Treatment of Experimental Anterior and Intermediate Uveitis by a Dexamethasone Intravitreal Implant

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PURPOSE. To assess the efficacy of a dexamethasone (DEX) intravitreal implant in a rabbit model of anterior and intermediate uveitis.

METHODS. Experimental anterior and intermediate uveitis was induced by a unilateral intracameral injection of Mycobacterium tuberculosis H37Ra antigen in preimmunized rabbits. Four days after uveitis induction, rabbits received DEX implant or underwent a sham procedure (no implant). Clinical and histopathologic signs of uveitis were assessed for 13 days, and levels of inflammatory markers in the iris/ciliary body were measured after 21 days.

RESULTS. All signs of anterior and intermediate uveitis were reduced by the DEX implant compared with sham procedure. At day 13, mean anterior chamber cell scores ± SD for the DEX implant versus the sham procedure were, respectively, 1.9 ± 1.3 versus 4.0 ± 0.0 (P = 0.04), and mean total histologic inflammatory scores were 3.9 ± 2.5 versus 15.4 ± 6.0 (P = 0.026). Similarly, at day 13, mean vitreous haze severity scores (SD) for the DEX implant versus the sham procedure were, respectively, 0.1 ± 0.2 versus 2.7 ± 1.5 (P = 0.026), and mean vitreous inflammatory cell infiltration scores were 0.0 ± 0.0 versus 1.5 ± 1.3. Treatment with the DEX intravitreal implant also significantly reduced the proinflammatory immune response, as measured by cytokine levels in iris/ciliary body.


Uveitis is an inflammatory disorder that is often classified according to the location of inflammation (anterior, intermediate, posterior, pan uveitis).1 Anterior uveitis, the most common form, is characterized by inflammation in the anterior chamber, whereas in intermediate uveitis, inflammation is confined primarily to the vitreous.1,5 Anterior uveitis can be chronic or recurrent,2,3 whereas intermediate uveitis is usually chronic.4 Corticosteroids remain the mainstay of therapy for uveitis. First-line therapy for chronic anterior or intermediate uveitis is periorcular or systemic corticosteroids. However, both routes of administration are associated with an increased risk of side effects,5 and corticosteroids given periorcularly are rapidly cleared, resulting in low intraocular drug levels within 2 weeks of injection.6 Therefore, frequent periocular injections are required in some patients to control chronic inflammation. In addition, some patients have disease resistant to topical steroids and require periocular administration or treatment with other immunosuppressive agents. This is especially true for more chronic forms of anterior uveitis, such as that associated with juvenile rheumatoid arthritis. Another concern with intermediate and posterior uveitis is that many patients have coexistent anterior segment inflammation. To overcome the disadvantages of periocular or systemic corticosteroids, sustained-release corticosteroid intravitreal implants are being developed7 for patients who have chronic or recurrent uveitis.

The dexamethasone (DEX) intravitreal implant (Ozurdex; Allergan, Inc., Irvine, CA) is a novel sustained-release corticosteroid intravitreal implant that has recently been approved by the United States Food and Drug Administration for the treatment of macular edema after retinal vein occlusion.

The objective of this study was to assess the efficacy of the DEX intravitreal implant in an experimental model of anterior and intermediate uveitis. The goal of our model was to mimic the main features of human anterior and intermediate uveitis: unilateral disease, inflammation confined to the anterior chamber and vitreous, histopathologic presence of inflammatory cells, upregulation of inflammatory markers, and disease progression.

METHODS

Study Design

This study complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and was approved by the local Institutional Animal Care and Use Committee. Young adult Dutch-belted pigmented rabbits weighing approximately 2.5 kg each were obtained from Covance Research Products Inc. (Denver, PA). Animals were provided with laboratory rabbit diet (product code 5326; LabDiet, Richmond, IN) and water ad libitum.

