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Literature Review

Use of non-TNF biologics for the treatment of neuro-Behçet's disease: Literature review and 2 refractory cases of monoclonal anti-TNFs treated with tocilizumab

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Abstract

Neurological complications of BD (neuro-Behçet's disease [NBD]) are life-threatening and disabling manifestations. Neurological involvement occurs in approximately 5% to 18% of patients with BD. Most patients with NBD respond well to glucocorticoids, cyclophosphamide, or anti-tumor necrosis factors (TNFs), but there are some resistant cases refractory to these drugs. This study aims to summarize the existing data on the management of NBD, with special focus on patients resistant to anti-TNFs. The study included a short review of early treatment steps. In addition to a literature review of treatment with non-TNF biologics, we present 2 NBD cases with neurological involvement that are resistant to standard high-dose steroid therapy and anti-TNF treatment. Both patients responded well to the tocilizumab therapy, and there was no serious adverse event.

Keywords: Behçet's disease, tocilizumab, neurological involvement

Introduction

Behçet's disease (BD) is a multisystemic disorder of unknown etiology and vessel vasculitis that involves the skin, mucosa, joints, eyes, arteries, veins, nervous system, and the gastrointestinal system.[1,2] BD as an autoinflammatory disorder has certain clinical features, which depend on the organ systems involved.[3] Although a mild course can be observed in the mucocutaneous form of the disease, organ damage or life-threatening features may be encountered, especially in cases of major organ involvement or vascular involvement. Moreover, neurological complications of BD (neuro-Behçet's disease [NBD]) are among the life-threatening and disabling manifestations.[4] NBD involvement occurs in approximately 5% to 18% of patients with BD.[5,6] According to 2018 European League Against Rheumatism (EULAR) recommendations for the management of BD, acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressive drugs such as azathioprine. Monoclonal anti-tumor necrosis factor (TNF) antibodies should be considered in severe cases of the disease as first-line treatment or in refractory patients.[1,7] Most patients with NBD respond to glucocorticoids, cyclophosphamide, or anti-TNFs, but there are some resistant cases refractory to these drugs.[8] Recent EULAR recommendation on the management of BD address the role of anti-TNFs, but further steps for the resistant cases are not clearly mentioned on account of insufficient clinical data.[1]

This study aims to summarize the existing data on the management of NBD, especially focusing patients resistant to anti-TNFs. To that end, we conducted a short review of early treatment steps. After a literature review of treatment with non-TNF biologics, we present 2 NBD cases with neurological involvement that are resistant to standard high-dose steroid therapy and anti-TNF treatment. Since there are recently published case reports focusing on the efficacy of tocilizumab, we herein aimed to show the value of interleukin (IL)-6 blockade and potential agents in the treatment of NBD.

Case 1

A 32-year-old male patient consulted our neurologist with complaints of double vision following increasing headaches and vision disorder for the last 6 months. Neurological evaluation did not consider primary neurological disease after comprehensive examinations of cranial magnetic resonance imaging (MRI) and other evaluations. Bilateral papillary edema was seen in ophthalmic consultation, and due to the gradual deterioration of the general condition of the patient and the high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), rheumatology consultation was requested. In rheu-

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Table 1. Non-TNF biologics used in refractory NBD cases.

Drug	Mechanism of action	Dose in case report	Adverse events	Reference
Tocilizumab	IL-6 receptor-monoclonal antibody	4-8 mg/kg IV infusions every 4 weeks	Hepatotoxicity, infusion site reactions, abnormalities in lipid profile, low platelet count, gastrointestinal perforations	- Addimanda et al. (8) - Urbaniak et al. (11) - Shapiro et al. (10)
Rituximab	Anti-CD20 antigen, monoclonal antibody	1000 mg IV infusions every 2 weeks, and every 6 months in follow-up	Infusion site reactions, hepatitis B reactivation, infusion reaction, infections, multifocal leucoencephalopathy, - late onset neutropenia	- Kidd (16) - Enriquez et al. (19) - Jade et al. (17) - Messina et al. (18) - Garcia Estrada C, 2020
Ustekinumab	Human monoclonal anti-IL-12/IL-23 antibody	Preload injections of ustekinumab at 90 mg at week 0, week 4, and week 16. 90 mg every 3 months follow-up dose.	Upper respiratory tract infection, nasopharyngitis, injection-site reactions, headache and fatigue	- Baerveldt et al. (21) - Terrier (22) NCT02648581*

