A Pharmacokinetic and Safety Evaluation of an Episcleral Cyclosporine Implant for Potential Use in High-Risk Keratoplasty Rejection

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PURPOSE. To determine the short and long-term pharmacokinetics and assess the toxicity of a cyclosporine (CsA) episcleral implant for the prevention of high-risk keratoplasty rejection.

METHODS. CsA episcleral implants were made with a high (implant A) or low (implant B) release rate, and in vitro release rates were performed. Short-term pharmacokinetics were performed in rabbits using implant B, and the spatial and temporal spread of drug was observed by sampling from multiple corneal and conjunctival sites at 3 and 72 hours. Implant A was used in long-term pharmacokinetic studies in dogs aged more than 1 year. An ocular toxicity study was performed in dogs older than 1 year.

RESULTS. A high release rate was observed with both implants over the initial 5 months followed by a steady state release. The cumulative release over the 400-day assay period from implants A and B was 3.8 ± 0.3 and 2.3 ± 0.3 mg, respectively. In the short-term pharmacokinetic studies, the cornea had CsA concentrations of 0.15 ± 0.06, 0.07 ± 0.02, and 0.05 ± 0.02 μg/mg at sites centered 8, 13, and 18 mm away from the implant site, respectively. In the long-term pharmacokinetic studies, corneal CsA levels ranged from 0.18 ± 0.06 to 0.009 ± 0.004 μg/mg during the 1-year study. There were no signs of ocular toxicity at 1 year.

CONCLUSIONS. Episcleral implants are safe and effective at delivering therapeutic CsA levels to the cornea to potentially prevent corneal allograft rejection. The implant can be surgically inserted at the time of penetrating keratoplasties, since the implant achieves therapeutic levels as early as 3 hours. In an earlier publication, we described a sustained-release CsA episcleral implant principally used to deliver therapeutic drug levels to the lacrimal gland in patients with ocular graft-versus-host disease. Consequently, in the present study, we examined a similar implant to determine whether a single device could deliver therapeutic drug levels throughout the entire cornea, and how rapidly therapeutic drug levels could be achieved. In addition, we report the results of a 1-year pharmacokinetic and toxicity evaluation of the implant.

METHODS Implant Manufacturing

We developed two implants with release rate profiles based on the typical immunosuppression therapy for prevention of corneal allograft rejection, starting with a high dose followed by a tapering maintenance dose. The goal was to deliver CsA to the cornea for 12 months from a silicone-based matrix-style implant release system, using previously described methods of implant preparation. The implants were designed to achieve high and low release rates. The higher release implant, implant A, measured 0.75 in. (19.05 mm) long, 0.08 in. (2.03 mm) wide, and 0.04 in. (1.02 mm) high (width was measured on the flat side; height was measure from the flat surface to the bottom of the rounded depression). The lower-release implant, implant B, measured 0.50 in. (12.7 mm) long and had identical height and width dimensions as implant A. The implants were both made in a polytetrafluoroethylene mold with impressions on the surface. When implanted, the flat side is applied to the episclera and the rounded side toward the overlying conjunctiva. CsA powder (Xenos Bioresources, Inc., Santa Barbara, CA) was thoroughly mixed with medical grade silicone with a platinum cure system (Nusil Technology, Carpinteria, CA) so that the weight of the drug as a percentage of the total weight of the implant (wt/wt) was 30%. The impressions were filled with the CsA silicone paste using a metal spatula and cured for a minimum of 24 hours at room temperature. The implants were sterilized with gamma irradiation (25–30 kGy).

In Vitro Release Rate

In vitro release rate determination was continued from our previously reported experiment, to study 1-year pharmacokinetics of the CsA implants. This in vitro experiment only determined the release rates of

