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ORIGINAL ARTICLE

TRActional DIabetic reTInal detachment surgery with co-adjuvant intravitreal dexamethasONe implant: the TRADITION STUDY

Matias Iglicki[1] · Dinah Zur[2,3] · Adrian Fung[4,5,6] · Pierre-Henry Gabrielle[7] · Marco Lupidi[8] · Rodrigo Santos[1] · Catharina Busch[9] · Matus Rehak[9] · Zafer Cebeci[10] · Martin Charles[11] · Dua Masarwa[2,3] · Shulamit Schwarz[2,3] · Adiel Barak[2,3] · Anat Loewenstein[2,3,12] · for the International Retina Group (IRG)

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Abstract

Aim Main failure of diabetic tractional retinal detachment (TRD) surgery is the development of proliferative vitreoretinopathy (PVR), causing higher re-detachment rates. We investigated whether the use of dexamethasone (DEX) implant at the end of pars plana vitrectomy (PPV) with silicone oil tamponade might have an impact on these outcomes.

Design Comparative, nonrandomized, retrospective study.

Participants A total of 148 eyes from 148 patients that underwent PPV with silicone oil tamponade for diabetic TRD (with DEX implant, $n=52$; without DEX implant, $n=96$).

Methods Consecutive patients' records were reviewed for time between TRD diagnosis and surgery; lens status before surgery and after 6, 12, and 24 months; retina attachment rate after primary PPV; change in postoperative PVR severity; rate of re-detachment at 6, 12, and 24 months; use of IOP lowering treatment after 6, 12, and 24 months; surgery details; intra- and postoperative complications. Correlations between outcome measures, postoperative PVR severity, and re-detachment rates were analyzed.

Main outcome measures Change in postoperative PVR severity and retinal re-detachment rates with and without the adjuvant use of DEX implant.

Results Retinal re-detachment rates were significantly higher in the group of patients that did not receive DEX implant [11/96 (11.5%) vs. 0/52 (0%), $p=0.049$; 11/84 (12.9%) vs. 4/52 (7.7%), $p=0.007$; 14/71 (19.7%) vs. 5/52 (10%) $p<0.001$ at 6, 12, and 24 months, respectively]. PVR severity correlated with retinal status at 12 and 24 months ($p=0.018$ and $p=0.027$, respectively). The difference in PVR severity between the two groups was statistically significant at 6, 12, and 24 months ($p<0.001$).

Conclusions DEX implant at the end of PPV in patients with diabetic TRD improves PVR severity and decreases re-detachment rates. This should be considered as an option in the customized treatment of TRD.

Keywords Steroid · Pars plana vitrectomy with silicone oil · Traction retinal detachment · Pars plana vitrectomy for complex retinal detachment · Pars plana vitrectomy for diabetic retinopathy

Introduction

Diabetes mellitus is a major healthcare concern in people of working age. Worldwide, about 93 million are estimated to have diabetic retinopathy (DR) [1]. Among diabetic patients, proliferative diabetic retinopathy (PDR) is the most common cause of severe visual loss [2], presenting with retinal neovascularization of the disk (NVD) or elsewhere in the retina (NVE). Vitreous hemorrhage and tractional retinal detachment (TRD) are sight-threatening complications of

Managed by Massimo Porta.

Matias Iglicki and Dinah Zur have contributed equally to this work.

✉ Matias Iglicki
matiasiglicki@gmail.com

Extended author information available on the last page of the article

PDR, potentially leading to irreversible severe vision loss or blindness within 5 years.

Small-gauge pars plana vitrectomy (PPV) has been shown to be effective and safe in the management of TRD and has become the common practice even in the presence of complicated ocular conditions [3–6]. In addition to membrane dissection and release of traction during the surgery, intraoperative panretinal photocoagulation (PRP) is mandatory in all cases in order to induce the regression of retinal neovascularization [7].

