Outcomes of femtosecond laser-assisted Descemet membrane endothelial keratoplasty for failed penetrating keratoplasty

Nir Sorkin, MD,* Tanya Trinh, MBBS, FRANZCO,* Adi Einan-Lifshitz, MD,†
Zale Mednick, MD, FRCSC,* Gisella Santaella, MD,* Alexandre Telli, MD,* Avner Belkin, MD,*
Clara C. Chan, MD, FRCSC, FACS,* David S. Rootman, MD, FRCSC*

ABSTRACT • RÉSUMÉ

Objective: To analyze the outcomes of femtosecond laser-enabled Descemet membrane endothelial keratoplasty (FE-DMEK) in treatment of failed penetrating keratoplasty (PK) grafts.
Study Design: Retrospective, interventional case series.
Participants: Patients with a failed PK graft who underwent FE-DMEK at Toronto Western Hospital, Canada, between 2014 and 2016.
Methods: Outcome measures were best spectacle-corrected visual acuity (BSCVA), endothelial cell density (ECD), rates of graft detachment, rebubbling, rejection, and failure.
Results: Eight eyes of 8 patients were included. Mean age was 64.7 ± 14.5 years. Average follow-up time was 27.5 ± 8.6 months (range 15–36 months). There were no intraoperative complications and no issues with the creation of the descemetorhexis—all descemetorhexis cuts were complete. There were no significant graft detachments and no need for rebubbling. There were no primary or secondary graft failures and all grafts were viable at the final follow-up. BSCVA worsened from 0.41 ± 0.33 logMAR (Snellen equivalent ~20/50) to 1.37 ± 0.91 logMAR (Snellen equivalent ~20/460) after PK failure ($p = 0.012$), and improved significantly after FE-DMEK to 0.34 ± 0.14 logMAR (Snellen equivalent ~20/45), 0.42 ± 0.12 logMAR (Snellen equivalent ~20/50), 0.27 ± 0.14 logMAR (Snellen equivalent ~20/35), and 0.25 ± 0.16 logMAR (Snellen equivalent ~20/35) at 6 months, 12 months, 24 months, and at final follow-up, respectively ($p = 0.013$, $p = 0.027$, $p = 0.022$, and $p = 0.008$, respectively). ECD decreased from 2837 ± 229 cells/mm^2 preoperatively to 1069 ± 413 cells/mm^2 (61.4% cell-loss rate) and 974 ± 344 cells/mm^2 (64.8% cell-loss rate) at 12 months and 24 months, respectively ($p < 0.001$). Cell loss was higher than in historical controls.
Conclusions: FE-DMEK was effective in the management of PK graft failure, showing very low detachment and rebubble rates.

Objectif: Analyser les résultats de la kératoplastie endothéliale de la membrane de Descemet au laser femtoseconde (FE-DMEK, pour *femtosecond laser-enabled Descemet's membrane endothelial keratoplasty*) dans la prise en charge de l'échec de la kératoplastie transfixiante (KT).
Nature: Étude rétrospective d'intervention d'une série de cas.
Participants: Patients chez lesquels la KT a échoué et qui ont subi une FE-DMEK au Toronto Western Hospital, au Canada, entre 2014 et 2016.
Méthodes: Au nombre des paramètres de mesure, citons la meilleure acuité visuelle corrigée (MAVC), la densité cellulaire endothéliale (DCE) ainsi que les taux de décollement du greffon, de réinjection postopératoire d'une bulle d'air (*rebubbling*), de rejet du greffon et d'échec de la greffe.
Résultats: Huit yeux de 8 patients dont l'âge moyen était de 64,7 ± 14,5 ans ont été inclus dans cette étude. Le suivi moyen s'étalait sur 27,5 ± 8,6 mois (fourchette : 15–36 mois). On ne déplore aucune complication intraopératoire ni de difficulté au moment du descemetorhexis : toutes les ablations de la membrane de Descemet étaient complètes. Il ne s'est produit aucun décollement significatif du greffon ni de besoin de procéder à une nouvelle injection de bulle d'air. On n'a enregistré aucun échec primaire ou secondaire de la greffe, et tous les greffons étaient viables au moment du suivi final. Après l'échec de la KT, la MAVC s'était détériorée, passant de 0,41 ± 0,33 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/50) à 1,37 ± 0,91 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/460) ($p = 0,012$), pour s'améliorer significativement après la FE-DMEK et atteindre 0,34 ± 0,14 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/45), 0,42 ± 0,12 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/50), 0,27 ± 0,14 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/35) et 0,25 ± 0,16 logMAR (équivalent sur l'échelle de Snellen : ≈ 20/35) à 6 mois, à 12 mois, à 24 mois et lors du suivi final, respectivement ($p = 0,013$; $p = 0,027$; $p = 0,022$ et $p = 0,008$, respectivement). La DCE est passée de 2837 ± 229 cellules/mm^2 avant l'intervention à 1069 ± 413 cellules/mm^2 (soit un taux de perte cellulaire de 61,4 %) et à 974 ± 344 cellules/mm^2 (soit un taux de perte cellulaire de 64,8 %) à 12 mois et à 24 mois, respectivement ($p < 0,001$). La perte cellulaire était plus prononcée que chez les témoins historiques.
Conclusions: La FE-DMEK a permis une prise en charge efficace d'un échec de la greffe sous KT et s'est soldée par de très faibles taux de décollement du greffon et de réinjection de bulle d'air.