*NCT02648581: This is an ongoing clinical study with unpublished clinical data.
IL: interleukin; IV: intravenous; NBD: neuro-Behçet's disease; TNF: tumor necrosis factor.

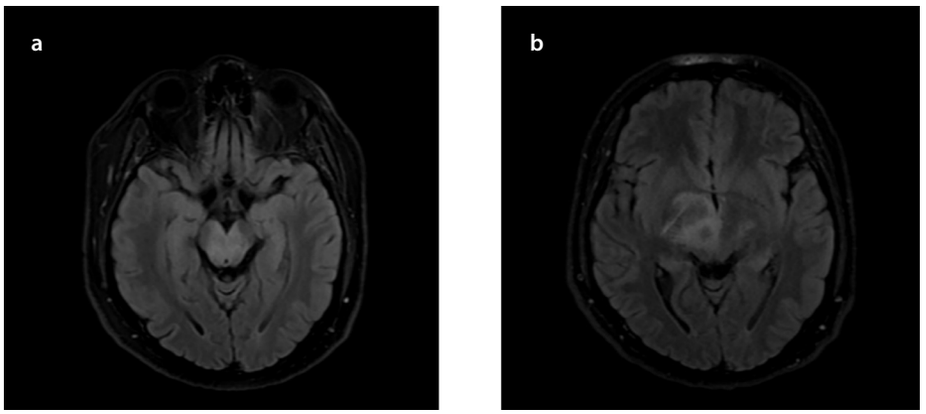

Figure 1. a, b. Symmetrical signal increase in flair sequence and Mesencephalon involvement of NBD (a) and Irregular signal increase observed in the right thalamus and internal capsule flair sequence (b).

matology examination, recurrent oral aphtha, recurrent genital ulceration, and skin lesions that may be compatible with erythema nodosum were detected for the last 5 years. In light of these symptoms, BD was considered as a preliminary diagnosis for the patient. The patient was transferred to a rheumatology clinic for further investigation. Human leukocyte antigen (HLA)-B51 genes are important in the pathogenesis of the disease. Therefore, HLA B51 and pathergy tests of the patient were requested.

When we looked at the radiological evaluation of the patient, in the cranial MRI, there was an increase in signal intensity in the T2A and FLAIR sequence, representing basal nuclear involvement, right thalamus and internal capsule posterior leg involvement, which was pathognomonic for BD, as well as mesencephalon and posterior colliculus involvement (Figure 1). Genetic and pathergy tests were inconsistent with clinical findings. Both HLA and pathergy tests were carried out. Pathergy test results were positive. The patient was started on 1 g/day steroids for a week, followed by 1 mg/kg/day steroid and 2.5 mg/kg/day azathioprine treatment. There was a rapid decrease in the patient's headache complaints and an improvement in visual impairment. At the end of the first month, the patient's clinical findings deteriorated under steroid and azathioprine treatment. In addition to severe headache, visual impairment, double vision, nausea, and vomiting, the patient's CRP and ESR levels were elevated. The previous steroid treatment of 1 g/day steroids was repeated for 3 days; however, symptoms were persistent and the patient's complaints gradually worsened. Alternatively, cyclophosphamide therapy was recommended, but the patient did not give consent after we provided information about the risk of developing oligospermia or azoospermia, which are normally associated with increased gonadotropin but normal testosterone secretion.