Diabetic retinopathy severity and progression correlate with intraocular levels of vascular endothelial growth factor (VEGF) [8]. However, the pathogenesis is complex and multifactorial: Pro-inflammatory cytokines and chemokines significantly contribute to the disease development [9–11] and promote ischemic changes in the retina [12–14]. Therefore, there is a potential role for intravitreal steroids in disease modification. Corticosteroids reduce not only leukostasis and inflammatory cytokine production, but also VEGF expression. Recently, our group published the 'DR ProDEX study' which provided the first long-term evidence that DEX implant has the potential to not only delay progression of DR and PDR development, but may also improve DR severity over 24 months [15]. Recently, dexamethasone was shown to be effective to inhibit PVR formation in a preclinical trial [16]. In a PVR animal model, intravitreal slow release dexamethasone intervened eyes had minimal PVR, compared to control groups.

The purpose of this study was to investigate whether the addition of intravitreal dexamethasone (DEX) implant at the end of PPV for diabetic TRD can improve the rate of retinal attachment over time.

Methods

This was an international multicenter study involving 11 centers.

Institutional review board (IRB) approval was obtained through the individual IRBs at the participating institutes for a retrospective consecutive chart review. Approval for data collection and analysis was obtained from the individual IRBs and ethics committee. The research adhered to the tenets of the Declaration of Helsinki. All data discussed in this study were fully anonymized before they were accessed.

Patient records from January 1, 2012, to December 1, 2016, were reviewed for consecutive cases of TRD treated by standardized PPV, endolaser and silicone oil tamponade with or without DEx implant at the end of the surgery. In study sites where dexamethasone was available for intraoperative use, all patients that fulfilled the inclusion criteria were offered the co-adjuvant treatment of dexamethasone implant at the end of the surgery. PPV and DEX implant at the end of the surgery as the first-line therapy for TDR were offered and discussed extensively with patients. After informed consent was signed, the procedure was done by the surgeon. There was no case selection by the surgeon.

Study participants

The following were set as the study inclusion criteria: (1) age 18 years or older; (2) type 1 or 2 diabetes mellitus; (3) macula-off treatment-naïve TRD second to PDR causing visual loss; (4) treated by standardize PPV, endolaser and silicone oil tamponade with or without DEx implant at the end of the surgery within 12 months from diagnosis of TRD; (5) minimum of 12 months of follow-up after surgery.

Exclusion criteria were: (1) other concomitant ocular diseases that cause RD (i.e., rhegmatogenous retinal detachment, exudative retinal detachment, other causes for TRD); (2) any previous injection of DEX implant or; (3) abnormalities of the vitreoretinal interface, such as epiretinal membrane, vitreomacular traction without RD.

Consecutive patient records were reviewed for demographic data; HbA1c values; best-corrected visual acuity (BCVA) and intraocular pressure (IOP) before surgery and after 6, 12, and 24 months; time between TRD diagnosis and surgery (in days); lens status before surgery and after 6, 12, and 24 months; retina attachment rate after primary PPV; rate of re-detachment at 6, 12, and 24 months; use of IOP lowering treatment after 6, 12, and 24 months; surgery details (PPV or combined cataract extraction with PPV and with or without DEX Implant at the end of the surgery); intra- and postoperative complications; any additional treatment after surgery; cataract progression and surgery after 12 and 24 months; time of silicone oil removal.

Seven ETDRS fields fundus images from baseline 6, 12 and 24 months were graded independently by two experienced Retina specialist examiners (MI and DZ), masked to group assignment and date of images. As there is no standardized PVR classification for TRD, the authors have chosen to grade PVR severity according to the updated Retina Society Classification [17] and retina status (attached/detached).

Surgery procedure

23G or 25G PPV was performed using the CONSTELLATION Vision System (Alcon Laboratories, Inc. Fort Worth, Texas, USA). In all eyes, a central vitrectomy was performed. The posterior vitreous was separated from the retina by active aspiration with the vitrectomy probe, and any visible vitreous strands that were adherent to the retina were removed. Intravitreous triamcinolone (40 mg/mL, Triesence®, Alcon, Fort Worth, Texas, USA) was systematically used in all cases as a marker to facilitate visualization and removal of the adherent posterior cortical vitreous.

