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Descemet's Membrane Endothelial Keratoplasty

Risk of Immunologic Rejection Episodes after Discontinuing Topical Corticosteroids

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Purpose: To assess the risk of immunologic rejection episodes if topical corticosteroids are discontinued 1 year after Descemet's membrane endothelial keratoplasty (DMEK) compared with continued once-per-day use.

Design: Prospective, longitudinal, parallel-group study.

Participants: A total of 400 eyes of 259 DMEK recipients, aged 23 to 90 years.

Methods: Patients were enrolled 1 year after DMEK and allowed to choose whether to stop or continue once-daily topical corticosteroids to maximize compliance. Fellow eyes were eligible for enrollment because the donor grafts were independent. Participants were examined at 1, 3, 6, and 12 months during the second year after DMEK. Results were assessed using Kaplan–Meier survival analysis.

Main Outcome Measures: Incidence of immunologic rejection episodes.

Results: Steroids were discontinued in 277 eyes (no steroid group) and continued once per day in 123 eyes (steroid group). The subject demographics were well balanced across groups; 99% of the subjects were white, and 95% of the grafts were performed to treat Fuchs' dystrophy. The cumulative incidence of rejection episodes was significantly greater in the no steroid group (6% vs. 0% in the steroid group; $P = 0.013$). Thirteen of 14 rejection episodes (all in the no steroid group) resolved with resumption of topical corticosteroids. Overall, 1 of 277 grafts (0.4%) failed in the no steroid group and none failed in the steroid group during the second year after DMEK ($P = 0.49$). The endothelial cell loss between 1 and 2 years was comparable in the no steroid and steroid groups (6.4%±12% vs. 5.6%±14%, respectively; $P = 0.67$).

Conclusions: Continued once-per-day use of a topical corticosteroid, even a weak one, was protective against rejection episodes during the second year after DMEK, whereas 6% experienced a rejection episode when steroids were discontinued. Among the 364 eyes that completed 12 months' follow-up, only 1 graft (0.27%) failed. *Ophthalmology 2016;■:1–5 © 2016 by the American Academy of Ophthalmology.*

Immunologic graft rejection is a leading cause of cornea transplant failure.[1–3] To prevent corneal graft rejection, topical corticosteroids are used for an extended period and often indefinitely.[4]

The incidence of transplant rejection episodes is remarkably low with the transplant procedure known as Descemet's membrane endothelial keratoplasty (DMEK), which involves implantation of minimal donor tissue, just the endothelial cell layer and Descemet's membrane.[5,6] In prospective studies involving 558 eyes, only 2 (0.4%) experienced an immunologic rejection episode in the first year after DMEK.[7,8]

We typically advise cornea transplant recipients to continue once-per-day use of topical corticosteroids indefinitely to prevent corneal graft rejection. Given the low risk of rejection with DMEK, we hypothesized that discontinuing topical corticosteroids at 1 year might be reasonably safe and more convenient and cost-effective for patients. To test this hypothesis, we designed a study to compare the risk of immunologic rejection episodes in the second year after DMEK with discontinuation versus continuation of topical corticosteroids.

Methods

This prospective, single-center, longitudinal, parallel-group study enrolled 259 participants between August 2012 and December 2014. An institutional review board approved the study, and all participants provided written informed consent. The study was Health Insurance Portability and Accountability Act compliant and adhered to the tenets of the Declaration of Helsinki.

Inclusion/Exclusion Criteria

The DMEK recipients were eligible to enroll at the 1-year postoperative examination. Exclusion criteria were active intraocular inflammation, corneal ulceration, keratitis, or conjunctivitis, a history of herpetic keratitis, abnormal eyelid function, ocular disease that would interfere with evaluation of the main outcomes, a

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prior rejection episode in the potential study eye, uncontrolled systemic disease, best-corrected vision <20/200 in the fellow eye, or a medical condition requiring use of topical or systemic corticosteroid medications. Fellow eyes were eligible for enrollment because the donor grafts in the 2 eyes were independently assigned.

Study Procedures

Participants were using a topical corticosteroid once per day in the DMEK eye(s) before enrolling. After enrollment, subjects were given a choice whether to discontinue topical corticosteroids (no steroid group) or continue once-per-day use (steroid group) for the 1-year study duration. Subjects were examined 3, 6, and 12 months after enrollment, and those in the no steroid group also were examined at 1 month.

The evaluations at each examination included medical and ophthalmic histories, documentation of any adverse events, manifest refraction and measurement of corrected distance visual acuity with Snellen projector charts, measurement of intraocular pressure (IOP) by Goldmann applanation, measurement of central corneal thickness by ultrasonic pachymetry, and slit-lamp examination to assess the health of the transplant and document any conjunctival or lid hyperemia, stromal inflammation, superficial punctate keratitis, other surface toxicity of the cornea, neovascularization of the cornea, keratic precipitates, or any cells or flare in the anterior chamber. Endothelial cell density (ECD) was measured by specular microscopy (manual centers method, Noncon Robo; Konan Medical, Inc., Hyogo, Japan) at the screening examination and at study completion. Subjects were instructed to come in for extra examinations if they noticed any problems with the eye or any early signs of a possible rejection episode, such as a change in vision, redness to the eye, increased light sensitivity, burning sensation, or foreign body sensation.

