# Behçet's Disease:
# Treatment of Neuro-Behçet's Disease - An Update

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## ABSTRACT

Neurological manifestations of Behçet's disease (neuro-Behçet's disease) present in 5-30% of cases. They are classified into parenchymal and non-parenchymal categories. Poor prognostic factors include multifocal involvement, spinal presentations, more than two attacks per year, progressive course and increased cerebrospinal fluid cell count and protein content at the time of neurologic manifestations. For patients with parenchymal neuro-Behçet's disease without any poor prognostic factor, azathioprine or methotrexate and corticosteroids are recommended as the first-line treatment. For high-risk patients, intravenous cyclophosphamide and corticosteroids are recommended. If these regimens failed, TNF-a-blocking drugs, such as infliximab or etanercept, should be added. Alternating IFN-a and then chlorambucil or experimental treatments are the last resorts for most refractory patients. Treatment of venous sinus thrombosis is achieved by using anticoagulation and short-term corticosteroids with or without immunosuppressants.

Figure 1. Axial FLAIR, axial T2-weighted image and coronal T2-weighted image showing typical neuro-Behçet's disease lesions extending from right thalamus to midbrain. Brainstem and cerebellar atrophy, and periventricular and subcortical lesions can also be noted. FLAIR: Fluid attenuated inversion recovery.

Neuro-Behçet's disease (NBD) is the constellation of neurologic symptoms and/or signs as a direct result of Behçet's disease (BD), and is usually confirmed by neuroimaging and/or evaluation of the cerebrospinal fluid (CSF)[1]. The frequency of neurologic manifestations of BD ranges from 5 to 30%[1,2].

The prevalence of BD per 100,000 population has been reported to be as high as 370 in Turkey and as low as 0.64 in Western Europe[3]. However, the globalization process is changing this epidemiological profile and more patients with NBD from European and North American countries are being diagnosed[4]. Therefore, all neurologists should be knowledgeable about the prompt diagnosis and accurate treatment of NBD.

## Clinical manifestation

Both the CNS and PNS can be involved in BD. The CNS manifestations can be divided into two main groups:

• Parenchymal manifestations that include brainstem presentations, hemispheric manifestations, spinal cord lesions and meningoencephalitic presentations;

• Nonparenchymal manifestations, such as dural sinus thrombosis, pseudotumor cerebri, arterial occlusion and/or aneurysms[1,2,5-7].

There are some patients with mixed features of parenchymal involvement and intracranial hypertension [8]. Brainstem manifestations, the most common presentations in parenchymal NBD, present as various combinations of sensory/motor long tract signs, cranial nerve palsies, cerebellar signs and, eventually, as pseudobulbar palsy and emotional instability[1,2,5-9].

Hemispheric manifestations include headache, focal sensory/motor signs, speech disorders, altered level of consciousness[1,2,5-9] and, less frequently, seizures[10] and movement disorders[11].

Although migraine and tension-type headaches are the most prevalent types of headaches in patients with BD, NBD must be meticulously investigated in patients with BD who present with headache[12,13]. Psychological presentations are much more prevalent than previously thought[14].

Aseptic meningitis with CSF pleocytosis and increased protein content commonly exists as a background of many cases of parenchymal CNS involvement in BD but there are also reports of pure meningoencephalitis as a presentation of NBD[15]. Tumorfactive NBD is defined as a tumor-like clinical and radiological manifestation of NBD[16,17].

Spinal manifestations, observed in 10-30% of patients with NBD, have a worse prognosis compared with the other types of parenchymal NBD[18].

Nonparenchymal NBD or neurovascular BD mainly includes cerebral venous thrombosis[2,7,8,19], but arterial stenosis, aneurysm formation or dissection of major cerebral arteries do occur rarely[20]. Cerebral venous thrombosis is the main cause of intracranial hypertension but it may not be confirmed by radiological investigations[19]. It manifests as acute or, more commonly, subacute evolution of headache, nausea, vomiting, visual obscurations associated with bilateral papilledema, sixth nerve palsy, alteration of the level of consciousness, seizure and/or focal neurologic deficits[2,7,19]. Peripheral neuropathy and myopathy are relatively rare manifestations of BD[1].