Uveitis was induced using a protocol modified from a rabbit model of panuveitis by Cheng et al.8 Rabbits were preimmunized with two subcutaneous injections of Mycobacterium tuberculosis H37Ra antigen (10 mg; Difco, Detroit, MI) suspended in mineral oil (500 μL) approximately 7 days apart, 3 to 4 weeks before treatment (Fig. 1). Four days before treatment, each rabbit was given a unilateral intracameral injection of M tuberculosis antigen suspended in sterile saline (20 μg; 1 μg/μL). Eyes were prepared for injection with 5% povidone iodine (Betadine Sterile Ophthalmic Prep Solution; Alcon, Fort Worth, TX) and proparacaine hydrochloride ophthalmic solution, USP 0.5% (Wilson Ophthalmic, Mustang, OK). The antigen was delivered to the anterior chamber of the eye using a Hamilton syringe with a 31-gauge needle. Eyes were treated with a triple antibiotic ointment and 1% atropine immediately after injection to prevent infection and maintain postoperative cyclopia.

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Physiology and Pharmacology
One treatment group received a unilateral intravitreal implant (700-μg DEX intravitreal implant) in the same eye that was injected with antigen. The second treatment group underwent the same procedure but did not receive an implant (sham procedure). Before implantation, rabbits were lightly anesthetized with an intravenous injection of ketamine (15 mg/kg, Ketaset; Fort Dodge Animal Health, Fort Dodge, IA) and acepromazine (1 mg/kg, Prom Ace; Fort Dodge Animal Health). Eyes were prepared for injection with 5% povidone iodine (Betadine Sterile Ophthalmic Prep Solution; Alcon) and praparacaine hydrochloride ophthalmic solution, USP 0.5%. A 22-gauge needle of a preloaded DEX implant applicator was introduced through the sclera, 4 mm from the limbus. The needle was advanced tangentially through the sclera, parallel to the limbus, for 1 to 2 mm. The needle was then turned to the perpendicular position and advanced to enter the vitreous chamber, where the implant was deployed. Eyes were treated with a triple antibiotic ointment and 1% atropine immediately after injection to prevent infection and to maintain postoperative cycloplegia. Healthy, untreated rabbits were preimmunized but did not receive any intraocular antigen or treatment intervention.

One cohort of rabbits (n = 9 for sham, n = 10 for DEX implant) was assessed for clinical and histopathologic changes. To confirm the histology results and to test two different lots of DEX Implant, a second cohort of rabbits (n = 6 for sham, n = 12 for DEX implant) was studied. Eyes from this second cohort were used not only to evaluate changes in corneal thickness but also to measure the iris/ciliary body thickness. Different eyes from healthy, untreated rabbits (n = 6) were used as a control group for histopathology, corneal thickness, and inflammatory marker assessments.

Clinical Assessment

External ocular appearance was documented on days −1, 3, and 13. Photographs (color 50°) of the eyes were taken with a digital Zeiss fundus camera (FF450 IR; Carl Zeiss Meditec, Dublin, CA). These photographs were assessed for the appearance of the fundus. Clinical severity of uveitis was assessed by a masked ophthalmologist on days −1, 3, 7, and 13 by measuring anterior chamber cells and vitreous haze. The same ophthalmologist assessed clinical severity throughout the study. Eyes were examined by slit lamp microscopy, and anterior chamber cells were graded by cell number from 0 to 4+ (where 0 = <1 cell in field, 0.5+ = 1–5 cells in field, 1+ = 6–15 cells in field, 2+ = 16–25 cells in field, 3+ = 26–50 cells in field, 4+ = >50 cells in field).1 Eyes were also examined using an indirect ophthalmoscope (with a 20D aspherical lens), and vitreous haze was graded by examination of the posterior pole and visibility of the optic nerve from 0 to 4 (where 0 = no inflammation, +0.5 = trace inflammation, +1 = mild blurring of retinal vessels and optic nerve, +2 = moderate blurring of optic nerve head, +3 = marked blurring of optic nerve head, +4 = optic nerve head not visible, or visibility of the posterior pole was prevented by corneal swelling).9