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γ-irradiated implants, as unpublished data demonstrated that gamma radiation causes no significant change in release rate and HPLC chromatograms. In vitro release rates were performed on randomly selected implants from each lot of implants A and B and placed in individual glass scintillation vials with 10 mL of phosphate-buffered saline (PBS; pH 7.4). Each vial was placed in a shaking water bath at 37°C, and the PBS in each vial was replaced every 24 hours, 5 days a week. In vitro release rates from the implants were determined by assaying the CsA concentrations in the vial over time with a reversed-phase HPLC assay. The analytical method was a modified USP assay procedure for CsA analysis, and no internal standard was used. Samples or standards with volumes of 5 to 200 μL were injected with an autosampler (model G1329A; Agilent Technologies, Palo Alto, CA). A 250 × 4.6-mm (5-mm) C18 polymeric column (Vydac, Hesperia, CA) was heated to 80°C in a column heater (model G1316A; Agilent). Separation was conducted by 1 mL/min isocratic elution with an acetonitrile/water/methanol/α-phosphoric acid (600:325:75:0.5) mobile phase and a pump (model G1312A; Agilent). The concentrations of the samples were monitored at 210 nm with an ultraviolet (UV) detector (model G115A; Agilent) and analyzed with Agilent Chemstation software. The standard curve was linear ($r^2 = 1.000$) over the range of 46 to 23,360 ng/mL, and the deviation between replicate samples was <5%. The drug detection limit for CsA in solvent was 0.01 μg/mL. The cumulative release of drug from the implants was determined by calculating the area under the release rate curve with the trapezoidal rule and recording it in milligrams ± 1 SD (SD). Sampling time points were daily for the first 2 weeks (for 5 days a week), twice weekly for 1 month, and weekly thereafter for approximately 1 year.

**Ocular Pharmacokinetics**

All procedures adhered to the guidelines in the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

**Short-Term Pharmacokinetics.** Twelve New Zealand White (NZW) rabbits of either sex, 6 to 12 months of age and weighing 2 to 3 kg (Covance Laboratories, Inc., Vienna, VA) were anesthetized with ketamine hydrochloride (35 mg/kg intramuscularly; Fort Dodge Animal Health, Inc., Division of Wyeth Pharmaceuticals, Overland Park, KS) and xylazine (5 mg/kg intramuscularly; Phoenix Scientific, Inc., St. Joseph, MO); proparacaine 1% ophthalmic drops (Allergan America, Horimigueros, PR) were used topically on the right eye. Toothed forceps were used to lift the conjunctiva and Tenon’s fascia in the superotemporal quadrant and a 3-mm incision was made with Wescott scissors. A pocket was formed in the sub-Tenon’s space and implant B was placed on the episclera, 5 mm posterior and parallel to the limbus. No sutures were used to secure the implants. The conjunctiva and Tenon’s fascia were reapproximated with a single 9-0 Vicryl suture. Animals were euthanatized at 3 and 72 hours after implantation with an intracardiac pentobarbital overdose (Beuthanasia-D Special; Scheming-Plough Animal Health Corp., Kenilworth, NJ). Animals were also euthanatized at 1 hour and 1 week to determine CsA concentrations in the buccal lymph node, the first lymph node in the cervical lymph node chain. After euthanasia, the implanted eye was enucleated and 5 × 5-mm sections of bulbar conjunctiva adjacent to the limbus were removed superiority and inferiorly, to examine the relative difference in CsA concentrations around the eye. The globes were immediately frozen at −70°C for later dissection and drug extraction. The time from enucleation to freezing was rapid (<10 seconds) which limited postmortem drug redistribution. Three contiguous circular sections of cornea were also removed with a 6-mm diameter trephine with the center of the sections 8, 13, and 18 mm away from the center of the implant to study the rate and amount of CsA distribution at various distances from the implant (Fig. 1). The frozen globe was then cut 360° around the limbus with a razor blade and the remainder of the cornea was lifted cleanly off of the frozen aqueous humor. A razor blade was passed parallel to the front surface of the iris, and the frozen aqueous humor lifted off the iris–lens diaphragm in two to three frozen pieces. CsA was extracted by placing the ocular tissues in HPLC-grade acetonitrile (Fisher Scientific, Pittsburgh, PA) in sealed vials for 24 hours at room temperature, sonicated with a (GEX 600 Ultrasonic processor; Daigger, Lincolnshire, IL) for 60 seconds, and stored in sealed vials for another 24 hours at room temperature. The samples were spun down in a centrifuge (Centra C12; Thermo IEC, Needham Heights, MA) for 30 minutes at 3500 rpm, and the supernatants were submitted for HPLC analysis. The same analytical method was used for cyclosporine analysis in ocular tissues as for in vitro samples. An internal standard was not used, though spiking of cyclosporine into some samples was applied to confirm the cyclosporine peak. A calibration curve for cyclosporine over the concentration range of 57.1 μg/mL down to 0.111 μg/mL was created by dissolving cyclosporine in acetonitrile and established with a correlation coefficient 1.000. The limit of quantification is approximately 0.05 μg/mL with injection volume of 10 μL. The SD for back-calculated standard concentration is <5% for concentration at 0.9 μg/mL and <10% for concentration at 0.1 μg/mL. The CsA concentrations in tissues were expressed as micrograms per milligram of tissue. Because of the small sample sizes, statistical analysis of tissue concentrations was performed using the bootstrap method, and statistical significance was assigned to $P < 0.05$.  

