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Incidence and Clinical Course of Immune Reactions after Descemet Membrane Endothelial Keratoplasty

Retrospective Analysis of 1000 Consecutive Eyes

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Purpose: To analyze the incidence and clinical course of graft rejection episodes after Descemet membrane endothelial keratoplasty (DMEK).

Design: Retrospective analysis of a consecutive, interventional case series.

Participants: One thousand eyes that underwent DMEK from July 2011 through August 2015 at the Department of Ophthalmology, University of Cologne.

Methods: All cases with follow-up of at least 1 month were included (mean follow-up, 18.5 months). Patients with a graft rejection episode were followed up for 1 additional year.

Main Outcome Measures: Incidence of graft rejection, best spectacle-corrected visual acuity (BSCVA), central corneal thickness (CCT), endothelial cell density (ECD), and need for regraft.

Results: Nine hundred five cases met the inclusion criteria. A graft rejection episode developed in 12 patients (estimated probability of rejection at 1 year, 0.9%; at 2 years, 2.3%; at 4 years, 2.3%). At time of rejection, 9 of 12 patients had stopped corticosteroids. Five patients were symptomatic and 7 did not note the rejection episode. Intensified topical corticosteroid therapy was started immediately after diagnosis of rejection. Two eyes decompensated and required a regraft, whereas the remaining 10 eyes required no regraft (BSCVA, 0.27±0.28 logarithm of the minimum angle of resolution [logMAR]; CCT, 554.1±39.1 μm at last visit before rejection vs. BSCVA, 0.21±0.15 logMAR; CCT, 540.0±15.0 μm 3 months after rejection). One year after the rejection episodes, BSCVA and CCT in these eyes remained unchanged when compared with the last visit before rejection (BSCVA, 0.15±0.11 logMAR; CCT, 533.8±26.0 μm). Significant changes were observed for ECD values (1741±274.5 cells/mm^2 at last visit before rejection vs. 1356±380.3 cells/mm^2 after 3 months [$P = 0.04$] and 1290±359.0 cells/mm^2 after 1 year [$P = 0.01$]).

Conclusions: The risk for graft rejection after DMEK is low, and an even smaller minority requires a regraft. After intensified local corticosteroid therapy, most patients show stable visual acuity and CCT, although ECD decreases. The occurrence of immune reactions up to 2 years after surgery predominantly in patients not receiving corticosteroids supports the prolonged use of corticosteroids after DMEK. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology*

Posterior lamellar keratoplasty techniques such as Descemet stripping automated endothelial keratoplasty (DSAEK) or Descemet membrane endothelial keratoplasty (DMEK) largely have replaced full-thickness penetrating keratoplasty (PK) for the treatment of corneal endothelial disorders such as Fuchs' endothelial dystrophy or pseudophakic bullous keratopathy.[1–3] Descemet stripping automated endothelial keratoplasty and DMEK offer faster visual rehabilitation, less postsurgical astigmatism, and lower risk of transplant rejection compared with PK.[4–7] Because the DMEK graft consists of only the Descemet membrane with corneal endothelium and, in contrast to the DSAEK graft, lacks any adhering corneal stroma, DMEK provides faster and more complete visual rehabilitation compared with DSAEK.[8]

Within the first 2 years after corneal grafting, studies with similar postoperative corticosteroid regimens have shown that the risk of immune rejection is 5% to 17% for PK, 8% to 12% for DSAEK, and 1% to 5% for DMEK.[5–7,9–12] Thus, although the risk of immune reactions after DSAEK is comparable with that of PK, the risk of immune reactions after DMEK is significantly lower, probably because less antigenic tissue is transplanted, as well as because of the generally lower antigenicity of the endothelium.[13] Compared with PK, immune reactions after DSAEK and DMEK often present without

http://dx.doi.org/10.1016/j.ophtha.2016.12.017
ISSN 0161-6420/16

a classical Khodadoust line, but mostly with diffuse endothelial precipitates, and are clinically subtle and often even asymptomatic.[4,6,14]

Several studies have reported the incidence of graft rejection after DMEK. Anshu et al[6] reported a single graft rejection episode among 140 DMEK cases; this patient was followed up for 3 months after the rejection episode and showed a clear graft after the last visit. In addition, Guerra et al[7] reported 131 DMEK cases, among which 7 eyes had an immune rejection episode. In 6 eyes, the rejection completely resolved with conservative therapy, whereas 1 eye required a regraft. Baydoun et al[15] reported a total of 352 eyes that were evaluated up to 8 years after DMEK, in which 2 immune reaction episodes occurred. Recently, Price et al[16] reported 277 patients for whom corticosteroids were discontinued 1 year after DMEK. In this cohort, 14 rejection episodes were observed and only 1 eye required a regraft. Although these studies indicate that immune reactions after DMEK are rare and often do not lead to secondary graft failure with the requirement of a regraft, detailed information on the subsequent clinical course of eyes with immune reaction episodes—including visual acuity, central corneal thickness (CCT), and endothelial cell density (ECD)—in a larger group of DMEK procedures are still missing. Therefore, the aim of this study was to characterize the incidence and subsequent 1-year clinical course of immune reactions occurring after a large number of DMEK surgeries.

