

# Intravitreal Ketorolac for Chronic Uveitis and Macular Edema

## A Pilot Study

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**Objective:** To investigate the adverse ocular effects of intravitreal ketorolac (4 mg) in patients with chronic uveitis and complications of chronic inflammation (macular edema).

**Methods:** We conducted a prospective phase 1 clinical trial involving 10 eyes of 10 adult patients with chronic inflammation and/or macular edema for whom previous treatment failed or who could not tolerate corticosteroids because of adverse ocular effects. Baseline (day 0) electroretinography, fluorescein angiogram, spectral domain optical coherence tomography (OCT), Goldmann visual field, and complete ophthalmic examination were performed, and then a single intravitreal injection of ketorolac (4 mg) was administered. Another ophthalmic examination with OCT was performed on day 3. Ophthalmic examination with fluorescein angiogram and OCT was repeated on days 7 and 30, and ophthalmic examination with fluorescein angiogram, OCT, electroretinography, and Goldmann visual field was performed on day 90. The study took place from March 1, 2010, through February 28, 2011.

**Results:** On the basis of ophthalmic examination findings, visual field, and electroretinography testing, there were no observed adverse ocular effects of intravitreal ketorolac. In 2 of 2 eyes with active intraocular inflammation, there was early resolution of inflammation, and in 4 of 8 eyes with macular edema, there appeared to be transient reduction in OCT thickness and/or fluorescein angiogram leakage.

**Conclusion:** A single intravitreal injection of ketorolac (4 mg) appeared to be well tolerated.

**Clinical Relevance:** Intravitreal ketorolac requires further clinical trials to determine whether it is an effective means to treat posterior segment inflammation as a safer alternative to corticosteroids in patients at increased risk of cataract formation and increased intraocular pressure.

**Trial Registration:** clinicaltrials.gov Identifier: NCT01164085

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**U**VEITIS IS ESTIMATED TO ACCOUNT for more than 10% of all cases of severe vision loss in developed countries, which makes it possibly the fourth leading cause of blindness in the United States.<sup>1,2</sup> Macular edema (ME) is a frequent cause of vision loss in patients with uveitis and complicates many other conditions.<sup>3-5</sup> Both intraocular inflammation and ME are promoted in part by prostaglandins (PGs).<sup>6</sup>

Cyclooxygenase (COX) is a critical enzyme in the inflammatory process and catalyzes the biosynthesis of PGs.<sup>7</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes and thereby the synthesis of PGs. Within the eye, PGs disrupt the blood-ocular barrier, increase vasodilation, and facilitate leukocyte migration.<sup>7</sup> Consequently, their inhi-

bition has favorable effects on both intraocular inflammation and ME.

Corticosteroids effectively treat uveitis and ME by means of their anti-inflammatory properties, and intraocular administration provides targeted delivery but is associated with higher rates of elevated intraocular pressure (IOP) and cataract formation. Ketorolac is a potent NSAID with known analgesic, antipyretic, and anti-inflammatory properties.<sup>7</sup> Despite its proven efficacy in reducing postoperative inflammation and ME, ketorolac does not reach significant levels in the vitreous or retina after topical or systemic application.<sup>7,8</sup> Therefore, intravitreal administration may allow greater therapeutic effects. More important, ketorolac does not cause cataract formation or increase IOP and offers a potentially safer alternative to corticosteroids.<sup>7</sup>

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**Table 1. Baseline Demographic Information and Visual Acuity**