**Long-Term Pharmacokinetics.** Fifteen normal research beagles received implant A, which was also placed in the sub-Tenon’s space of the superotemporal quadrant in one eye 5 mm from the limbus, and the animals were killed at 1, 3, 6, 9, and 12 months subsequent to implantation. Ocular tissues of the implanted eye, including the cornea, conjunctiva, sclera, lacrimal gland, third-eyelid gland, lens, ciliary body, aqueous humor, vitreous humor, upper and lower eyelid tarsus and tarsal conjunctiva were separated for drug

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**Figure 1.** Placement of episcleral CsA implant (arrow) (A) superotemporally, 5 mm from the limbus. Circular sections (B) of the cornea were removed to measure the drug concentration at different regions. Distances were measured from the implant (arrow) which was superotemporal.
weights were 40.6 implants from each lot of implants A and B, and total mean In vitro release rates were performed on five randomly selected

**RESULTS**

**In Vitro Release Rate**

In vitro release rates were performed on five randomly selected implants from each lot of implants A and B, and total mean weights were 40.6 ± 1.8 and 25.8 ± 1.6 mg, respectively, and the amount of CsA initially loaded into the implants was 12.2 and 7.7 mg. The in vitro release pattern of all implants was typical of a matrix implant with release kinetics that are governed by diffusion from dispersed drug in a polymer (Fig. 2A). A high and declining release rate over the initial 5 months was followed by a steady state release over the 400-day assay period. The cumulative release from implants A and B was 3.8 ± 0.3 and 2.3 ± 0.3 mg, respectively, representing approximately 30% of the initial drug loading (Fig. 2B). Drug released from the implant over an 18-month period showed no signs of degradation, and the physical structure of the implant was not altered (Robinson MR, unpublished data, 2006). Implant A and B are projected to release 90% of the drug load for approximately 6 and 7 years, respectively.

**Short-Term Pharmacokinetics**

Twelve NZW rabbits received implant B superotemporally and 5 mm posterior to the limbus in their right eyes. Drug extraction was performed on the implanted eye of 3 rabbits at each time point studied. Three hours after implantation, the cornea had CsA concentrations of 0.15 ± 0.06, 0.07 ± 0.02, and 0.03 ± 0.02 µg/mg at sites centered 8, 13, and 18 mm away from the implant site, respectively (Fig. 3). Seventy-two hours after implant placement, the corneal CsA concentrations were 0.10 ± 0.06, 0.09 ± 0.03, and 0.05 ± 0.03 µg/mg at 8, 13, and 18 mm away from the implant site, respectively. The concentration of the superior and inferior conjunctiva at 3 hours was 0.11 ± 0.03 and 0.04 ± 0.01 µg/mg, respectively (Fig. 4). At 72 hours, the superior and inferior conjunctiva concentrations were 0.13 ± 0.06 and 0.15 ± 0.03 µg/mg. The drug concen-
trations in the buccal lymph node were evaluated on three rabbits at each time point. The lymph node concentration of CsA was 0.10 ± 0.04 and 0.06 ± 0.02 μg/mg at 1 hour and 1 week, respectively.

Long-Term Pharmacokinetics

The right eyes of 15 dogs received one implant A, and they were euthanatized at 1, 3, 6, 9, or 12 months for ocular drug extraction in the implanted eye. Corneal CsA levels ranged from 0.18 ± 0.06 to 0.009 ± 0.004 μg/mg during the 1-year study period. Drug levels, $C_{\text{max}}$, $T_{\text{max}}$, and AUC$_{0–12\text{months}}$ in all the ocular and surrounding tissues are reported in Table 1.

