

Use of an intravitreal sustained-release cyclosporine delivery device for treatment of equine recurrent uveitis

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Objective—To evaluate the use of an intravitreal sustained-release cyclosporine (CsA) delivery device for treatment of horses with naturally occurring recurrent uveitis.

Animals—16 horses with recurrent uveitis.

Procedures—Horses with frequent recurrent episodes of uveitis or with disease that was progressing despite appropriate medication were selected for this study. Additional inclusion criteria included adequate retinal function as determined by use of electroretinography, lack of severe cataract formation, and no vision-threatening ocular complications (eg, retinal detachment, severe retinal degeneration, and posterior synechia). Sustained-release CsA delivery devices (4 µg of CsA/d) were implanted into the vitreous through a sclerotomy at the pars plana. Reexaminations were performed 1, 3, 6, and 12 months after implantation, then continued annually. Ophthalmic changes, number of recurrent episodes of uveitis, and vision were recorded.

Results—The rate of recurrent episodes after device implantation (0.36 episodes/y) was less than prior to surgery (7.5 episodes/y). In addition, only 3 horses developed episodes of recurrent uveitis after surgery. Vision was detected in 14 of 16 affected eyes at a mean follow-up time of 13.8 months (range, 6 to 24 months).

Conclusions and Clinical Relevance—This intravitreal sustained-release CsA delivery device may be a safe and important tool for long-term treatment of horses with chronic recurrent uveitis. (*Am J Vet Res* 2001;62:1892–1896)

Equine recurrent uveitis (ERU) is a painful ocular condition resulting from inflammation of the uveal tract. It is the leading cause of blindness in horses worldwide.^{1,2} In the United States, 8 to 25% of horses are affected with recurrent uveitis.^{1,2} Equine recurrent uveitis is characterized by episodes of intraocular inflammation that develop weeks to months after an initial episode of uveitis subsides.¹⁻⁵ In active recurrent episodes of ERU, the blood-ocular barrier breaks down, resulting in infiltration of inflammatory cells

and protein, miosis, iris hyperemia, corneal edema, and ocular discomfort. These active episodes may last days or weeks, gradually resolving to a relatively comfortable quiescent period. Each recurrent episode imparts permanent damage to the eye. Ultimately, even with aggressive treatment, many horses develop a chronically painful eye and blindness as a result of secondary cataract formation, synechia (intraocular adhesions), scarring, glaucoma, and phthisis bulbi.^{1,2,5}

Treatments commonly used for ERU (eg, corticosteroids and nonsteroidal anti-inflammatory medications) are aimed at reducing inflammation and minimizing permanent ocular damage during each active episode. However, treatments are not effective in preventing recurrence of disease. A mononuclear cell infiltrate has been detected in eyes from horses with chronic recurrent uveitis. This infiltrate consists predominantly of CD4⁺ T-lymphocytes, the T-helper (Th) cell subset.⁶ Cytokine profiles from these cells indicate that they are primarily Th1 cells; that is, they release high concentrations of interleukin- (IL-) 2 and γ -interferon and low concentrations of IL-4.⁶ This suggests that in horses with chronic recurrent uveitis, ocular inflammation is nonspecific and immune-mediated and does not develop in response to specific microorganisms.

Cyclosporine A (CsA) is a 1.2-kd cyclic peptide that blocks the transcription of IL-2 and, therefore, decreases the responsiveness of T-cells to inflammatory stimuli.^{7,8} Cyclosporine A may be the ideal drug to prevent the activation of T-lymphocytes and recurrence of active episodes of uveitis in horses with recurrent uveitis.^{6,9} However, available methods of delivery of CsA to the eye are inadequate. Cyclosporine A is hydrophobic and does not penetrate into the eye when applied topically,^{10,11} and systemic administration may be costly and promote serious adverse effects such as renal, hepatic, and neurologic toxicoses.¹² Therefore, a polyvinyl alcohol/silicone-coated intravitreal sustained delivery CsA device, which has been shown to result in sustained concentrations of CsA in ocular tissues of rabbits,¹³⁻¹⁵ has been evaluated for use in horses. The CsA device was implanted into eyes of clinically normal horses for up to 1 year and was not associated with ocular inflammation or complications.¹⁶ In horses with experimentally-induced uveitis, implantation of the CsA device decreased the duration and severity of inflammation, cellular infiltration, tissue destruction, and transcription level of pro-inflammatory cytokines.⁹ The purpose of the study reported here was to evaluate the use of the intravitreal sustained-release CsA device for treatment of horses with naturally occurring recurrent uveitis by describing the surgical procedure for implantation of the device, complications during and

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after surgery, and the long-term effects of surgery and the device on recurrence of active episodes of uveitis.

