INTRAVITREAL INJECTION OF RANIBIZUMAB DURING CATARACT SURGERY IN PATIENTS WITH DIABETIC MACULAR EDEMA

PAULO I. RAUEN, MD,* JEFFERSON A. S. RIBEIRO, MD,* FELIPE P. P. ALMEIDA, MD,* INGRID U. SCOTT, MD, MPH,† ANDRÉ MESSIAS, MD, PHD,* RODRIGO JORGE, MD, PHD*

Purpose: To investigate macular thickness and visual acuity changes after 1 intravitreal injection of 0.5-mg ranibizumab during phacoemulsification cataract surgery in eyes with diabetic macular edema refractory to laser treatment.

Methods: Eleven eyes of 11 patients with diabetic macular edema refractory to modified Early Treatment Diabetic Retinopathy Study laser therapy received intravitreal during phacoemulsification cataract surgery. Comprehensive ophthalmic evaluation was performed preoperatively and at 1, 4, 8 ± 1, and 12 ± 2 weeks postoperatively. Main outcome measures included central subfield thickness and best-corrected Early Treatment Diabetic Retinopathy Study visual acuity.

Results: Eleven patients completed the 12-week study visit. Mean central subfield thickness (±SEM) was 399.82 ± 29.50 μm at baseline and did not change significantly at any postoperative study visit ($P > 0.05$). Mean (±SEM) best-corrected Early Treatment Diabetic Retinopathy Study visual acuity was 0.95 ± 0.13 logarithm of the minimum angle of resolution (20/200) at baseline and was significantly improved at Weeks 1 (0.38 ± 0.13), 4 (0.38 ± 0.11), 8 (0.35 ± 0.08), and 12 (0.46 ± 0.12) after treatment ($P < 0.05$).

Conclusion: In this case series of patients with diabetic macular edema refractory to laser therapy, intravitreal ranibizumab administered during cataract surgery was associated with no significant change in central subfield thickness postoperatively. Significant improvement in best-corrected Early Treatment Diabetic Retinopathy Study visual acuity was observed after treatment, likely because of cataract removal.

RETINA 32:1799–1803, 2012

Macular edema is a leading cause of decreased visual acuity in patients with diabetic retinopathy.[1,2] Moreover, patients with diabetic retinopathy have a higher risk than non–diabetic patients for macular edema onset or worsening after cataract surgery.[3–5] This susceptibility is related to the association between perioperative inflammation and breakdown of the blood–retinal barrier, especially in patients with previous microvascular changes secondary to diabetic retinopathy.[6–8] To decrease the risk of macular edema worsening after cataract surgery, preexisting diabetic macular edema (DME) is often treated before cataract surgery.[9]

After publication of the Early Treatment Diabetic Retinopathy Study (ETDRS), laser photocoagulation became the standard of care treatment for clinically significant DME.[10] More recently, the Diabetic Retinopathy Clinical Research Network reported improved visual acuity outcomes in patients with center-involved DME treated with intravitreal ranibizumab with prompt or deferred laser compared to patients treated with prompt laser alone.[11]

In the view of these results, we conducted an open-label prospective study to evaluate the morphologic and visual acuity outcomes associated with a single intravitreal injection of ranibizumab during cataract surgery for the management of clinically significant DME.

From the *Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; and †Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, PA.

The authors declare no conflict of interest.

Reprint requests: Rodrigo Jorge, MD, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Avenida Bandeirantes, 3900, Ribeirão Preto, São Paulo, 14049-900, Brazil; e-mail: rjorge@fmrp.usp.br

Methods

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board, and all participants gave written informed consent before entering into the study. All patients with at least 1 eye with cataract and clinically significant DME refractory to modified ETDRS laser therapy who were evaluated at the Retina Section of the Department of Ophthalmology, School of Medicine of Ribeirão Preto, and scheduled to undergo phacoemulsification cataract surgery in at least 1 eye with refractory DME between December 2009 and September 2010, were invited to participate in the study.