Due to the lack of expected improvement on the 45th day of treatment, the azathioprine treatment was discontinued, and infliximab therapy of 5 mg/kg/every 6 weeks was added to the treatment. Steroid dosage was stabilized as 20 mg/day, and dose reduction could not be achieved since there was no significant improvement in clinical findings. In addition, due to weight gain, high blood sugar, and uncontrolled hypertension, the dose could not be increased when needed.

Infliximab was given to the patient 3 times every 6 weeks. Even if partial response was obtained, the steroid dose could not be reduced. Although the patient's headache and visual impairment complaints decreased compared with those in the past, it still did not reach the expected level. The patient was followed up with a partial response and in the 8th month of treatment, a new attack was observed.

Main Points

- Neurological complications of BD (neuro-Behçet's disease [NBD]) are life threatening and disabling.
- Neurological involvement occurs in about 5% to 18% of patients with BD.
- Glucocorticoids, cyclophosphamide, and/or anti-tumor necrosis factors (TNFs) are the primary treatment choices.
- Some NBD cases are refractory to anti-TNFs, and there is no specific guidance to anti-TNF-resistant cases.
- Tocilizumab can be the last resort in refractory NBD cases.

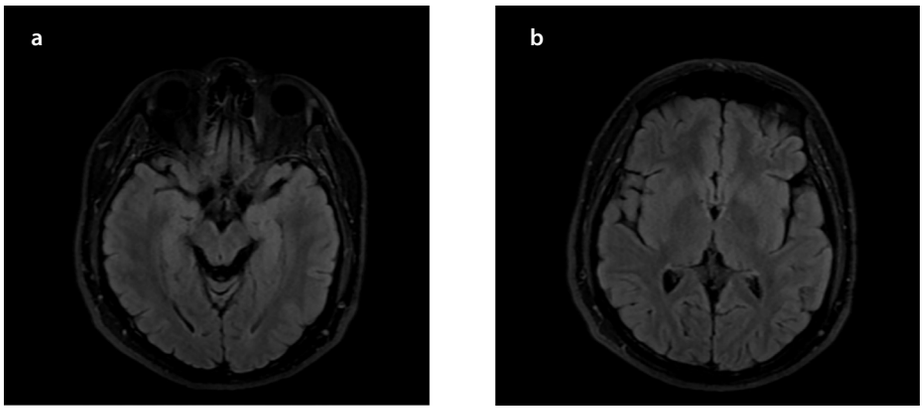

Figure 2. a, b. The mesencephalon signal disappeared completely after treatment and returned to normal (a). Also, thalamus and internal capsule signal was not observed again (b).

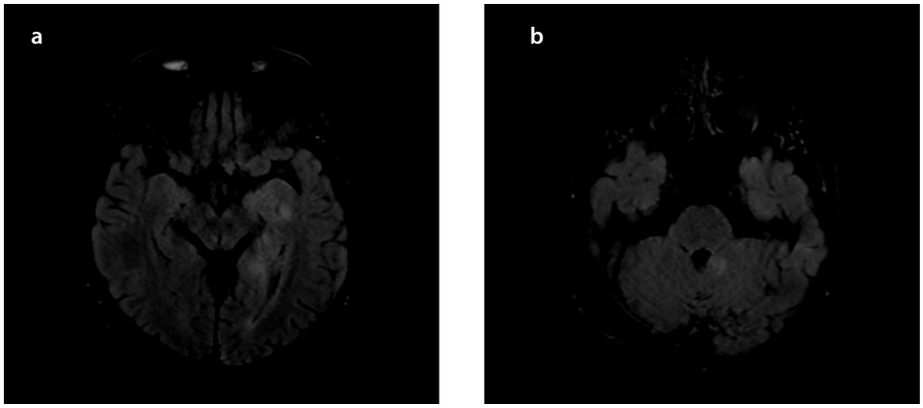

Figure 3. a, b. Significant signal increase in the left temporoparietal and peritrigonal region of the NBD flair sequence (a), and signal increase representing NBD associated involvement in left inferior cerebellar pedicle (b).