After that, tractional membranes were peeled off using bimanual technique under chandelier lights (Alcon, Fort Worth, Texas, USA) and with the help of serrated forceps in one hand and the vitrectomy probe in the other hand. Triamcinolone was fully washed out before instilling perfluorocarbon to re-attach the retina. Then, PRP was applied using endolaser. After checking that there was no retinal tear using indentation, a total air–fluid exchange was performed, followed by air-silicon exchange using 1000csts Silicone oil (SIL-1000, DORC, Dusseldorf, Germany). Prior to cannula removal, DEX implant (Ozurdex, Allergan, Inc., Irvine, CA) was injected in the treated group, 3.5 mm in phakic or 4.00 mm in pseudophakic patients, posterior to the limbus. At the end of surgery, the cannulae were removed, and sclerotomy sites were sutured with vicryl 7.0. Postoperatively, topical antibiotic and antiinflammatory therapy were administered four times daily over 1 month.

Outcome measures

Main outcome measures were (1) the rate of retinal reattachment after primary PPV, (2) the rate of re-detachment over 24 months, and (3) progression of PVR from baseline to the study endpoint of 24 months.

Statistical analysis

The demographics and clinical characteristics of our study cohort were evaluated using traditional descriptive methods. Fisher's exact test and Pearson Chi-square test were used to test for association between retina status (attached yes/no) and PVR severity at 6, 12, and 24 months and baseline variables: DEX implant (yes/no), PVR severity, new diagnosis of PDR, previous treatments for PDR or DME, and time from diagnosis to surgery. Changes in BCVA from baseline were tested by paired *T* test and ANOVA with repeated measures.

Statistical analysis was performed by the Statistical Laboratory School of Mathematics, Tel Aviv University, Tel Aviv, Israel. All statistics were computed with SPSS statistical package version 25.0.

Results

This study included 148 eyes from 148 patients, with mean age of 61.6 ± 15.8 years. Demographic and baseline characteristics are detailed in Table 1. Fifty-two patients (35.1%) received DEX implant at the end of the surgery, and 96 patients (64.9%) were not treated with DEX implant. PVR severity at baseline was well balanced between both groups ($p = 0.70$).

Table 1 Descriptive statistics—demographic data and baseline characteristics

	All ($n = 148$)	PPV+ DEX− group ($n = 52$)	PPV without DEX group ($n = 96$)	p value*
Age (years), mean ± SD	62.0 ± 15.7	65.0 ± 14.3	60.0 ± 16.1	0.047
Male gender, *n* (%)	85 (57.4)	27 (51.9)	58 (60.4)	0.47
New diagnosis of PDR	108 (73.0)	51 (100)	57 (59.4)	< 0.001
Previous treatment for PDR				< 0.001
None	119 (80.4)	52 (100)	67 (69.8)	
PRP	25 (16.9)	0	25 (26.0)	
Anti-VEGF	4 (2.7)	0	4 (4.2)	
Previous treatment for DME				
None	141 (95.3)	52 (100)	91 (92.7)	
Anti-VEGF	5 (3.4)	0 (0)	5 (5.2)	
DEX Implant	2 (1.4)	0 (0)	2 (2.1)	
HbA1c (%), mean ± SD	8.06	8.63	7.63	0.008
Time from diagnosis until surgery (weeks), mean ± SD	1.27 ± 0.4	1.19 ± 0.4	1.36 ± 0.5	0.180
Lens status at baseline, *n* (%)				0.104
Phakic	142 (95.9)	52 (100)	90 (93.7)	
Pseudophakic	6 (4.1)	0 (0)	6 (6.3)	
BCVA at baseline, logMAR, mean ± SD	0.97 ± 0.45	0.86 ± 0.12	1.06 ± 0.58	0.154
BCVA at 24 months, logMAR, mean ± SD	1.04 ± 0.56	0.57 ± 0.11	0.83 ± 0.48	< 0.001

BCVA best-corrected visual acuity, *DEX* dexamethasone, *PDR* proliferative diabetic retinopathy, *PPV* pars plana vitrectomy, *PRP* panretinal photocoagulation, *VEGF* vascular endothelial growth factor

*Difference between PPV+ DEX− group and PPV without DEX group tested by Fisher's exact test and Pearson Chi-square test

Table 2 Retina attachment rate over time

Retina attached	6 months	12 months	24 months
DEX− *n* (%)	85/96 (88.5)	74/85 (87.1)	57/71 (80.3)
DEX + *n* (%)	52/52 (100)	48/52 (92.3)	47/52 (90)
*p value	0.049	0.007	0.001

DEX dexamethasone, *PVR* proliferative vitreoretinopathy

DEX− patients that did not receive DEX implant at the end of the surgery; DEX+ patients that did receive DEX implant at the end of the surgery