## Pathology

Top of FIt is apparent that the main pathological feature of CNS lesions caused by BD is the perivascular infiltration of mononuclear, polymorphonuclear and, rarely, eosinophilic cells[21]. Interestingly, perivascular cuffing was not seen in some reports[22,23].

The most inconsistent aspect in pathological reports of NBD is the presence of necrosis. While it was obviously present in some studies[22,24], there was no evidence of necrosis in other reports[21,23,25].

The heterogeneity observed in histopathological presentations of NBD may be justified by different stages of the disease. However, heterogeneous etiopathologic mechanisms may be contributory[26].

## Diagnosis

Diagnosis of NBD is not problematic when neurological manifestations present in a patient fulfilling the diagnostic criteria for BD[27]. Diagnostic difficulties appear in the patients who present with isolated neurologic attack(s) preceding the onset of BD. Under-diagnosis also occurs when history taking or physical examination are incomplete and general manifestations of BD are neglected.

Over-diagnosis is also possible. Since BD is a chronic and sometimes crippling disease, it may induce some psychological distress and probably conversion

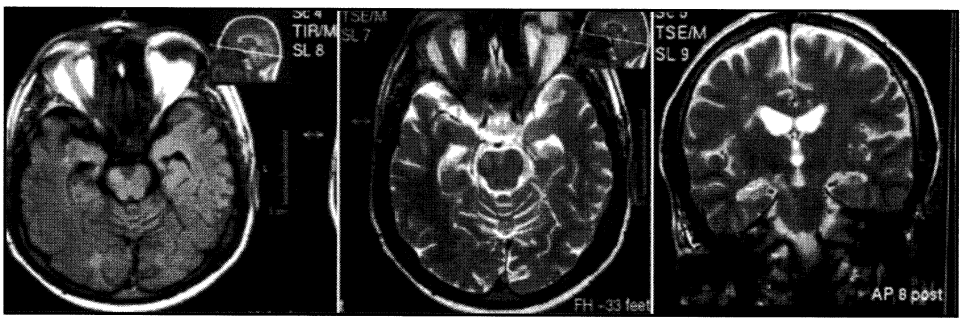


*Figure 1. Axial FLAIR, axial T2-weighted image and coronal T2-weighted image showing typical neuro-Behçet's disease lesions extending from right thalamus to midbrain. Brainstem and cerebellar atrophy, and periventricular and subcortical lesions can also be noted. FLAIR: Fluid attenuated inversion recovery*

reaction. In a recent study, patients with BD had significantly higher scores in somatization scales in comparison with healthy controls [28].

However, NBD should be kept in mind for any patient who develops stroke at a young age, intracranial hypertension and intracerebral venous occlusive disease, multiple sclerosis and spinal cord syndromes, especially in çountries where BD is prevalent.

By far the most helpful investigatory tools for the evaluation of NBD is MRI. Conventional techniques, such as T1-weighted, T2-weighted, fluid-attenuated inversion recovery and proton-density images, are enough for routine assessment, but diffusion-weighted MRI and MR spectroscopy have also been used in some studies [29,30]. It should be stressed that all MRIs that are requested for the diagnosis of NBD must be performed by the administration of gadolinium to evaluate the pattern of contrast enhancement.

As shown in Figure 1, a typical presentation of acute NBD is an iso-, hypo- or hyperintense medium-size lesion in T1/T2/fluid-attenuated inversion recovery-weighted images, with or without contrast enhancement, which extends from the thalamus and basal ganglia to the brainstem (mostly in the midbrain). Meanwhile, periventricular and juxtacortical lesions can also be found. Cerebral atrophy (especially in the brainstem) can also be seen in patients with chronic disease [31,32].

Spinal cord MRI reveals similar signal characteristics and enhancement properties. Segmental enlargement of the spinal cord has also been reported [18].

Cerebral venous thrombosis usually presents with bilateral cortical infarctions with or without hemorrhages. Signs such as delta sign (a triangular area of enhancement with a low-attenuating center in the area of the superior sagittal sinus) or cord signs (increased attenuation in either the dural sinuses or a vein filled with thrombus) may also be present in brain MRI. Its definite diagnosis can only be confirmed by computerized tomographic angiography, magnetic resonance angiography or digital subtraction angiography [2,7,19].