Toxicity Evaluation

Six dogs each received one implant A in one eye. Over the 1-year period, clinical examinations showed no signs of ocular toxicity. There were no significant changes in the ERG recordings compared with baseline during the 1-year study in both eyes. The histopathologic appearance by light microscopy in all eyes showed normal ocular tissues. There was a fine fibrous encapsulation surrounding the implant securing it to the episclera. There were no signs of retinal toxicity in all quadrants of the eye. In two of six dogs, there was a mild lymphoplasmacytic reaction around the implants at 12 months; however, there was no clinically observable inflammation. The laboratory data collected at each clinical examination (serum chemistries, renal and liver function tests, complete blood count) showed no signs of abnormalities.

**DISCUSSION**

CsA inhibits T-cell activation and vascular endothelial cell proliferation at in vitro drug concentrations of 0.0001 to 0.001 and 0.0012 to 0.06 μg/mg, respectively.$^{20–28}$ In the present study, corneal CsA concentrations were 0.09 ± 0.05 μg/mg at the 3-hour time point and remained in the inhibitory range for a minimum of 1 year for both these cell types, which are important in the evolution of the allograft rejection response. Investigators have also expressed the importance of suppressing T-cell activation in the draining lymph nodes of eyes after a corneal allograft because the generation of an alloresponse occurs in these lymph nodes in both low- and high-risk cases.$^{29,30}$ The episcleral implant delivered concentrations of 0.1 ± 0.04 and 0.12 ± 0.09 μg/mg of CsA to the buccal lymph node of rabbits at 1 hour and 1 week, respectively, which were 2 to 3 log units higher than the range necessary to inhibit T-cell activation in vitro. In addition to potentially inhibiting the generation of effector cells to the corneal graft, the corneal CsA concentrations were in the therapeutic range for direct inhibition of angiogenesis and therefore potential inhibition of vascularization of the graft.$^{31}$

The rapid rate at which the episcleral implant delivered high concentrations of CsA to the cornea, conjunctiva, and buccal lymph node, suggests that diffusion may not be the only drug-dispersion mechanism present. The CsA concentration ($C$) due to diffusion in one dimension and in the absence of clearance processes, can be predicted with the following solution to Fick’s Second Law$^{32}$:

**FIGURE 3.** Cornea CsA concentrations at increasing distances from implant B at 3 and 72 hours. **Histograms:** experimentally measured CsA concentrations at the corresponding sites on the cornea; **lines:** predicted concentrations if drug dispersion in the cornea were due to diffusion alone as a function of distance.

**FIGURE 4.** Conjunctiva CsA concentrations at increasing distances from implant B at 3 and 72 hours. **Histograms:** experimentally measured CsA concentrations at the corresponding sites on the conjunctiva; **lines:** predicted concentrations due to drug diffusion across circular distances around the cornea, which were calculated based on the 13-mm radius from implant to the center of the cornea.
for the boundary conditions

\[ C(x;0) = 0 \]

and

\[ C(0,t) = C_\text{in} \]

where \( C_\text{in} \) is the constant concentration in the tissue adjacent to the source (implant), \( D \) is the coefficient for solution diffusion through the tissue, \( t \) is time, \( \text{erfc} \) is the complementary error function, and \( x \) is the distance between the source and the measurement position. The coefficients for diffusion of CsA through rabbit cornea and conjunctiva were estimated from measurements of a wide range of hydrophilic and lipophilic model solutes to be \( 1.0 \times 10^{-6} \) and \( 4.4 \times 10^{-7} \) cm²/s, respectively.33–36 The distances from the implant to the sampling site (\( x \)) on the cornea were 8, 13, and 18 mm, corresponding to the trephined sections of the cornea. For the conjunctiva, circular distances around the cornea were calculated based on the 13-mm radius (from the center of the cornea to the implant; Fig. 1). The origin was taken to be at the implant site in the superior conjunctiva giving \( 13 \times \pi = 40.8 \) mm as the location of the inferior conjunctiva. The theoretical concentrations on the cornea due to diffusion alone were significantly less than the experimental concentrations (\( P < 0.05 \)) at 13 and 18 mm away from the implant site at 3 and 72 hours (Figs. 2, 5). The inferior conjunctiva exhibited a significantly higher CsA concentration at 72 hours than predicted for movement by diffusion alone.

