CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Efficacy of infliximab in treatment of refractory panuveitis associated with Behçet disease

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SUMMARY

Introduction Behçet disease (BD) is a chronic multi-system disorder with manifestations in the ocular, urological, articular, and vascular systems. Tumor necrosis factor alpha is believed to play a pivotal role in BD. Therapeutic blockade of its activity by infliximab is a novel therapeutic approach and has successfully led to remission of the disease.

The aim is to report two cases of refractory BD-associated panuveitis (PU) treated with infliximab. The patients were followed for 12 months. The main therapy assessment parameters were the best corrected visual acuity (BCVA) in the better eye, slit lamp and fluorescein angiography (FAG) from baseline findings and from the final examination.

Case outline A male patient (45 years old, 25 years of BD history) and a female patient (45 years old, 15 years of BD history), both with posterior synechia, 3+ flare and complicated cataract, while the female also had hypopyon, were treated with infliximab administered at the dose of 5 mg/kg at weeks 0, 2, 6, and 14. The results for the male patient were as follows (baseline vs. the final examination): BCVA – 0.5 vs. 0.8; cellular reaction – 3+ vs. 1+; FAG – 1/2 vs. 0. The results for the female patient were as follows: BCVA – 0.1 vs. 0.3; FAG – 2/3 vs. 0. After 12 months, relapses or side-effects were not observed.

Conclusion Infliximab is an effective and promising drug in treating refractory BD-associated PU. It promptly reduces acute symptoms of PU, but it still remains to be seen if a long-term remission in a great number of patients will be achieved.

Keywords: Behçet disease; TNF-α; infliximab; retinal vasculitis; panuveitis

INTRODUCTION

Behçet disease (BD) is a chronic, relapsing, multisystem inflammatory disorder characterized by recurrent oral and genital ulcerations and uveitis, with varying other manifestations associated with vascular inflammation [1, 2]. After the initial BD description by Hulusi Behçet, additional target organ involvements, including vascular, neurological, and gastrointestinal manifestations, have been recognized and added to the disease spectrum. BD is found most often in young, adult males between the ages of 20 and 40 of Mediterranean, Middle Eastern, or Japanese extraction [2]. The etiology of BD remains unknown, but it is accepted that genetic and environmental factors play a role in its pathogenesis. The ocular inflammation associated with BD represents one of the most challenging forms of uveitis to treat. Initial manifestations include recurrent attacks of anterior uveitis, with or without hypopyon, retinal vasculitis, retinal infiltrates and hemorrhage, disc hyperemia, and vitreous opacification. Late complications may include cataract, iris synechia, glaucoma, retinal vascular occlusion, retinal neovascularization, and optic atrophy [2, 3, 4].

BD is one of the most difficult forms of uveitis to treat. Variety in disease presentation and severity, as well as regional differences in the standard of care, demand a tailor-made approach [5–8]. The preferred treatment modality is combined drug therapy, which includes corticosteroids, non-steroid anti-inflammatory drugs, colchicine, immunosuppressive and cytotoxic agents. Anti-tumor necrosis factor (TNF) monoclonal antibodies have recently attracted attention as a novel therapeutic approach [5, 6, 8, 9].

Infliximab is a chimeric monoclonal antibody composed of mouse variable domains of monoclonal antibody cA2 and human constant domains. It is being used increasingly in refractory (to corticosteroids and immunosuppressive agents) inflammatory eye diseases [10]. Several short-term follow-up studies have demonstrated the efficacy and safety of TNF-α antagonist drugs in the treatment of refractory posterior uveitis [11, 12, 13].

The aim of this paper is to report our experience on using infliximab in treating two patients with refractory BD-associated posterior uveitis (PU) with a comprehensive literature review.

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CASE REPORTS

We present two patients with refractory PU associated with BD who received infliximab intravenously at the dose of 5 mg/kg of body mass at weeks 0, 2, 6. and 14.

The diagnosis of BD fulfilled the criteria of the International Study Group [14]. Both patients had had more than five recurrences yearly and had been treated with corticosteroids (10–20 mg of prednisone) and with immunosuppressive therapy (cyclosporine 5 mg/kg and methotrexate 15–20 mg/week).

Both patients had chronic, bilateral sight-threatening retinal vasculitis resistant to high doses of corticosteroids. At admission, they demonstrated acute retinal vasculitis and cystoid macular edema in both eyes.

