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Does adalimumab prevent the loss of visual acuity in patients with uveitis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences-Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not adalimumab prevents the loss of visual acuity in patients with uveitis.

STUDY DESIGN: Review of three English language primary studies published between 2013-2016.

DATA SOURCES: Two randomized controlled phase 3 trials and one retrospective study were found using PubMed. The RCT's compared treatment with adalimumab to placebo in patients with noninfectious uveitis, while the retrospective study solely assessed outcomes in patients with noninfectious uveitis receiving adalimumab treatment.

OUTCOMES MEASURED: For the two RCT's, the clinical outcome of time to treatment failure due to worsening visual acuity was measured by calculating logMAR from the Early Treatment Diabetic Retinopathy Study (EDTRS) chart in each eye. For these two studies visual Functioning questionnaires (VFQ-25) were also administered. In the retrospective study visual acuity was measured using Snellen charts.

RESULTS: The randomized controlled phase 3 trials found a statistically significant decrease in treatment failure due to a worsening of visual acuity in the patients treated with adalimumab over placebo. In Jaffe et al. the mean change in best corrected visual acuity (BCVA) was significantly less for the adalimumab group, however, in Nguyen et al the difference was not statistically significant. The VFQ-25 was in favor of the adalimumab group in both studies but was not significant in Nguyen et al. A larger number of serious adverse events were associated with the adalimumab group compared to placebo, but no new safety issues were identified. The retrospective study also showed improvement in visual outcomes for noninfectious uveitis patients treated with adalimumab.

CONCLUSION: Adalimumab can help prevent loss of visual acuity in adult patients with noninfectious intermediate, posterior or panuveitis.

KEYWORDS: Adalimumab, uveitis

INTRODUCTION

Uveitis is an inflammatory condition of the uveal tract. The uvea is the middle layer of the eye and uveitis is classified based on the location of the inflammation within the uveal tract. Anterior uveitis includes inflammation of the iris and ciliary body and is the most common form of the condition. Intermediate uveitis involves the vitreous and peripheral retina, while posterior uveitis manifests as inflammation in the choroid or retina. Inflammation throughout all of these structures is termed panuveitis. These four classifications of uveitis can also be subtyped into more specific diagnoses if the inflammation is localized to a specific portion of either the anterior, intermediate or posterior segment of the uvea.

The development of uveitis is influenced by systemic inflammatory diseases, infections, trauma and genetics.¹ A prompt diagnosis of uveitis and referral to an ophthalmologist is essential as the complications of the inflammatory process can deteriorate one's vision.¹ Complications from uveitis include blindness, glaucoma, macular edema, adhesions, band keratopathy and optic nerve damage.² Up to 40 percent of cases are due to an underlying systemic inflammatory disease, which are often treated with systemic corticosteroids.¹ Corticosteroids are also the current mainstay of treatment for non-infectious uveitis and chronic therapy can further contribute to complications like cataracts, glaucoma, osteoporosis, metabolic syndrome and immunosuppression.¹ Uveitis currently accounts for 10-15 percent of cases of blindness in Western countries and can be prevented by early diagnosis and adequate treatment.³

The presenting symptoms of uveitis vary based on the location of the inflammation, contributing to its difficult diagnosis. Patients are more likely to present to the emergency department with significant pain and injection in anterior uveitis, while posterior and intermediate uveitis is more commonly painless with vision changes.¹ Uveitis is estimated to

account for 5 million health care visits per year, with an annual incidence of 17-52 cases per 100,000 persons.⁴ Racial predispositions to uveitis are related to the autoimmune diseases that are more prevalent in certain ethnic populations.¹ The underlying systemic inflammatory conditions associated with uveitis like systemic lupus erythematosus and inflammatory bowel disease are often debilitating diseases themselves and are associated with significant medical costs. An additional diagnosis of uveitis has been estimated to cost \$935 to \$1,738 per month depending upon the treatments pursued.⁴