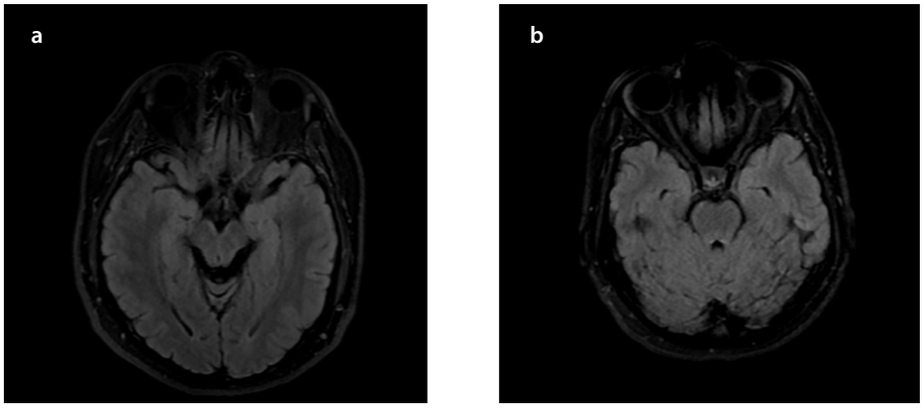

Figure 4. a, b. After the treatment, the signal increase in left temporoparietal and peritrigonal region was completely disappeared (a) and cerebellar pedicle was observed in normal view (b).

Due to increased CRP levels and accompanying steroid dose and worsening clinically compatible findings, such as oral aphthae, headache, and visual impairment, it was decided to start tocilizumab 8 mg/kg once a month. After adding tocilizumab to steroid 20 mg/day (steroid dose was determined during infliximab therapy, and due to relapses in symptoms, lower doses were not preferred), a significant improvement was observed in the patient's clinical and laboratory findings. At the sixth dose of tocilizumab, the patient's laboratory and clinical findings normalized. The patient's steroid dose was decreased to 2.5 mg/every-other-day. In the last control cranial MRI of the patient, it was observed that the signal increase in the T2A and FLAIR sequence, which represents involvement in the basal ganglion and brain stem monitored during diagnosis, completely declined after treatment (Figure 2). The patient is currently in clinical laboratory and radiological remission receiving under 2.5 mg/every-other-day steroid and tocilizumab 8 mg/month treatment.

Case 2

A 36-year-old male patient consulted the neurologist with complaints of headaches, visual impairment, intermittently monitored joint pain, joint swelling, and mobility limitations. Rheumatology evaluation was requested regarding the joint complaints. The patient had a history of recurrent neurologist evaluations and a history of nonspecific analgesic and migraine treatment. The rheumatology evaluation revealed that the patient had recurrent oral and genital ulcers for the last 3 years. In addition, there was intermittent recurrent nondestructive arthritis in the right knee. CRP and ESR test results were in normal ranges. Septic arthritis and gout were ruled out with joint puncture applied to the knee. BD was considered clinically. HLA B51 and pathergy tests were requested to reach a final diagnosis. In the cranial MRI of the patient; there was an increase in signal intensity in the left inferior cerebellar pedicle, left thalamus lateral and left peritrigonal region in T2A and FLAIR tab (Figure 3). The patient's existing radiological and clinical symptoms with laboratory findings were thought to be due to central nervous system involvement of BD. The pathergy test result of the patient was negative, and the HLA B51 test result was positive.

The patient was started on 1 g/day steroid for 3 days followed by concomitant 2.5 mg/kg/day azathioprine treatment with 0.5 mg/kg/day maintenance steroid treatment. The patient's headache, visual impairment, arthritis, and aphthae findings improved rapidly. In the third month of the treatment, the patient's clinical findings showed a deterioration under 10 mg/day steroid and 150 mg/day azathioprine treatment. In addition to severe headache, vomiting, and joint pain, the CRP and ESR levels were increased significantly. Following 1 g/day steroid lasting 3 days, 0.5 mg/kg/day maintenance steroid treatment was implemented.

