Intravitreal Infliximab in Refractory Uveitis in Behçet's Disease: A Safety and Efficacy Clinical Study

Thesis

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By

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ABSTRACT

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Purpose: To assess the safety and efficacy of intravitreal infliximab, an anti-tumor necrosis factor antibody, in 20 eyes of 20 patients with refractory posterior uveitis in Behçet's disease.

Methods: Three consecutive intravitreal injections of infliximab (1 mg/0.05 mL) 6 weeks apart were given to 20 patients with refractory posterior uveitis in Behçet's disease. Best corrected visual acuity (BCVA), intraocular pressure (IOP), vitritis (graded 0 to 4) and posterior segment active vasculitis, active retinitis and papillopathy (presence or absence) were assessed at baseline, day 1 and 2, 4, 6, 8, 12, and 18 weeks post first injection. Optical Coherence Tomography (OCT) and Electroretinogram (ERG) were done at baseline and 4, 12, and 18 weeks. Fluorescein Angiography (FA) was done at baseline and at the discretion of the examiner, not at every post-injection evaluation.

Results: There were no ocular or extra-ocular side effects observed during the study period. Baseline BCVA (mean logarithm of the minimum angle of resolution 0.94) improved significantly at week 2 (mean logMAR 0.6, $P < 0.0001$) and continued to improve (mean logMAR 0.36, $P < 0.0001$) at the end of follow up. Profound decrease in vitritis grading from baseline mean 2 to 0.2 at the end follows up ($P < 0.001$). Active vasculitis was present in 15 patients and cleared in 14 patients at the end of follow up ($P< 0.001$). Active retinitis was present in 9 patients and cleared in all of them at week 4 ($P< 0.001$).

Papillopathy was present in 2 patients and cleared in both of them at week 4 (P< 0.001). Central foveal thickness decreased significantly from baseline mean 361 to 180.5 microns at the end of follow up (P< 0.0001). No significant electrophysiological changes were observed after repeated intravitreal infliximab injections.

Conclusions: These findings suggest that intravitreal infliximab is safe and effective in treatment of refractory posterior uveitis in Behcet's disease. Intravitreal infliximab should be considered when the systemic use of standard treatments for ocular Behcet are not effective, contraindicated or not feasible.

Contents

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List of figures

List of tables

List of abbreviations

AMD: Age Realated Macular Degeneration

BCVA: Best Corrected Visual Acuity

CFT: Central Foveal Thickness

CME: Cystoid Macular Edema

CMT: Central Macular Thickness

CRVO: Central Retinal Vein Occlusion

DR: Diabetic Retinopathy

EAU: Experimental Autoimmune Uveoretinitis

ERG: Electroretinogram

FA: Fluorescein Angiography

IFN-γ: Interferon gamma

IL: Interleukin

IP-10: Immune Protein 10

LogMAR: Logarithm of Minimum Angle of Resolution

MCP-1: Monocyte Chemoattractant Protein-1

MIP-1β: Macrophage Inflammatory Protein-1 beta

NFL: Nerve Fiber Layer

OCT: Optical Coherence Tomography

RPE: Retinal Pigment Epithelium

SD: Standard Deviation

TNF-α: Tumor Necrosis Factor α

VEGF: Vascular Endothelial Growth Factor

Introduction

Tumor necrosis factor alpha (TNF-α) blockers are relatively new drugs of biological therapy which are in extensive clinical use for inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and ankylosing spondylitis. The three main drugs are infliximab, etanercept and adalimumab.[1, 2] Due to their success in treating immune-mediated joint diseases, the use of these drugs in other immune-mediated diseases is growing.[3, 4, 5]

Anti tumor necrosis factor drugs can be used safely through intra-lesion injection like intra-articular injection of infliximab in cases of psoriatic arthritis which was safe and well tolerated by patients.[6]

Uveitis can be also immune mediated. It can be organ specific (i.e. appears to only involve the eye) or associated with other relevant systemic diseases such as ankylosing spondylitis, psoriatic arthropathy, inflammatory bowel disease, sarcoidosis and Behçet's disease.

For years, the treatment of choice for this type of noninfectious uveitis has been systemic immune suppression with steroids or immunosuppressive agents such as cyclosporin A, azathioprine, methotrexate, cyclophosphamide, chlorambucil, or tacrolimus.

However, in a large number of patients, relapses occur despite aggressive treatment with these drugs, and this can lead to a significant, or even permanent, loss of vision.

The uveitis animal models[7] have helped to study the immunology of uveitis and investigate possible treatment modalities. TNF- α appears to play a key role in the regulation of this inflammatory process[8] and the proliferative response to retinal antigens.[9] TNF-α has also been detected in human eyes with a variety of inflammatory conditions[10]. Thus its central role in ocular inflammation makes TNF-α an attractive target for immune therapy.[11]

Behçet's disease is a multisystem vasculitis of unknown cause primarily involving eyes, mucosal surfaces, and skin.