Materials and Methods

Animals—Criteria for inclusion of horses in the study included a documented history and ocular clinical signs typical of ERU,^{1-5,17,18} a complete vaccination and deworming history, positive menace response, minimum B-wave amplitude of 100 μ V determined by use of electroretinography (ERG), and owner compliance (eg, willingness to return horses for reevaluation, maintenance of an observation log) and consent. Cataract formation over 10% of the total area of the lens or other ocular conditions other than signs of uveitis disqualified the horse from this study. Horses with chronic but non-vision-threatening signs of recurrent uveitis such as corpora nigra degeneration, mild iris fibrosis, peripapillary depigmentation without optic nerve degeneration, and mild vitreous degeneration were included in the study. In addition, negative or low (< 1:200) serum antibody titers to *Leptospira interrogans* serovars pomona, icterohemorrhagiae, bratislava, canicola, autumnalis, and grippotyphosa¹⁹⁻²² were also required for inclusion in the study.

Ophthalmic examinations—Complete ophthalmic examinations (tonometry, biomicroscopy, direct ophthalmoscopy, and ERG) were performed at the initial and all follow-up examinations. Ocular clinical signs were recorded and included the following: corneal cloudiness, hypopyon, aqueous flare, miosis, lens opacification (cataract), synechia, vitreous opacity, and retinal and optic nerve degeneration.

Horses were tranquilized with detomidine (0.01 mg/kg of body weight, IV) prior to scotopic ERG.^a Horses were dark adapted for 5 minutes, and a photostimulator^b was placed 5 cm from each eye and used to produce single flashes (2.3 \times 10⁶ J/cm²; 0.01-ms duration). Channel amplifiers were set at a bandpass of 5 to 250 Hz. The response to 10 flashes (signal averaged) was recorded, and B-wave latency and amplitude were measured.

Construction of CsA delivery devices—Cyclosporine A devices^c were constructed as described.^{9,14,16} Briefly, 10 mg of CsA powder^d was compressed into custom-built 3-mm tablet dies.^e Each pellet was coated with several layers of silicone^f and allowed to dry overnight. Coated pellets were covered with a sheet of ethylene vinyl acetate^f sufficient to cover the sides of the pellets leaving 1 face open. The completed device was treated at 104 C for 1 hour. The final silicone coating was fine tuned to provide a release rate of 4 μ g of CsA/d. The completed devices were sterilized by gamma irradiation prior to use.

Implantation of the CsA device—Ocular surgery was performed during the quiescent phase of uveitis. If signs of active uveitis were detected (eg, aqueous flare, hypopyon, extreme miosis, peripapillary chorioretinitis), the horse was treated with anti-inflammatories administered topically and orally, and surgery was delayed. Devices were implanted as described,^{9,16} except that horses in this study were maintained under general anesthesia with isoflurane and oxygen until completion of surgery. To ensure precise placement of each device, surgery was performed with the use of an operating microscope. Following preparation of the eye for surgery, a 5-mm-long conjunctival incision was made at the superior-temporal aspect of the eye, approximately 1 cm posterior and parallel to the limbus. A full-thickness 4-mm sclerotomy was made 1 cm posterior to the limbus at this dorsolateral conjunctival incision, thereby placing the incision through the pars plana. A small vitrectomy was done at the incision site to remove vitreous prolapsing from the scleral incision. The 2 \times 3-mm device was placed into the vitreous through the