In penetrating keratoplasty (PK), secondary graft failure from late endothelial decompensation is not an uncommon occurrence and becomes increasingly likely with aging of the graft. Traditionally, a repeat PK procedure was necessary to replace the full-thickness failed graft. In recent years, the use of endothelial keratoplasty allows for replacement of the decompensated endothelium with a new endothelial graft, obviating the need for a full-thickness transplant. This reduces the risk of rejection, improves the visual outcome, induces minimal refractive changes, and avoids risks associated with "open-sky" surgery.[1–6]

Descemet membrane endothelial keratoplasty (DMEK) has been shown to promote faster and better visual recovery than

https://doi.org/10.1016/j.jcjo.2019.04.003
ISSN 0008-4182

Descemet stripping automated endothelial keratoplasty[7,8] with reduced rejection rates.[8] Recent literature shows that DMEK is a viable option to manage secondary PK graft failure with acceptable outcomes. However, the use of DMEK in this scenario is associated with a high rate of postoperative rebubbling, ranging between 26% and 100%,[3–6,9] and with subsequent early and late graft failure.[2–4,6,9,10]

Recently, the femtosecond laser has been suggested as a novel tool for performing precise descemetorhexis in DMEK surgery.[11,12] We previously reported promising DMEK outcomes using femtosecond laser-enabled Descemet membrane endothelial keratolasty (FE-DMEK) in Fuchs' endothelial dystrophy, showing similar efficacy to manual descemetorhexis with lower postoperative graft detachment, rebubble, and cell-loss rates.[12,13] In this study, we present the outcomes of FE-DMEK performed in patients with a failed PK graft.

Methods

A retrospective medical chart review was performed on consecutive patients with a failed PK graft who underwent FE-DMEK at the Kensington Eye Institute and were followed up at Toronto Western Hospital (Toronto, Ontario, Canada) between 2014 and 2016. Included were 8 eyes of 8 patients. All eyes had at least 15 months of postoperative follow-up (1 eye, 15 months; 1 eye, 18 months; 3 eyes, 24 months; 3 eyes, 36 months). Patients with failed PK were suitable for DMEK surgery if there was no significant stromal or subepithelial scarring and the patient possessed suitable anterior chamber anatomy. This retrospective interventional case series received Research Ethics Board approval by the University Health Network (Toronto Western Hospital, Toronto, Ontario, Canada) and was conducted in compliance with the tenets of the Declaration of Helsinki.

The data collected in this study included demographic characteristics, host and donor characteristics, intra-operative and postoperative complications, best spectacle-corrected visual acuity (BSCVA), endothelial cell density (ECD) obtained using a noncontact specular microscope (Robo, KSS 300; Konan Medical, Hyogo, Japan), and data on graft detachment, rebubbling, rejection, and failure. All donor tissues used were stored in corneal storage solution (Optisol; Bausch & Lomb, Rochester, NY) and received from the Eye Bank of Canada, Ontario division.