The ophthalmological evaluation included the best corrected visual acuity (BCVA) measurement by Snellen, a slit lamp biomicroscopy evaluation, tonometry, ocular fundus ophthalmoscopy, and fundus fluorescein angiography (FAG) at baseline, at weeks 7 and 14, and after 12 months.

Both patients underwent an examination by a pulmonologist, including chest X-ray and purified protein derivate; they were also examined by a rheumatologist before the infliximab administration. Blood and urine analyses were performed as listed: complete blood count, erythrocyte sedimentation rate, kidney and liver function testing, C-reactive protein and autoimmune antibodies (monthly), and a check-up with the rheumatologist every three months.

After infliximab, no immunosuppressive agent was administered; prednisone with dose tapering was scheduled in the following manner: 10 mg/day over the first three months, followed by 5 mg/day in the next three months until withdrawal.

Before the therapy, the patients were fully informed and signed an informed consent regarding its possible side effects and the fact that the long-term risks of infliximab are unknown.

Complete remission was defined as the presence of less than 1+ cellular reaction (scale 0–4) and a score of 0 at FAG (score 0 – absence of active vasculitis; 1 – peripheral vasculitis; 2 – posterior pole vasculitis; 3 – vasculitis with retinal necrosis) [15].

Case 1

A 45-year-old man with a 25-year-long history of BD had complaints about blurred vision in the right eye (RE) starting two days before the admission. Due to retinal vasculitis and longstanding cystoid macular edema, a complete loss of vision occurred in the left eye (LE). At admission, BCVA of the RE was 0.5, while the LE exhibited no light perception. Slit lamp biomicroscopy reveled posterior synechia at 3, 4, and 7 o'clock positions, 3+ cellular reaction in the anterior chamber, and complicated cataract. At the retina, active vasculitis with infiltrates was observed; FAG demonstrated peripheral and posterior pole vasculitis (1–2). A dermatologist identified huge oral and genital ulcerations. Infliximab was administrated as stated above. After 24 hours, the retinal infiltrates decreased in number;

seven days later, oral and genital ulcerations decreased and the patient gained one Snellen line. The infusions were repeated at weeks 2, 6 and 14. There were no signs of recurrences. Six months later, oral and genital ulceration appeared completely resorbed, BCVA of the RA was 0.8 Snellen with no signs of PU, 1+ cellular reaction and FAG 0 (absence of active vasculitis). By the end of the follow-up, at 12 months, there were no recurrences, nor adverse effects of the therapy.

Case 2

A 45-year-old female patient had a 15-year-long history of BD with complaints of redness and a decrease of visual acuity in both eyes. At admission, BCVA of the RE was 0.1; LE hand movement at 1 m. At slit lamp examination, on both eyes, hypopyon was demonstrated, 3+ flare in anterior chamber, complicated cataract, normal intraocular pressure. The FAG finding was defined as score 2–3. Just before administering infliximab, the patient presented acute swelling of the right knee joint and oral ulceration. Just 24 hours after the infusion, BCVA of the RE was 0.2 and the joint was less swollen. The infusions were repeated at weeks 2, 6, and 14. After the fourth infusion of Infliximab, BCVA of the RE was improved by two Snellen lines and BCVA of the LE was 0.1. At 12 months, no relapse was registered, flare was 1+, FAG score 0, BCVA remained stable (RE 0.3; LE 0.1). There were neither relapses of the disease, nor immediate side-effects of the therapy by the end of the follow-up.

DISCUSSION

The infliximab molecule is a chimeric antibody whose variable regions are monoclonal, derived from mouse cells, while the constant regions are of human origin. It is administered by intravenous infusion, and TNF-α binding and blocking are central to its mechanism of action. TNF-α is active in many places in the immune cascade, and is crucial in a number of immune diseases [16]. Infliximab therapy has been reported as being generally effective in anecdotal case series of BD patients with various refractory manifestations, including mucocutaneous lesions, uveoretinitis, arthritis, and gastrointestinal involvement [10, 13]. Sfikakis et al. [17, 18] were among the first to show that infliximab leads to remarkably rapid and effective suppression of almost all manifestations of Behçet's disease, at least in the short term, including acute sight-threatening PU. The recent studies have shown that remission is maintained in 75% of patients [11, 16, 19, 20]. However, there are different literature data on the number of infusions that would lead to disease remission. In one study, no patients received more than six infusions, and in another one, 75–78% of patients receiving nine infusions achieved disease remission in one year and 50% of subjects remained in remission for a further 12 months [15, 21]. Furthermore, in a small retrospective controlled case series, infliximab-treated patients maintained improved

visual acuity in the two-year follow-up after a course of six infusions over three months [22].