The current treatment regimen for acute non-infectious uveitis is to provide anticholinergic eye drops to induce cycloplegia and mydriasis to help reduce pain. Topical or systemic corticosteroids are also administered to reduce inflammation.¹ Approximately half of patients with uveitis will not have remission of symptoms with corticosteroid use alone.¹ Once a patient begins to require more than 10mg/day of prednisone, an immunosuppressive drug is considered.⁴ Antimetabolites and cytotoxic agents are used help reduce inflammation and preserve vision, however, long-term treatment with methotrexate, cyclosporine and azathioprine have complications like renal insufficiency, hypertension, thrombocytopenia and hepatic toxicity.⁴ Adalimumab has been shown to reduce the inflammation associated with uveitis and can be an effective treatment, limiting the amount of corticosteroid use and preventing the visual deterioration associated with uveitis as well as the complications from glucocorticoid use.

OBJECTIVE: The objective of this systematic review is to determine whether or not adalimumab prevents the loss of visual acuity in patients with uveitis.

METHODS: The population of the studies used in this review included patients with active or inactive noninfectious uveitis and their ages ranged from 4-81 years old. Two randomized controlled trials and one retrospective study were used in this review. In the RCT's, patients

were given either a subcutaneous injection of placebo or 80mg of adalimumab at baseline, followed by 40 mg every two weeks. A burst of prednisone was also administered at baseline and then tapered over two weeks. Treatment was continued for 80 weeks or until the patient experienced treatment failure. The retrospective study by Dobner et al. evaluated patients that were given 40 mg of adalimumab every two weeks with an average follow up of 87.9 weeks. Measurements of the patients change in visual acuity over the course of treatment was the clinical outcome looked at for selection of these studies.

The keywords used for research were “adalimumab” and “uveitis”, in the databases PubMed and Cochrane Systematic Review. The included articles were published in English and in peer reviewed journals between 2013-2016. The studies selected for this review were chosen based on their evaluation of patient oriented outcomes (POEMs). Inclusion criteria were studies that were published within 10 years and at least two of them were RCT’s. Exclusion criteria included studies that did not evaluate POEMs or evaluated patients with infectious causes of uveitis. Statistics reported in this review include p values, hazard ratios, mean change and numbers needed to harm.

Table 1. Demographics and Characteristics of included studies

Study	Type	#pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dobner, 2013 (4)	Retrospective	60	4-71	Patients with uveitis refractory to other immunosuppressive treatment	Infectious uveitis	13	Adalimumab 40mg every 2 weeks
Jaffe, 2016 (5)	RCT	217	18-81	18 years or older with active noninfectious intermediate, posterior, or panuveitic uveitis. despite the use of Prednisone. No previous, active or latent TB.	Isolated anterior uveitis. Confirmed or suspected infectious uveitis. Contraindication pupil dilation. Corneal or lens opacity that impaired visualization of the fundus. Previous exposure to anti-TNF therapy or any biologic therapy with a potential therapeutic impact on	17	Adalimumab 80mg at baseline and 40mg doses every 2 weeks. 60mg/d prednisone burst followed by taper.

					non-infectious uveitis. Using >1 immunosuppressive therapy (not including corticosteroids) within the last 28 days prior to baseline visit.		
Nguyen, 2016 (6)	RCT	227	18-75	18 years or older with inactive noninfectious intermediate, posterior, or panuveitic uveitis. Inactive uveitis for at least 28 days before the baseline visit. Use of 10-35 mg/d PO Prednisone. Documented history of at least 1 disease flare within 18 months of the screening visit. No previous or active TB.	Same exclusion criteria as Jaffe et al.	18	Adalimumab 80 mg at baseline and 40 mg doses every 2 weeks. 10-35mg/d PO Prednisone at baseline. Followed by a taper starting at week 2.