TABLE 1. Drug Concentration of Ocular Tissues over 1 Year with a CsA Episcleral Implant in Dogs

<table>
<thead>
<tr>
<th>Drug Location</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>1 month AUC 0–12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper eyelid tarsus and tarsal conjunctiva</td>
<td>0.171 ± 0.004</td>
<td>0.140 ± 0.003</td>
<td>0.113 ± 0.003</td>
<td>0.104 ± 0.004</td>
<td>0.098 ± 0.005</td>
<td>0.813 ± 0.051</td>
</tr>
<tr>
<td>Lower eyelid tarsus and tarsal conjunctiva</td>
<td>0.148 ± 0.025</td>
<td>0.146 ± 0.027</td>
<td>0.145 ± 0.027</td>
<td>0.148 ± 0.025</td>
<td>0.146 ± 0.027</td>
<td>0.726 ± 0.051</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>0.085 ± 0.042</td>
<td>0.091 ± 0.043</td>
<td>0.093 ± 0.043</td>
<td>0.091 ± 0.042</td>
<td>0.085 ± 0.043</td>
<td>0.667 ± 0.045</td>
</tr>
<tr>
<td>Third eyelid gland</td>
<td>0.096 ± 0.044</td>
<td>0.091 ± 0.043</td>
<td>0.094 ± 0.044</td>
<td>0.091 ± 0.043</td>
<td>0.096 ± 0.044</td>
<td>0.667 ± 0.045</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>0.080 ± 0.044</td>
<td>0.079 ± 0.043</td>
<td>0.078 ± 0.043</td>
<td>0.079 ± 0.044</td>
<td>0.080 ± 0.044</td>
<td>0.667 ± 0.045</td>
</tr>
<tr>
<td>Sclera</td>
<td>0.074 ± 0.045</td>
<td>0.079 ± 0.044</td>
<td>0.078 ± 0.044</td>
<td>0.079 ± 0.045</td>
<td>0.074 ± 0.045</td>
<td>0.667 ± 0.045</td>
</tr>
<tr>
<td>Aquous Humor</td>
<td>0.141 ± 0.025</td>
<td>0.146 ± 0.027</td>
<td>0.145 ± 0.027</td>
<td>0.148 ± 0.025</td>
<td>0.146 ± 0.027</td>
<td>0.726 ± 0.051</td>
</tr>
</tbody>
</table>

Data are expressed as the mean micrograms per milligram of tissue ± 1 SD. AUC are micrograms per milligram per month.

Figure 5. Top: theoretical drug concentrations from implant B due to diffusion alone at 3 and 72 hours. Bottom: experimental drug concentrations from implant B at 3 and 72 hours imply that diffusion alone does not provide for drug movement across the cornea.
In contrast, when the experimental data are taken to be due to diffusion alone, the diffusion coefficient for diffusion of CsA across the cornea is estimated to be $1.8 \times 10^{-7}$ cm$^2$/s, which is an unrealistic four orders of magnitude greater. This large discrepancy in diffusion coefficient estimates cannot be attributed to the difference between lateral diffusion within the cornea and the transverse diffusion within the cornea described by the previous experimental measurements.

Other mechanisms probably contributed to the rapid lateral drug movement in our study.

We hypothesize that conjunctival lymphatic vessels contribute to the rapid distribution of the drug around the cornea, since high levels of CsA were detected in the buccal lymph node at 1 hour and 1 week. Previous investigations of drug concentrations in the ipsilateral cervical lymph nodes have also shown significant lymphatic clearance from the sub-Tenon’s space of low-molecular-weight hydrophilic compounds such as gadolinium-DTPA (diethylenetriamine penta-acetic acid), and compounds as large as albumin.

A role for conjunctival lymphatics in facilitating drug delivery to the anterior segment was first suggested in 1957 with tracor compounds injected subconjunctivally. It has also been suggested that the conjunctival lymphatics play a role in drug elimination after injection of triamcinolone acetonide in the sub-Tenon’s space. Here, trabecular diffusion of drug occurred into the vitreous only when the lymphatic circulation was interrupted at the injection site with sharp dissection of the conjunctiva.