The treatment of azathioprine 150 mg/day continued, however, due to the absence of expected improvement in the first month of the treatment, azathioprine was discontinued. The patient's steroid dose could not be reduced, and the complaints continued to a large extent. Infliximab 5 mg/kg every 6 weeks was added to the treatment. Before starting anti-TNF treatment, we also recommended cyclophosphamide therapy; however, the patient did not give consent due to gonadal side effect risks. The steroid dose was continued at 0.5 mg/kg/day. According to the clini-

cal response, the steroid dose was gradually reduced. Infliximab was applied to the patient 4 times every 6 weeks. The treatment change was decided due to the decrease in the initial good response at the sixth month of treatment and the new recurrent attacks that followed (oral major aphthae, headache, nausea, vomiting, visual impairment, and accompanying increment in acute-phase reactants).

In addition to the 0.5 mg/kg/day steroid treatment, the patient was started on tocilizumab 8 mg/kg once a month. According to the clinical improvement, the dose of the steroid was gradually decreased again. After the fourth tocilizumab treatment, the patient was found to have fully recovered per the clinical, laboratory and radiology findings. In the control cranial MRI, the baseline brainstem basal ganglionic and peritrigonal involvement completely regressed (Figure 4).

Discussion

The BD is a multisystemic disorder of unknown etiology and vessel vasculitis that may involve the nervous system as well.[1,2] BD's features depend on the organ system involved.[3] NBD is associated with life-threatening and disabling manifestations of BD.[4] According to recent literature, NBD involvement occurs in approximately 5% to 18% of patients with BD.[5,6] There have been no controlled or comparative trials on the treatment of any aspect of NBD. However, retrospective studies have shown the efficacy of steroids, azathioprine, and anti-TNFs.[8]

According to 2018 EULAR recommendations for the management of Behçet's syndrome; acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressive such as azathioprine. Monoclonal anti-TNF antibodies should be considered in severe cases of the disease as first-line treatment or in refractory patients.[1,7] Most patients with NBD respond to glucocorticoids, cyclophosphamide, or anti-TNFs, but there are some resistant cases refractory to these drugs.

Refractory cases can be treated with IL-6 inhibitors, B-cell inhibitors and other drugs such as interferon alpha. IL-6 concentrations seem to be associated with the pathogenesis of NBD[8] because patients with NBD had elevated cerebrospinal fluid (CSF) levels of IL-6 in contrast to unaffected controls.[9] Due to the proven pathogenetic role of IL-6 in NBD, clinicians tried IL-6 blockade as an alternative option to treat manifestations in refractory patients.[10,11] Since increased IL-6 concentrations seem to be associated with the pathogenesis of NBD, IL-6 inhibition is the primary option for the patients with NBD who are refractory to anti-TNFs.[12] However, there are reports with rituximab and interferon alpha, too. We herein presented 2 cases of NBD resistant to treatment options listed in 2018 EULAR recommendations and a comprehensive literature review of resistant cases treated with non-TNF biologics. Both patients were resistant to anti-TNF antibodies and were successfully treated with tocilizumab.

