Forcefulness of Infliximab in Patients with Neuro-Behçet’s Disease

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DOI: 10.21276/sjmps.2019.5.2.14

Abstract

Behçet’s disease is a systemic vasculitides, characterized clinically by recurrent mucocutaneous lesions but vital organs may be affected like central nervous which can increased the morbidity-mortality especially among young patients. Infliximab, is a promising therapeutic approach for this disease especially in those with manifestations refractory to the standard immunosuppressive therapy. We report 3 cases of refractory neuro-Behçet’s disease with a dramatical clinical improvement under infleximab.

Keywords: Neuro-Behçet’s disease, Infliximab, Behçet’s disease.

INTRODUCTION

Behçet’s disease (BD) is a rare systemic vasculitis of unclear aetiology, it can involve both arteries and veins of all sizes. For this reasons, all organ systems can potentially be affected.

The recurrent oral and genital ulcerations and uveitis are the hallmarks of the disease. Whatever patients may also present arthralgia, venous or arterial thrombosis and neurological involvement.

The neurological involvement in BD, also known as neuro-Behçet’s disease (NBD) is one of the most serious complications of BD. It is one of the main causes of morbidity and mortality and occurs in approximately 5–14% of patients with BD [1]. It was described for the first time in 1941 [2].

In NBD, the central nervous system involvement can be classified into parenchymal-NBD characterized by inflammation of small venous structures that produces focal or multifocal CNS involvement and non-parenchymal-NBD characterized by the involvement of extra-axial venous vasculopathy that produces venous sinus thrombosis, the distinction between the parenchymal-NBD and the non-parenchymal-NBD is fundamental for the treatment choice decision.

The treatment of NBD remains empirical. Currently, no treatment option has been supported by randomized controlled trials (RCTs). Corticosteroid and immunosuppressive agents are widely used but may not control the disease adequately. Infliximab (IFX) is one of the tumor necrosis factor α (TNFα) inhibitors that begins to be used during the last 2 decades in treating patients with BD. IFX is expected to be an efficient strategy for treatment of NBD.

In this article, we report the experience of our center in administration of IFX for treatment of NBD.

CASE SERIES

Case 1:

A 41-year-old man was admitted two years before for headache with severe weakness in his left leg. His medical history revealed otherwise that he suffered from recurrent oral ulceration and genital ulceration. His skin exam showed multiple scar of genital ulceration, ophthalmologic examination demonstrated a total posterior synechiae in both eyes.

He had positive pathergy reaction, so he fulfilled the International Behçet’s disease Study Group criteria.

On neurological exam, he had left hemiparesis without facial paralysis and cerebellar ataxia. Cranial nerve examination was normal.

Results from blood tests were unremarkable and cerebrospinal fluid (CSF) analysis demonstrated increased lymphocytes (110 cells/mm3) and protein (58 mg/dl). CSF IgG oligoclonal banding was negative.
His cranial MRI revealed multiple signal lesions involving the right internal capsule and right cerebellar hemisphere.

We diagnosed NBD and treatment with intravenous methylprednisolone at 1,000 mg/day for 5 days was started with improved symptoms. A maintenance dose of 50 mg/day of oral prednisolone was administered for 8 weeks before to decrease the dose gradually (mean dosage 10 mg/day) associated with colchicine at 1 mg daily. He received also pulse cyclophosphamide (1g/month for 6months) and subsequently azathioprine 150 mg/day. The neurologic symptoms were improved. Seven months later, his gait gradually deteriorated with severe ataxia.

Azathioprine was withdrawn and IFX was started (5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter). A dramatic improvement in his gait remained stable throughout the observation period without any serious side effect. During the 12 months, the patient remained clinically steady.

Case 2:

A 35-year-old man, admitted in 2006 for headache, diplopia, vomiting and left hemiparesis. The patient reported that he had recurrent oral ulceration and genital ulceration during two years. His cerebral MRI revealed right temporal lobe inflammatory lesion.

Cerebrospinal fluid (CSF) analysis demonstrated increased lymphocytes (70 cells/mm3) and increased protein (55 mg/dl).

The diagnosis of NBD was made, and he received intravenous methylprednisolone 1 g per day for 5 days. A maintenance dose of 50 mg/day of oral prednisolone was prescribed. He received also pulse cyclophosphamide (1g/2months) for 2 years; relay with daily azathioprine (150 mg/day).

The patient was followed in our daily hospital with a stable course for 11 years. In 2017, he presented with severe left flaccid hemiplegia, dysarthria, difficulty swallowing and cerebellar ataxia.

After he received intravenous methylprednisolone, the symptoms of the patient were resolved partially and we decided to start IFX with a dose of 5 mg/kg administered by infusions at weeks 0, 2, 6, and every 8 weeks. The patient improved, became stable with no recurrent attack. He has been treated by IFX for 1 year and half, without any serious side effect.

Case 3:

A 48-year-old man, admitted in 2015, for sudden left weakness with ataxia. The neurological exam revealed cerebellar syndrome, left hemiparesis with bilateral paralysis of the VI cranial nerve.

His medical history revealed recurrent oral ulceration and genital ulceration; his ophthalmologic examination demonstrated an anterior synechiae in both eyes. He had positive pathergy reaction, so he fulfilled the International Behçet’s disease Study Group criteria but he didn’t receive any treatment before.

The cerebral MRI showed multiple inflammatory lesions involving the righ medial temporal lobe and mesencephalon. Cerebrospinal fluid (CSF) analysis demonstrated increased lymphocytes (85cells/mm3) and protein (75 mg/dl).

