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Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☎ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: srparhiv@bvcom.net, Web address: www.srpskiarhiv.rs

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Case Report / Приказ случаја

Maja Živković[1,†], Marko Zlatanović[1], Gordana Zlatanović[1], Vesna Jakšić[2] , Aleksandra Hristov[3] , Svetlana Jovanović[4]

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

Ефикасност инфликсимаба у лечењу рефракторног панувеитиса удруженог са Бехчетовом болешћу

[1]Eye Clinic, Clinical Center Niš, Niš, Serbia;
[2]School of Medicine, University of Belgrade, Belgrade, Serbia;
[3]Eye Clinic "Maja", Niš, Serbia;
[4]Eye Clinic, Clinical Center Kragujevac, Serbia

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† **Correspondence to:**
Maja ŽIVKOVIĆ
Eye Clinic, Clinical Center Niš, Bulevar dr Zorana Đinđića 48, 18000 Niš, Serbia
E-mail: **maculareader@gmail.com**

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SUMMARY

Introduction Behçet disease (BD) is a chronic multi-system disorder with ocular, urological, articular and vascular systems manifestations. 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 was to report two cases of refractory BD associated panuveitis (PU) treated by infliximab. Patients were followed 12 months.

The main outcomes were best corrected visual acuity (BCVA) in a better eye, slit lamp and fluorescein angiography (FAG) findings at baseline and final examination.

Case report Male patient (45 years old, 25 years of BD history) and female patient (45 years old, 15 years of BD history) both with posterior synechia, 3+flare and complicated cataract while female had hypopion too, were treated by Infliximab administered at the dose of 5 mg/kg at weeks 0, 2, 6 and 14. Results were the following: male patient -baseline vs. last examination visual acuity 0,5 vs. 0,8; cellular reaction 3+ vs.1+; FAG 1/2 vs.0; for female patient- visual acuity 0.1 vs.0.3; FAG 2/3 vs 0. After 12 months, relapses or side-effects were not observed.

Conclusion Infliximab is effective and promising drug in a treatment of 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

САЖЕТАК

Увод Бехчетова болест (ББ) је 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).

Главни параметри праћења ефикасности лечења су били најбоље коригована оштрина вида на бољем оку, налаз на предњем сегмент и на флуоресцеинској ангиографији (ФАГ).

Приказ случаја Мушкарац (стар 45 година, болује од ББ 25 година, налаз: задње синехије, 3+фларе и компликована катаракта) и жена (стара 45 година, БД болује 15 година, налаз: хипопион, 3+ фларе и компликована катаракта) лечени су инфликсимабом у дози од 5 мг/кг телесне масе у недељама 0, 2, 6 и 14. Резултати на почетку и крају лечења су били: Болесник: БЦВА 0,5 вс. 0,8; фларе 3+ вс. 1+; ФАГ 1 и 2 вс. 0; Болесница: БЦВА 0.1 вс. 0.3; ФАГ 2/3 с вс 0 . После 12 месеци, рецидиви или нежељени ефекти нису уочени.

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

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

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 Behcet, additional target organ involvement, including vascular, neurological, and gastrointestinal manifestations, has 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 [2–4].

Behçet's disease is one of the most difficult forms of uveitis to treat. Variety in disease presentation and severity, as well as regional differences in standard of care, demand a tailor-made approach [5–8]. The preferred treatment modalities are combined drug therapy and include corticosteroids, non-steroid anti-inflammatory drugs-NSAIDs, colchicine, immunosuppressive and cytotoxic agents. Anti TNF monoclonal antibodies have recently attracted attention as 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 [11–13].

The aim of this study is to report our experience using infliximab in treatment two patients with refractory BD–associated posterior uveitis (PU) with comprehensive literature review.

CASE REPORT

We present two patients with refractory PU associated with BD who were received Infliximab intravenously at the dose of 5 mg/kg body mass at weeks 0, 2,6,14 and 22.