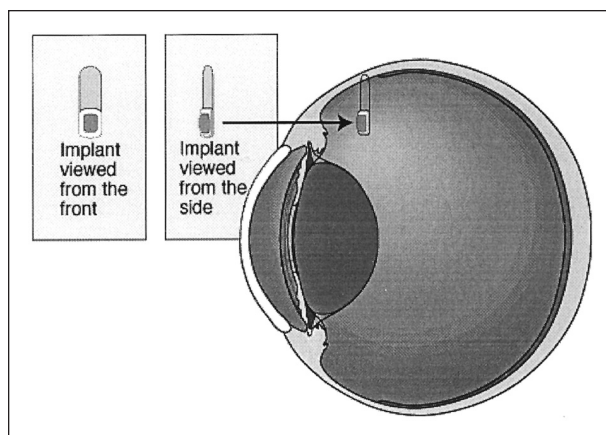


Figure 1—Site of surgical implantation of an intravitreal sustained-release cyclosporine A (CsA) delivery device in horses. Following a dorsolateral conjunctival incision, a full-thickness 4-mm sclerotomy was made 1 cm posterior to and parallel to the limbus. The 2 \times 3-mm device was placed into the vitreous through the incision and pars plana and anchored the sclera with a single suture.

incision and pars plana and anchored into place by suturing the stem of the device into the scleral incision, using 6-0 nylon^g (Fig 1). This suture was also used to close the sclerotomy with an additional 1 or 2 simple interrupted sutures. The conjunctival incision was closed with 6-0 polyglactin 910^h in a simple continuous pattern. All horses received a single IV dose of 500 mg of flunixin meglumineⁱ at the conclusion of surgery. Postoperative medications included flunixin meglumine (1 mg/kg, PO, q 24 h) for 5 days, triple antibiotic ophthalmic ointment^j administered topically every 12 hours for 10 days, and atropine ointment^k administered topically once a day for 7 days. Flunixin meglumine and atropine were administered to minimize any discomfort associated with surgery.

Follow-up—Following surgery, owners were requested to maintain a logbook to record ocular appearance, signs of pain, medications administered, and visual performance of their horses. Horses were reevaluated 1, 3, 6, and 12 months after implantation of the device and then annually. At each reevaluation, a complete ophthalmic examination, including ERG, was performed.

Results

Animals—Sixteen horses (mean \pm SD) age, 10.1 \pm 4.6 years) with unilateral recurrent uveitis met the inclusion criteria. Eight horses were castrated males, and 8 were sexually intact females. Seven breeds were represented, the most common of which were Thoroughbreds (n = 6) and Hanoverians (4; Table 1). The right eye was affected in 9 horses and the left eye in 7. All horses had a history of recurrent episodes of uveitis that included all or most of these typical clinical signs: ocular pain (blepharospasm, epiphora), periorcular swelling, corneal edema, aqueous flare, miosis, and hypopyon. All horses had chronic recurrent uveitis, with a mean duration of 2.7 \pm 1.5 years (range, 4 months to 5 years).

Initial clinical signs—During the initial examination, all horses had clinical signs of chronic recurrent uveitis, which included corpora nigra atrophy (n = 9), vitreous degeneration (8), focal cataract (3), peripapillary depigmentation (3), and corneal opacity or edema

Table 1—Signalment, preoperative clinical signs, and history of horses included in a study evaluating an intravitreal sustained-release cyclosporine delivery device for use in horses with chronic recurrent uveitis

Breed (sex; age [y])	Duration (y)	Initial clinical signs	Mean duration between episodes (wk)
Thoroughbred (F; 1)	0.33	CN atrophy, mild VD	0*
Hanoverian (F; 6)	5	CN atrophy, iris fibrosis	12
Warm blood (F; 9)	3	Moderate VD	5
Morgan (F; 8)	3	Mild PD, CN atrophy	14
Thoroughbred (F; 15)	0.5	CN atrophy	0*
Thoroughbred (CM; 11)	2	Mild AF, mild CE, VD, cataract	6
Hanoverian (CM; 15)	4	CN atrophy, VD	0*
Thoroughbred (F; 10)	5	Mild CO, CN atrophy	0*
Thoroughbred (CM; 9)	3	CN atrophy	0*
Quarter Horse (F; 15)	2	CN atrophy, iris fibrosis	0*
Appaloosa (CM; 16)	3	Focal PRD	5
Hanoverian (F; 5)	1	CN atrophy	10
Appaloosa (CM; 18)	5	VD, focal cataract	16
Thoroughbred (CM; 9)	2	Corneal CD, glauc, sub lens, focal cataract, VD	12
Hanoverian (CM; 6)	2	ALC pigment, VD, CN atrophy	16
Mixed breed (CM; 9)	2	CN degeneration, VD, PD	8