Cerebrospinal fluid analysis has different patterns in parenchymal and nonparenchymal subdivisions of NBD. In patients with parenchymal manifestations, pleocytosis (neutrophilic and/or lymphocytic) and elevated protein levels and normal glucose contents are usually found. However, CSF can be entirely normal [1,2]. In patients with cerebral venous thrombosis, the CSF profile is usually normal except for an elevated opening pressure [19].

### *Course & prognosis*

Parenchymal NBD has monophasic, relapsing-remitting and chronic progressive courses, but nonparenchymal NBD rarely relapses [1,5,6]. Poor prognostic factors include young age at onset, 'brainstem +' involvement, spinal cord involvement, frequent attacks (more than two per year), dependence on corticosteroids, progressive course and increased cell count and protein content at the time of neurologic manifestations. The presence of abnormal CSF findings at the time of neurologic manifestations necessitates more potent immunosuppression [2,33,34].

### *Treatment*

The European League Against Rheumatism (EULAR) recommendations for the management of Behçet's disease states, "there are no controlled data to guide the management of CNS involvement in BD" [35]. The literature on treatment of NBD mostly includes case reports, small series and a limited number of open label studies. Small sample size and different inclusion criteria make these studies barely comparable. In this milieu, the current evidence of therapeutic efficacy is low grade.

Corticosteroids and immunosuppressive drugs have traditionally been the main treatments for different manifestations of BD. Theoretically, any agent used for the treatment of general BD can also be administered for NBD. However, the difference in pathological and prognostic properties of NBD compared with general BD necessitates the selection of an NBD-tailored immunosuppressive regimen.

Recently, targeted therapy has been developed for highly selective suppression of proinflammatory immune mediators.

In proposing a therapeutic guideline for NBD, pathological, clinical, prognostic and even medico-economical aspects should be considered [36]. Treatment of acute attacks (first attack or relapses) is usually conducted successfully by administration of corticosteroids and short-term immunosuppressive drugs. A hierarchical use of immunosuppressive drugs and targeted therapy should be considered for patients with a relapsing-remitting or primary progressive course. Patients who enter a relentlessly progressive course should be treated with more potent regimens and sometimes with combination therapy.

Treatment of cerebral venous thrombosis is based on anticoagulation with or without immunosuppression and should be studied differently.

## Treatment of parenchymal NBD

### *Corticosteroids*

Although corticosteroids have been the mainstay of treatment for BD for many years, there is no large randomized clinical trial to support their use. Some studies have even debated their efficacy [37].

For acute attacks of NBD, EULAR recommendations for the management of BD suggest intravenous pulse therapy with methyl prednisolone 1000 mg/day for 3-7 days and then shifting to oral prednisolone in a single morning dose of 1 mg/kg/day [35]. A tapering schedule should be started when the therapeutic effect is achieved. Tapering should be conducted over 2-3 months [35]. In the author's view, a tapering schedule is completely case dependent. Tapering should be conducted with 5-mg/week decrements and dose adjustment according to the clinical responses. Side effects of corticosteroids should be monitored cautiously. Neuropsychiatric adverse effects, including seizures, depression, mania, schizophreniform psychosis and myopathy, can mimic exacerbation of primary disease.

### *Azathioprine*

Although some authorities are doubtful about its efficacy, azathioprine has been used for the treatment of NBD in different countries [6,38]. In a trial performed in Turkey, the combined treatment with glucocorticoids and either azathioprine or placebo was evaluated in general BD. The inadequate number of patients with neurologic involvement in that study prevented reaching a conclusion regarding the role of azathioprine in NBD [39]. In the long-term extension of that trial, five out of the 23 patients in the placebo group and two out of the 25 patients in the azathioprine group developed neurologic involvement [40].

Oral azathioprine 2-3 mg/kg/day is recommended for remission induction. The major side effects of the drug are bone marrow suppression and dose-dependent hepatotoxicity, which should be monitored, particularly in the early months of the treatment. The measurement of thiopurine methyltransferase activity has been recommended for prevention of azathioprine toxicity [41]; however, it is not available in all centers.

### *Methotrexate*

The remission of NBD is usually achieved by oral methotrexate 12.5-25 mg/week. Subcutaneous methotrexate has also been administered for rheumatologic diseases [42]. Drug monitoring should be performed by pretreatment and regular examination of serum transaminase, complete blood count and chest radiography for diagnosis of hepatotoxicity, bone marrow suppression and pneumonitis, respectively [43].