OUTCOMES MEASURED: Jaffe et al. and Nguyen et al. evaluated the efficacy of adalimumab over placebo based on comparison of time to treatment failure. Treatment failure was determined when changes in the eye indicative of uveitic flare were noticed, or a decrease in the patients best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Study visits were done at baseline and weeks one, four, six, eight and every four weeks thereafter. Visits were continued until treatment failure was determined or until 80 weeks was reached. The primary clinical outcome being assessed in this review is visual acuity, which in the RCT's was calculated using the logarithm of minimum angle of resolution (logMAR) of each eye. Visual functioning questionnaires (VFQ-25) were also administered at these study visits to further compare patient outcomes in placebo versus the treatment group. The VFQ-25 provides a detailed assessment of a patients perceived visual quality and evaluation of ocular pain. The questionnaire consists of a VFQ-25 composite score, VFQ-25 distance vision sub-score, change in VFQ-25 near vision sub-score, and change in VFQ-

25 ocular pain sub-score. Jaffe et al. and Nguyen et al. also monitored for adverse events at each study visit, starting from the first administration of treatment and until 70 days after the last dose.

In the retrospective study, Dobner et al. evaluated the effectiveness of adalimumab by reviewing the outcomes of patients at multiple institutions treated with adalimumab for noninfectious uveitis. Improvement of uveitis was determined by an enhanced visual acuity of two or more lines on Snellen chart, a decrease in inflammatory markers, macular edema and uveitic flares or the prednisone dose the patient was previously on could be reduced to less than 10 mg. At least one of these criteria had to improve, while none of the others could worsen to determine the treatment effective.

RESULTS: Jaffe et al. is a phase 3 trial undertaken in 18 countries from 2010 through 2014.

The study analyzed effectiveness of adalimumab in adult patients that were 18-81 years old and had active noninfectious intermediate uveitis, posterior uveitis or panuveitis. The patients chosen had active infections despite the use of prednisone 10-60 mg per day and further inclusion and exclusion criteria is available in Table 1. Active infection was recognized based on the National Eye Institute criteria and the Standardization of Uveitis Nomenclature Working Group.

Patients were randomly assigned to receive adalimumab (80mg at baseline and 40mg every two weeks) or placebo and all patients were given a prednisone burst of 60mg per day followed by a taper, in which all had discontinued prednisone by 15 weeks. The intention to treat analyses included 217 of the 223 patients randomly assigned (110 in adalimumab group and 107 in placebo) because six patients were omitted due to poor compliance with treatment.

In this systematic review the outcome being assessed from Jaffe et al. is change in visual acuity. The efficacy of adalimumab in this study was determined by time to treatment failure and the adalimumab group had a significantly lower incidence of treatment failure due to a

decrease in best corrected visual acuity. When comparing treatment failure due to a worsening of best corrected visual acuity (BCVA), a hazard ratio of 0.56 was calculated with a 95% CI (0.32-0.98) and $P=0.04$. This represents that at any time during the study, half as many patients that were receiving adalimumab experienced treatment failure due to worsening vision than in the placebo group. In Jaffe et al. the mean change in BCVA using logMAR was also calculated comparing the treatment and placebo groups per eye (Table 2). The data collected represents the change from the BCVA before week 6 to the state of vision at the final visit. The mean between group difference was -0.07 with a 95% CI (-0.11 to -0.02) and a p value of 0.003. The mean between group difference of -0.07 represents a significantly smaller change in logMAR, demonstrating significantly more stable vision for the patients receiving adalimumab over placebo. The VFQ-25 filled out by the patients favored the adalimumab group in the composite and all sub-score categories except the change in distance vision sub-score.

Throughout the Jaffe et al. study, there were six serious adverse events in the placebo group and 18 serious events in the adalimumab group. Injection site reactions and allergic reactions were the most common adverse events, therefore, calculations were made regarding the incidence of serious adverse events (Table 3). The calculated numbers needed to harm (NNH) for the intervention group is 24 which means that for every 24 patients treated with adalimumab, one more patient will experience a serious adverse event. Some of the serious adverse events found in the adalimumab group included various infections, lupus and cancer. One death was reported in the adalimumab group due to end stage chronic renal disease but was judged by the investigators to be unrelated to the intervention.