*Active uveitis immediately recurred when high doses of anti-inflammatory medications were discontinued (calculated as 1 episode/wk).
 F = Sexually intact female. CN = Corpora nigra. VD = Vitreous degeneration. PD = Peripapillary depigmentation. CM = Castrated male. AF = Aqueous flare. CE = Corneal edema. CO = Corneal opacity. PRD = Peripapillary retinal depigmentation. glauc = Glaucoma. sub = Subluxated. ALC = Anterior lens capsule.

(3; Table 1). Mean interval between active episodes of uveitis was 6.9 ± 5.7 weeks. However, 6 horses had constant uveitis, meaning that once high doses of anti-inflammatory medications (ie, phenylbutazone or flunixin meglumine) were discontinued or tapered, active uveitis immediately developed. An ERG was performed on 11 of 16 horses prior to surgery. Mean latency and B-wave amplitude were 8.5 ± 1.4 ms and 164.6 ± 18.3 μ V, respectively, which were within reference ranges for horses established at the North Carolina State University.¹⁶

Surgery—In most cases, the surgical procedure was uncomplicated. The duration of each procedure was typically < 15 minutes. No major complications developed during surgery. However, liquefied vitreous, which extruded through the 4-mm scleral incision, was present in 10 of 16 horses, and mild vitreal hemorrhage from the incision was detected during surgery in 6 horses. Vitreal hemorrhage stopped prior to the completion of surgery and was not evident at the 1-month reevaluation. One horse did develop complete hyphema during recovery from anesthesia. Hyphema was also resolved at the 1-month reevaluation.

Outcome—Mean follow-up time for the 16 horses was 13.8 ± 5.3 months (range, 6 to 24 months). Only 3 of the 16 horses developed signs of recurrent episodes of uveitis after surgery. These episodes were judged by owners to be less severe, briefer, and more responsive to topical or oral administration of anti-inflammatory medications (0.1% dexamethasone,^l q 8 h, or phenylbutazone,^m 1 g, q 12 to 24 h, respectively) than episodes prior to surgery. Overall, during the follow-up period, 6 recurrent episodes were reported (mean number of episodes per horse, 0.38 ± 0.9). Thus, the mean rate of recurrent episodes of uveitis determined for these 16 horses was 0.36 episodes/y. The recurrence rate after implantation of the CsA

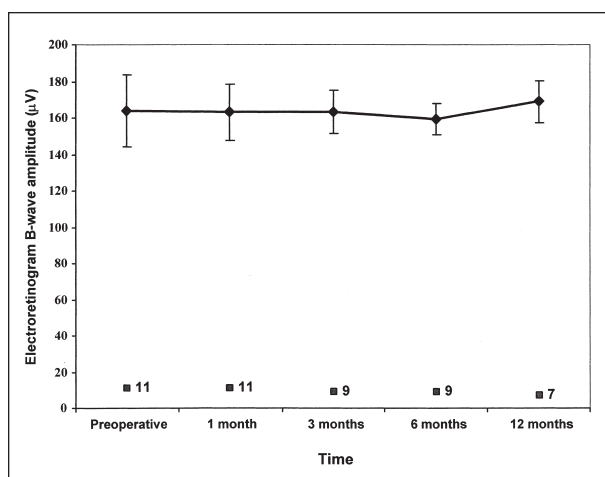


Figure 2—Results of electroretinography before (preoperative) and after surgical placement of an intravitreal sustained-release CsA delivery device in horses with chronic recurrent uveitis. The upper line indicates the mean (\pm SD) amplitude of the B wave of the electroretinogram. The lower data points indicate the number of horses evaluated.

delivery device was substantially less than the rate prior to surgery (7.5 episodes/y). Vision was detected in 14 of 16 affected eyes during the follow-up period. Electroretinography results after surgery were similar to results prior to surgery (Fig 2).