Japanese investigators recommended low-dose methotrexate (7.5-12.5 mg, orally, weekly) for patients with chronic progressive NBD. Their recommendation was based on some studies that evaluated the clinical responses by neuropsychiatric findings, brain MRI and CSF IL-6 levels [44,45]. Paradoxical neurological adverse effects, such as aseptic meningitis, transverse myelitis and leukoencephalopathy, may be major obstacles. Although these drug hazards have mostly been reported with intrathecal and intravenous administration, evidence of CNS toxicity with oral methotrexate has also been reported [46].

### *Cyclophosphamide*

In the Cochrane database (1998) there was not sufficient evidence to support the use of cyclophosphamide in the treatment of BD and/or ocular BD [47]. However, there are some studies that support its use, particularly in NBD [48,49]. Monthly intravenous pulse therapy with cyclophosphamide has been widely used for the treatment of NBD [50,51]. In addition to routine monthly administration, trials of daily very-high-dose [52], as well as low-dose pulse therapy (St Thomas' protocol) [53], have been reported for the treatment of NBD.

Although oral administration of cyclophosphamide 1-3 mg/kg/day has also been recommended, intravenous pulse therapy with the dose of 500-1000 mg/m2 of body surface area is better tolerated. Cyclophosphamide pulses also cause lower cumula-

tive doses and consequently have lower risk of secondary malignancies.

By prescribing the drug in a once-monthly fashion, the total duration of the treatment is tailored according to the severity of the disease and response of the patient. The cumulative dose should be kept below 20 g [54]. The major adverse effects of cyclophosphamide are hemorrhagic cystitis and risk of bladder cancer. Vigorous hydration with 2-3 l of fluid on the days of administration may prevent such effects. Blood counts and urine analysis should be performed every month before each pulse.

### *Chlorambucil*

Chlorambucil 0.2 mg/kg/day has been used in some small series [55]. Efficacy of chlorambucil 0.1 mg/kg/day in the treatment of meningoencephalitis or recurrent meningitis in patients with BD was approved on the basis of clinical response and improvement in CSF pleocytosis [56]. Owing to the severe adverse effects, such as carcinogenicity, its use should be limited to the situations when no other immunosuppressive drug and/or targeted therapy is effective.

### *IFN-α*

Although IFN-α has had very promising results in ocular, articular and mucocutaneous manifestations of BD [57,58], the data for the efficacy of IFN-α in NBD are limited [59,60].There is also a report of successful treatment of NBD in a pediatric-age group with IFN-$\alpha_{2a}$ [61].

Variations in the dose and interval of administration (from 3 million IU three-times per week to 9 million IU/day) and the type of IFN-α (a or b) make a final recommendation somewhat difficult. Irritating side-effects, mainly 'influenza-like syndrome and injection-site reactions, are the other obstacles for considering IFN-α as a first-line drug.

### *TNF-α blockade*

TNF-α is believed to play a pivotal role in the immunopathogenesis of BD [62]. TNF-α blockade has been recommended for the treatment of various inflammatory diseases since the 1990s. Some anti-TNF-α drugs, such as infliximab, etanercept, adalimumab and certolizumab, have been marketed since then [63]. Some case reports and small series have reported the usefulness of infliximab, etanercept and adalimumab in the treatment of NBD [64-70].

In a study in Italy, infliximab was effective as an adjuvant therapy in the treatment of eight patients with refractory NBD [71]. In another study in Japan, the therapeutic effect of infliximab on patients with progressive NBD was revealed through a reduction in CSF IL-6 levels but not in TNF-α [72].

Although the results of these studies were promising, therapeutic responses were sometimes partial [66] or nonsustained [69]. Formation of antibodies to infliximab should be considered in cases of drug failure.

An expert panel recommended infliximab for patients who are refractory to treatment with pulse cyclophosphamide and prednisolone, or in those who relapse while receiving maintenance treatment with azathioprine and prednisolone [73].