The diagnosis of NBD was made and we decided to start intravenous methylprednisolone for 5 days. Maintenance dose of 65 mg/day of oral prednisolone with colchicin 1mg/day and pulse cyclophosphamide 1g/2 month was administered, with partial improvement.

After1 years of therapy with cyclophosphamide, he reported worsening of the ataxia with left hemiparesis. Cerebral MRI showed inflammatory lesion of the right internal capsule with brain stem atrophy.

Cyclophosphamide was withdrawn and treatment with IV methylprednisolone pulses. IFX with a dose of 5 mg/kg was started by infusions at weeks 0, 2, 6, and every 8 weeks. The neurological state was improved without recurrent attack or any serious side effect and he has still been treated with IFX for 1 year.

DISCUSSION

BD is a potentially sight-threatening condition and one of the most feared complications is the neurological involvement.

In a study of the 430 BD patients, 121 patients (28.1%) had neurologic symptoms: 74 patients had a parenchymal involvement (61%); 41 patients became dependent; 5 patients had no improvement with severe disability; and 3 died [2]. In another study, the mortality rate of NBD was 10.4% [3].

The etiology of BD is still unclear, but it is known that immune systems are activated in BD. T lymphocytes are the principal element in the development of BD by releasing cytokines (such as TNFα), resulting in damage to the affected tissues. The aims of BD treatment are to control inflammation [4]. TNFα is believed to play an important role in BD. Many studies have shown an over production of TNFα in this condition [4]. This makes think of the possible effectiveness of anti-TNFα treatment in BD.

Considering the high rate of morbidity and mortality in NBD, rapid introduction of immunosuppressive treatment is critical.
The treatment of parenchymal forms of NBD is poorly coded, due to the lack of prospective RCTs in this pathology.

The European League Against Rheumatism (EULAR) recommendations in 2018 proposed for the management of Acute attacks of parenchymal involvement, high doses of pulsed glucocorticoids for rapid suppression of inflammation, followed by slow tapering, to gather with immunosuppressives to prevent recurrences and progression [5].

The dose and duration of the initial intravenous treatment and the subsequent oral therapy vary between different centers [5]. In the EULAR 2018, it recommended to start with daily pulses of intravenous methylprednisolone 1 g/day that may be continued for up to 7 days followed by oral prednisolone (or prednisone) at 1mg/kg/day for 1 month and tapered by 5–10mg every 10–15 days [4].

Retrospective studies have shown that two-thirds of patients with brainstem lesions or cerebral lesions make good recovery in response to the courses of steroids, but the other third have recurrence of relapses or progressive course [5]. Another alternative for the relapses is the plasma exchange (PE), especially when high dose steroid fails. There have been some reports suggesting that PE is effective when it used in a group of autoimmune diseases including BD. Also there has been a recommendation to use PE in BD in the guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis 2016 [6].

The treatment with glucocorticoids should never be used alone. The rationale to start a disease modifying therapies is to help in controlling the inflammatory process, to prevent or reduce the frequency of further neurological relapses, to reduce steroid exposure, and possibly to control the other systemic features of this multisystem disease.

None of the agents, including intravenous cyclophosphamide (750 mg / m2 / month) and azathioprine (2-3 mg / kg / day) that are commonly used, in analogy to other vasculitis with cerebral involvement have been shown beneficial in NBD in a RCTs (7). Otherwise in clinical practice, it is classical to add an immunosuppressant drug such as azathioprine or monthly pulse cyclophosphamide.

IFX, a recombinant chimeric monoclonal antibody which effectively neutralizes both the soluble and membrane binding forms of TNF-α, has been shown an effective agent in the treatment of rheumatoid arthritis, Crohn’s disease and spondylarthopathies [8]. The efficacy and safety of IFX in patients with refractory BD has been reported [9], with the drug leading to a good outcome of neuro-Behçet manifestations [10, 11].

NBD may be refractory to the classical drugs (glucocorticoids and immunosuppressive therapies). The International Neuro-Behçet Syndrome Advisory Group recommended TNF-α blockers as second-line options after first-line therapy failure, intolerance, or an aggressive course [12].

Zeydan et al., reported 16 patients of NBD switched to IFX (5 mg/kg in weeks 0, 2, and 6, then once every 8 weeks; minimum follow-up duration ≥ 12 months) from common immunosuppressive drugs. For 15 patients, neurologic relapses were ended and no worsening under IFX [12]. For one patient the treatment was stopped because of pulmonary and CNS tuberculosis (TB) [11]. It is well known that drugs like IFX is possibly associated with reactivation of latent TB or other serious infections. Testing for latent TB is important to prevent infection.

In our cases, we confirmed the efficacy of IFX in a refractory NBD, the treatment stopped the progression of the disease and no relapse has been seen for all the cases. Also, no infection has occurred, IFX was pretty tolerated. For the long-term effects, there are few publications for a possible positive effect of IFX for NBD [13, 14].

For the optimal duration of anti-TNFα in BD patients in clinical remission, there is no data but some authors recommend a minimal treatment period of 2 years [4].

There are two doses of IFX that are used in NBD, 3mg/kg and 5mg/kg but no study showed the superiority of one compared to the other but it was some cases showed that a 5 mg/kg regimen had better clinical responses [15].

CONCLUSION

Our cases support that IFX, anti TNF-α agent, is a good candidate for NBD treatment when it is resistant to conventional immunosuppressive agents such as corticosteroids or azathioprine. IFX seems to be safe and effective in controlling the disease.

REFERENCES


