Successful Treatment with Infliximab for Refractory Uveitis in a Hemodialysis Patient with Behçet’s Disease and a Review of the Literature for Infliximab Use in Patients on Hemodialysis

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Abstract

A 36-year-old man with a 16-year history of refractory Behçet’s disease (BD)-associated uveitis and chronic renal failure requiring hemodialysis suffered from frequent ocular attacks despite treatment with systemic corticosteroids and cyclosporine A. Following infliximab administration, the patient’s BD ocular attack score 24 and visual acuity improved. Although he developed mild acute gastroenteritis, he did not experience any other adverse events. In our review of the literature, we identified seven patients on hemodialysis with inflammatory disease successfully treated with infliximab. Infliximab may be effective and safe in cases of BD and other diseases, including in patients under hemodialysis.

Key words: Behçet’s disease, uveitis, hemodialysis, infliximab

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Introduction

Behçet’s disease (BD) is a systemic inflammatory disorder of unknown etiology characterized by a relapsing-remitting course. Although the clinical manifestations of BD vary greatly, 25% to 75% of BD patients develop uveitis (1). While oral aphthous ulcers commonly occur in BD patients, individuals without this symptom are reported to exhibit more prevalent ocular involvement (2). Uveitis associated with BD occurs in a variety of patterns of attacks, and Nussenblatt et al. reported that repeated attacks may result in severe visual obstruction (1). The administration of infliximab to treat BD-associated refractory uveitis has been shown to be effective and in 2008 gained the recommendation of the European League Against Rheumatism (EULAR) (3).

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor α (TNFα) and has been proven to be very effective when used in combination with immunosuppressive agents, such as methotrexate (MTX), particularly in patients with rheumatoid arthritis (RA) (4, 5). However, the efficacy and safety of infliximab have not been sufficiently explored in patients with renal impairment or a history of treatment with regular hemodialysis, due to the difficulties in applying combination therapies with immunosuppressant drugs in these patients. To the best of our knowledge, there are no reports regarding the use of treatment with infliximab for BD-associated uveitis in patients undergoing hemodialysis. We herein report our experience with treating such a patient with infliximab and provide a review of the literature on the use of infliximab in patients on hemodialysis.

Case Report

A 36-year-old Japanese man was admitted to our hospital...
with reduced visual acuity (VA). He had been diagnosed with complete BD 16 years earlier based on the presence of oral aphthous ulcers, pseudofolliculitis, genital ulcers and uveitis. In addition, he was found to have HLA-B40/B59 on human leukocyte antigen typing. At that time, his best-corrected visual acuity (BCVA) (expressed in decimals) was 1.2 for both the oculus dexter (OD) and oculus sinister (OS) measurements. For one year, he experienced recurrent ocular attacks, despite receiving treatment with oral colchicine and a topical corticosteroid. Although he showed a partial response to oral cyclosporine A (CsA) prescribed 14 months after his initial presentation, which achieved a reduction in the frequency of the attacks, his loss of vision had already severely progressed. His VA findings included light perception (OD) and 0.1 (OS) five years after the first attack, and fundoscopy revealed optic atrophy in the left eye (Fig. 1A).

Three years before presenting to our department, the patient had developed renal impairment leading to end-stage renal disease (ESRD) that required regular hemodialysis. A renal biopsy was not performed because he refused this procedure. A laboratory examination showed an elevated urine β2-microglobulin level, whereas the titers for anti-nuclear antibodies, anti-DNA antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) were all negative. Ultrasonography revealed the kidneys to be highly echogenic without vascular thrombosis, although gallium scintigraphy detected no abnormal accumulation in the bilateral kidneys. These findings were insufficient to confirm the etiology of ESRD, including IgA nephropathy and renal amyloidosis. Treatment with CsA was subsequently discontinued due to suspicion that nephrotoxicity was the cause of the patient’s renal impairment. One year before presenting to our hospital, the administration of CsA was resumed at a dose of 25 mg/day and oral prednisolone (PSL) (30 mg/day) was prescribed, due to relapse of the ocular attacks. The BD ocular attack score 24 (BOS24) (6) subsequently decreased from 3 to 0 in the left eye: however, the attacks again relapsed after PSL tapering (Fig. 2).

At the time of admission, the patient’s VA was light perception for both OD and OS, with anterior chamber cells and vitreous haze in the left eye. Therefore, the BOS24 for the left eye was calculated to be 4 (anterior chamber cells: 1 point, vitreous haze: 3 points). The presence of severe cataracts prevented an examination of the right eye (Fig. 2).