Infliximab 5 mg/kg should be administered by intravenous infusion at weeks 0, 2 and 6, and then every 8 weeks. Etanercept 50 mg should be injected subcutaneously every week. The author suggests simultaneous administration of monthly cyclophosphamide or oral methotrexate and prednisolone with TNF blockade [71-73]. If these regimens induce remission, the dosage of either anti-TNF agent or the concomitant immunosuppressive drug(s) may be reduced further [73]. Cardiac failure, hepatic diseases, tuberculosis and other infections are major contraindications for TNF-blockade therapy. Opportunistic infection should be monitored cautiously.

### *Intravenous immunoglobulin & plasmapheresis*

Although Guillain-Barre syndrome, chronic inflammatory demyelinating neuropathy, polymyositis and myasthenia gravis have been rarely reported with BD [1], intravenous immunoglobulin and plasmapheresis can be used as the first-line therapeutic options for these presentations.

### *Other drugs*

Thalidomide [74,75], dapsone [76], colchicines [77] and sulfasalazine [78] have also been used in different manifestations of BD. They can be used in patients with NBD with simultaneous other manifestations of BD.

### *Contraindicated Drugs*

#### *Cyclosporine & Tacrolimus*

Cyclosporine A has shown beneficial responses in the treatment of ocular, mucocutaneous and articular manifestations of BD [79]. However, there are some debates about its use in NBD. There are reports of its inferiority to other agents in the treatment of NBD [80]. Differentiation between the neurological adverse effects of cyclosporine and the symptoms of NBD itself may be difficult [81]. More importantly, cyclosporine may exacerbate or even induce neurological complications of BD [82,83].

In patients taking cyclosporine for refractory uveitis, neurological complications can be due to both NBD and the drug toxicity. Although peak and true blood levels are not always parallel to the drug toxicity, they can be helpful indications. Concurrent evolution of general presentations of BD is in favor of NBD rather than cyclosporine encephalopathy. When either entity is contributing in neurological manifestations, alteration of cyclosporine with another potent immunosuppressive drug is mandatory.

CNS toxicity related to tacrolimus (FK 506) has also been reported in patients with BD [84,85].

## Future perspectives

### *Targeted therapy*

A recent advance in the management of rheumatic diseases is the use of biological agents that block certain immunological molecules that have crucial roles in the pathogenesis of the diseases.

Alemtuzumab is a monoclonal antibody against CD52 antigen, which induces depletion of T cells, especially the CD4+ subset. There is a report of a long-term remission in a cohort of patients with BD, most of whom were refractory to corticosteroids and immunosuppressive drugs. Eight out of the 18 patients had CNS involvement. Five out of the eight patients with CNS involvement developed remission 6 months after alemtuzumab infusion. After 6-53 months of follow-up, four patients had complete remission. Owing to the possibility of opportunistic infections, oral acyclovir and nystatin mouthwash were also prescribed for the patients [86].

Among new biologics, tocilizumab is a very promising agent. Tocilizumab is a humanized antibody that binds both to soluble and membrane-bound IL-6 receptors. There are several studies that revealed a significant elevation of IL-6 in the CSF of patients with NBD in comparison with healthy controls [44,72,87]. These studies may justify a pivotal role of IL-6 in the in situ pathogenesis of NBD. Consequently, we can hypothesize that tocilizumab may be an efficacious adjuvant drug for the treatment of NBD [88].

Rituximab (anti-CD20 monoclonal antibody), abatacept (a fusion protein of cytotoxic T-lymphocyte antigen 4 and immunoglobulin), anakinra (anti-IL-1 monoclonal antibody), daclizumab (monoclonal anti-

**Table 1. Size of treatment effects and strength of recommendation of major therapeutic options for neuro-Behçet's disease.**

| Drug | Study | Strength of recommendation | Size of treatment effect | Ref. |
|---|---|---|---|---|
| Corticosteroids | No trial was done particularly on NBD | Level C | Class IIa | |
| Azathioprine | Controlled trial on general BD (six patients and nine controls with NBD) with long-term follow-up | Level C | Class IIa | [39,40] |
| Methotrexate | Open trial (six patients) with long-term follow-up | Level C | Class IIa | [44,45] |
| Cyclophosphamide | Open trials: eight patients and seven patients | Level C | Class IIa | [48,49] |
| TNF-α-blocking drugs | Case series: eight patients and five patients | Level C | Class IIa | [71,72] |
| IFN-α | Open trial on general BD (three patients with NBD) | Level C | Class IIa | [59] |
| Chlorambucil | Open trial on patients with meningoencephalitis or recurrent meningitis (14 patients) | Level C | Class IIb | [56] |
| Cyclosporine and tacrolimus | Expert opinion recommendation | Level C | Class III | [35] |

