interleukin-2 (IL-2). It is highly effective in transplanting organs and in many autoimmune diseases.^{1,2} Its efficacy was demonstrated in BD.^{72,73} New formulation in microemulsion, as we use today, was tested in ocular lesions with good results, where the ocular attacks decreased in 78.6% of patients.⁷⁴ Cyclosporine was used in pyoderma gangrenosum of BD⁷⁴ and found, in 2003, to be very effective in unresponsive to other treatments.⁷⁵ These results were later confirmed in 2008.⁷⁶ It was also used in recurrent cutaneous polyarthritides nodosa-like lesions.⁷⁷ However, the main indication is ocular lesions, especially uveitis.⁷⁸⁻⁸² The mechanism of action has been broadened in BD. It has been shown, in BD uveitis that when combined to prednisolone, it down-regulates the natural killer cell-like effector functions of CD8brightCD56+ T cells.⁷⁸ Importantly, the production of interleukin-17, which plays an important role in all autoimmune diseases, is inhibited by cyclosporine A.⁸² Cyclosporine is used as 5 mg/kg by oral route. As soon as a therapeutic response is obtained, the drug must be reduced to the minimum dose that keeps the patient in remission. Side effects are important; especially nephrotoxicity that leads to renal insufficiency.⁸³ The use of cyclosporine in BD is associated with the occurrence of neurological manifestations, which appear as a complication of the treatment and necessitate the interruption of cyclosporine therapy.⁸¹⁻⁸⁵

All immunosuppressive drugs are efficient in major organ involvements of BD, mainly ocular manifestations.^{21,58,59,79,86-90} A study comparing the efficacy of all immunosuppressive drugs among 1494 patients with ocular manifestations of BD (posterior uveitis and/or retinal vasculitis) followed the patients longitudinally for up to 15 years (7685 eyes-years of treatment). It showed that there was no statistically significant difference between their efficacies on visual acuity. However, combination therapy of PCP (1 g monthly) + azathioprine (2-3 mg/kg daily) + prednisolone (0.5 mg/kg daily) was more effective on retinal vasculitis than the others.

Methotrexate, on the other hand, was mainly effective on uveitis, and had the least efficacy on retinal vasculitis.⁸⁹

Biological Agents

Interferon alpha (INF- α -2a and INF- α -2b) was the first biological agent used for BD in 1986 by Tsambaos *et al.*⁹¹ It was first used in milder forms of the disease (mucocutaneous and articular manifestations) but the real indication is ocular manifestations. Kotter *et al.* used INF in high doses of 9 million international units (IU) daily. However, lower doses of 3 million IU three times a week have also used, but with fewer efficacies. Kotter *et al.* recommended to start the treatment with 6-9 million IU per day (subcutaneous injections) and to reduce the dose to 4.5 million IU daily after 4 weeks. After another 4 weeks, they recommended to reduce the dose to 3 million per day. The maintenance dose after complete remission will be 3 million IU three times per week. It is recommended to continue INF at least for 8 weeks after complete remission.⁹²

Side effects are numerous, mainly a flu-like syndrome necessitating the use of NSAIDs to overcome the reaction. The local reaction on the site of injection is very frequent and varies from a rash to pyoderma gangrenosum (although the latter is of exception). A case of pathergy has also been reported on the site of injection.⁹³

Results on eye lesions (from different reports) seem very good. Kotter *et al.* evaluated the highest number of patients (50 patients) and reported the response rate as 92%. The mean visual acuity rose from 0.46 to 0.81 after 6 months.⁹⁴ In 2006, INF was used for refractory cystoid macular edema with good results in 11 out of the 15 eyes.⁹⁵ In a study in 2008, only 71.9% of the eyes responded.⁹⁶ While, in another study in the same year, the improvement was 88% of the eyes⁹⁷ (very close to the rate reported by Kotter *et al.*⁹⁴). Findings on mucocutaneous and articular manifestations are less impressive and less complete.^{98,99} Many recurrences are seen during the treatment, Kotter *et al.* concluded that INF should be reserved for more serious lesions of the disease like ocular lesions.⁹⁴

Anti TNF- α has recently been used in BD. There are sparse reports on few cases.