Table 2. Mean change in best corrected visual acuity for Jaffe et al.

	Placebo group (N=107)		Adalimumab group (N=110)		Mean Between Group Difference (95% CI)	P value
	Number of patients	Value (logMAR)	Number of patients	Value (logMAR)	-0.07 (-0.11 to -0.02)	0.003
Left eye	103	0.12	101	0.07		
Right eye	103	0.13	101	0.04		

Table 3. Calculations for harm from Jaffe et al.

Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	NNH
12%	16%	33%	4%	24

Nguyen et al. is another phase 3 trial that was conducted at 62 study sites in 21 countries. The primary outcome measured in this double blinded, randomized, placebo controlled trial was to assess time to treatment failure in patients with inactive noninfectious uveitis. Patients were either given a baseline loading dose of adalimumab 80mg followed by 40mg every two weeks or placebo. Trial participants were also given 10-35 mg/d of oral prednisone at baseline and underwent a steroid taper starting at week two, in which all participants had completed by week 19. The main inclusion criteria stated patients must be 18 years of age or older with inactive noninfectious intermediate, posterior or panuveitis. Inactivity was required for 28 days prior to the baseline visit and patients must have been using 10-35mg/d of prednisone to maintain inactivity. Disease inactivity was based on the absence of inflammation and criteria from the Standardization of Uveitis Nomenclature. Further inclusion and exclusion criteria is available in Table 1. The intention to treat population included 226 patients, 111 in placebo and 115 in the treatment group.

In the Nguyen et al. study the adalimumab group had significant less treatment failure compared to placebo and the greatest between group difference was treatment failure caused by a decrease in visual acuity (21% in the placebo group and 9% in the adalimumab group). When comparing treatment failure due to a worsening of visual acuity, a HR of 0.33 was calculated with a 95% CI of 0.16-0.70 and a p value of 0.002. This calculation states that one third as many of the adalimumab treated patients at any given time had treatment failure caused by worsening vision when compared to the placebo group. This is an equivalent reduction in risk of 67 percent. The change in BCVA was also calculated for each eye and compared between groups. The results favored the adalimumab group but was not statistically significant. All of the VFQ-25 were in favor of adalimumab except the near vision subset, but these differences between groups were also not significant.

Out of the 111 patients in the intention to treat population of the placebo group, 95 completed the study. Sixteen of the participants discontinued the study, seven of which were due to adverse events, three were lost to follow up, three withdrew because of lack of efficacy and three for other reasons. In the adalimumab intention to treat population, 101 completed the study and 10 discontinued due to adverse events, two withdrew and two discontinued for other reasons. The occurrence of adverse and serious adverse event was similar between groups. Calculations were made using the incidence of serious adverse events in treatment groups, with the adalimumab group reporting 13 serious adverse events and placebo reporting 10. The NNH for adalimumab is 34 which means for every 34 patients given this intervention, one more patient would experience a serious adverse event (Table 5). One malignancy of squamous cell carcinoma was reported in the adalimumab group. There were four cases of latent tuberculosis, one of which was in the placebo group and the remaining three in the adalimumab patients. One

death was reported in the adalimumab population due to aortic dissection and cardiac tamponade but was determined to not be related to the intervention.

Table 4. Mean change in BCVA for Nguyen et al.

	Placebo group N=111		Adalimumab group N=115		Mean difference (95% CI)	P value
	Number of patients	Value (logMar)	Number of patients	Value (logMAR)	-0.04	0.096
Left eye	110	0.06	115	0.01		
Right eye	110	0.02	115	-0.01		

Table 5. Calculations for harm from Nguyen et al.