Class I: conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa: weight of evidence or opinion is in favor of the procedure or treatment. Class IIb: usefulness/efficacy is less well established by evidence or opinion. Class III: conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Strength of recommendation: A: data derived from multiple randomized clinical trials; B: data derived from a single randomized trial or nonrandomized studies; C: expert opinion or case studies
BD: Behçet's disease; NBD: Neuro-Behçet's disease.

body to the IL-2 receptor, CD25) and SP600125 (a kinase inhibitor that inhibits signaling of TNF-α) are other potential weapons against BD and NBD.

### *Tolerization therapy*

The strategy of tolerization therapy was adopted in a Phase I/II clinical trial by the oral administration of p336-351 cholera toxin B subunit three-times weekly in eight patients with BD. The administration of p336-351 cholera toxin B subunit had no adverse effects, and withdrawal of the immunosuppressive drugs did not result in the relapse of uveitis in most patients. The control of uveitis was paralleled by a lack of peptide-specific CD4 T-cell proliferation, as well as by a decrease in pathogenic Th1 cells and the inflammatory cytokines IFN-γ and TNF-α compared with patients in whom uveitis had relapsed. More importantly, after tolerization was discontinued, two patients remained free of uveitis at the follow-up visit [89]. Further investigations are indicated for evaluation of this therapeutic modality for the treatment of different aspects of BD, including NBD.

### *Stem cell transplantation*

There is a report of the prevention of disease progression in two patients with severe progressive NBD who underwent autologous CD34+ selected peripheral blood stem cell transplantation after high-dose immunosuppressive chemotherapy. Although findings of brain MRI were similar in both patients, single photon-emission computed tomography showed an increase in blood flow in the hypoperfused cerebral areas in one of the patients who showed disability improvement [90].

## Treatment of nonparenchymal NBD

### *Cerebral venous sinus thrombosis*

For cerebral venous sinus thrombosis associated with BD, concurrent use of corticosteroids and anticoagulants has been suggested [19,91,92]. Meanwhile, some investigators recommended immunosuppressive drugs (with or without anticoagulation) for the treatment of venous thrombosis in NBD [93,94].

Initially, either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin can be used. Heparin or heparinoids should be continued for at least 5 days and warfarin should be used simultaneously from the third or fourth days. The heparin product can be discontinued on day 5 or 6 if the international normalizing ratio equals 2.5-3 for 2 consecutive days. Duration of anticoagulation is a matter of debate. Risk of hemorrhage of pulmonary artery aneurism should be kept in mind. The author recommends a period of 6 months of anticoagulation and tapering of warfarin. A few weeks after discontinuation of warfarin, a thorough thrombophilia profile should be investigated. If, for example, a robust thrombophilic state, such as deficiency of protein C, protein S, antithrombin III, plasminogen or tissue plasminogen activator, activated protein C resistance, elevated plasminogen activator inhibitor-1, dysfibrinogenemia and hyperhomocysteinemia, are not present, long-life anticoagulation is not necessary.

### *Arterial involvement*

Arterial involvement can present as stenosis, aneurysm formation, both stenosis and aneurysm formation or dissection of the cerebral arteries. These pathologies cause intracerebral and/or subarachnoid hemorrhage or arterial infarction [1]. Any invasive approach to the arterial system, including repairs by autologous veins or synthetic grafts, may cause pseudoaneurysms [95]. As this pathergy-like phenomenon may exacerbate vascular pathology, aggressive surgical or endovascular interventions are not recommended. Treatment of these arterial complications could be similar to that of the high-risk group of parenchymal NBD [96].