Etanercept is a soluble receptor intercepting circulating TNF- α before it reaches its receptors on the cell surface. Only a double-blind, controlled study by Melikoglu *et al.* in Turkey has assessed the efficacy of etanercept on mucocutaneous lesions. Patients received 25 mg injections twice weekly for 3 months. There was a statistically significant reduction in mucocutaneous and articular attacks during the therapy. It is important to note that not all lesions responded to the treatment and after discontinuation, there was an exacerbation of attacks.¹⁰⁰ The latter will largely limit the use of etanercept in treatment of BD as the disease is chronic and lasting for several decades. Melikoglu *et al.* also tested etanercept for ocular lesions in an open study on 10 cases. Patients were already receiving already azathioprine, cyclosporine, and prednisolone. All medications continued with the adjunction of etanercept, except cyclosporine. The results were not satisfactory after 9 months of treatment since there was no statistically significant improvement of visual acuity (mean before 0.34, mean after 0.54).¹⁰¹

Infliximab is a monoclonal antibody for TNF- α . It was used by Sablé-Fourtassou *et al.* in 2002. They used it in a dosage of 5 mg/kg by infusion. It was given on the classic schedule of week 1, 2, 6, 14, and then, after every 8 weeks. They used it in 3 patients for duration of 5 to 9 months and reported an excellent result. Visual acuity improved significantly reaching almost the normal value in nearly all patients. The patients were on INF before getting infliximab. They were obliged to stop it because of side effects or inefficacy.¹⁰² Sfrikakis *et al.* presented the effects of short-term use of infliximab on uveitis in 5 patients. The treatment response was dramatic.¹⁰³ Many case reports have clarified the effects of infliximab in few patients. There are 11 reports on 10 cases or more,¹⁰⁴⁻¹¹⁴ all on ocular manifestations except one.¹¹¹ Among them, only 2 reports are on more than 20 cases.^{106,113} Infliximab is also effective in the treatment of other manifestations, and among them, intractable

gastrointestinal manifestations.¹¹⁵⁻¹¹⁷ Arida *et al.* reviewed 88 articles on a total of 325 cases treated with infliximab. They reported the improvement of oral ulcers 91%, genital ulcers 96%, skin lesions 77%, erythema nodosum 81%, ocular lesions 89%, gastrointestinal manifestations 91%, neurological manifestations (central) 90%, joint manifestations 94%, and thrombophlebitis 70%.¹¹⁷

Adalimumab is a humanized anti-TNF- α monoclonal antibody. Arida *et al.* could find 13 articles on adalimumab (on a total of 28 patients). The results of improvement were 73% in oral ulcers, 86% in genital ulcers, 80% in skin lesions, 100% in erythema nodosum, 100% in ocular lesions, 100% in gastrointestinal manifestations, 100% in neurological manifestations (central), and 60% in joint manifestations.¹¹⁷ The same authors also reviewed 12 articles on etanercept (totally on 37 patients) and reported improvements in 82% of oral ulcers, 71% of genital ulcers, 67% of skin lesions, 100% of erythema nodosum, 60% of ocular lesions, 100% of neurological manifestations (central), and 100% of joint manifestations.

Rituximab is an anti-CD20 antibody which depletes B-lymphocytes.^{118,119} It was used in connective tissue diseases and vasculitides, but not in BD. Recently it was used for intractable eye lesions of BD in one case with good results.¹²⁰ A randomized controlled study of patients with intractable retinal vasculitis with cystoid macular edema resistant to immunosuppressive drugs compared rituximab (10 cases) with combination therapy of PCP and azathioprine (10 cases). Patients on rituximab improved while patients on immunosuppressive combination therapy did not.¹²¹

As suggested by the above-mentioned experiences, etanercept may be partially effective in mucocutaneous lesions of BD but not much effective in ocular manifestations. Infliximab was effective in short- and mid-term studies of ocular manifestations (maximum 3 years of follow-up in prospective studies). However, all the presented experiences are on few cases and practically short-term treatment.

Since attacks of ocular lesions in BD continue for many years, it is important to have a controlled study on a large number of patients lasting for several years to judge the real efficacy of infliximab (as has been performed in case of immunosuppressive drugs). For now, the best indication of anti-TNF therapy will be the control of intractable ocular attacks, mainly the retinal vasculitis. Adalimumab was effective in the few studied cases, but only on short-term therapy. None of the previous studies were a randomized, controlled trial comparing the drug with a gold standard. The only study of this kind was with rituximab.

How to treat patients in the daily practice

It is important to keep in mind that: 1. BD progresses by repeated cycles of attack and remission, 2. not all patients with BD need treatment, and 3. not all of those needing treatment require aggressive treatment.^{1,2,37} The aim of the treatment is to: 1. accelerate the healing process, 2. prevent from sequels, and 3. prolong or maintain remission.¹²² BD lesions are of two kinds: 1. Those producing some burden, like the majority of mucocutaneous lesions, joint manifestations, and some vascular manifestations like superficial phlebitis. For these lesions, complete healing is not indispensable. Faster healing, shorter healing time, fewer attacks, and longer remissions are sufficient. 2. Those producing high morbidity, like ocular manifestations, neurological manifestations, and the majority of vascular lesions especially large vein thrombosis and arterial aneurysm, and many of gastrointestinal manifestations.^{3,19,123} For these lesions, quick and complete healing along with is mandatory; otherwise sequels will appear. Apart quick and complete healing, long or definitive remission to prevent sequels are necessary. In case of slow healing process and frequent attacks, lesions accumulate from one attack will persist until the next and lead to another, leading to sever impairment of the involved organ. A good

example is eye lesions that progress toward severe loss of vision or blindness in few years.¹