Patient No.	Age, y	Eye	Lens Status	Diagnosis	Best Corrected Snellen Visual Acuity				
					Day 0	Day 3	Day 7	Day 30	Day 90
1	69	R	Pseudophakic	Postsurg CME	20/400	20/400	20/400	20/400	20/400
2	77	L	Pseudophakic	Postsurg CME	6/200	4/200	20/400	6/200	6/200
3	77	R	Pseudophakic	Uveitis	20/50 <sup>-2</sup>	20/70 <sup>-2</sup>	20/50	20/50 <sup>+2</sup>	20/150
4	73	L	Pseudophakic	Uveitic CME	20/40 <sup>-2</sup>	Missed appt	20/30 <sup>-1</sup>	20/70 <sup>+2</sup>	20/70
5	73	R	Pseudophakic	Postsurg CME	20/30 <sup>+2</sup>	20/40 <sup>-1</sup>	20/50 <sup>+2</sup>	20/40 <sup>+1</sup>	20/40
6	50	L	Phakic	Uveitis	20/30 <sup>-2</sup>	20/30 <sup>+2</sup>	20/40 <sup>-1</sup>	20/30 <sup>-1</sup>	20/20 <sup>-1</sup>
7	63	L	Phakic	Diabetic CME	20/70 <sup>+2</sup>	20/40 <sup>+2</sup>	20/40 <sup>-1</sup>	20/50 <sup>+2</sup>	20/30 <sup>+2</sup>
8	67	L	Pseudophakic	Uveitic CME	20/50 <sup>-1</sup>	20/40 <sup>+2</sup>	20/40 <sup>-2</sup>	20/40 <sup>-1</sup>	20/30 <sup>+2</sup>
9	88	R	Pseudophakic	Postsurg CME	20/50 <sup>-2</sup>	20/50 <sup>+1</sup>	20/50 <sup>-2</sup>	20/50 <sup>-1</sup>	20/50 <sup>+2</sup>
10	75	R	Pseudophakic	Postsurg CME	20/100	20/60	20/80	20/70 <sup>+2</sup>	20/40 <sup>-2</sup>

Abbreviations: appt, appointment; CME, chronic macular edema; postsurg, postsurgical.

Previous studies have demonstrated that intravitreal ketorolac is safe, effectively inhibits inflammation, and results in therapeutic levels of drug in the retina.<sup>9-11</sup> We report the results of a phase 1 study designed to assess the safety of intravitreal ketorolac in patients with chronic inflammation and/or ME.

## METHODS

An Investigational New Drug Application was submitted to the US Food and Drug Administration for intraocular use of ketorolac. The Vanderbilt University Institutional Review Board approved this study, and patients gave informed consent before enrollment. The study complied with all aspects of the Health Insurance Portability and Accountability Act. The trial is registered at [clinicaltrials.gov](http://clinicaltrials.gov): Identifier NCT01164085.

Ketorolac tromethamine (Professional Compounding Centers of America) was compounded in preservative-free normal saline on the day of treatment by the Vanderbilt Investigational Drug Service at a concentration of 30 mg per 0.75 mL in single-use syringes.

Ten eyes of 10 adult volunteers, age 18 or older, with chronic intraocular inflammation and/or complications of chronic inflammation (ME) for whom maximal medical treatment failed or who were unable to tolerate corticosteroids because of adverse ocular effects were consecutively enrolled from March 1, 2010, through February 28, 2011. Baseline electroretinography, fluorescein angiogram (FA), spectral domain optical coherence tomography (OCT), Goldmann visual field, and complete ophthalmic examination, which included best-corrected Snellen visual acuity by a combination of pinhole and refraction, IOP measurement, slitlamp examination, and dilated funduscopic examination, was performed on day 0. Intravitreal injection of ketorolac (4 mg) was administered on the same day after baseline testing was completed. A dose of 4 mg was derived from a recent safety study in Dutch-belted rabbits.<sup>10</sup> All intravitreal injections were performed using standard sterile technique, and no complications were observed.

Slitlamp and funduscopic examinations were repeated after the injection, and IOP was remeasured. On day 1, patients were contacted by telephone and asked to grade their level of eye pain (none, mild, moderate, or severe) and visual acuity (same, worse, or better). A subsequent ophthalmic examination with OCT was performed on day 3. Ophthalmic examination with FA and OCT was given again on days 7 and 30, and ophthalmic examination with FA, OCT, electroretinography, and Goldmann visual field was performed on day 90 upon exit.