Surgical Technique

All procedures were performed at the Kensington Eye Institute, Toronto, Ontario, Canada. DMEK grafts were prepared using a modification of the original Melles technique.[14,15] After preparation, the donor Descemet membrane was loaded into either a glass cartridge (Geuder Medical, Heidelberg, Germany) or an intraocular lens (IOL) cartridge (Monarch, Alcon, Fort Worth, TX). The size of the PK graft was measured, and the sizes of the donor DMEK graft and the descemetorhexis were chosen accordingly. In all patients, the descemetorhexis was at least 0.25 mm smaller than the PK graft to avoid graft dehiscence with further diameter reduction in the presence of peripheral graft-host junction opacities that could have caused an incomplete femtosecond incision (descemetorhexis diameter range was 6.00−7.75 mm). Five eyes (62.5%) had a DMEK graft that was 0.25 mm larger than the PK graft, 1 eye (12.5%%) had same-sized DMEK and PK grafts, and 2 eyes (25%) had a DMEK graft that was 0.25 mm smaller than the PK graft. Five DMEK grafts were 8.00 mm in diameter and 3 DMEK grafts were 7.75 mm in diameter.

A temporal 2.4-mm incision and 3 paracenteses were performed in the host peripheral corneal rim without penetrating the PK graft, to prevent potential graft-host wound dehiscence.[9] A descemetorhexis was performed with the assistance of the Intralase iFS femtosecond platform (Abbott Medical Optics, Abbott Park, IL), creating a vertical ring cut whose depth extended from 100 μm above the thinnest measured corneal depth to 100 μm below the thinnest measured corneal depth. Corneal depth was measured using a Palmscan P2000U pachymeter (MicroMedical Devices, Calabasas, CA) at 8 points along the circumference of the planned descemetorhexis incision.[12] Descemet membrane was subsequently dissected from the stroma using a reverse Sinskey hook. Care was taken to avoid deep dissection into stromal tissue. One procedure was combined with phacoemulsification and IOL implantation.

No peripheral iridectomies were performed. All patients remained strictly supine for 2 hours and then "as much as possible" at home until the next morning. All patients were examined 2 hours after surgery and, if necessary, some of the air was released if the bubble was completely filling the anterior chamber and pupillary block was deemed to be likely. The following day, 0.1% dexamethasone sodium phosphate and 0.3% tobramycin antibiotic (Tobradex; Alcon, Mississauga, Ontario, Canada) eye drops were administered 4 times daily for a week. Then, antibiotic drops were discontinued and 0.1% dexamethasone sodium phosphate (Maxidex; Alcon) eye drops were tapered down to once daily during a 3-month period. Postoperative examinations were performed at day 0, day 1, week 1, month 1, every 3 months for the first postoperative year, and every 6 months thereafter.

Rebubbling criteria: Rebubbling is performed within 24 hours in eyes with Descemet membrane detachment of more than one third of the DMEK graft if no air bubble is left in the anterior chamber. Rebubbling is also performed later on if there is unresolved Descemet membrane detachment that is causing persistent corneal edema either limiting rapid visual recovery or causing significant ocular surface discomfort. In cases of uncertainty, anterior segment optical coherence tomography (Spectralis, Heidelberg Engineering GmbH., Heidelberg, Germany) is performed to determine whether there is graft detachment.

Statistical Analysis

Data were recorded in Microsoft Excel (2016) and analyzed using XLSTAT (version 2019.1.2). BSCVA results

were converted to logarithm of the minimum angle of resolution (logMAR). Continuous variables were compared within subjects using the Wilcoxon signed-rank test and paired *t* test. All tests were 2-tailed, and the threshold for statistical significance was defined as a *p*-value <0.05.

Results

Eight eyes of 8 patients were included. Average age was 64.7 ± 14.5 years. There were 6 male eyes (75.0%) and 3 right eyes (37.5%). Three patients were phakic (37.5%) and 5 were pseudophakic (62.5%). The mean number of PK procedures performed before FE-DMEK was 1.4 ± 0.7 (range 1–3) and the mean time between PK and FE-DMEK surgeries was 16.9 ± 10.0 years. Average follow-up time after FE-DMEK was 27.5 ± 8.6 months (range 15–36 months). Indications for PK are shown in Table 1. There were no intraoperative complications and no issues with the creation of the descemetorhexis—all descemetorhexis cuts were complete.

