

Study of the Impact of the Use of a Thiazolidinedione or a DPP-4 Enzyme Inhibitor as an Adjuvant to Standard Immunosuppressive Therapy on the Rate of Recurrent Exacerbations in Behçet's Disease Patients with Uveitis.

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Abstract:

Introduction: Uveitis in Behçet's disease is a potentially blinding condition. It may lead to anterior and posterior synechiae which may lead to secondary glaucoma, cataract, and macular oedema. Posterior segment involvement in Behçet's disease includes posterior uveitis, retinal, macular, and optic disc oedema, and retinal vasculitis. Adequate control of activity of the disease with systemic immune-suppressive therapy in order to salvage vision is of utmost importance, hence the necessity of the combined internal medicine and ophthalmic approach. **Subjects and methods:** The study included 45 subjects, who were divided into three groups, with 15 subjects in each group. After signing the informed consent, each patient was assigned to one of the following three treatment arms: standard immunotherapy (systemic corticosteroids plus azathioprine) alone, standard immunotherapy with Pioglitazone 15 mg per os per day, or standard immunotherapy with

Sitagliptin 100 mg per os per day. **Results:** on comparing the mean improvement in visual acuity at the end of 1 year follow up among the three study groups, the group receiving adjuvant Pioglitazone showed a statistically significant improvement over the group receiving systemic steroids and azathioprine alone, the $t = 2.5$, level of significance 0.05, degree of freedom 55. Whereas the group receiving adjuvant Sitagliptin showed no statistically significant improvement over the group receiving systemic steroids and azathioprine alone, the $t = 0.54$, level of significance 0.05, degree of freedom 57. **Conclusion:** A statistically significant improvement in the control of uveitis in Behçet's disease patients was obtained by addition of Pioglitazone to systemic steroids and Azathioprine, but not by addition of Sitagliptin to the same combination.

Keywords: Uveitis, Behçet's disease, Azathioprine, Pioglitazone, Sitagliptin.

Introduction:

Behçet's disease (BD) is a multiorgan disease characterized by an immune-mediated occlusive vasculitis. Major symptoms of BD consist of oral aphthous ulcers, genital ulcerations, skin lesions, and ocular lesions. Due to its poor visual prognosis, eye involvement, which affects approximately 60-80% of patients, is, along with CNS involvement, the most serious manifestation of BD.⁽¹⁾

So far, the a etiology and pathogenesis of BD remain unclear, with the background of HLA-B51 as the major important predisposing genetic factor.⁽¹⁾

Uveitis in Behçet's disease is a potentially blinding condition. Common complications of recurrent anterior uveitis in Behçet's disease include anterior and posterior synechiae which may lead to secondary glaucoma, cataract, and macular oedema.^(2,3) Posterior segment involvement in Behçet's disease includes posterior uveitis, retinal, macular, and optic disc oedema, and retinal vasculitis.⁽⁴⁾ The need for adequate control of activity of the disease with systemic immune-suppressive therapy in order to salvage vision cannot be overemphasized.⁽⁵⁾

Systemic corticosteroids are widely used in the therapy of ocular BD. However, they are not suitable as a monotherapy for longer treatment durations because their doses, necessary to maintain remission of ocular disease, will be too high resulting in unacceptable side effects. Thus, in most cases it will be necessary to add a steroid-sparing immunosuppressive drug as Azathioprine or cyclosporine.⁽³⁾

Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders recommend 1 mg/kg/day of prednisone for severe uveitis. Control of acute inflammation usually takes 2–4 weeks and steroids then need to be slowly tapered for approximately 6 months until their withdrawal.⁽⁶⁾

Azathioprine, cyclosporine, and methotrexate are the immunosuppressive agents that are most frequently used to treat auto-immune uveitis. In a randomized double-blind placebo-controlled trial in Behçet's disease, 2.5 mg/kg/day azathioprine was found to have a significantly preventative effect on new flares of uveitis in patients with previous episodes and patients who had never experienced a flare of uveitis before inclusion in the study.⁽³⁾

Thiazolidinediones are a class of drugs originally used for the treatment of type 2 diabetes. They bind avidly to peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake in peripheral fat. By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, these drugs improve the patient's sensitivity to insulin. These compounds have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs. In addition to their antidiabetic effect, thiazolidinediones have got a number of other biological effects including anti-inflammatory effects. Studies have found that these drugs can be useful in controlling the inflammatory process in Behçet's disease.⁽⁷⁾

Sitagliptin is an inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4). Since DPP-4 mediates pro-inflammatory signals, Sitagliptin exerts an anti-inflammatory effect. Sitagliptin induces a reduction in the expression of

a series of pro-inflammatory genes and a reduction in plasma concentrations of CRP, TNF- α , and IL-6 in a comprehensive anti-inflammatory effect.⁽⁸⁾

Subjects and Methods:

The subjects who were enrolled in the study were Behçet's disease patients with uveitis, requiring treatment with systemic immunomodulatory therapy to control their intraocular inflammation or to ameliorate their ocular disease course.