Throughout the study, measurement of best-corrected Early Treatment Diabetic Retinopathy Study visual acuity and central subfield thickness (CSFT) quantified using third-generation optical coherence tomography (OCT) was performed before other study procedures by a masked certified examiner. Ophthalmic evaluation, fundus photography, and fluorescein angiography were performed by one retina specialist (P.I.R.), and study data were collected, interpreted, and analyzed by other investigators (J.A.S.R., F.P.P.A., A.M., I.U.S., and R.J.).

Patient Eligibility and Baseline Evaluation

Patients with refractory diffuse DME and cataract in at least 1 eye based on clinical examination, fluorescein angiography, and OCT were identified. If both eyes were eligible for treatment, then the eye with worse visual acuity was included. Inclusion criteria include 1) refractory DME (defined herein as the presence of "clinically significant macular edema"—as per ETDRS criteria—despite at least 1 session of macular laser photocoagulation performed at least 3 months previously) and diffuse fluorescein leakage involving the foveal center and most of the macular area on fluorescein angiography; 2) BCVA between 0.3 logarithm of the minimum angle of resolution (logMAR) (20/40) and 1.6 logMAR (20/800); 3) central subfield thickness greater than 300 μm on OCT; and 4) presence of cataract with Grade 2 or higher nuclear opalescence[12] and sufficient to impede adequate grid laser retreatment.

Exclusion criteria include 1) aphakia or pseudophakia; 2) history of glaucoma or ocular hypertension (defined as an intraocular pressure [IOP] higher than 22 mmHg); 3) an ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., retinal vein occlusion, uveitis, or other ocular inflammatory disease, neovascular glaucoma); 4) focal/grid or panretinal photocoagulation in the study eye within 6 months before study entry; 5) systemic corticosteroid therapy; 6) uncontrolled hypertension (according to guidelines of the seventh report of the joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure); and 7) any condition that may interfere with follow-up or documentation.

Each patient received a detailed ophthalmologic examination including measurement of BCVA according to a standardized refraction protocol using a retroilluminated Lighthouse for the Blind distance visual acuity test chart (using modified ETDRS charts 1, 2, and R), applanation tonometry, undilated and dilated slit-lamp biomicroscopic examination, indirect fundus examination, as well as blue and infrared reflectance, autofluorescence pictures and fluorescein angiography.

Cataract grading was performed according to the Lens Opacity Classification System III,[12] which consists of slit-lamp evaluation of the lens opacity giving scores, in a decimal scale, for nuclear color, nuclear opalescence, cortical cataract, and posterior subcapsular cataract. For intraocular lens power measurement, keratometry was done with a Topcon autorefractor (KR8800; Topcon, Tokyo, Japan), and axial length was measured using Alcon OcuScan RXP A-Scan Biometry (Alcon, Fortworth, TX).

Third-generation OCT evaluation (Stratus Tomographer, Model 3000; Carl Zeiss Ophthalmic Systems, Inc., Humphrey Division, Dublin, CA) was performed in all patients and consisted of 6 linear 6.00-mm scans orientated at intervals of 30° and centered on the foveal region. To optimize accuracy of OCT data, automatic delineation of the inner and outer boundaries of the neurosensory retina generated by OCT built-in software was verified for each of the six scans using the "retinal thickness (single eye)" analyses protocol.[13] Central subfield thickness values were automatically calculated as the average thickness of a central macular region 1,000 μm in diameter centered on the patient's foveola by built-in OCT3 software using "retinal thickness/volume" analysis protocol.

Good reproducibility of these measurements using this method and its feasibility to monitor and detect DME[14] and macular edema after cataract surgery[15] have been described elsewhere.

Treatment

Each patient received 1 intravitreal injection of 0.5 mg/0.05 cc of ranibizumab at the conclusion of phacoemulsification cataract surgery, which was performed within 1 week of baseline, using a technique described

elsewhere.[16] The phacoemulsification procedure included the following steps: 3.0-mm clear corneal incision, "stop and chop" phacoemulsification technique (Legacy; Alcon), type 7B foldable intraocular lens (Alcon) insertion, and 1 NYLON 10.0 stitch to close the clear corneal incision.