Graft detachment smaller than 1/3 of the graft area was seen in 1 of 8 eyes (12.5%) and did not require rebubbling. No rebubble procedures were needed. There were no primary or secondary graft failures and all grafts were viable at the final follow-up with a clear and compact PK graft. Two eyes had acute graft rejection (at 4 and 12 months), which resolved completely with the use of topical steroids. There were no intraocular pressure elevations.

Table 1—Indications for penetrating keratoplasty

Keratoconus	4/8 (50.0%)
Previous graft failure*	1/8 (12.5%)
Scarred ulcer	1/8 (12.5%)
Fuchs' dystrophy	1/8 (12.5%)
Chemical burn	1/8 (12.5%)

*Original indication for the failed graft was keratoconus.

BSCVA before PK graft failure was 0.41 ± 0.33 logMAR (Snellen equivalent ~20/50) and worsened significantly to 1.37 ± 0.91 logMAR (Snellen equivalent ~20/460) after PK failure ($p = 0.012$). After FE-DMEK, BSCVA improved significantly to 0.34 ± 0.14 logMAR (Snellen equivalent ~20/45), 0.42 ± 0.12 logMAR (Snellen equivalent ~20/50), 0.27 ± 0.14 logMAR (Snellen equivalent ~20/35), and 0.25 ± 0.16 logMAR (Snellen equivalent ~20/35) at 6 months, 12 months, 24 months, and at final follow-up, respectively ($p = 0.013$, $p = 0.027$, $p = 0.022$, and $p = 0.008$, respectively) (Fig. 1). Postoperative BSCVA was not significantly different from prefailure BSCVA at any time period ($p = 0.440$, $p = 0.698$, $p = 0.582$, and $p = 0.347$ for 6 months, 12 months, 24 months, and final follow-up, respectively).

Mean preoperative ECD was 2837 ± 229 cells/mm^2, decreasing at 12 months and 24 months to 1069 ± 413 cells/mm^2 (61.4% cell-loss rate, $p < 0.001$) and 974 ± 344 cells/mm^2 (64.8% cell-loss rate, $p < 0.001$), respectively.

Discussion

In recent years, DMEK has evolved as a tool for management of PK graft endothelial failure with a good clinical outcome. However, rates of detachment and rebubbling in this setting are high compared with primary DMEK, with rebubbling rates ranging between 26% and 100%.[3–6,9] In our study, the rebubbling rate after FE-DMEK for failed PK was 0% and only one eye (12.5%) had a small detachment that did not affect graft clarity or visual outcome and therefore did not require rebubbling. This is consistent with a lower detachment and rebubble rate found by our group in a comparison between FE-DMEK and manual DMEK in Fuchs' endothelial dystrophy patients.[12] The reason for the lower detachment and rebubble rate is unknown but may be related to a more complete removal of the host's Descemet with less remnant Descemet tags and islands due to the precise and

