Infliximab Therapy in Ocular Manifestations of Behcet's Disease

Thesis

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Abstract

Objective: This study was designed to assess the efficacy and safety of Infliximab (IFX) in the treatment of ocular manifestations in patients with Behcet's disease, namely BD-associated refractory posterior uveitis (PU) as expressed by VA improvement from baseline and to investigate the efficacy of IFX to reduce disease flare-up, to assess the proportion of relapse free subjects at the end of follow-up, and the percentage of patients achieving a complete or partial remission, and to evaluate the tolerability and safety of the treatment.

Methods: Twenty patients with refractory Behcet uveitis PU (17 males and 3 females) were included in this study. patients were subjected to full history taking, physical examination, purified protein derivative (PPD) test, laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood cell count with differential count, renal and liver function, antinuclear antibody titer .Ophthalmologic evaluation consisted of a complete ocular examination including best-corrected VA , slit-lamp biomicroscopy, tonometry and ophthalmoscopy, optical coherence tomography (OCT), & fundus fluorescein angiography (FFA).

Results: By the end of week 8 (induction), we observed a highly significant improvement inVA (right eyes: 0.1±0.09 vs 0.6±0.2, *P*=0.001) (Left eyes: 0.19±0.17 vs 0.6±0.3, *P*=0.001), and by the end of week 32 there was further improvement in VA**, (**right eye: 0.6±0.2 vs 0.8±0.2, *P*=0.001**), (**left eyes: 0.6±0.3 vs 0.8±0.2, *P*=0.001**)**, but this improvement was nearly the same by the end of week 58**, (**right eyes: 0.8±0.2 vs 0.8±0.2**) (**left eyes: 0.8±0.2 vs 0.8±0.2**)**. It was noted that improvement in VA was more evident in group A than in group B ($P<0.05$). At the end of a follow-up of 12 months, 16/20 (80%) patients showed a complete remission, 4/20(20%) showed partial response, none of the patients were non-responders. All of the patients (20) who were taking corticosteroids were able to stop it by week 22 during infliximab treatment, and all showed a reduction in extraocular manifestations of Behçet's disease. None of the patients had worsening VA or new onset ocular complications.

Conclusions: Infliximab seems to be a useful alternative therapy for patients with sight-threatening uveitis unresponsive to the standard immunosuppressive therapy. Although infliximab can be used as first-line medications in bilateral OBD, unilateral case with visual acuity below (6/60) may also need initial infliximab infusion as the first-line drug. Azathioprine can be used as a long-term therapy to control recurrent attacks upon first suppression of ocular inflammation by biologicals. Infliximab is also effective treatment in ocular Behcet disease regarding long term therapy.

Key Words: Anti-tumor necrosis factor, Behcet's disease uveitis.

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CONTENTS

List of Abbreviations

adhesion molecules (ICAM-1 and VCAM-1)
antigen-presenting cells (APCs)
Anti-IL-17 (AIN457)
Antinuclear antibodies (ANA)
Aqueous humor (AH)
Azathioprine (AZA),
Behçet's disease (BD)
Chronic infantile neurological cutaneous articular syndrome (CINCA)
Complete remission (CR)
Corticosteroids (CS)
Cyclosporine (CsA),
Cystoid macular edema (CME)
Cytotoxic combination therapy group (CCTG)
Experimental autoimmune uveo- retinitis (EAU)
Follicular helper T (TFH)
Fundus fluorescein angiography (FFA)
Helper T-cell (Th cell)
High-dose (HD)
Immunoglobulin G1 (IgG1)
Indocyanine green angiography (ICGA)
Induced regulatory T(iTreg)
Infliximab (IFX)
Isoniazide (INH)
Interferon gamma (IFN-gamma)
Interleukin-2 (IL-2)
International Study Group (ISG)
Lipopolysaccharides (LPS)
Low-dose (LD)
Matrix metalloproteinases (MMPs)
Mitomycin C (MMC)
Moderate-dose (MD)
Natural killer (NK)
Natural regulatory T (nTreg)
Nitric oxide (NO)
Ocular Behçet's disease (OBD)
Optical coherence tomography (OCT)
Oral ulcers (OU)
Partial remission (PR)
Periphral blood mononuclear cells (PBMCs)
Plasmacytoid dendritic cells (PDC)

Plasmacytoid dendritic cells (PDC)
Posterior uveitis (PU)
Regulatory T-cells (Tregs)
Retinal vasculitis (RV)
Retinoic acid-related orphan receptor-gamma t (ROR-gamma t)
Rituximab group (RG)
SOLUBLE FasL (sFasL)
SOLUBLE TNF-α (sTNF- α)
THP precursor Th cell
Transforming growth factor (TGF)
Transmembrane TNF-α (tTNF- α)
Tuberculosis {TB}
Tumor necrosis factor alpha(TNF-alpha)
Tumor necrosis factor receptor 1 (TNFR1)
Tumor necrosis factor receptor 2 (TNFR2)
Ultrasound biomicroscopy (UBM)
VASCULAR Endothelial Growth Factor (VEGF)
VISUAL acuity (VA)
VITROUS humor (vh)
VOGT-Koyanagi-Harada (VKH)