All treatments were performed by the same physician (R.J.) under sterile conditions. In addition, 0.3% ciprofloxacin 4 times a day for 2 weeks and 0.1% methylprednisolone for 4 weeks were prescribed post injection.

Rescue Treatment

Focal/grid laser could be performed at any study visit after surgery if CSFT was higher than the baseline value and if additional spots were possible to be placed at the discretion of the treating physician.

Follow-up Examinations and Outcome Measures

Patients were scheduled for follow-up examinations at Weeks 1, 4, 8 (±1), and 12 (±2) after injection. At these visits, the patient underwent complete ophthalmic examination using the same procedures as at baseline, with the exception of fluorescein angiography, which was performed only at the final (Week 12) follow-up visit.

Main outcome measures include 1) change from baseline in OCT-measured CSFT and 2) change from baseline in ETDRS BCVA.

Statistical Analysis

Comparisons were performed using multiple analysis of variance for repeated measures. Data are shown as absolute values, and intraindividual differences to baseline of BCVA (logMAR) and intraocular pressure (IOP) at the 4 postinjection study visits (e.g., BCVA – BCVA at baseline) were calculated to show the effect of treatment on visual acuity during follow-up, whereas the percentage change between CSFT values at the 4 periods after treatment and at baseline, calculated as ([follow-up CSFT – baseline CSFT]/baseline CSFT) × 100%, was used to show OCT data. Statistical significance was considered if P was <0.05.

Results

Between November 2009 and September 2010, 11 patients (8 women) completed the 12-week study period (Table 1). Six eyes had proliferative diabetic retinopathy treated with panretinal photocoagulation at least 6 months before initial evaluation. Baseline characteristics and lens opacity scores are summarized in Table 1.

Outcome Measures

Central subfield thickness. Mean ± SE baseline CSFT was 399.82 ± 29.50 μm (range, 289–567 μm) and did not change significantly at 1 week (397.82 ± 30.03 μm), 4 weeks (429.18 ± 32.64 μm), 6 weeks (412.82 ± 34.45 μm), and 12 weeks (405.60 ± 38.78 μm) after surgery (Table 2). In some eyes, CSFT increased and, in these cases, focal laser was performed. Macular laser was performed in 1 patient at Week 1, in 6 at Week 4, and in 3 at Week 12. Laser was not performed in only 1 patient during the 12 weeks of follow-up. A reduction in CSFT greater than 11% was observed in only 1 eye at Weeks 1, 4 and 8, and in 2 eyes at Week 12.

Best-corrected Early Treatment Diabetic Retinopathy Study Visual Acuity. Mean ± SE BCVA was 0.95 ± 0.13 logMAR (20/200) at baseline and significantly improved at Weeks 1, 4, 8, and 12 after treatment ($P > 0.05$). The maximal BCVA

Table 1. Patient Demographic Data, Baseline Characteristics, and Cataract Grading According to the Lens Opacity Classification System III

Number of patients	n = 11
Age (mean ± SD), years	68.8 ± 13
Gender	8 Women
Duration of diabetes (mean ± SD), years	18.0 ± 9.2
Treatment regimen (n)	5 no insulin/6 insulin
Diabetic retinopathy classification	5 NPDR/6 PDR treated with PRP
Macular edema duration (mean ± SD), months	12.0 ± 8.0
Number of laser (grid) sections (mean ± SD)	1.2 ± 0.4
Severity of cataract (LOCS) (mean ± SD)	
Cortical cataract	2.64 ± 1.03
Nuclear color	2.82 ± 0.98
Nuclear opalescence	2.82 ± 0.98
Posterior subcaspular cataract	2 ± 1
Sum score	10.27 ± 1.35

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

Table 2. Mean ± SE of BCVA, CSFT (Absolute Values and Percentage of Baseline), and IOP at Baseline and Follow-up Visits