*p value indicating the difference between DEX− and DEX+ group at the different time points by Fisher's exact test

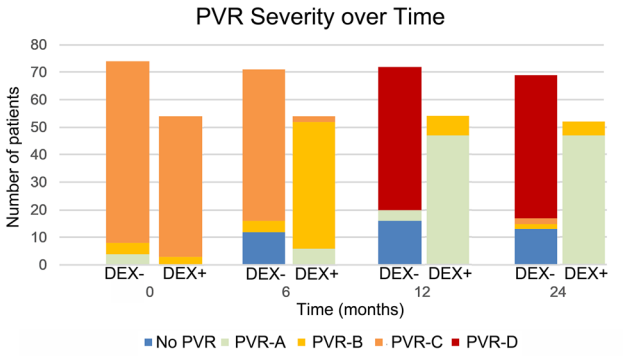

Fig. 1 Change in severity of proliferative vitreoretinopathy (PVR) over 24 months follow-up. DEX+: patients treated with dexamethasone (DEX) implant ($n=52$). DEX−: patients not treated with DEX implant at the end of the surgery ($n=74$). Portions of patients with different PVR severity grades are shown at baseline, at 6, 12, and 24 months after pars plana vitrectomy

Outcomes

Baseline PVR severity was not correlated with retinal status after the surgery ($p=0.136$, $p=0.316$, $p=0.424$ at 6, 12, and 24 months, respectively). Retinal re-detachment rates were significantly higher in the group of patients that did not receive DEX implant [11/96 (11.5%) vs. 0/52 (0%), $p=0.049$; 11/84 (12.9%) vs. 4/52 (7.7%), $p=0.007$; 14/71 (19.7%) vs. 5/52 (10%) $p<0.001$ at 6, 12, and 24 months, respectively, Table 2]. Patients in the DEX group presented significantly less progression in PVR severity compared with patients in the group without DEX implant: At 24 months, 13 eyes (18.6%) in the DEX− group did not have PVR, compared to no eyes in the DEX+ group. The frequency of eyes with PVR severity grade A was 0 versus 45 (86.5%), grade B 2 (2.8%) versus 7 (13.5%), grade C 2 (2.8%) versus no eyes, 52 (75.4%) versus no eyes ($p<0.001$; Fig. 1).

PVR severity correlated with retinal status at 12 and 24 months ($p=0.018$ and $p=0.027$, respectively). The difference in PVR severity between the two groups was statistically significant at 12 and 24 months ($p<0.001$ and $p<0.001$, respectively, Table 3). There was no statistically significant correlation between the performance of treatment for PDR or DME previous to the surgery and the retinal status over time ($p=0.572$, $p=0.768$, $p=0.280$ for PDR; $p=0.161$, $p=0.431$, $p=0.083$ for DME).

Interestingly, time between silicone oil removal and change in PVR severity did not correlate ($p=0.17$).

Central macular thickness (CMT) was measured only in cases when the retina was attached during follow-up and available at all time points in 63 cases in the DEX− group and in 52 cases in the DEX+ group. The CMT was significantly lower in the DEX implant group at 6, 12, and 24 months (282 ± 25 µm, 281 ± 25 µm, and 303 ± 41 µm, respectively) compared to the cohort that did not receive

Table 3 Severity of proliferative vitreoretinopathy over time

PVR severity	Baseline		6 months		12 months		24 months	
	DEX− $n=74$	DEX+ $n=52$	DEX− $n=71$	DEX+ $n=52$	DEX− $n=72$	DEX+ $n=52$	DEX− $n=69$	DEX+ $n=52$
0	0	0	12 (16.9)	0	16 (22.2)	0	13 (18.6)	0
A	4 (5.4)	0	0	4 (7.7)	4 (5.6)	45 (86.5)	0	45 (86.5)
B	4 (5.4)	3 (5.8)	4 (5.6)	46 (88.5)	0	7 (13.5)	2 (2.8)	7 (13.5)
C	66 (89.2)	49 (94.2)	55 (77.5)	2 (3.8)	0	0	2 (2.8)	0
D	0	0	0	0	52 (72.2)	0	52 (75.4)	0
*p value	0.748		<0.001		<0.001		<0.001	

Out of 96 patients in the DEX− group, PVR severity grading was available in 74, 71,72, and 69 cases at baseline, 6, 12, and 24 months, respectively

DEX dexamethasone; *PVR* proliferative vitreoretinopathy

DEX− patients that did not receive DEX implant at the end of the surgery; DEX+ patients that did receive DEX implant at the end of the surgery

*p value indicating the difference between DEX− and DEX+ group at the different time points tested by Fisher's exact test

DEX implant (441 ± 141 µm, 441 ± 147 µm, 427 ± 138 µm, respectively, $p = 0.002$).