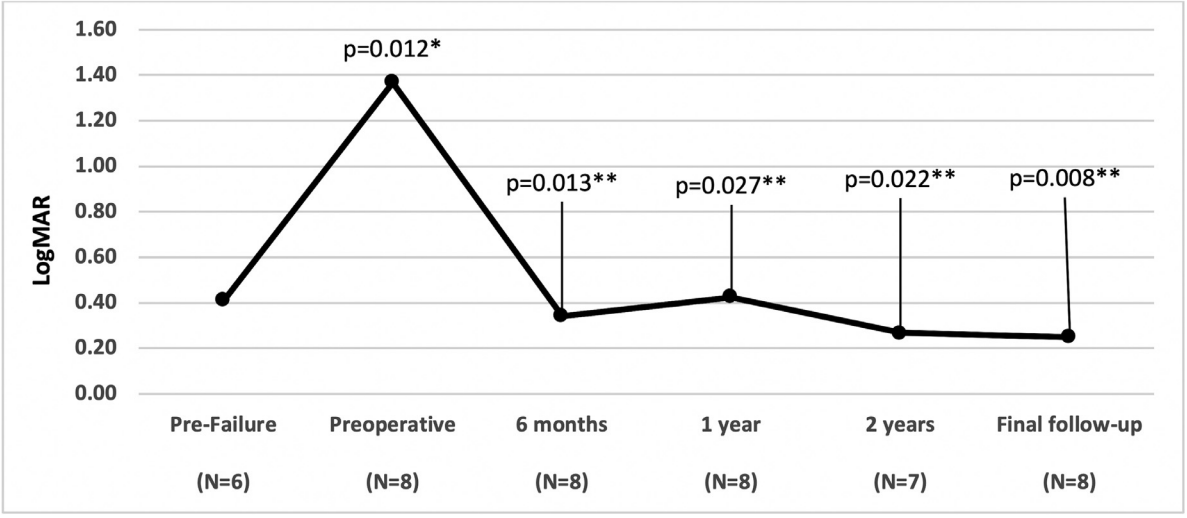

Fig. 1—Mean best spectacle-corrected visual acuity (BSCVA) in logMAR before graft failure, pre- and postoperatively. *Compared with pre-failure BSCVA. **Compared with preoperative BSCVA.

deep ring cut performed by the femtosecond laser. Lavy et al. described outcomes of DMEK in 11 failed PK grafts, including histology analysis of one of the grafts.[4] One of their conclusions was that making complete descemetorhexis across the PK graft may be more difficult than in virgin corneas so that remnant Descemet may contributed to incomplete graft adherence. In this setting, FE-DMEK might offer an advantage. In addition to mechanical interference, residual host Descemet in the interface might produce a different attachment profile and affect the wound healing response. Lavy et al. found that although histology of DMEK under PK showed a virtually normal interface between the donor Descemet and the host posterior stroma in areas with uncomplicated graft attachment, in areas that had clinically shown detachment, a layer of newly formed fibrotic tissue was visible overlying the DMEK graft, extending from the posterior PK wound toward the central and peripheral graft areas. They concluded that although formation of scar tissue may be part of the normal wound-healing response in graft detachment, this fibrotic response seemed to be more extensive than in primary DMEK eyes and attributed this to the presence of the PK wound and/or chronic inflammation associated with PK graft failure. Therefore, it is possible that a more uniform apposition of the DMEK graft in FE-DMEK cases, with less "micro-detachment" pockets, could alter the wound-healing response and promote better attachment. It should be noted that there were no eyes with glaucoma drainage devices, or filtering blebs in our cohort. History of previous glaucoma surgery in eyes undergoing manual DMEK has been found to be a significant risk factor for DMEK graft detachment in post-PK eyes.[10] This should be further evaluated in FE-DMEK also.

In addition to risks associated with the rebubble procedure itself, higher rates of detachment and rebubbling may lead to higher rates of primary and possibly also secondary graft failure. Recent literature shows that rates of primary failure in DMEK for failed PKP range between 5% and 29%.[3,4,6,9,10] In our cohort, there were no primary or secondary graft failures. This could be explained in part by the lack of significant detachments and no performance of rebubbling. Endothelial cell-loss rates after DMEK for failed PK range in the literature between 44% at 12 months and 59% at 16 months.[4,9,10] This is higher than 12-month cell-loss rates of 38%−40% and a 24-month cell-loss rate of 45% recently described in large cohorts of DMEK patients with varying surgical indications.[16,17] Possible mechanisms contributing to higher cell loss in post-PK DMEK are increased procedure complexity, high detachment rates, chronic inflammation or low-grade rejection associated with PK graft failure, and presence of ocular comorbidities. In our cohort, endothelial cell-loss rate was 61.4% at 1 year and 64.8% at 2 years. This shows that cell-loss rate after FE-DMEK for failed PK remained high despite the low detachment and rebubble rates, and differs from lower endothelial cell-loss rates found in FE-DMEK compared with manual DMEK performed in Fuchs' endothelial dystrophy patients.[13] A possible explanation for this is that because endothelial cell deficiency in failed PK grafts is profound, more endothelial cells migrate peripherally from the DMEK graft, thereby reducing DMEK cell density. Although rates found in our study seem slightly higher than those reported in manual DMEK for failed PK, it should be noted that cell-loss calculations in those studies excluded cases of primary and early graft failures—cases where endothelial cell-loss rate would be maximal. Nevertheless, endothelial cell loss in either FE-DMEK or manual DMEK for failed PK should be further investigated.

Limitations of this study include its small cohort and retrospective nature. Nevertheless, it is, to the best of our knowledge, the first study describing the use of FE-DMEK in cases of failed PK. Larger-scale prospective studies can further evaluate outcomes of FE-DMEK in cases of failed PK.