## RESULTS

The primary purpose of this study was safety, and there were no observed adverse ocular effects after intraocular injection of ketorolac. Slitlamp and funduscopic examinations immediately after treatment and on subsequent study visits (days 3, 7, 30, and 90) demonstrated no anterior chamber reaction, media opacity, rapid cataract formation (2 of 10 patients were phakic), or retinal or optic nerve changes suggestive of toxicity. There were no increases in IOP or recorded cases of severe pain or subjective vision loss following treatment. On the basis of Goldmann visual field and electroretinography testing, no prominent changes in visual field or in the amplitude and latency of a-waves and b-waves compared with baseline were observed at 3 months.

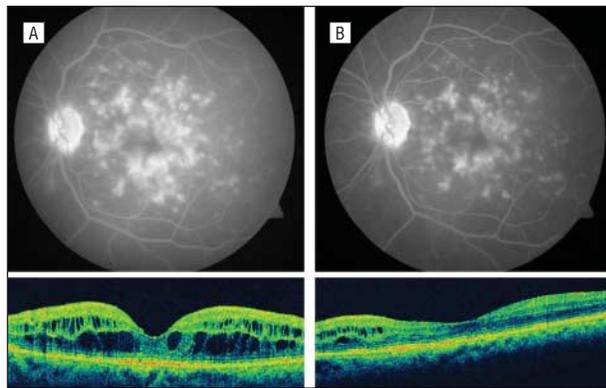
Baseline demographic information and best-corrected Snellen visual acuity at baseline and subsequent study visits are listed in **Table 1**. Both study eyes with chronic uveitis (patients 3 and 6) demonstrated favorable responses in regard to inflammation after treatment with ketorolac. The right eye of patient 3 had end-stage glaucoma and IOP of 21 mm Hg with persistent grade 0.5<sup>+</sup> (1-5 cells in a 1 × 1-mm slit beam) anterior chamber inflammation despite systemic immunosuppression with methotrexate and topical therapy with loteprednol etabonate, 0.5% (Lotemax; Bausch & Lomb) 4 times daily. Three days after treatment, there was grade 0 (<1 cell in a 1 × 1-mm slit beam) anterior chamber inflammation, and IOP was 16 mm Hg. During follow-up, there were no recurrences of inflammation. The left eye of patient 6 had an immediate reduction of anterior chamber inflammation from grade 2<sup>+</sup> (16-25 cells in a 1 × 1-mm slit beam) at baseline to grade 0 on day 7 following treatment, with corresponding subjective improvement in vision from 20/30<sup>-2</sup> at baseline to 20/30<sup>+2</sup> on day 3. However, the patient's inflammation recurred by day 30.

Of the remaining 8 patients with ME, 4 patients (1, 2, 5, and 7) did not demonstrate any apparent decrease in edema after treatment (**Table 2**). Patient 1, however, had chronic ME for more than 1 year and showed no response to previous intraocular injection of triamcinolone acetonide (4 mg) (Kenalog-40; Bristol-Myers Squibb). Pa-

**Table 2. OCT Thickness of 8 Patients With Macular Edema**

Patient No.	Diagnosis	Central Subfield Thickness, $\mu\text{m}$				
		Day 0	Day 3	Day 7	Day 30	Day 90
1	Postsurg CME	676	646	708	626	625
2	Postsurg CME	450	483	499	552	570
4	Uveitic CME	320	Missed appt	275	386	376
5	Postsurg CME	321	404	331	398	328
7	Diabetic CME	447	416	405	421	368
8	Uveitic CME	254	245	246	278	326
9	Postsurg CME	491	428	533	553	499
10	Postsurg CME	679	624	698	549	513

Abbreviations: appt, appointment; CME, chronic macular edema; OCT, optical coherence tomography; postsurg, postsurgical.