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Introduction

Ocular Behcet disease (OBD) is an idiopathic, immune disorder that produces unpredictable outbreaks of aggressive and exaggerated ocular inflammations. It clinically presents as episodic and recurrent hypopyon iridocyclitis along with vitreitis, retinitis, occlusive panuveitic vasculitis, and cystoid macular edema (CME), alternating with periods of inactive phases. Complications such as band keratopathy, glaucoma, vitreoretinal hemorrhage or detachment, macular degeneration, epiretinal membrane, vein occlusion may be encountered ***(Evereklioglu, 2005).***

OBD comes in bursts and typically affects young adults in their most productive ages between 20 and 40 years with pediatric cases ***(Borlu et al., 2006).*** However, its pathogenesis is still unclear and there is no laboratory screening profile to recognize and confirm disease activity ***(Turko¨ et al., 2005).*** But still, recent investigations reveal some new insights into the cause in a genetic basis ***(Borlu et al., 2009).***

Behcet symptoms occur wherever there is a patch of inflammation. Therefore, it affects almost all tissue or organ in the body without exception. In its full spectrum, some prefer to call this disorder as "oculo-articulo-oromucocutaneous syndrome ***(Evereklioglu., 2011).***

Infliximab is a chimeric (mouse/human) monoclonal antibody to tumor necrosis factor α that binds to TNF-α and prevents it from binding to its receptor ***(Taylor, 2010).*** Evidence suggests increased levels of TNF-α in serum and aqueous fluid in patients with intraocular inflammation due to Behçet's disease ***(Evereklioglu., 2002).***

It is not altogether surprising, then, that TNF-α inhibitors have been effective in the management of uveitis in these patients. The first clinical evidence for this in the literature came in the form of a case series by ***Sfikakis et al., (2001)*** who treated five patients with relapsing BD panuveitis with infliximab; they achieved remission within 24 hours of the first infusion and complete suppression by 7 days in all 5 patients (including no anterior chamber cell, no vasculitis, and no retinal lesions in any patient).

A report the following year described remission lasting up to 8 weeks after a series of 4 infusions in one patient ***(Triolo et al., 2002)***. An interventional case series using a total of 3 infliximab infusions (at weeks 0, 2, and 6) to treat posterior uveitis in 5 patients with previous treatment failures included 3 patients with BD, all of whom demonstrated improved visual acuity in both eyes following treatment and essentially complete remission of ocular disease. Although patients were given additional infusions as needed, some experienced treatment-free remissions of up to 5 months ***(Joseph et al., 2003).***

The first report of longer-term use of infliximab for BD uveitis described a patient who had active disease despite cyclosporine A, azathioprine, and prednisolone and then had rapid resolution of inflammation on infliximab. With ongoing infusions every 8 weeks he was able to gradually taper and discontinue all other immunosuppressive medications (over the course of 14 months) and had no disease activity during the 16 months he was monitored; the final two months were under infliximab monotherapy ***(Katsiari et al., 2001).***

Encouraged by the early successful case reports, other groups began treating difficult cases of Behçet's uveitis with infliximab and the number of case reports and series increased exponentially.

Aim of the Work

Assess the efficacy and safety of Infliximab therapy in treatment of ocular manifestations in patients with Behcet's disease.

Ocular Manifestations of Behçet's Disease

Behçet's disease (BD), first described by ***Hulusi Behçet in (1937)*** is a chronic multisystem disorder characterized by recurrent episodes of uveitis, oral aphthous lesions, genital ulcers, and skin lesions, with underlying vasculitis ***(Tugal et al., 2004).***

Although the most frequent initial manifestations are oral and genital ulcerations, the majority of patients present with more severe ocular, joint, gastrointestinal system, vascular system, or central nervous system involvement ***(Kansu et al., 2005).***

There is no pathognomonic finding or test for BD, and thus the diagnosis remains primarily clinical. Various sets of diagnostic criteria for BD have been suggested, and the criteria of the Japanese BD Research Committee and the 1990 classification of the International Study Group for BD are widely employed **.**

BD affects males more than females (2–10:1) along the silk route that extends from Mediterranean regions to Japan, where the disease is seen more commonly than in other areas. However, the male: female ratio is reversed in Western Europe and the US. The estimated prevalence of BD is between one in 10 000 and one in 1000 in the Mediterranean, the Middle East, and the Far East, with the highest prevalence being in Turkey where there are 80–300 cases per 100 000 population ***(Evereklioglu, 2005).***