The study included 45 subjects, who were divided into three groups, with 15 subjects in each group. After signing the informed consent, each patient was assigned to one of the following three treatment arms:

- Standard immunotherapy (systemic corticosteroids plus azathioprine) alone.
- Standard immunotherapy with Pioglitazone 15 mg per os per day.
- Standard immunotherapy with Sitagliptin 100 mg per os per day.

Inclusion criteria:

1. The diagnosis of Behçet's disease, according to the International Classification Criteria:

- Recurrent oral ulceration.

Plus at least 2 of the following criteria:

- Recurrent genital ulceration.
- Eye lesions: active uveitis or retinal vasculitis.
- Skin lesions: erythema nodosum or papulopustular lesions
- Positive pathergy test.

2. Active uveitis secondary to Behçet's disease in at least one eye.

3. Male and female subjects older than 18 years of age.

Exclusion criteria:

1. Patients treated at any time with chlorambucil or cyclophosphamide.
2. Treatment with intravitreal anti-VEGF agents administered to the study eye within 3 months prior to study screening.

3. Treatment with any injected or implantable corticosteroid-releasing device within the last 3 years.
4. Intraocular surgery or laser photocoagulation in the study eye within the last 6 weeks.
5. Ocular disease that would interfere with ocular evaluations (e.g. corneal scarring, cataract, vitreous hemorrhage, uncontrolled glaucoma, toxoplasma scar, macular scarring).
6. Treatment with any live or live-attenuated vaccine in the last 2 months.
7. Any systemic biologic therapy (e.g. interferon, infliximab, daclizumab, etanercept, or adalimumab) given intravenously or subcutaneously within 3 months prior to screening
8. History of lymphoproliferative disease or any known malignancy within the past 5 years.
9. Heart failure and/or coronary heart disease

The patients were subjected to:

1. History taking.
2. Ophthalmologic examination:
 - Visual acuity (uncorrected and corrected).
 - Slit lamp examination.. to detect anterior chamber cells.
 - Direct ophthalmoscopy.. to detect vitreous haze.
 - Fundus examination using a slitlamp biomicroscope plus a non contact fundus lens.
 - Intraocular pressure measurement using Goldmann applanation tonometer.
3. Systemic evaluation:
 - Systemic manifestations of Behçet's disease eg. oral ulcers, genital ulcers, erythema nodosum.
 - Vital signs: temperature, pulse, blood pressure, respiration.
 - Adverse events of the administered drugs.
 - Laboratory investigations: CBC, urea, creatinine, lipid profile, liver enzymes, high sensitivity CRP.

Follow up was done for a period of 12 months.

The data was statistically analyzed using SPSS program version 18. The following statistical tests were used: descriptive statistics (including mean and SD), t-test, ANOVA test, and multiple regression analysis. Probability or p value of <0.05 was considered statistically significant, while p>0.05 was considered statistically non-significant.

Results:

The study included 45 Behçet's disease patients with uveitis, requiring treatment with systemic immune-modulatory therapy to control their intraocular inflammation or to ameliorate their ocular disease course. The subjects were divided into three groups, with 15 subjects in each group. The groups received either

- Standard immunotherapy (systemic corticosteroids plus azathioprine) alone.
- Standard immunotherapy with Pioglitazone 15 mg per os per day.
- Standard immunotherapy with Sitagliptin 100 mg per os per day.

Follow up of the 3 groups has been done for a period of 12 months.