In the present study, it is speculated that the pericorneal lymphatic ring, which is the major lymphatic trunk in the conjunctiva concentric with the cornea, and its afferent lymphatic vessels around the implant site, absorb the CsA near the implant site. Because lymphatic vessels are leaky, allowing for two-way passage, some quantities of CsA can diffuse out of the lymphatic vessels into the surrounding tissues en route to being eliminated either via the medial or cervical lymph node chain. Thus, the lymphatic flow surrounding the cornea may contribute to the rapid CsA dispersion across the cornea and conjunctiva. Nonetheless, one should be cautious in using diffusion coefficients determined in vitro to predict drug transport in vivo which will neglect the contribution of other coexisting modes of drug transport, such as lymphatics.

In the literature, there are currently two CsA-releasing implants studied for the prevention of high-risk corneal allograft rejection. Apel et al. studied a polylactic-glycolic acid (PLGA) disc-shaped CsA implant in a high-risk rabbit model, and showed that these devices implanted at the time of transplantation improved the survival time of the grafts. In vitro, these implants exhibited stable release for <100 days before reaching an unstable phase characterized by bulk degradation of PLGA. Unlike our episcleral implant, which maintained stable drug release for a minimum of 400 days, the in vitro release from PLGA is difficult to predict beyond the first 100 days. The corneal concentration achieved from the PLGA implant was 0.4 ng/mg at 35 days, which is below the therapeutic range for as peak corneal concentration achieved from the PLGA implant was 0.4 ng/mg at 35 days, which is below the therapeutic range for CsA levels from episcleral implants at 42 days. Xie et al. reported experiments with a CsA polylactide-co-glycolide (PLG) implant that was implanted in the aqueous humor and subconjunctival region of rat models of PKP rejection. Although the PLG delivery system significantly prolonged corneal allograft survival in a high-risk corneal graft rejection model in rats compared with controls, the CsA concentrations achieved were below the therapeutic range. Furthermore, even though the PLGA subconjunctival implant and the PLG implant are biodegradable, Apel et al. showed the bulk degradation of the polymer to be disadvantageous in generating a long-term release profile.

Several other drug delivery methods have been investigated for preventing corneal allograft rejection. Topical eye drops delivering CsA to the cornea have been investigated, but these formulations result in maximum tissue levels that are significantly lower than those achieved with an episcleral implant. In a rabbit study of maximum tissue concentration after a single dose of 0.05% CsA emulsion, Acheampong et al. reported that peak CsA concentrations in the cornea, upper conjunctiva, and lower conjunctiva were below the therapeutic range. Furthermore, even though the tissue levels from the episcleral implant short-term rabbit study resulted in peak concentrations two to three orders of magnitude higher, as peak cornea, upper conjunctiva, and lower conjunctiva concentrations were 0.07, 0.13, and 0.12 μg/mg, respectively. Local injections of CsA formulations into the subconjunctival space have shown very low corneal levels and thus a short-lived therapeutic effect. Collagen shields and fragments appeared to be more effective than systemic formulations; however, the effects last only up to 12 hours. Microspheres, liposomes, and nano-capsules also do not provide the prolonged release required to prevent high-risk PKP rejection.

There are a few limitations to our studies, including the usage of rabbits for the short-term pharmacokinetic studies and dogs for the long-term pharmacokinetic studies and toxicity studies. Direct comparisons of tissue drug concentrations may not be possible across species. Nevertheless, the results of the ocular drug distribution in a 6-month rabbit pharmacokinetic study using the same CsA implants showed similar results in the dog data presented in the present study. A second limitation was that draining lymph node drug concentrations were not measured beyond the 1-week time point, and even though ocular drug tissues remained stable over 1 year, we cannot assume that drug was present in the lymph nodes for the long term.

Our experiments have shown that episcleral implants are safe and effective at delivering therapeutic CsA levels to the cornea and surrounding tissues to prevent corneal allograft rejection. The implant can be surgically placed on the episclera at the time of PKP, since the implant achieves therapeutic levels as early as 3 hours. Although these episcleral CsA implants are expected to be therapeutic, further studies are needed to determine the clinical efficacy of the devices in PKP models.

References
Episcleral Cyclosporine Implant for Keratoplasty Rejection