At present, there is not a specific guideline or recommendation for the management of NBD, and it is generally included in BD treatment protocol.[1,4] Treatment alternatives used for BD are also used for the management of NBD, but owing to its unique nature and characteristics, it is not always true to extrapolate to NBD. There are 2 important guidelines addressing the management of NBD.[1,4] According to the 2018 EULAR recommendations for the management of BD, acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressive drugs such as azathioprine.[1] Efficacy of cyclosporine A in BD is widely accepted, but it is avoided in NBD given the unique nature of the disease. Monoclonal anti-TNF antibodies should be considered in severe cases of the disease as first-line treatment or in refractory patients. It is already known that there are patients resistant to anti-TNFs and existing guidelines do not address the resistant cases. Although there have been no controlled or comparative drug studies on NBD, there is enough clinical experience and case reports showing efficacy of non-TNF biologics (Table 1). Table 1 summarizes the existing data on non-TNF biologics used in treatment of refractory NBD cases.[9]

Elevation of plasma IL-6 levels has been one of the key laboratory finding in patients with BD. In addition, it is mainly used to show evidence of neurologic involvement. Significant changes in IL-6 suggest a correlation with disease activity.[13] Because of increased IL-6 levels, monoclonal antibody against IL-6 is regarded as a new treatment for the management of NBD. Addimanda et al[8] presented 3 resistant cases successfully treated with tocilizumab where all patients attained low disease activity. There are recent case reports and reviews showing the efficacy of IL-6 in NBD.[8,10,11] Tocilizumab as an IL-6 inhibitor is widely used as monotherapy or in combination with corticosteroids.[13] The reported dosage of tocilizumab was 8 mg/kg every 4 weeks.[8,10,11] As in treatment with anti-TNF drugs, there is increased risk of activating latent tuberculosis among patients using tocilizumab. Tuberculosis screening should be conducted before starting tocilizumab and isoniazid prophylaxis (300 mg/day) should be prescribed for 9 months in patients with latent tuberclosis.[4,9] In addition, during the treatment process, allergic reactions, hypercholesterolemia, and bowel perforation are other important adverse effects, and therefore, close clinical follow-up is needed.[9] Our clinical findings were in parallel with the recent case reports of resistant NBD cases treated with tocilizumab.

There are certain studies suggesting potential pathogenetic role of B cells in patients with BD.[14] The interaction of B cells with T cells and T-cell involvement in BD make B-cell inhibitors such as rituximab a potential treatment modality for refractory NBD. Rituximab is a chimeric monoclonal antibody against CD-20, and it is one of the most off-label used drug in immune-mediated diseases.[13] There are recent studies showing efficacy of rituximab in ocular manifestations of BD. Although there have been no controlled studies in NBD, rituximab was investigated in a single-blind randomized controlled trial of refractory BD patients with eye involvement.[15] Rituximab was efficient in severe ocular manifestations of BD. Patients' Total Adjusted Disease Activity Index improved significantly after 6 months of rituximab treatment.[15] Rituximab's use in NBD is limited to case presentations and needs further evidence.[16-19] According to a recent review by Borhani et al,[9] rituximab shown as Class IIA and level C recommended treatment alternative for the management of NBD. Rituximab doses vary in terms of patients' conditions, and mostly it is used IV 1000 mg/every six months.[16-19] If there is loss of response to tocilizumab, rituximab can be an alternative option in resistant NBD cases.

IL-17 inhibitors are not eligible for the treatment of NBD. Recently, there have been case reports showing the role of IL-17 blockade in triggering BD reactivation.[20] However, there are increased serum levels of IL-12 and IL-23 in patients with BD with ocular involvement.[13,21] Ustekinumab as an IL-12 and IL-23 inhibitor can be an alternative treatment for NBD cases. There are ongoing studies assessing the safety and efficacy of ustekinumab, in patients with Behçet's disease (STELABEC).[22] The results can be extrapolated to NBD cases.

Conclusion

In the absence of recommendations and guidelines, non-TNF biologics including IL-6 inhibitors,

B-cell inhibitors, and IL-12/23 inhibitors have been reviewed. Considering the role of IL-6 in the pathogenesis of NBD, inhibition of this pathway can be a successful treatment option. Due to the absence of randomized studies on NBD, recent recommendations produced by global authorities did not put tocilizumab in the treatment algorithm. However, clinical findings and literature show future promising results.

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflict of interest to declare.

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