Lopez-Gonzalez et al. [12] described the use of Infliximab in patients with refractory posterior uveitis in a seven-year follow-up study, and used different numbers of infusions in patients' treatment to calm the disease down and to achieve remission. They concluded that a possible dosing interval could be three infliximab infusions of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks for a year, along with other immunosuppressive agents such as methotrexate. It is significant in their investigation that all patients with posterior uveitis within BD had positive tolerance to the therapy, while no improvement was observed in chorioretinal lesions associated with multifocal choroiditis and birdshot retinochoroidopathy [12].

Of course, infliximab therapy should not be used as the initial therapy, nor in minor cases where the treatment of an acute attack and long-term remission could be achieved by conventional standard therapy. European League Against Rheumatism has published important guidelines based on expert consensus and systematic review of the literature [23, 24]. Arguably, azathioprine is recommended as the initial immunosuppressant of choice to prevent ocular complications. Additional therapy with cyclosporine and/or infliximab is indicated when there is severe eye disease [24]. Fresko and Yazici [8] suggest that if the patient has severe eye disease (defined as > 2 lines of drop in visual acuity on the 10/10 scale) and/or retinal disease (retinal vasculitis or macular edema), fast-acting drugs such as cyclosporine A or infliximab should be used in combination with azathioprine or corticosteroids. No other additional therapy with infliximab was administered to our patients – only prednisolone monotherapy over the first six months, although the literature data suggest the use of the therapy in combination with an immunosuppressive, like methotrexate, is more efficient [12, 16]. Fresko and Yazici emphasize rapid occurrence of relapsing if infliximab is used alone [8].

Infliximab has side effects. Patients treated with TNF-α blockers incur the risk of reactivation of latent tuberculosis and other infections, demyelinating disease, and congestive heart failure [25]. We did not find any adverse effects of this drug. Suhler et al. [20] described a broad range of side effects potentially attributable to infliximab, including lupus-like reaction, pulmonary embolus, and congestive heart failure. The most recent study from Sakai et al. [26] suggests that relief of uveitis attacks and extraocular manifestations by infliximab therapy significantly improved the health-related and vision-related quality of life in patients with BD.

Infliximab seems to be effective in treatment of refractory PU associated with BD. It promptly reduces acute visual symptoms, but it still remains to be seen whether it will produce long-term remission in a great number of patients. We did not observe any adverse effects. So, to answer all the raised questions, more trials are needed to be done. Yet, we do hope this new therapy will lead to a more effective treatment of BD, will reduce the incidence of relapses, and consequently, long-term therapy will be reduced as well.

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Ефикасност инфликсимаба у лечењу рефракторног панувеитиса удруженог са Бехчетовом болешћу

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САЖЕТАК

Увод Бехчетова болест (ББ) јесте хронични мултисистемски поремећај са очним, уролошким, зглобним и васкуларним манифестацијама. Фактор туморске некрозе – алфа има кључну улогу у патогенези ББ. Инфликсимаб блокира његову активности и то је нови терапијски приступ у лечењу ББ. Циљ овог рада је да прикаже исход лечења инфлуксимабом код два болесника са ББ који су имали рефракторни панувеитис (ПУ). Пацијенти су праћени у периоду од 12 месеци. Главни параметри праћења ефикасности лечења су били најбоље коригована оштрина вида на бољем оку, налаз на предњем сегменту и на флуоресцеинској ангиографији (ФАГ).

Приказ болесника Мушкарац (стар 45 година, болује од ББ 25 година, налаз: задње синехије, 3+ *flare* и компликована катаракта) и жена (стара 45 година, од ББ болује 15 година, налаз: хипопион, 3+ *flare* и компликована катаракта) лечени су инфликсимабом у дози од 5 *mg/kg* телесне масе у недељама 0, 2, 6 и 14. Резултати на почетку и крају лечења су били следећи: мушкарац са ББ – видна оштрина 0,5 *vs.* 0,8; *flare* 3+ *vs.* 1+; ФАГ 1/2 *vs.* 0; жена са ББ – видна оштрина 0.1 *vs.* 0.3; ФАГ 2/3 *vs.* 0. После 12 месеци рецидиви или нежељени ефекти нису уочени.

Закључак Инфликсимаб је ефикасан и обећавајући лек у лечењу ПУ код болесника са ББ. Њиме се постиже брзо смиривање акутних симптома ПУ.

Кључне речи: Бехчет; TNF-*α*; инфликсимаб; мрежњача; васкулитис; панувеитис