Methods

In this retrospective study, we reviewed clinical records of 1000 consecutively performed DMEK surgeries between July 1, 2011, and August 31, 2015, at the Department of Ophthalmology, University of Cologne, Cologne, Germany. The data were compiled within the Cologne DMEK database using Research Electronic Data Capture electronic data capture tools. Research Electronic Data Capture is a web-based application designed to support data capture for research studies.[17] The study was performed in conformance with the tenets of the Declaration of Helsinki, was approved by the local institutional review board (no. 14-373), and adhered to all German federal and state laws. Written informed consent was obtained from all patients before surgery.

Inclusion and Exclusion Criteria

All DMEK surgeries between July 1, 2011, and August 31, 2015, were reviewed. Descemet membrane endothelial keratoplasty surgery alone in phakic or pseudophakic eyes, as well as triple procedures (DMEK combined with phacoemulsification and posterior chamber lens implantation) for coexistent cataract were included. All patients with available postoperative follow-up data of at least 1 month at our department were included in the study. Patients with insufficient follow-up or follow-up solely at external sites were excluded. Eyes that required repeat DMEK during follow-up after resurgery were considered new cases. Eyes that required a full-thickness regraft or DSAEK during follow-up were excluded afterward. Routine visits were scheduled at 1, 3, 6, 12, 18, and 24 months after surgery and thereafter annually.

Indication for Descemet Membrane Endothelial Keratoplasty Surgery

Indications for DMEK surgery were Fuchs endothelial dystrophy (n = 803), pseudophakic bullous keratopathy (n = 85), other endothelial diseases including congenital hereditary endothelial dystrophy and posterior polymorphous corneal dystrophy (n = 28), pseudoexfoliation-related bullous keratopathy (n = 5), and graft failure or rejection after previously performed DMEK, DSAEK, or PK (n = 79).

Surgical Technique and Postoperative Medication

Descemet membrane endothelial keratoplasty or triple DMEK surgery was performed under general or local anaesthesia by 2 experienced surgeons (C.C. or B.O.B.), as described previously.[18–20] Before surgery, all patients received neodymium:yttrium–aluminium–garnet (Nd:YAG) laser iridotomy (VisuLas YAG II plus; Carl Zeiss Meditec, Jena, Germany) to avoid pupillary block or Urrets–Zavalia syndrome. In the case of coexisting cataract, first a conventional phacoemulsification with implantation of an acrylic intraocular lens into the capsular bag was performed. Thereafter, descemetorhexis and insertion of the previously prepared donor endothelium–Descemet membrane graft (8 mm in diameter) was performed as described in detail previously.[1,19]

All patients received standardized postoperative management. Eyes were treated with lubricants (Hylo-Care; Ursapharm, Saarbrücken, Germany) 5 times daily, ofloxacin eye drops (Floxal EDO; Mann, Berlin, Germany) 4 times daily for 1 week, pilocarpine 1% eye drops (Bausch & Lomb, Irvine, CA) 3 times daily for as long as air was in the anterior chamber, and corticosteroid eye drops (prednisolone acetate 1%; Inflanefran forte; Pharm Allergan, Ettlingen, Germany). Before April 1, 2014, corticosteroids were applied 5 times daily for the first postoperative month and afterward tapered 1 drop per month (the last drop to be applied for at least 1 year). Based on publications indicating that intensified topical corticosteroids can reduce the risk of cystoid macular edema, we changed our therapy regimen to hourly corticosteroids for the first postoperative week after April 1, 2014.[21,22] Corticosteroids subsequently were reduced to 5 times daily for the rest of the first month and thereafter again tapered 1 drop per month (the last drop to be applied for at least 1 year).

Preoperative and Postoperative Clinical Assessment

Standardized eye examinations, including best spectacle-corrected visual acuity (BSCVA), tonometry, slit-lamp examination, funduscopy, slit-lamp–adapted optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany) to measure CCT, and ECD measurements (Tomey EM-3000 Specular Microscope; Tomey Corporation, Nagoya, Japan) were performed routinely before and at 1, 3, 6, 12, 18, and 24 months after surgery and thereafter annually and at any additional visit. Preoperative donor graft ECD was provided by the provider eye bank. In the case of an immune reaction episode, BSCVA, CCT, and ECD were analyzed for the following time points: before surgery, at the last visit before the onset of immune reaction, and 3 and 12 months afterward.

Detection and Treatment of Corneal Graft Rejection

Corneal graft rejection was diagnosed clinically by slit-lamp evaluation and was defined as new retrocorneal precipitates on