The use of infliximab was discussed with the patient, and, after obtaining his consent, treatment was initiated at a dose of 5 mg/kg body weight on weeks 0, 2 and 6 then every eight weeks thereafter. On week 17, his VA had improved from light perception to 0.03 for OS, and anterior chamber cells and vitreous haze were no longer detected; the resulting BOS24 decreased to 0 (Fig. 1B). After six months of treatment and follow-up, no ocular attacks occurred and he remained in clinical remission. During this period, he continued regular hemodialysis sessions three times per week, and his renal function remained stable, with no electrolyte or cardiovascular complications. On week 15, after the third administration of infliximab, he developed mild acute gastroenteritis, resulting in a one-week postponement of the fourth cycle of treatment. However, he did not experience any other adverse events, and the concomitant dose of corticosteroids was gradually tapered and CsA was discontinued without the recurrence of ocular symptoms. On week 24, just before the fifth administration of infliximab, the serum trough concentration of the drug was 9.81 μg/mL (Fig. 2).

**Review of literature**

Our search of the PubMed database revealed only seven cases of hemodialysis treated with infliximab published to date. In addition, to the best of our knowledge, the current case is the first case of BD-associated uveitis in a patient on hemodialysis treated with infliximab (Table). Cases involving sarcoidosis (7), rheumatoid arthritis (8, 9), juvenile idiopathic arthritis (10), psoriatic arthritis (11), ankylosing spondylitis (12) and Crohn’s disease (13) have been previously reported. Importantly, infliximab was effective in all seven reported cases, as in our BD patient. Moreover, Yee et al. (7) reported the success of infliximab treatment in a sarcoidosis patient. In that case, despite resolution of the enteropathic and myopathic symptoms, the patient developed a hypercoagulable state associated with circulating antikeratin antibodies, which subsequently led to the cessation of infliximab therapy (7). Although the current patient dever-
Figure 2. Clinical course of the disease before and after infliximab administration. PSL: prednisolone, p.o.: per os, CSA: cyclosporine A, i.o.: intraocular, IFX: infliximab, sCr: serum creatinine level, BOS24: Behçet’s disease ocular attack score 24, VA: visual acuity

Table. Summary of Patients on Hemodialysis Treated with Infliximab.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying disease</th>
<th>Duration of follow-up</th>
<th>Effectiveness</th>
<th>Adverse event</th>
<th>Concomitant drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>2001</td>
<td>72</td>
<td>Female</td>
<td>Sarcoidosis</td>
<td>6 weeks</td>
<td>effective</td>
<td>hypercoagulable state</td>
<td>CS</td>
</tr>
<tr>
<td>8</td>
<td>2002</td>
<td>60</td>
<td>Female</td>
<td>RA</td>
<td>2 years</td>
<td>effective</td>
<td>No</td>
<td>CS</td>
</tr>
<tr>
<td>9</td>
<td>2006</td>
<td>45</td>
<td>Female</td>
<td>RA</td>
<td>unknown</td>
<td>effective</td>
<td>No</td>
<td>CS, NSAIDs</td>
</tr>
<tr>
<td>10</td>
<td>2007</td>
<td>34</td>
<td>Female</td>
<td>JIA</td>
<td>24 months</td>
<td>effective</td>
<td>No</td>
<td>unknown</td>
</tr>
<tr>
<td>11</td>
<td>2010</td>
<td>52</td>
<td>Male</td>
<td>PsA</td>
<td>6 months</td>
<td>effective</td>
<td>No</td>
<td>SASP, NSAIDs</td>
</tr>
<tr>
<td>12</td>
<td>2010</td>
<td>46</td>
<td>Male</td>
<td>AS, IgA nephropathy</td>
<td>2 years</td>
<td>effective</td>
<td>No</td>
<td>SASP, NSAIDs</td>
</tr>
<tr>
<td>13</td>
<td>2011</td>
<td>33</td>
<td>Male</td>
<td>CD</td>
<td>5 years</td>
<td>effective</td>
<td>No</td>
<td>CS, IS</td>
</tr>
</tbody>
</table>

| Our case  | 2014 | 36  | Male  | BD                | 6 months             | effective | Acute gastroenteritis | CS |


BD is an inflammatory systemic disorder characterized by a number of symptoms, including recurrent oral and genital ulcers, specific skin rashes and recurrent attacks of uveitis. The BOS24 was developed to evaluate the severity of ocular attacks (6). It consists of a total 24 points for the following six parameters: anterior chamber cells, vitreous haze, peripheral retina lesions, posterior pole lesions, foveal lesions and optic disc lesions. Kaburaki et al. concluded that the BOS24 score is highly correlated with the specialist’s impression of the uveitis disease activity (6). We therefore employed the BOS24 to evaluate our patient’s condition, and, notably the score decreased dramatically from 4 to 0 after the initiation operated mild acute gastroenteritis, as described above, the six other patients identified in the literature search did not experience any adverse events (Table).