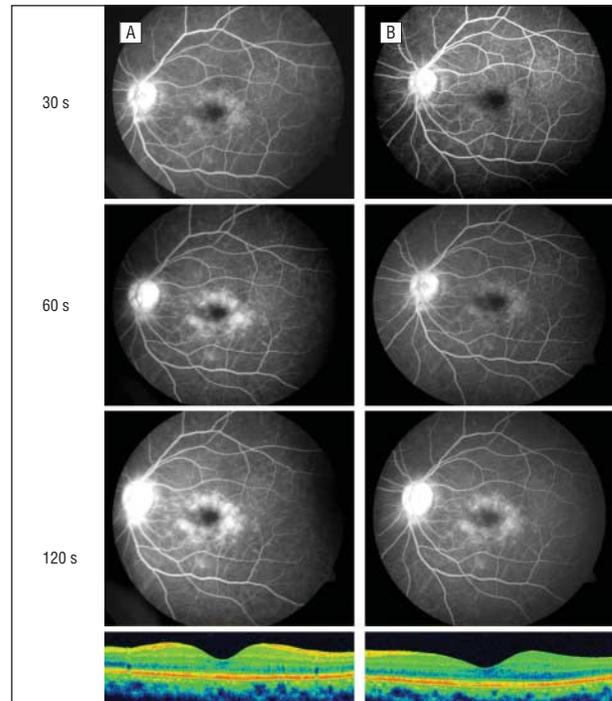
**Figure 1.** Baseline (A) and day 7 (B) of fluorescein angiogram (FA) and optical coherence tomography images of patient 4, demonstrating reduction in FA leakage and macular thickening after intravitreal injection of ketorolac.

tient 2 had ME in the setting of mechanical traction from an epiretinal membrane, and patient 5 had a history of previous vitrectomy that may have limited the efficacy of ketorolac by decreasing its half-life. Finally, although patient 7 did experience subjective improvement in vision after treatment ( $20/70^{+2}$  on day 0 to  $20/40^{+2}$  on day 3) and reduction in central subfield thickness ( $447 \mu\text{m}$  on day 0 to  $416 \mu\text{m}$  on day 3 and  $405 \mu\text{m}$  on day 7), there was no concomitant reduction of leakage observed on FA.

Four other patients (4, 8, 9, and 10) with ME appeared to show a more favorable response. Patient 4 demonstrated reduced macular thickness from  $320 \mu\text{m}$  on day 0 to  $275 \mu\text{m}$  on day 7 with concomitant reduced leakage on FA and corresponding subjective improvement in vision from  $20/40^{-2}$  on day 0 to  $20/30^{-1}$  on day 7 (**Figure 1**). Patient 8 had minimal thickening on OCT at baseline but demonstrated reduced leakage on FA by day 7 (**Figure 2**). Patients 9 and 10 (**Figure 3**) demonstrated reduced thickness on OCT from  $491 \mu\text{m}$  and  $679 \mu\text{m}$  at baseline to  $428 \mu\text{m}$  and  $624 \mu\text{m}$  by day 3, respectively. In all 4 patients, reduction of thickness was transient.