Histopathologic Assessment

The inflammatory response was assessed on days 4 and 13 by histopathology and ocular section grading. To prepare the tissue for sectioning, eyes were enucleated immediately after rabbits were euthanatized by intravenous injection of 390 mg/mL pentobarbital sodium and 50 mg/mL phenytoin sodium (Euthalol; Virbac Animal Health Inc., Fort Worth, TX). The eyes were fixed overnight in modified Davidson’s fix (BBC Biochemical, Standwood, WA). Fixative was changed to 50% ethanol (for 5–24 hours), 70% ethanol (for 12–48 hours), and then 10% neutral buffered formalin for storage. Before sectioning, eyes were trimmed with a cut perpendicular to the large blood vessel, approximately 2 mm before the disc. Tissue was processed overnight in an automatic processor (Tissue-Tek VIP; Sakura Finetek Europe B.V., Zoeterwoude, The Netherlands) and then embedded nasal-side down in paraffin. Sections of 4-μm thickness were cut sequentially at the equator so that all tissues of the eye, from the anterior to the posterior segment, were represented. Sections were stained in hematoxylin-cosin using an automatic stainer (Tissue-Tek VIP; Sakura Finetek Europe B.V.). Sections were assessed by a masked pathologist for inflammatory cell infiltration and ocular histopathology. The conjunctiva, cornea, anterior chamber, trabecular meshwork, iris, and ciliary body were scored from 0 (normal) to 4 (marked)10 for signs of inflammation. The signs of inflammation scored included edema/congestion (conjunctiva, ciliary body, cornea), inflammatory cell infiltration (conjunctiva, cornea, anterior chamber, trabecular meshwork, iris, ciliary body), and neovascularization (cornea). Scores were combined to give a total inflammatory score for each section (maximum score, 40). The vitreous, choroid, and retina were scored from 0 (normal) to 4 (marked) for signs of inflammatory cell infiltration. The vitreous was also assessed (present/absent) for signs of fibrin. Morphometric measurements were taken of the ciliary body to assess edema. Corneal thickness was assessed on day 21 using an OCT system (Visante; Carl Zeiss Meditec).

Inflammatory Marker Quantification

Changes in the iris/ciliary body levels of proinflammatory markers were assessed on day 21 by multi-analyte profile (MAP) analysis. The entire panel of 89 proinflammatory markers from a multiplex immunoassay (HumanMAP, version 1.6; Rules-Based Medicine, Inc., Austin, TX) were tested.11 All markers that were increased threefold or greater were reported. To prepare the tissue for analysis, eyes were enucleated immediately after rabbits were euthanatized, as described. The iris/ciliary body tissue was isolated from the eye and snap-frozen in liquid nitrogen. Protein was isolated from the iris/ciliary body tissue by homogenization in lysis buffer (T-Per; Pierce, Merck, Darmstadt, Germany) containing protease inhibitors (Roche, Indianapolis, IN). Samples were centrifuged at 3000 rpm for 10 minutes, and supernatants were collected and frozen. Frozen samples were sent to a certified service laboratory (Rules-Based Medicine) for antigen analysis by the human antigen MAP (LumineX Human MAP, version 1.6) system, which is a multiplex bead immunoassay that detects the expression of 89 proteins. Briefly, samples were added to the multiplex microspheres and incubated at room temperature for 1 hour. Cocktails of biotinylated reporter antibodies were then added, mixed, and incubated at room temperature for 1 hour. Multiplexes were developed by the addition of excess streptavidin-phycocerythrin, incubation at room temperature for 1 hour, and analysis by the LumineX system.
The eye at day 13 after DEX implant treatment appears normal.

The clinical grading of uveitis (anterior chamber cell score and vitreous haze) was lower in DEX implant-treated eyes than in sham-treated eyes. Figure 2 shows photographs of the external ocular appearance of sham-treated eyes and DEX implant-treated eyes before and after treatment. By day 13, there were no external signs of uveitis in DEX implant-treated eyes. In contrast, the external ocular appearance of sham-treated eyes was characterized by extensive corneal edema, pupil synechiae, conjunctival vascular dilation, and corneal vascularization. The fundus appeared normal in both DEX implant-treated eyes and sham-treated eyes at day 3 and day 13 (in all eyes in which the fundus was evaluable).