Complications—Decreased vision was detected in 1 horse after implantation of the CsA delivery device. Vision loss was attributable to progressive glaucoma, which was present prior to surgery. Intraocular pressure and progression of glaucoma in this horse was controlled with topical administration of timolol.ⁿ A second horse developed glaucoma approximately 3 months after surgery. Glaucoma in this horse was well controlled with a combination of laser photocoagulation and topical administration of

antiglaucoma medications. Vision was still detected in this horse at the end of the follow-up period. Vision loss in a third horse was attributed to the sudden development of a mature cataract 9 months after surgery. Although the affected eye was nonvisual, active signs of inflammation were not detected, and no recurrent active episodes of uveitis developed. The owner of this horse elected not to have the lens extracted as a treatment for cataract because of the possibility of increased inflammation and complications following surgery. A fourth horse developed a complete retinal detachment 3 months after surgery and became blind. Vitreous degeneration progressed in this horse, although no signs of active inflammation or recurrent episodes of uveitis were observed.

Discussion

The purpose of this study was to describe the selection of cases, the surgical technique, and results after implantation of an intravitreal sustained-release CsA delivery device for the treatment of ERU. Few complications developed during and after surgery. Only 2 horses developed severe complications after surgery that resulted in vision loss. Vision loss was attributable to retinal detachment in 1 horse and mature cataract formation in the other. Few active episodes of uveitis were noted at a mean follow-up time of 13.8 months, and only 3 horses developed any evidence of uveitis after device implantation.

Equine recurrent uveitis is a panuveitis with inflammation in the iris, ciliary body, and choroid, although the ciliary body and nonpigmented ciliary epithelium are affected primarily and most severely.^{8,23} Because the ocular inflammatory response appears to be T-cell mediated, and because CsA acts to decrease responsiveness of T cells to inflammatory stimuli, sustained-release CsA drug delivery devices may be an important tool for the long-term control of ERU. The device used in this study is expected to deliver 4 µg of CsA/d for approximately 5 years. If recurrent episodes develop after 5 years, a second device could be implanted. Because the device delivers medication constantly, reliance on owners to treat potentially painful eyes is eliminated, thus increasing the likelihood of success for the long-term treatment of ERU. Moreover, delivery of a constant amount of CsA to the eye may prevent recurrence of uveitis, and CsA can thus replace other medications commonly used (eg, aspirin, phenylbutazone) to treat ERU with limited efficacy and potential detrimental effects on the gastrointestinal and hematologic systems. Cyclosporine A released from slow-release intravitreal devices is primarily contained within the eye and ocular tissues; cyclosporine was not detected in the blood of horses treated by use of an intravitreal CsA delivery device.^{9,16} Systemic immunosuppressive or toxic effects as a result of intravitreal administration of CsA are thus unlikely.¹⁶

Selection of appropriate horses to receive the CsA delivery device is important for long-term success after surgery. Chronic irreversible uveitic changes in the eye such as synechiae, corneal edema, glaucoma, vitreal degeneration, and retinal atrophy will result in

decreased vision over time and decreased long-term success of device implantation. The goal of sustained intravitreal administration of CsA is to prevent further inflammatory episodes, thereby preventing additional chronic damage to eyes. Horses with fewer chronic ocular changes are better candidates for surgery, because vision-threatening complications may be prevented by use of the delivery device, making it easier to monitor the success of surgery. Horses with cataracts should be avoided when selecting patients for implantation. In a previous study⁹ evaluating a device that released 2 µg of CsA/d in the vitreous of horses, cataracts involving approximately one fourth of the lens or more continued to progress despite the decrease in number or complete elimination of recurrent episodes of uveitis. In the present study, surgery was performed only on horses without active ocular inflammation. This was done to minimize intraoperative surgical complications and to help prevent severe inflammation following surgery. To further limit surgically induced inflammation and help prevent the induction of a recurrent episode of inflammation, horses were treated with anti-inflammatory agents administered orally or intravenously prior to and for 5 days after surgery. One horse did develop complete hyphema during recovery from anesthesia. However, there was no vitreal hemorrhage during or after surgery in this horse. Therefore, we believe that hyphema developed because of trauma during recovery and not as a result of the surgical procedure. Hyphema resolved by 1 month after surgery.