CER	EER	RRI	ARI	NNH
8.8%	11.7%	33%	2.9%	34

In the retrospective study by Dobner et al., 60 patients receiving adalimumab treatment for various forms of noninfectious uveitis were identified from tertiary care centers in Vienna, Munster and Heidelberg. All of the patients had received prior immunosuppressive treatment without improvement, which included etanercept and infliximab. A majority of the patients evaluated had active anterior uveitis and systemic disease. All of the patients in this study were receiving adalimumab 40mg every other week. Fifty nine percent of the patients had improvement of their visual acuity, 36 percent had stable vision, while 5 percent experienced worsening vision. At the last follow up visit 47 out of the 60 patients were still receiving adalimumab treatment. Eight of the patients discontinued because of inefficacy, two discontinued treatment because of liver enzyme elevation, one because of furunculosis, one

patient became pregnant, and one death due to a heart attack which was determined to not be related to the treatment.

Table 6. Changes in visual acuity in patients receiving adalimumab from Dobner et al.

Change in visual acuity	Number of patients	Percent %
Improvement	35	59
Stable	21	36
Worsening	3	5

DISCUSSION: Prior to the two RCT's discussed in this systematic review, there has been a lack of controlled studies on the efficacy of immunomodulatory drugs for the treatment of noninfectious uveitis.^{5,6} The added benefits of these studies included the diverse types of uveitis in the population as well as evaluating the ability of adalimumab to prevent uveitic flare while tapering patients off glucocorticoids. The rapid discontinuation of glucocorticoid therapy in these studies was a limitation, because in clinical practice patients often take glucocorticoids as needed to help control symptoms.⁵

Indication of adalimumab treatment has been evaluated and proven effective in various other inflammatory diseases, such as rheumatoid arthritis, psoriasis, hidradenitis suppurativa, ankylosing spondylitis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis.⁷ No new precautions for adalimumab treatment were noted in these studies on noninfectious uveitis.^{5,6} Following the publication of the RCT's included in this systematic review, FDA approval of adalimumab for the treatment of noninfectious intermediate, posterior and panuveitis in adults was granted.⁷ Black box warnings for adalimumab treatment include the risk of serious infections, however, most patients who developed life threatening infections were concomitantly

taking other immunosuppressive treatment.⁷ The warning recommends testing patients for latent TB infection and to closely monitor patients for signs of opportunistic infection throughout treatment.⁷ Increased risk of lymphoma and other malignancies is also included in the warning but states that it is currently unclear if the risk is associated solely with adalimumab or adalimumab in combination with other immunosuppressive treatment.⁷ Other risks associated with adalimumab include reactivation of hepatitis B in chronic carriers, rare cases of new onset or reactivation of neurologic disorders, infrequent cases of pancytopenia have been reported and rarely the development of a lupus like syndrome.⁷ Data suggests adalimumab crosses the placenta but there are no known impacts on the fetus with in utero exposure or through breast feeding.⁷

CONCLUSION: The result of this systematic review of the literature shows that adalimumab can help prevent the loss of visual acuity in adult patients, specifically with noninfectious intermediate, posterior or panuveitis.^{5,6} Both the RCT's demonstrated statistically significant reduction in treatment failure due to worsening BCVA.^{5,6} No new safety concerns were identified for adalimumab treatment compared to its indication in other disease, however, patient risk factors need to be considered prior to initiating adalimumab treatment. An open-label extension study is being done for long-term safety studies in patients with noninfectious uveitis receiving adalimumab.^{5,6} A limitation of the studies was the wide variety of uveitis diagnoses as this impaired the ability to evaluate the efficacy in specific conditions. These studies controlled for the location and activity of uveitis but further research could involve studies that analyze the efficacy of treatment for specific causes of uveitis. Currently adalimumab is the only FDA approved non-glucocorticoid therapy for noninfectious uveitis and, therefore, further study can be done to compare the efficacy of adalimumab and other immunomodulatory agents.

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