#### COMMENT

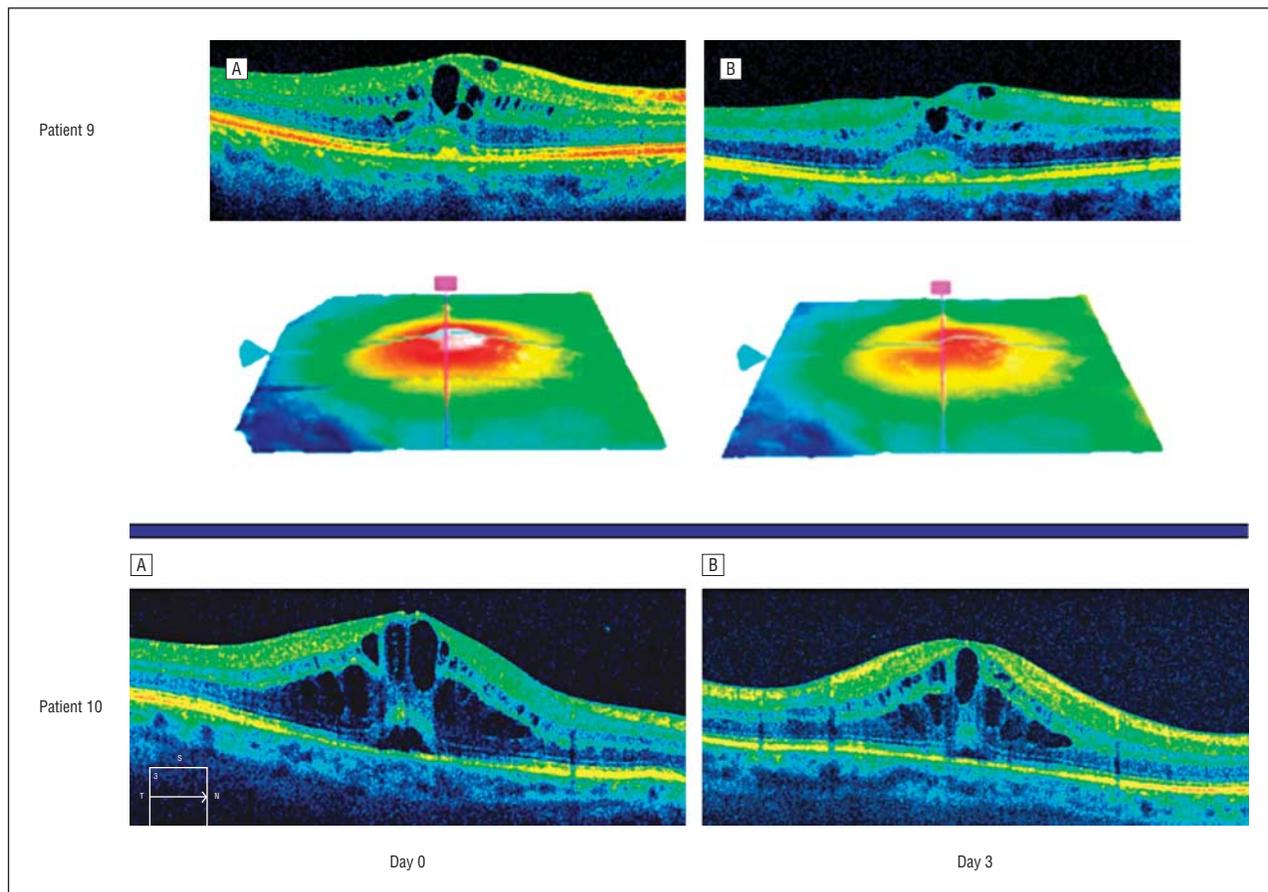
The results of this initial phase 1 human study suggest that a single intravitreal injection of ketorolac (4 mg) is well tolerated. To our knowledge, this is the first study evaluating the safety of intravitreal ketorolac in humans.<sup>12</sup>



**Figure 2.** Baseline (A) and day 7 (B) of comparable fluorescein angiogram (FA) images taken at roughly 30, 60, and 120 seconds after injection of fluorescein of patient 8, demonstrating qualitative reduction of leakage on early and mid-FA images after intravitreal injection of ketorolac. Despite leakage on FA, optical coherence tomography demonstrated minimal cystoid changes at baseline and day 7.

Cyclooxygenase is a critical enzyme in the inflammatory process and catalyzes the biosynthesis of PGs. Within the eye, PGs disrupt the blood-ocular barrier, increase vasodilation, and facilitate leukocyte migration. The ciliary body, iris epithelium, vascular endothelium, Muller cells, retinal pigment epithelium, and other cells within the eye express COX enzymes and are possible sources of endogenous PGs.<sup>7,11,13</sup> Because NSAIDs are potent inhibitors of COX enzymes, they inhibit the synthesis of PGs. Consequently, ophthalmic formulations of ketorolac (Acular, Acular LS, and Acuvail; Allergan) have been shown in several well-designed clinical studies to reduce pain, inflammation, and ME after cataract, vitreo-retinal, and refractive surgery.<sup>7,12,14</sup>