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

Both patients had a chronic, bilateral sight threatening retinal vasculitis resistant on high dose corticosteroids. At admission, they demonstrated acute retinal vasculitis and cystoid macular edema in both eyes.

The ophthalmological evaluation included: 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.

To both patients, exam at pulmonologist, including chest X-ray and purified protein derivate (PPD) as well as rheumatologist exams were done before 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 a rheumatologist every three months.

After Infliximab, no immunosuppressive agent was administered, prednisone with dose tapering was scheduled: 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 written consent on its possible side-effects and the fact that the long-term risks of Infliximab are unknown.

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

Case 1: A 45-years-old man with a 25-years long history of BD had complains about blurred vision in the right eye starting two days before admission. Due to retinal vasculitis and longstanding cystoid macular edema, a complete loss of vision occurred in the left eye. At admission BCVA of the right eye (RE) was 0.5; left eye (LE) - no light perception (NLP). Slit lamp biomicroscopy reveled posterior synechia at 3,4 and 7 o'clock position, 3+cellular reaction in anterior chamber and complicated cataract. At the retina, active vasculitis with infiltrates were observed; FAG demonstrated peripheral and posterior pole vasculitis (1-2). A dermatologist identified huge oral and genital ulcerations**.** Infliximab (Remicade®) was administrated as it has been mentioned above. After 24 hours the retinal infiltrates decreased in number; seven days later, oral and genital ulcerations decreased and patient gain one Snellen line more. 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, visual acuity of right eye 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-years old female patient had a 15-years history of BD with complains of redness and decrease visual acuity in both eyes. At admission, BCVA of the RE was 0,1; LE hand movement at 1m. At slit lamp examination, on both eyes, hypopion was demonstrated, 3+ flare in anterior chamber, complicated cataract, normal intraocular pressure. FAG finding was defined as 2-3 scale. Just before administering Infliximab, the patient presented acute swelling of the right knee joint and oral ulceration. Only 24 hours after infusion, BCVA RE was 0.2 and the joint was less swollen. The infusions were repeated at weeks 2,6,14. After the fourth infusion of Infliximab, BCVA of the RE was improved for two Snellen lines and BCVA of the LE was 0.1. At 12 months period, no relapse were registered, flare was 1+, FAG 0 scale, BCVA remains 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 infiximab molecule is a chimeric antibody of which the variable regions are monoclonal derived from mouse cells, while the constant regions are of human origin.. It is administered by intravenous infusion, and binding and blocking TNF-α are central to its mechanism of action. TNF-α

is active at 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]. Sifkakis [17,18] was one of the first to show that Infliximab leads to remarkably rapid and effective suppression of almost all manifestations of Behcet's disease, at least in the short term, including acute sight-threatening panuveitis. The recent studies have shown that remission is maintained in 75% of patients [11,16,19,20]. But, there are different literature data on the number of infusions that would lead to disease remission. In one study, no patients received more than 6 infusions and in another one, 75–78% of patients receiving 9 infusions achieved disease remission in 1 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 2-year follow-up after a course of 6 infusions over 3 months [22].

Lopez-Gonzalez et al. [12] described the use of Infliximab in patients with refractory posterior uveitis in a 7-year follow up study, and used different number 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 8 weeks for 1 year, along with other immunosuppressive agents such as methotrexate. It is significant in their investigation that all the 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 initial, or in minor cases where the treatment of an acute attack and long-term remission could be achieved by conventional standard therapy. EULAR (European League Against Rheumatism) has published important guidelines based on expert consensus and systematic review of literature [23,24]. Arguably, azathioprine is recommended as the initial immunosuppressant of choice to prevent ocular complications. Additional therapy with cyclosporine or/and 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 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, just prednisolone monotherapy over the first six months, although literature data suggest the use of the therapy in combination with certain immunosuppressive, like methotrexate, 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

efects 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 (HR-QoL and VR-QoL) 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 incidence of relapses, and consequently, long-term therapy will be reduced as well.

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