Discussion

BD is an inflammatory systemic disorder characterized by a number of symptoms, including recurrent oral and genital ulcers, specific skin rashes and recurrent attacks of uveitis. The BOS24 was developed to evaluate the severity of ocular attacks (6). It consists of a total 24 points for the following six parameters: anterior chamber cells, vitreous haze, peripheral retina lesions, posterior pole lesions, foveal lesions and optic disc lesions. Kaburaki et al. concluded that the BOS24 score is highly correlated with the specialist’s impression of the uveitis disease activity (6). We therefore employed the BOS24 to evaluate our patient’s condition, and, notably the score decreased dramatically from 4 to 0 after the initiation
of infliximab.

Several trials have demonstrated the beneficial effects of CsA in treating ocular involvement in cases of BD, and this drug is therefore widely used (3, 14, 15). However, evidence in the literature regarding the safety of this agent in ESRD patients is scarce. Furthermore, the use of CsA carries a risk of renal impairment (16). CsA nephrotoxicity is divided into acute and chronic categories. Acute nephrotoxicity is usually reversible with the cessation of CsA, whereas the chronic form is often irreversible. Hence, the use of CsA in ESRD patients is controversial. The administration of TNF-α inhibitors is considered in BD patients who exhibit an inadequate response to topical and/or conventional systemic therapies, such as corticosteroids, CsA and colchicine, or those with refractory ocular involvement. Although there are no controlled trials, several open-label clinical trials and non-randomized comparative studies have reported the efficacy of intravenous infliximab for BD-associated uveitis (17-21), among TNF-α inhibitors, only infliximab is approved for the treatment of BD-associated uveitis in Japan. However, little is known about the efficacy of infliximab in ESRD patients on hemodialysis. Another subcutaneous TNF-α inhibitor, adalimumab, is approved for BD-associated enteritis, but not BD-associated uveitis in Japan. Although adalimumab has been reported to be effective and safe in ESRD patients with RA (22), to the best of our knowledge, there are currently no reports regarding treatment with adalimumab in BD patients undergoing hemodialysis.

The current case report and review of the literature suggest the potential efficacy and safety of infliximab for patients undergoing hemodialysis, although the possibility of an undesirable serum infliximab concentration and increased incidence of adverse events, such as infection, must be considered. The serum trough infliximab concentration observed in our patient before the fifth administration (9.81 μg/mL) is comparable to that noted in patients with inflammatory bowel disease possessing a normal renal function treated with 5 mg/kg of infliximab (mean trough level: 3.0 μg/mL, range: <2.0-13.0) (23), suggesting that hemodialysis does not eliminate infliximab from the body. We speculate that infliximab is unable to penetrate the pores of hemodialyzers, as the molecular weight of infliximab (149,000 Da) is much larger than the pore size of the hemodialyzer. Kume et al. also examined the infliximab concentration in a Crohn’s disease patient with ESRD, reporting that the maximum and minimum serum levels remained essentially unchanged by hemodialysis (13). Hueber et al. retrospectively analyzed 11 patients with renal impairment treated with TNF-α inhibitors, concluding that the use of TNF-α inhibitors has no effect on the renal function in patients with renal disease or induce any increases in the incidence of adverse events, such as susceptibility to infection (10). Likewise, in the present patient, the serum creatinine level did not change during infliximab treatment. To our knowledge, the current case report is the first to document infliximab treatment in a BD patient with refractory uveitis on regular hemodialysis. As observed in other patients treated with infliximab, our patient responded well to the therapy and, despite developing mild acute gastroenteritis during the course of treatment, tolerated and continued the drug.

In conclusion, the current case and review of the literature provide support for the efficacy and safety of infliximab in patients undergoing hemodialysis. Although larger trials are required, infliximab is a promising treatment option for patients with refractory BD-associated uveitis.

The authors state that they have no Conflict of Interest (COI).

References
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