Of the commercially available ophthalmic NSAIDs, ketorolac has the greatest body of evidence supporting its



**Figure 3.** Baseline (A) and day 3 (B) of optical coherence tomography (OCT) images from patient 9 and patient 10 demonstrating reduction in OCT thickness after intravitreal injection of ketorolac.

safety and efficacy, which makes it a compelling choice for intraocular delivery.<sup>7,12</sup> A recent pilot study on the safety of intravitreal diclofenac did not observe any favorable effects on ME, but this was not the study's primary objective.<sup>15</sup> Diclofenac is also much more toxic to the retina than ketorolac, and thus safe injectable doses are limited to 400 to 500  $\mu\text{g}$ .<sup>10,16</sup> At these doses, diclofenac is completely eliminated from the vitreous and retina by 24 hours.<sup>11,17</sup>

The results of this small phase 1 human study provide the basis for future larger studies. Such future studies would be informative because ketorolac's lack of association with elevated IOP or cataract formation grant it a distinct therapeutic advantage over corticosteroids in patients at increased risk of these complications.<sup>18</sup> Moreover, intravitreal ketorolac achieves peak drug concentrations in the vitreous (234  $\mu\text{g}/\text{mL}$ ) and retina (280  $\mu\text{g}/\text{g}$ ) more than 100-fold greater than what can be obtained with topical or systemic administration and considerably exceeding levels necessary to inhibit COX activity in both anterior and posterior tissues.<sup>11</sup>

Ketorolac's intraocular half-life is profoundly limited by its high water solubility. Forty-eight hours after intravitreal injection, the vitreous concentration of ketorolac remains barely therapeutic (but rapidly decreasing), but the retinal concentration is below the inhibitory concentration of 50% for both isoforms of COX (COX-1 and COX-2).<sup>11</sup> The lack of a uniform and sustained thera-

peutic effect of ketorolac on ME observed in this study may be due to its short half-life in conjunction with more treatment-resistant disease in patients selected for this safety study. Nevertheless, even a temporary therapeutic effect of ketorolac may still be clinically useful in situations in which an immediate anti-inflammatory effect is needed until slower-acting therapies take effect. Furthermore, sustained intraocular delivery of ketorolac is feasible with current drug technology and may dramatically improve its efficacy.

In addition to its role in inflammation, considerable evidence indicates that COX is a promoter of angiogenesis.<sup>7,19-23</sup> Cyclooxygenase-2 is present in choroidal neovascular membranes and in other highly vascularized lesions, and it is significantly upregulated in the retinal pigment epithelium in response to proinflammatory cytokines.<sup>24,25</sup> Pharmacologic inhibition or genetic deletion of COX-2 inhibits choroidal neovascularization in animal models by reducing retinal vascular endothelial growth factor expression.<sup>13,24,26</sup> These results suggest that NSAIDs may be useful for the prevention and treatment of choroidal neovascularization due to inflammatory or degenerative conditions but that intraocular delivery may be necessary to achieve therapeutic drug levels.

As with all uncontrolled studies, our results should be interpreted with caution. Although we did not observe any adverse ocular effects of ketorolac, this was a phase 1 study and designed only to assess frank toxic-

ity, and more subtle adverse ocular effects could have been missed. In addition, because this was not a controlled study, we cannot rule out the possibility that our observations were due to bias, chance, or natural history. Finally, this study was neither intended nor adequately designed to assess efficacy, but considerable clinical and scientific evidence already exists demonstrating the anti-inflammatory and anti-ME effects of ketorolac for ocular disease, which provides strong rationale for this therapeutic approach.

In conclusion, the results of this phase I human study suggest that a single intravitreal injection of ketorolac (4 mg) is well tolerated and safe. Ketorolac possesses distinct therapeutic advantages over corticosteroids because of its superior safety profile, but larger controlled studies are needed to confirm and expand upon these initial findings.

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