In conclusion, FE-DMEK was effective in treatment of PK graft failure, showing very low detachment and rebubble rates.

References

1. Price FW, Price MO. Endothelial keratoplasty to restore clarity to a failed penetrating graft. *Cornea*. 2006;25:895–9.
2. Anshu A, Price MO, Price FW. Descemet's stripping endothelial keratoplasty under failed penetrating keratoplasty: visual rehabilitation and graft survival rate. *Ophthalmology*. 2011;118:2155–60.
3. Anshu A, Price MO, Price FW. Descemet membrane endothelial keratoplasty and hybrid techniques for managing failed penetrating grafts. *Cornea*. 2013;32:1–4.
4. Lavy I, Liarakos VS, Verdijk RM, et al. Outcome and histopathology of secondary penetrating keratoplasty graft failure managed by descemet membrane endothelial keratoplasty. *Cornea*. 2017;36:777–84.
5. Gundlach E, Maier AKB, Riechardt AI, et al. Descemet membrane endothelial keratoplasty as a secondary approach after failure of penetrating keratoplasty. *Exp Clin Transplant*. 2015;13:350–4.
6. Heinzelmann S, Böhringer D, Eberwein P, Lapp T, Reinhard T, Maier P. Descemet membrane endothelial keratoplasty for graft failure following penetrating keratoplasty. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:979–85.
7. Tourtas T, Laaser K, Bachmann BO, Cursiefen C, Kruse FE. Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty. *Am J Ophthalmol*. 2012;153:1082–90.
8. Goldich Y, Showail M, Avni-Zauberman N, et al. Contralateral eye comparison of Descemet membrane endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty. *Am J Ophthalmol*. 2015;159. 155−159.e1.
9. Einan-Lifshitz A, Belkin A, Sorkin N, et al. Descemet membrane endothelial keratoplasty after penetrating keratoplasty: features for success. *Cornea*. 2018;37:1093–7.
10. Pasari A, Price MO, Feng MT, Price FW. Descemet membrane endothelial keratoplasty for failed penetrating keratoplasty. *Cornea*. 2019;38:151–6.
11. Pilger D, von Sonnleithner C, Bertelmann E, Joussen AM, Torun N. Femtosecond laser-assisted descemetorhexis: a novel technique in Descemet membrane endothelial keratoplasty. *Cornea*. 2016;35:1274–8.
12. Einan-Lifshitz A, Sorkin N, Boutin T, et al. Comparison of femtosecond laser-enabled descemetorhexis and manual descemetorhexis in descemet membrane endothelial keratoplasty. *Cornea*. 2017;36:767–70.
13. Sorkin N, Mednick Z, Einan-Lifshitz A, et al. Three-year outcome comparison between femtosecond laser-assisted and manual Descemet membrane endothelial keratoplasty. *Cornea*. April 2019.
14. Borovik AM, Perez M, Lifshitz T, et al. Peripheral blunt dissection: using a Microhoe-facilitated method for Descemet membrane endothelial keratoplasty donor tissue preparation. *Cornea*. 2017;36:1270–3.
15. Melles GRJ, Ong TS, Ververs B, van der Wees J. Descemet membrane endothelial keratoplasty (DMEK). *Cornea*. 2006;25:987–90.

16. Peraza-Nieves J, Baydoun L, Dapena I, et al. Two-year clinical outcome of 500 consecutive cases undergoing Descemet membrane endothelial keratoplasty. *Cornea*. 2017;36:655–60.
17. Schrittenlocher S, Schaub F, Hos D, Siebelmann S, Cursiefen C, Bachmann B. Evolution of consecutive Descemet membrane endothelial keratoplasty outcomes throughout a 5-year period performed by two experienced surgeons. *Am J Ophthalmol*. 2018;190:171–8.

Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

From the *Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ont; †Ophthalmology Department, Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Originally received Jan. 14, 2019. Final revision Apr. 11, 2019. Accepted Apr. 15, 2019.

Correspondence to Nir Sorkin, MD, Department of Ophthalmology and Vision Sciences, Toronto Western Hospital, 399 Bathurst St, 6th Floor East Wing, Reception 1, Toronto, Ont. M5T 2S8. nir.sorkin@gmail.com