The clinical grading of uveitis (anterior chamber cell score and vitreous haze) was lower in DEX implant-treated eyes than in sham-treated eyes (Fig. 3). At day –1, 8 of 9 sham-treated eyes and 9 of 10 DEX implant-treated eyes had an anterior chamber cell score of ≥3. By day 3, only 4 of 10 DEX implant-treated eyes had an anterior chamber cell score of ≥3 (compared with 9 of 9 sham-treated eyes), and at day 13, the mean anterior chamber score was significantly lower in DEX implant-treated eyes (1.9 ± 1.3 vs. 4.0 ± 0.0, DEX implant versus sham; *P = 0.04) (Fig. 3). By day 13, only 1 of 5 DEX implant-treated eyes had an anterior chamber cell score of 4. Similarly, the severity of vitreous haze was significantly lower in DEX implant-treated eyes (at day 13, 0.1 ± 0.2 vs. 2.7 ± 1.5, DEX implant versus sham; *P = 0.026) (Fig. 3).

At day 4, DEX implant-treated eyes had moderate histopathologic signs of inflammation with cell infiltration in the cornea (score of 1.0 ± 0.6), iris (1.2 ± 0.6), ciliary body (2.0 ± 0.7), and trabecular meshwork (1.7 ± 0.4). In contrast, in sham-treated eyes at day 4, inflammation was observed in the anterior angle chamber and extended posteriorly into the ciliary body, suprachoroidal space, and muscle (Fig. 4). Cell infiltration was present in all tissues of the anterior segment, including the cornea (score of 1.9 ± 0.5), anterior chamber (0.7 ± 0.3), iris (1.2 ± 0.4), ciliary body (2.0 ± 0.4), and trabecular meshwork (2.4 ± 0.4).

By day 13, there was little evidence of inflammation or cell infiltration in DEX implant-treated eyes, and most eyes had a histopathology similar to that of healthy, untreated eyes (Fig. 4). Only 1 of 5 DEX implant-treated eyes showed moderate to severe signs of corneal infiltration (score of 1.5) and ciliary

**RESULTS**

**Clinical Signs of Uveitis**

Eyes that received the DEX intravitreal implant had fewer clinical signs of uveitis than sham-treated eyes. Figure 2 shows photographs of the external ocular appearance of sham-treated eyes and DEX implant-treated eyes before and after treatment. By day 13, there were no external signs of uveitis in DEX implant-treated eyes. In contrast, the external ocular appearance of sham-treated eyes was characterized by extensive corneal edema, pupil synechiae, conjunctival vascular dilation, and corneal vascularization. The fundus appeared normal in both DEX implant-treated eyes and sham-treated eyes at day 3 and day 13 (in all eyes in which the fundus was evaluable).

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**Histopathology**

Treatment with the DEX intravitreal implant reduced histopathologic signs of uveitis compared with sham-treated eyes (Fig. 4). Overall, the total inflammatory score was similar in DEX implant-treated eyes and sham-treated eyes at day 4 (12.1 ± 3.4 vs. 15.8 ± 2.4; *P = 0.09) but was significantly lower in DEX implant-treated eyes at day 13 (3.9 ± 2.5 vs. 15.4 ± 6.0; *P = 0.026; Fig. 5).

At day 4, DEX implant-treated eyes had moderate histopathologic signs of inflammation with cell infiltration in the cornea (score of 1.0 ± 0.6), iris (1.2 ± 0.6), ciliary body (2.0 ± 0.7), and trabecular meshwork (1.7 ± 0.4). In contrast, in sham-treated eyes at day 4, inflammation was observed in the anterior angle chamber and extended posteriorly into the ciliary body, suprachoroidal space, and muscle (Fig. 4). Cell infiltration was present in all tissues of the anterior segment, including the cornea (score of 1.9 ± 0.5), anterior chamber (0.7 ± 0.3), iris (1.2 ± 0.4), ciliary body (2.0 ± 0.4), and trabecular meshwork (2.4 ± 0.4).

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**FIGURE 2.** Representative photographs of the external ocular appearance of sham- and DEX implant-treated eyes. Photographs were taken at day –1 (3 days after uveitis induction), day 3, and day 13. Corneal edema, pupil synechiae, conjunctival vascular dilation, and corneal vascularization are present in sham-treated eyes. The eye at day 13 after DEX implant treatment appears normal.