## Follow-up

### *Drug efficacy*

The author proposes some definitions for remission and exacerbation in NBD. Clinical remission is defined as subjective diminishment or disappearance of attributed symptoms and objective diminishment or disappearance of signs. CSF remission is defined as normalization of cell counts of the CSF, change from polymorphonuclear- to lymphocyte-dominant pleocytosis and significant decrease in CSF protein level (>50% reduction from the baseline). Radiologic remission is defined as a decrease in the number of hyperintense lesions in T2-weighted MRI, decrease in MRI burden (total surface area of hyperintense lesions in T2-weighted images) and absence of enhancing lesions in contrast-administered T1 technique. Complete remission is defined as fulfilling the criteria of clinical, CSF and radiological remission. Incomplete remission is defined as fulfilling some but not all the above targets.

Clinical, CSF and radiologic exacerbation are defined as aggravation or reappearance of signs and symptoms, CSF pleocytosis or increased protein content, and an increase in MRI burden or evolution of enhancing lesions, respectively.

If clinical remission is achieved, CSF and MRI evaluation should be performed 3-6 months after discontinuing the immunosuppressive drugs. If clinical exacerbation occurred, CSF and MRI studies should be conducted as soon as possible. It should be kept in mind that corticosteroid pulse therapy may diminish CSF and MRI abnormalities, especially CSF pleocytosis and gadolinium enhancement. Therefore, this kind of treatment should be postponed after diagnostic modalities.

### *Adverse drug effects*

All recommended drugs for NBD have more or less important adverse effects. Corticosteroids, immunosuppressive drugs and targeted therapies reduce immunological activities, making a opportunistic infections a major concern. As tuberculous meningitis, brucella meningitis, Lyme disease and other causes of chronic meningitis can mimic parenchymal NBD, the issue becomes more complicated. Thorough CSF cultures and other microbiological studies, such as PCR and ELISA for specific infectious agents, should be performed at the time of exacerbations. As some of the aforementioned drugs are hepatotoxic, nephrotoxic or bone marrow suppressants, liver and renal function tests, complete blood counts and urinalysis should be requested routinely. Bone mineral densitometry is also advised for patients who receive long-term corticosteroids.

Neuro-Behçet's disease per se, adverse effects of drugs (such as corticosteroids), opportunistic infections and psychological distress due to a chronic and sometimes crippling disease, can all induce some psychiatric manifestations. Therefore, collaboration of psychiatrists, neurologists and rheumatologists for the diagnosis and management of such manifestations is mandatory.

Immunosuppressive drugs can also induce paradoxical immunological side effects. Exacerbation or de novo development of psoriasis has been reported with both IFN-α [57] and infliximab [97]. Erythema nodosum has also been reported with thalidomide [74].

### *Recommendation*

Although significant improvement in the treatment of mucocutaneous, ophthalmic and pulmonary manifestations of BD has been achieved in the past decades, the treatment of NBD is still a major dilemma [94]. Due to the relapsing-remitting nature of BD, evaluation of the efficacy of different therapeutic options are somewhat difficult. Drug effects may be confused with the natural course of the disease. Considering the grave prognosis of NBD, the author recommends the policy of early institution of effective immunosuppressive drugs for reaching a better outcome. This policy is supported by some expert opinions [98] and by the results of a long-term study [40].

As mentioned earlier, when proposing a therapeutic guideline for NBD, the efficacy, safety and cost of drugs should be considered. Generally speaking, azathioprine, methotrexate and cyclophosphamide have been more extensively studied, are less hazardous and more affordable. TNF-α-blocking drugs and IFN-α are therapeutic options with higher prices and limited data on long-term adverse effects. Chlorambucil should be considered as a last resort due to its potentially hazardous effects. Biologics other than anti-TNF drugs and tolerization therapy, which have been used in case reports or small series or only hypothetically for use in NBD, are future weapons. Table 1 summarizes the size of treatment effects and the strength of recommendation of major therapeutic options for NBD.

Selection of treatment regimens for parenchymal NBD should be based on the presence of poor prognostic factors, including multifocal involvement, spinal presentations, more than two attacks per year, progressive course and increased CSF cell count and protein content at the time of neurologic manifestations.