The cohort that received DEX implant at the end of the surgery had never been treated for diabetic retinopathy, neither for PDR nor for DME (Table 1). In contrast, 29 patients (30.2%) that did not receive DEX implant had had previous treatment for PDR (PRP in 25 eyes, anti-VEGF injections in 4 eyes). Five patients were previously treated with anti-VEGF injections for DME, and 2 eyes with DEX implant.

In order to rule out bias confounding our results, we could confirm our results by performing a subanalysis on patients who did not receive any previous treatment for PDR or DME before PPV. Retinal re-detachment rates were significantly lower in the group that received DEX implant at the end of the surgery at 12 and 24 months ($p = 0.002$ and $p = 0.001$, respectively). Also, PVR severity was significantly lower in the DEX treated group at 12 and 24 months ($p < 0.001$ for both).

In order to rule out confounding factors, a statistical analysis was applied and there was no statistically significant difference neither in terms of baseline characteristics between patients with or without DEX implant ($p = 0.201$), nor for frequency of DEX implant use by the same surgeon ($p = 0.189$).

Baseline BCVA was well balanced between the groups ($p = 0.154$). After 24 months, BCVA was significantly better in the DEX treated group (0.57 ± 0.11 vs. 0.83 ± 0.48, $p < 0.001$).

All patients who underwent the procedure with DEX implant were followed up at 12 and 24 months, and none was excluded because of insufficient follow-up. In the DEX− group, 11 patients did not have data at 12 months follow-up. However, as all these 11 patients were followed up at 24 months, they were not excluded from the study.

The interobserver reliability for grading results were $\kappa = 0.83$, indicating good reliability.

Safety profile

Of 142 phakic patients at baseline, 17 patients (12.0%) underwent combined PPV with cataract extraction. Of the 125 patients left phakic, 6 patients (4.8%) underwent cataract extraction during 24 months follow-up. There was no significant difference in terms of cataract progression between both groups ($p = 0.17$).

None of the patients received any additional DME treatment including intravitreal therapy, macular and panretinal laser after PPV over the study period.

Six patients (4.1%) needed intraocular pressure (IOP) lowering medication over 24 months (4 in the DEX−, 2 in the DEX+ group). All were treated and well controlled with topical treatment only. No patient needed surgical intervention for glaucoma.

Six patients (4.1%) had intraoperative complications: One patient developed a paramacular hole, and five patients had an iatrogenic retinal tear which was treated by endolaser during the surgery.

Discussion

Our results indicate that sustained-release DEX implant at the end of surgery for diabetic TRD might have the potential to not only delay progression of PVR, but also improve retina attachment rates and anatomical outcomes over 24 months of follow-up. To our best knowledge, this is the first study to investigate the adjuvant use of intravitreal DEX implant in this setting.

Patients treated with intravitreal DEX implant at the end of the surgery had a statistically significant lower re-detachment rate and less PVR progression. In contrast, patients that did not receive adjuvant DEX implant had a 7.6%, 12.9%, and 19.7% rate of retinal re-detachment at 6, 12, and 24 months, respectively ($p = 0.049$, $p = 0.007$, and $p < 0.001$). Also, PVR progressed significantly more in the group that did not receive DEX implant ($p < 0.001$). Patients in the DEX group improved significantly more in vision 24 months after surgery compared with the DEX− group ($p < 0.001$). This can be explained by the higher rate of re-detachment in the DEX− group.

The most common complication of retinal re-attachment surgery with a preliminary silicone oil fill is a retinal re-detachment. In the literature, the re-detachment rates vary between less than 10% and over 70% [18, 19].