**FIGURE 3.** Clinical response of eyes to sham procedure and DEX implant treatment. Values represent the (A) mean anterior chamber scores and (B) mean vitreous haze scores for sham-treated eyes (*n = 9 at days –1 and 3; *n = 4 at days 7 and 13) and DEX implant-treated eyes (*n = 10 at days –1 and 3; *n = 5 at days 7 and 13). Error bars represent the SD. Differences in the mean scores observed between the sham- and DEX implant-treated eyes were evaluated using the Wilcoxon rank-sum test. *P < 0.05.
body infiltration (score of 2.0). There was no evidence of cell infiltration in the anterior chamber or iris. In contrast, in sham-treated eyes, the severity of inflammation increased from day 4. Both the ciliary body and the iris were markedly swollen and heavily infiltrated (Fig. 4). By day 13, cell infiltration was present in the cornea (score of 1.6 \( \pm \) 0.9), anterior chamber (0.9 \( \pm \) 0.9), iris (1.3 \( \pm \) 1.0), ciliary body (2.3 \( \pm \) 0.9), and trabecular meshwork (2.5 \( \pm \) 1.5).

Inflammatory cell infiltration into the vitreous was observed at day 4 in both DEX implant-treated eyes and in sham-treated eyes (Table 1). However, by day 13, cell infiltration in the vitreous had increased in sham-treated eyes and decreased (to normal) in DEX implant-treated eyes. At day 13, fibrin was present in the vitreous of 2 of 4 sham-treated eyes compared with 0 of 5 DEX implant-treated eyes.

Minor cell infiltration into the choroid was observed only in 2 of 4 sham-treated eyes at day 13 (Table 1). Inflammatory cell infiltration was not observed in the retina (Table 1).

At day 4, the size of the ciliary body in DEX implant-treated eyes was similar to the size of the ciliary body in sham-treated eyes (Fig. 5). However, by day 13, the size of the ciliary body was three times greater in sham-treated eyes than in DEX implant-treated eyes (0.73 \( \pm \) 0.13 mm\(^2\) vs. 2.47 \( \pm \) 1.45 mm\(^2\); Fig. 5). At day 21, corneal thickness was significantly lower in DEX implant-treated eyes than in sham-treated eyes (406 \( \pm \) 111 \( \mu \)m vs. 802 \( \pm \) 75 \( \mu \)m; \( P = 0.0009\); Fig. 5). At day 21, corneal thickness in DEX implant-treated eyes was similar to the corneal thickness of healthy, untreated eyes (353 \( \pm \) 14 \( \mu \)m; Fig. 5).

**Iris/Ciliary Body Levels of Inflammatory Markers**

Most inflammatory markers that were upregulated (more than threefold increase) after uveitis induction were significantly downregulated in DEX implant-treated eyes (Table 2).

Of the 89 inflammatory markers assessed, the levels of 10 markers were significantly higher in sham-treated eyes than in healthy, untreated eyes (Table 2; Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5939/-/DCSupplemental). Inflammatory markers that were significantly upregulated after uveitis induction in sham-treated eyes compared with healthy, untreated eyes were brain-derived neurotrophic factor (BDNF; 9-fold, \( P = 0.0051\)), CD40 (73-fold, \( P = 0.0037\)), interleukin-1\( \beta \) (IL-1\( \beta \); 16-fold, \( P = 0.0037\)), IL-8 (3-fold, \( P = 0.0051\)), macrophage inflammatory protein-1\( \alpha \) (MIP-1\( \alpha \); 3-fold, \( P = 0.0028\)), MIP-1\( \beta \) (3-fold, \( P = 0.0047\)), matrix metallopeptidase-2 (MMP-2; 9-fold, \( P = 0.0051\)), regulated on activation, normal T-cell expressed, secreted (RANTES; 1338-fold, \( P = 0.0048\)), vascular cell adhesion molecule-1 (VCAM-1; 3-fold, \( P = 0.0051\)), and vascular endothelial growth factor (VEGF; 4-fold, \( P = 0.0051\)). For all other inflammatory markers, the change was less than twofold, or the level was below assay detection limits. Compared with the sham procedure, treatment
The results of this study demonstrated that dexamethasone, when delivered intravitreally as a sustained-release implant, reduced inflammation in an animal model of anterior and intermediate uveitis. For this study, we modified the Cheng et al.8 rabbit model of panuveitis (in which the primary site of inflammation is the anterior chamber, vitreous, and retina or choroid)1 so that the ocular inflammation observed clinically was primarily in the anterior and intermediate uveitis.