There are many initiating causes for ERU, including systemic diseases such as leptospirosis.^{2,22,24} Therefore, horses included in the present study had low or no serum antibody titers to several *L interrogans* serovars. We also excluded horses with a possible leptospiral infection, because it is not known what effect an immunosuppressive drug such as cyclosporine will have on potential microbial infections within the eye.

There are few options available for the long-term control and prevention of recurrent episodes of uveitis in affected horses. One option is to administer anti-inflammatory medications orally or topically to help prevent recurrent episodes. Disadvantages of this approach include potential toxicities of the medications, a low degree of owner compliance, and, possibly, poor efficacy of the medications to prevent ERU. Another option is core vitrectomy (ie, removal of the vitreous). Although this procedure is commonly done in Europe, to our knowledge, there has been only 1 study describing this technique published in English. In that study,²⁵ there was a high rate of vision-threatening cataract formation after surgery. Despite this complication, many horses remained comfortable after vitrectomy, and the authors suggested that the technique was a suitable alternative to enucleation. Horses selected for CsA device implantation in the present study had clear ocular media and did not have chronic lesions (eg, severe cataract, retinal degeneration). The efficacy of the CsA delivery device in horses with more advanced disease is unknown. In more severe cases, there may be a role for the use of both core vit-

rectomy and CsA device implantation to assist in the long-term control of recurrent episodes of ocular inflammation.

The goal of the present study was to describe the surgical technique for implantation of intravitreal CsA delivery devices and the immediate and long-term complications of use of this device in horses with naturally occurring recurrent uveitis. Although the rate of recurrent episodes was less after implantation of the CsA device, we cannot definitively state that the device was responsible. Active episodes of ERU are extremely variable in severity, recurrence rate, progression, and duration, both within and between affected horses. A study evaluating a large number of horses over a prolonged period is needed to definitively determine the efficacy of any novel ERU treatment. The results of our study, however, are promising and suggest that further study of CsA delivery devices is warranted. In general, the CsA devices were well tolerated, with no apparent complications arising from the devices themselves. These results indicate that this device, which releases 4 µg of CsA/d, may be a safe and important tool for the long-term treatment of naturally occurring chronic recurrent uveitis in horses.

^aNicolet Spirit Expansion System, Nicolet Biomedical, Madison, Wis.

^bGrass Photostimulator, Model #PS33 C, Grass Medical Instruments, Quincy, Mass.

^cDonated by Drs. Paul Ashton and Tom Smith, Control Delivery Systems, Inc, Watertown, Mass.

^dXenos Pharmaceuticals, San Mateo, Calif.

^eParr Instruments, Moline, Ill.

^fPolysciences Inc, Warrington, Pa.

^gEthicon, Ethicon Inc, Somerville, NJ.

^hVicryl, Ethicon Inc, Somerville, NJ.

ⁱBanamine, Schering-Plough Corp, Kenilworth, NJ.

^jTriple antibiotic (neomycin, polymyxin, bacitracin) ophthalmic ointment, Bausch & Lomb, Tampa, Fla.

^kAtropine sulfate ophthalmic ointment, Bausch & Lomb, Tampa, Fla.

^lDexamethasone sodium phosphate ophthalmic solution USP 0.1%, Bausch & Lomb, Tampa, Fla.

^mPhenylzone paste, Schering Plough Animal Health Corp, Union, NJ.

ⁿTimoptic, Merck Pharmaceuticals, Whitehouse Station, NJ.

^oGilger BC, Wilkie DW, Ashton P, et al. Use of cyclosporine intravitreal implants in the control of naturally-occurring equine recurrent uveitis (abstr). *Invest Ophthalmol Vis Sci* 2000;41:2004.

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