In complex retinal detachment with macula involvement, the re-detachment rates after 1 year are as high as 52 and 64% with 5000 and 1000 cts silicone oil tamponade, respectively [20]. In the previous studies, no significant difference was found in terms of re-detachment rates between 1000 and 5000 cts tamponade [20, 21]. In our study, re-detachment rates were lower than in those previous reports and confirm more recent studies with small-gauge PPV [4, 22].

The major limitation of our study includes its retrospective nature and the lack of randomized control group. We did not correlate HbA1c levels over the follow-up period with outcome measures. Poor systemic diabetic control may have an impact on ocular disease progression. Moreover, we did not investigate the predictive value of other baseline factors such as insulin dependency, renal function, or high blood pressure. The surgical procedures were performed with 23 or 25G PPV. However, the previous studies showed comparable results with both techniques [6]. Future prospective investigations of these baseline factors will be useful to assess the role of DEX implant in PVR modification.

Recent studies have been targeting pharmacologic inhibition of cellular proliferation and membrane contraction

preventing PVR with drugs such as daunorubicin [23], 5-fluorouracil and heparin [24], oral low-dose isotretinoin [25], microRNAs [26], and PI5P4Kα and -β [27]. Although promising, neither of these have really showed promising results in order to stop or prevent PVR progression.

In a prospective randomized trial, DEX implant did not improve the primary anatomic success rate in eyes with rhegmatogenous retinal detachment undergoing PPV with silicone oil for PVR [28]. The potential role of intravitreal steroids in PVR grade change in the setting of diabetes has a significant rationale. Inflammation plays a major role in the process of PVR formation [29, 30]. Previously, triamcinolone acetonide intravitreal injection has been shown to be effective and safe when given as an adjunct to PPV with silicone oil tamponade in treating proliferative vitreoretinopathy [31, 32]. Recently, a small sustained-release DEX implant was used in a novel PVR animal model [16]. Compared to eyes treated with balanced saline solution or free dexamethasone, eyes with the sustained-release DEX had significantly less PVR formation [16]. We hypothesize that because of this pharmacological action, patients treated with DEX implant at the end of the surgery in the current study experienced less PVR progression and enjoyed better attachment rates over 24 months follow-up.

PVR pathophysiology is not well known. Finding the paths of PVR formation and progression might lead to develop an effective preventive adjunctive therapy. Our results remark the role of inflammation in PVR development and progression. The use of DEX implant at the end of the surgery in our study in patients with diabetic TRD shows an improvement in anatomical results and a reduced need for re-operation. This should be considered as an option in the customized treatment of TRD. A randomized control trial is needed in order to realize the current role of DEX implant in the treatment of diabetic TRD.

Compliance with ethical standards

Conflict of interest None.

Ethical approval The study was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee), nr. 0745-18-TLV.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Affiliations

Matias Iglicki[1] · Dinah Zur[2,3] · Adrian Fung[4,5,6] · Pierre-Henry Gabrielle[7] · Marco Lupidi[8] · Rodrigo Santos[1] · Catharina Busch[9] · Matus Rehak[9] · Zafer Cebeci[10] · Martin Charles[11] · Dua Masarwa[2,3] · Shulamit Schwarz[2,3] · Adiel Barak[2,3] · Anat Loewenstein[2,3,12] · for the International Retina Group (IRG)

1 Private Retina Service, University of Buenos Aires, 525 Aguirre St., 3rd Floor, Apt. A, 1414 Buenos Aires, Argentina

2 Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

3 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

4 Department of Ophthalmology, Westmead Hospital, Sydney, NSW, Australia

5 Faculty of Medicine and Health Sciences, Macquarie University Hospital, Sydney, NSW, Australia

6 Save Sight Institute, Sydney Eye Hospital, University of Sydney, Sydney, NSW, Australia

7 Ophthalmology Department, DIJON University Hospital, Burgundy, France

8 Eye Clinic, Department of Biomedical and Clinical Science, "Luigi Sacco", Luigi Sacco Hospital, University of Milan, Milan, Italy

9 Department of Ophthalmology, University of Leipzig, Leipzig, Germany

10 Ophthalmology Department Istanbul, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

11 Dr. Charles Ophthalmology Center, Buenos Aires, Argentina

12 Incumbent, Sydney A. Fox Chair in Ophthalmology, Tel Aviv University, Tel Aviv, Israel