In the pathogenesis of uveitis, although the vitreous cellular infiltration appeared to be less than haze in our model, fibrin (protein leakage) was present and contributed to the haze score, which combines the optical effect of cellular infiltration and protein leakage. In our model, ocular inflammation was unilateral and progressed from mild to severe over the experimental period. The key difference between the model in our study and that of Cheng et al.8 was that we used an intracameral injection of M. tuberculosis to localize inflammation to the anterior and intermediate vitreous rather than a vitreous cavity injection, which induced panuveitis in the Cheng model. In the Cheng model, sustained-release corticosteroids were implanted before uveitis was induced. In our model, the DEX implant was administered after uveitis was induced, which mimics treatment of uveitis in clinical settings. Other experimental models that closely resemble human anterior and intermediate uveitis have been developed in rats.12–15 However, for the purposes of our study, a larger animal model was necessary to enable implantation of the DEX implant. In addition, although there are anatomic and physiological differences between rabbit and human eyes, the pharmacokinetics of dexamethasone in the vitreous are similar between the species.16,17

Topical corticosteroids have long been known to suppress anterior chamber inflammation in various models of experimental uveitis.18–20 In a comparative study, anterior uveitis was reduced similarly by dexamethasone sodium phosphate 0.1%, fluorometholone 0.1%, loteprednol etabonate 0.5%, and prednisolone acetate 1% in rabbits.21 When given topically, corticosteroids are instilled multiple times a day as their aqueous concentrations drop to subtherapeutic levels in a few hours after each instillation.21,22 Multiple daily administration of corticosteroids is, however, complicated by toxicity to the corneal epithelium.23 As occurs with topical instillation, dexamethasone is rapidly eliminated from the eye after intravitreal injection, with a half-life of <4 hours.17 The chronic and recurrent nature of uveitis, however, necessitates sustained therapeutic tissue levels of corticosteroids. Pharmacokinetic studies in primates have shown that the sustained-release DEX implant delivers high retinal concentrations of dexamethasone for 2 months, followed by lower maintenance drug levels for up to 6 months.24 In clinical trials of patients with persistent macular edema, a single DEX implant improved visual acuity at month 3, which persisted to month 6.25,26 Our findings indicate that a single DEX implant can effectively suppress anterior chamber inflammation for 13 days in a rabbit model of anterior uveitis.

There is interest in the role that inflammatory cytokines play in the pathogenesis of uveitis. Although enzyme-linked immu-

### TABLE 1. Inflammatory Cell Infiltration into the Vitreous, Choroid, and Retina after Uveitis Induction

<table>
<thead>
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<th>Healthy, Untreated Eyes</th>
<th>Sham</th>
<th>DEX Intravitreal Implant</th>
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<tr>
<td></td>
<td>Day 13 (n = 2)</td>
<td>Day 4 (n = 5)</td>
<td>Day 13 (n = 4)</td>
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<tr>
<td>Vitreous</td>
<td>0.0 ± 0.0</td>
<td>0.8 ± 0.3</td>
<td>1.5 ± 1.3</td>
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<tr>
<td>Choroid</td>
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<td>0.0 ± 0.0</td>
<td>0.5 ± 0.3</td>
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<tr>
<td>Retina</td>
<td>0.0 ± 0.0</td>
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Values are mean ± SD scores. Eyes were scored from 0 (normal) to 4 (marked) for inflammatory cell infiltration.
The most commonly increased cytokines were interferon-γ in infectious uveitis in comparison to controls. In these studies, cytokine levels of patients with idiopathic, infectious or non-infectious, these studies collectively suggest that inflammatory mediators play a role in the onset or exacerbation of anterior or intermediate uveitis,30,31,34–38 which supports that inflammatory markers tested in this study, most were not detectable or were below the limits of detection, possibly because of poor cross-reactivity between rabbit samples and human antibodies.

Values are mean ± SD concentrations. Data for all 89 inflammatory markers are available in Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5939/DCSupplemental.

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