For the low-risk group without any poor prognostic factor, daily azathioprine or weekly methotrexate and corticosteroids are recommended as the first step. For the high-risk group and refractory patients of the low-risk group, intravenous pulse cyclophosphamide

and corticosteroids are recommended. Other anti-BD drugs, such as colchicines, sulfasalazine and dapsone, can be administered as adjuvant therapy in patients with NBD with simultaneous other manifestations of BD. If these regimens fail, TNF-α-blocking drugs, such as infliximab or etanercept, may be added. Shifting to other immunosuppressive drugs that had not been administered before can be used for patients resistant to the above regimens. Alternating IFN-α and then chlorambucil or experimental treatments are the last resorts for most refractory patients. Treatment of venous sinus thrombosis is based on anticoagulation and short-term corticosteroids with or without immunosuppressive drugs.

A systematic monitoring of the patient's clinical, CSF and radiological responses (as mentioned previously) at monthly and then 3-month intervals is necessary. If the patient developed complete remission, gradual tapering of immunosuppressive drugs and then corticosteroids should be followed. If incomplete remission or exacerbation is detected, shifting to more potent drugs is necessary.

Finally, the author restates the necessity of the multicentered, multidisciplinary randomized clinical trial for evaluation of the safety, efficacy and side-effect profile of different therapeutic options for the treatment of NBD. Head-to-head trials comparing different first-line drugs or first- versus second-line dugs are particularly recommended.

## *Expert commentary*

The literature on treatment of NBD mostly includes case reports, small series and a limited number of open label studies. Corticosteroids and immunosuppressive drugs have traditionally been the main stay of the treatment for NBD. Recently, targeted therapy has been developed for highly selective suppression of proinflammatory immune mediators. First-line drugs include corticosteroids, azathioprine, oral or pulsed intravenous cyclophosphamide and methotrexate. Second-line drugs include chlorambucil, IFN-α, anti-TNF monoclonal antibodies and thalidomide.

The author has proposed a therapeutic recommendation based on the type of manifestations, prognostic factors and response to other drugs. For patients with parenchymal NBD without any poor prognostic factor, daily azathioprine or weekly methotrexate and corticosteroids are recommended as the first step. For the high-risk group and refractory patients of the low-risk group, intravenous pulse cyclophosphamide and corticosteroids are recommended. If these regimens fail, TNF-α-blocking drugs, such as infliximab or etanercept, might be added. IFN-α or chlorambucil can be used for most refractory patients. Treatment of cerebral venous sinus thrombosis can be achieved by anticoagulation and short-term corticosteroids with or without immunosuppressants.

## *Five-year view*

As NBD is somehow rare, multicentered randomized clinical trials should be conducted for evaluation of its different therapeutic options. Head-to-head trials comparing azathioprine, methotrexate, cyclophosphamide and anti-TNF antibodies are especially recommended.

TNF-α-blocking drugs, including infliximab, etanercept, adalimumab and certolizumab, are promising drugs for refractory patients. However, the evidence of their efficacy is based on case reports and small series. If large head-to-head trials show their efficacy in comparison to conventional immunosuppressive drugs, these biologics can be administered not only for refractory patients but also as first-line drugs.

Although tocilizumab (anti-IL-6 antibody) has not been used for NBD yet, owing to persuading evidence on the role of IL-6 in the in situ pathogenesis of NBD, the author recommends a randomized clinical trial using this monoclonal antibody in the near future. Alemtuzumab, a monoclonal antibody against CD52 antigen, may be another potential weapon against NBD. High cost is the major obstacle for promotion of monoclonal antibodies in the field of NBD.

Table 1. Size of treatment effects and strength of recommendation of major therapeutic options for neuro-Behçet's disease.

## *Key issues*

- Neurological manifestations of Behçet's disease (neuro-Behçet's disease) present in 5-30% of patients.
- CNS involvement can be divided into two main groups: parenchymal involvement that presents with brainstem involvement, hemispheric manifestations, spinal cord lesions and meningoencephalitic presentations; and nonparenchymal involvement that includes cerebral venous thrombosis, arterial occlusion and aneurysms.
- Proposed treatment options for parenchymal neuro-Behçet's disease are corticosteroids, azathioprine, oral or pulsed intravenous cyclophosphamide, methotrexate, IFN-α and anti-TNF monoclonal antibodies.
- Treatment of venous sinus thrombosis is based on anticoagulation and short-term corticosteroids. Immunosuppressants can also be added.
- Cyclosporine A may exacerbate or even induce neurological complications of Behçet's disease.
- TNF-α blockade with infliximab or etanercept are promising therapeutic options for refractory patients.

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