Group I: On ophthalmic examination at the beginning of the study, the studied eyes in group I showed an uncorrected visual acuity ranging from Hand Movement to 0.4 and a corrected visual acuity ranging from Hand Movement to 0.5. Examination using the slit lamp biomicroscope was used to detect anterior chamber cells, which ranged from +2 cells to +4 cells with hypopyon. Direct ophthalmoscopy was used to depict vitreous haze which was present in 17 of the studied eyes. On systemic evaluation, all the 15 patients reported having recurrent attacks of oral ulcers, 9 patients having active oral ulcers at the time of examination. All the fifteen patients reported having genital ulcers, ranging from a single attack to 6 attacks.

The patients were started on systemic prednisolone 60 mg/day and azathioprine 100 mg/day. Several follow up visits were arranged with both ophthalmic and systemic evaluation

performed regularly. At the end of 12 months of follow up, the studied eyes in group one showed an uncorrected visual acuity ranging from Hand Movement to 0.6 and a corrected visual acuity ranging from Hand Movement to 0.7. The level of anterior chamber cells ranged from +1 cells to +3 cells (Figure II), and vitreous haze was persistent in 4 eyes. Two patients continued to suffer from oral ulcers, but no patients were still experiencing genital ulcers.

Group II: On ophthalmic examination at the beginning of the study, the studied eyes in group II showed an uncorrected visual acuity ranging from Hand Movement to 0.3 and a corrected visual acuity ranging from Hand Movement to 0.5. The slit lamp biomicroscope was used to detect anterior chamber cells, which ranged from +2 cells to +4 cells with hypopyon. The direct ophthalmoscope was used to assess vitreous haze which was present in 18 of the studied eyes. On systemic evaluation, all the fifteen patients stated having multiple attacks of oral ulcers, 11 patients having active oral ulcers at the time of examination. All the fifteen patients reported having genital ulcers, ranging from a single attack to 5 attacks.

The patients were started on systemic prednisolone 60 mg/day, azathioprine 100 mg/day, and Pioglitazone 15 mg/day. Several follow up visits were organized and both ophthalmic and systemic evaluation were done regularly. At the end of 12 months of follow up, the studied eyes in group two showed an uncorrected visual acuity ranging from Counting fingers at 60 cm to 0.7 and a corrected visual acuity ranging Counting fingers at 60 cm to 0.8 (Figure I). The level of anterior chamber cells ranged from zero cells to +1 cells, and vitreous haze was persistent in only one eye.

No patients continued to suffer from oral or genital ulcers. The patient with mediastinal vein syndrome experienced complete resolution of the face, neck, and upper limbs swelling during the course of follow up.

Group III: At the start of the study, the studied eyes in group III showed an uncorrected visual acuity ranging from Counting Fingers at 30 cm to 0.4 and a corrected visual acuity ranging from Counting fingers at 30 cm to 0.6. Examination using the slit lamp biomicroscope was used to detect anterior chamber cells, which ranged from +1 cells to +4 cells without hypopyon. Direct ophthalmoscopy was performed to examine for vitreous haze which was present in 15 of the studied eyes. On systemic evaluation, the 15 enrolled patients reported having recurrent attacks of oral ulcers, 7 patients having active oral ulcers at the time of examination. Fourteen patients reported having genital ulcers, ranging from a single attack to 6 attacks.

The patients were started on systemic prednisolone 60 mg/day, azathioprine 100 mg/day, and Sitagliptin 100mg/day. Several follow up visits were arranged with both ophthalmic and systemic evaluation performed regularly. At the end of 12 months of follow up, the studied eyes in group three showed an uncorrected visual acuity ranging from Counting Fingers at 50 cm to 0.6 and a corrected visual acuity ranging Counting Fingers at 50 cm to 0.7. The level of anterior chamber cells ranged from +1 cells to +2 cells, and vitreous haze was persistent in 3 eyes. One patient had an attack of oral ulcers and another attack of genital ulcers during the course of follow up that resolved with continuation of treatment.

Table I: Demographic characteristics and duration of disease of the study groups – before treatment.

	Group I (Steroids + Azathioprine) (n=15)	Group II (Steroids + Azathioprine + Pioglitazone) (n=15)	Group III (Steroids + Azathioprine + Sitagliptin) (n=15)
Age (mean, SD)	44 +/- 3 yrs, 3 ms	43 +/- 4 yrs, 1m	46 +/- 2 yrs, 2 ms
Sex (M/F)	12/3	13/2	13/2
Duration of disease	8- 12 years	8-14 years	7-12 years

Discussion:

In the present study, the results of the group of patients receiving systemic steroids and azathioprine, group I, came supportive of those published by these Nussenblatt³, as both the systemic manifestations (e.g. oral ulcers and genital ulcers) and the ocular manifestations (e.g. anterior chamber cells and vitreous haze) improved in most of the patients receiving the regimen.