For lesions producing some burden, the first line of treatment is colchicine (1 mg at bedtime). In case of resistance or side effects, the treatment is changed to levamisole. In resistant cases, combination of both is of help. MTX or AZA with low dose prednisolone, or thalidomide or dapsone will be other choices when higher resistance is observed. For patients having 3 or 4 attacks of oral aphthosis per year, there is no need for systemic treatment. Local treatment, in case of an abnormally painful attack, will usually suffice. The best local treatment (particularly Orabase) will be adequate for abnormally painful attacks. Pimecrolimus triamcinolone in Orabase, which is an ointment can be used in adheres to the oral mucosa. Pimecrolimus ointment can be used in case of isolated genital aphthosis or long duration aphthous ulcer.¹²⁴ Intralesional injection of triamcinolone acetonide may also be used for intractable genital aphthosis.

For articular manifestations, NSAIDs for few to several weeks are usually sufficient. If not, MTX at low dose (7.5 mg weekly) + low dose prednisolone is the best choice. However, other choices can be used like levamisole, AZA, or cyclosporine A.

For the second type of lesions, those with high morbidity, immunosuppressive drugs are mandatory for lesions with high morbidity. A short course of moderate-dose (20-30 mg/day) prednisolone should suffice a single for eye lesion (i.e. lesions, if the patient has only uveitis, and if uveitis is an isolated anterior uveitis). Usually prednisolone at moderate doses of 20 to 30 mg per day is largely sufficient. A short course of few weeks will suffice.

However, isolated anterior uveitis is rare in BD. Usually the patients have a panuveitis or posterior uveitis alone. In these cases, the first line immunosuppressive drug will be MTX at 15 mg weekly, with prednisolone 0.5 mg/kg daily in divided doses. After controlling the inflammation, the dose of prednisolone will be

tapered gradually, every month to every 3 months, to arrive to a maintenance dose of 7.5 mg weekly. It is wise to continue at this dose for several months before deciding to further taper and eventually stop the medicine. If the inflammation does not recur, MTX can be gradually tapered (by steps of 3 to 4 months) until it is stopped. At each level of tapering of the drugs, if the inflammation recurs, and depending on its importance, one or several steps are taken back.

If at the beginning of the treatment the eye does not respond, an escalation of drug is initiated as: increase of weekly dose of MTX will increase up to 25 mg, change of MTX will be replaced with AZA, change to combination therapy with PCP + AZA + prednisolone will be prescribed. Inefficacy of all these methods will necessitate the substitution of immunosuppressive + AZA + prednisolone as described before. If still no benefit, change of immunosuppressive strategy with to biological agents.

If eye lesions are retinal vasculitis, with or without posterior uveitis, the first line of treatment will be combination therapy with PCP + AZA + prednisolone (0.5 mg/kg daily). After controlling the inflammation, prednisolone dose will be tapered gradually, every month to every 3 months, to arrive to a maintenance dose of 7.5 mg daily. If the inflammation does not recur after 6 PCP, the rhythm of once monthly pulse is decreased to once every two months and then to once every 3 months. If still in remission, PCP will be stopped after 3 to 4 PCP, and the patient will continue on AZA alone. After several months at this regimen, the tapering will start again with prednisolone, exactly as for uveitis alone, and then with AZA.

At any step, if the inflammation recurs, the treatment will get one to several steps depending on the importance of the new attack. If the combination does not work, AZA can be changed to MTX or to cyclosporine A. If still no improvement, biological agents have to start, if the patient can afford it.

For neurological manifestations, the same treatment scheme as for retinal vasculitis is used,

except prednisolone is to be given as 1 mg/kg daily. In case of treatment escalation and change of immunosuppressive drugs, cyclosporine is to be avoided, because of its neurological side effects.

For vascular involvement, the classic strategy was the prescription of anticoagulants. However, new experiences and papers are more and more in favor of immunosuppressive drugs + prednisolone for these cases. Depending on the site and the form of the lesion, anticoagulation may be given, but not for longtime as in the past.¹²⁵⁻¹²⁹ Ahn *et al.* demonstrated that adding anticoagulants did not improve the results obtained by immunosuppressive drugs + prednisolone in deep vein thrombosis.¹²⁶ However, for superficial vein thrombosis and some restricted and mild forms of deep vein thrombosis, NSAIDs may be enough. In such cases, trying NSAIDs before opting for the aggressive treatment will be beneficial.

For gastrointestinal manifestations, the first treatment to try is sulfasalazine (2 g daily) + prednisolone in low to moderate doses. If not sufficient, immunosuppressive drugs are necessary. In case of resistance to the treatment, biological agents are the last resort.

Conflict of Interests

Authors have no conflict of interests.

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