Although Behçet's disease occurs worldwide, it is a particularly common cause of uveitis in countries that line the ancient Silk Road including Italy, Turkey, Greece, Saudi Arabia, Iran, China, Korea, and Japan.[12, 13] The age of onset of uveitis is usually in the third to fourth decades of life, with men being more commonly affected than women.[14]

In recent literature, systemic infliximab has been shown to be helpful in refractory cases of uveitis. Treatment of any ocular disease with TNF-α blockers should be considered off-label, and it is advisable to obtain informed written consent.[15, 16]

However, blocking TNF actions by systemic administration of infliximab has been associated with serious side effects such as reactivation of latent tuberculosis, opportunistic infections, exacerbation of preexisting multiple sclerosis and malignancies. Therefore, provided that therapeutic intraocular concentrations of infliximab can be achieved, an intravitreal injection of infliximab with minimal systemic absorption would minimize, if not eliminate, systemic adverse effects.[17, 18, 19]

References:

1. **Braun J & Sieper J**. Biological therapies in the spondyloarthritides: the current state. Rheumatology 2004;43:1072-84.

2. **Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, Gromnica-Ihle E, Kellner H, Krause A, Schneider M, Sörensen H, Zeidler H, Thriene W & Sieper J**. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multi-centre trial. Lancet 2002;359:1187-93.

3. **Atzeni F, Sarzi-Puttini P, Doria A, Iaccarino L & Capsoni F**. Potential off-label use of infliximab in autoimmune and non-autoimmune diseases. Autoimmune Rev 2005;4:144-52.

4. **Pascher A & Klupp J.** Biologics in the treatment of transplant rejection and ischemia / reperfusion injury. Biodrugs 2005;19(4):211-31.

5. **Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L & Benticuaga MN**. Treatment of therapy-resistant sarcoidosis with adalimumab. Clin. Rheumatol 2005 Oct 25:1-2.

6. **Bello S, Bonali C, Serafino L, Di Giuseppe P, Minosi A & Terlizzi N**. Intra-articular therapy with infliximab in psoriatic arthritis: efficacy and safety in refractory monoarthritis, Reumatismo 2010 Jan-Mar;62(1):46-50.

7. **Wacker WB & Lipton MM**. Experimental allergic uveitis: homologous retina as uveitogenic antigen. Nature 1965;206:253-4.

8. **Dick AD, Forrester JV, Liversidge J & Cope AP**. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res 2004; 23:617-37.

9. **Sartani G, Silver PB, Rizzo LV, Chan CC, Wiggert B, Mastorakos G & RR Caspi**. Anti tumour necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci 1996;37:2211-8.

10. **Franks WA, Limb GA, Stanford MR, Ogilvie J, Wolstencroft RA, Chignell AH & Dumonde DC**. Cytokines in human intraocular inflammation. Curr Eye Res 1992;11:187-91.

11. **Robertson M, Liversidge J, Forrester JV & Dick AD**. Neutralizing tumor necrosis factor-alpha activity suppresses activation of infiltrating macrophages in experimental autoimmune uveoretinitis. Invest Ophthalmol VisSci 2003;44:30344.

12. **Zouboulis C.C.** Epidemiology of Adamantiades-Behçet's disease. Ann Med Interne (Paris) 1999;150: 488-498.

13. **Sakane T, Takeno M, Suzuki N & Inaba G.** Behçet's disease. New Engl J Med 1999;341:1284-1291.

14. **Yazici H, Tüzün Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdoğan H, Serdaroğlu S, Ersanli M, Ulkü BY & Müftüoğlu AU**. Influence of age of onset and patient's sex on the prevalence and severity of Behçet's syndrome. Ann Rheum Dis 1984;43:783-789.

15**. Pleyer U, Mackensen F, Winterhalter S & Stubiger N**. Anti-TNF-α treatment for uveitis. Analysis of the current situation. Ophthalmologe 2011;108:13-20.

16. **Sharma SM, Nestel AR, Lee RW & Dick AD**. Clinical review: Anti-TNF alpha therapies in uveitis: perspective on 5 years of clinical experience. Ocul Immunol Inflamm 2009;17:403-414.

17. **Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD & Rosenbaum JT**. A prospective trial of therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 2005;123:903–912.

18. **Wegscheider BJ, El-Shabrawi L, Weger M, Ardjomand N, Hermann J, Aberer E & El-Shabrawi Y**. Adverse skin reactions to infliximab in the treatment of intraocular inflammation. Eye 2007; 21: 547–549.

19. **Keystone EC**. Safety of biologic therapies–an update. J Rheumatol Suppl 2005;74:8–12.

Aim of Work

The aim of this study is to assess the safety and efficacy of intravitreal infliximab injection (1 mg/0.05 mL) in cases of refractory uveitis in Behçet's disease by full clinical assessment, Electroretinogram (ERG), Fluorescein Angiography (FA) and Optical Coherence Tomography (OCT) after 3 consecutive intravitreal injections at six weeks intervals.