At the end of 12 months of follow up in the present study, the studied eyes showed a mean improvement of visual acuity of 0.1 over the pretreatment levels (SD: 0.02). This improvement was approximate to that reported by Yazici et al,^{9,10} who recorded a mean improvement in visual acuity of 0.15 over the pretreatment levels. Nine of the 29 examined eyes had persistent Anterior Chamber cells denoting persistence of anterior uveitis activity, while the remaining 20 eyes were free of cells at the end of the follow up period, with a 72.4% improvement rate, slightly lower than that achieved by Yazici et al¹¹, who mentioned a 79% improvement rate. The vitreous haze was persistent in 4 of the 17 eyes that had vitreous haze at the beginning of the study, and disappeared from the remaining 13 eyes. The rate of improvement in vitreous haze was 76.5 %, a percentage almost similar to that reported in the study by Kotter et al¹², who mentioned improvement in vitreous haze in about 76% of the eyes. The mean frequency of recurrence of attacks of oral ulcers was 2 attacks/ patient /1 year of follow up under treatment (SD: 0.2), and the mean frequency of recurrence of attacks of genital ulcers was 1 attack/ patient /1 year of follow up under treatment (SD: 0.1).

The patients in the second group, who received Pioglitazone in addition to systemic corticosteroids and Azathioprine showed, at the end of follow up, a mean improvement in visual acuity over the pretreatment levels

of 0.2 (SD: 0.05). This improvement is fairly lower than that mentioned by Kim et al¹³, who achieved a 0.3 mean improvement in visual acuity over the pretreatment levels. Only 2 of the 28 examined eyes had persistent Anterior Chamber cells denoting persistence of anterior uveitis activity, while the remaining 26 eyes were free of cells at the end of the follow up period, an improvement rate approaching 93%, and somewhat exceeding that reported by Kim et al, who reported 85% improvement in anterior uveitis.

Vitreous haze was persistent in only one of the 18 eyes that showed vitreous haze at the beginning of the study, and disappeared from the remaining 17 eyes, the latter representing 94% of the studied eyes, whereas Kim et al achieved disappearance of vitreous haze in 90% of the affected eyes. The mean frequency of recurrence of attacks of oral ulcers was 0.5 attack/ patient /1 year of follow up under treatment (SD: 0.2), and the mean frequency of recurrence of attacks of genital ulcers was 0.1 attack/ patient / 1 year of follow up under treatment (SD: 0.05).

In the third group, who received Sitagliptin in addition to systemic steroids and Azathioprine, there was a mean improvement in visual acuity over the pretreatment levels of 0.12 (SD: 0.05). This mean improvement is the same as that reported by Acacina et al¹⁴, who reported a mean improvement in visual acuity of 0.12 over the pretreatment visual acuity. Eight of the 30 examined eyes had persistent Anterior Chamber cells denoting persistence of anterior uveitis activity, while the remaining 22 eyes were free of cells at the end of the follow up period, a rate improvement of 70% similar to that achieved by Acacina et al^{15,16}.

On comparing the mean improvement in visual acuity at the end of 1 year follow up, the group receiving adjuvant Pioglitazone showed

a statistically significant improvement over the group receiving systemic steroids and azathioprine alone, the $t = 2.5$, level of significance 0.05, degree of freedom 55. Whereas the group receiving adjuvant Sitagliptin showed no statistically significant improvement over the group receiving systemic steroids and azathioprine alone, the $t = 0.54$, level of significance 0.05, degree of freedom 57.

Regarding the improvement in anterior chamber cells and vitreous haze, the group receiving adjuvant Pioglitazone obtained a statistically significant improvement over the group receiving systemic steroids and azathioprine alone, confidence interval (20.25-20.64). On the other hand, the group receiving Sitagliptin as an add-on therapy, achieved no statistically significant improvement over the control group, confidence interval (2.17 – 2.65).

In conclusion, addition of Pioglitazone to systemic steroids and Azathioprine in treating Behçet's disease patients with uveitis, achieved a statistically significant improvement in the control of uveitis over systemic steroids and Azathioprine alone. On the other hand, the addition of Sitagliptin to the same combination did not obtain a statistically significant improvement over systemic steroids and Azathioprine alone.

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