Statistical Analysis

The main outcome measure was the incidence of immunologic rejection episodes. The criteria for recording a rejection episode were the identification of keratic precipitates or an endothelial rejection line by slit-lamp examination, the observation of cells in the anterior chamber after the initial resolution of perioperative inflammation, or an increase of 30 μm or more in the central corneal ultrasonic pachymetry relative to the baseline measurement.

The null hypothesis was that the incidence of graft rejection episodes would not differ significantly between groups. The alternative hypothesis was that the incidence of graft rejection episodes would be greater in the group that discontinued topical corticosteroids. The secondary outcome measures were ECD and IOP.

To determine the required sample size, we used historical data that suggested the rate of rejection episodes between 12 and 24 months after DMEK would be approximately 0.5% in the group that continued topical corticosteroids.[5] We considered a 5% or greater difference in rejection rates between groups to be clinically significant. By assuming that approximately twice as many participants might choose to stop steroids as would choose to continue, a sample size of 372 eyes would provide 80% power to detect a clinically significant difference in rejection episode rates using a 1-sided test at a 5% significance level. Anticipating between 5% and 10% loss to follow-up during the 1-year study duration, we enrolled 400 eyes.

The cumulative probability of initial rejection episodes was assessed by Kaplan–Meier survival analysis and the log-rank test, which took loss to follow-up into consideration. The statistical analysis was conducted with SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and interpreted at a 5% significance level.

Results

Demographics and Subject Disposition

Topical corticosteroids were discontinued in 277 eyes and continued once per day in 123 eyes. The demographics were well balanced across the steroid and no steroid groups (Table 1). Most participants had Fuchs' endothelial corneal dystrophy, and the mean age was 67 years. More than 90% of the enrolled eyes in both groups completed the study per protocol (Table 2).

The topical corticosteroids used in the steroid group are listed in Table 1. The subjects in that group continued using whatever steroid they were using at the 1-year postoperative (baseline) examination. When the study started, the subjects were typically using prednisolone acetate 1% once per day at the baseline examination, unless a lower-strength steroid was required to manage IOP during the first postoperative year. After randomized trials showed that, compared with prednisolone acetate 1%, use of the weaker fluorometholone 0.1% or loteprednol 0.5% significantly reduced the risk of IOP elevation without substantially increasing the risk of rejection, patients were switched to a weaker steroid 1 to 2 months after DMEK.[7,8] As a result, the subjects enrolled later in the study were using fluorometholone 0.1% or loteprednol etabonate 0.5% at the baseline examination.

Rejection Episodes

Fourteen eyes, all in the no steroid group, experienced a possible or probable rejection episode. The cumulative proportion of eyes with a rejection episode was 0% (no eyes) in the steroid group versus 6% in the no steroid group ($P = 0.013$). An analysis restricted to the first enrolled eye per patient yielded similar results (0% vs. 6.7% cumulative proportions of rejection episodes in the steroid and no steroid groups, respectively; $P = 0.027$). Thus, potential confounding between fellow eyes did not significantly affect the results.

Table 1. Demographics of Study Subjects

	Steroid Group N = 123 Eyes	No Steroid Group N = 277 Eyes	*P* Value
Age (yrs)	67±10	67±11	0.59
Sex (female)	83 (67)	181 (65)	0.69
Race (white, non-Hispanic)	122 (99)	273 (99)	0.35
Indication for transplant (eyes)			0.44
Fuchs' dystrophy	114 (93)	264 (95)	
Pseudophakic/aphakic corneal edema	3 (2)	3 (1)	
Failed endothelial keratoplasty	6 (5)	9 (3)	
Failed penetrating keratoplasty	0 (0)	1 (0.4)	
Postoperative lens status			0.67
Posterior chamber intraocular lens	115 (94)	262 (95)	
Phakic	8 (6)	15 (5)	
Prior glaucoma diagnosis			0.10
Primary open-angle glaucoma	1 (0.8)	8 (2.9)	
Glaucoma suspect	3 (2.4)	1 (0.4)	
Steroid responsive	21 (17)	56 (20)	
Prior glaucoma surgery (trabeculectomy)	0 (0.0)	1 (0.4)	1.0
Topical corticosteroid used once per day			
Fluorometholone 0.1%	100 (81)		
Prednisolone acetate 1.0%	21 (17)		
Loteprednol etabonate 0.5% gel	2 (2)		

Data are mean ± standard deviation or number of eyes (%).

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