	Baseline	1 Week	4 Weeks	8 Weeks	12 Weeks
BCVA (logMAR)	0.9 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
P (MANOVA)		0.0257*	0.0135	0.0041*	0.0065*
CSFT (μm)	399.8 ± 29.5	397.8 ± 30	429.2 ± 32.6	412.8 ± 34.5	405.6 ± 38.8
CSFT baseline (%)		−0.1 ± 3.8	8.4 ± 5.8	4.4 ± 6.2	4.2 ± 8
P (MANOVA)		0.8580	0.0851	0.5336	0.7882
IOP (mmHg)	13.9 ± 0.9	13.1 ± 0.8	13.5 ± 0.7	13.5 ± 0.7	12.9 ± 0.9
P (MANOVA)		0.0629	0.6572	0.3673	0.2781

MANOVA, multiple analysis of variance.

improvement was observed at Weeks 1 and 4: 0.57 ± 0.08 logMAR (almost 6 ETDRS chart lines) (Table 2). Further, an improvement in BCVA greater than two ETDRS lines was observed in 8 eyes at Weeks 1, 4 and 8, and in 6 eyes at Week 12.

Intraocular pressure. Mean IOP at baseline was 13.91 ± 0.88 mmHg, and there was no statistically significant change in IOP at any of the postinjection study visits (Table 2).

No other adverse events, such as postoperative increased anterior chamber cells or flare or cases of endophthalmitis, were observed.

Discussion

Recent studies have investigated the use of anti-vascular endothelial growth factor (anti-VEGF) agents during cataract surgery for the treatment of DME. Cheema et al[17] reported lower rates of diabetic retinopathy progression when 1.25 mg of intravitreal bevacizumab was used at the end of the cataract surgery in patients with DME. Takamura et al[18] reported a significant decrease in CSFT from 355 μm at baseline to 327 μm at Month 1 and 330 μm at Month 3 after cataract surgery and perioperative injection of bevacizumab in patients with DME. Similarly, Chen et al[19] demonstrated, in a retrospective study, significant improvement in mean CSFT from 466 μm at baseline to 333 μm, 313 μm, and 333 μm at 4, 8, and 12 weeks, respectively, after cataract surgery with intravitreal injection of bevacizumab in eyes with DME. Akinci et al[20] reported improvement in mean CSFT from 387 μm at baseline to 292 μm and 275 μm at 1 month and 3 months, respectively, after cataract surgery and intravitreal injection of bevacizumab for DME. Despite these promising results, the present study did not show any significant reduction in CSFT after intravitreal ranibizumab during cataract surgery in patients with refractory DME during a 12-week follow-up period. Besides the fact that our study used a different anti-VEGF agent, our study included only patients with refractory DME, whereas the study reported by Akinci et al included only treatment-naive patients and the other studies[17–19] permitted inclusion of patients with no previous treatment; this may explain, at least in part, the differing results between the previous studies using bevacizumab and the present study in which ranibizumab was used. The 2 times higher half-life of bevacizumab in comparison to ranibizumab may contribute to a longer duration of bevacizumab, which may be important in cases of high VEGF upregulation (e.g. diabetic patients who never received anti-VEGF treatment and who experience the pro-inflammatory effects of cataract surgery).[21]

Best-corrected Early Treatment Diabetic Retinopathy Study visual acuity improved after cataract surgery and intravitreal injection of ranibizumab at all postoperative study visits. Similar results have been reported in other studies using bevacizumab.[17–20] However, in contrast to previous studies, BCVA improvement in the current study did not parallel macular thickness reduction and was probably related primarily to cataract removal.

For ethical reasons, and because there was no rationale for postponing the standard of care treatment, if additional laser spots were possible and the surgeon could obtain clear visualization of the fovea, rescue therapy with focal/grid laser was performed as soon as 1 week after cataract surgery if patients had a CSFT higher than baseline. Similarly, Cheema et al[17] also performed focal/grid laser within 1 week after cataract surgery. Despite the possibility of laser treatment as soon as 1 week after surgery, only 1 patient in the present study received laser during the first month of the study. This means that 10 patients had just the anti-VEGF treatment for DME during the first postoperative month, and CSFT results at Week 4 represent almost purely the anti-VEGF effect of ranibizumab in this cataract surgery–DME scenario. After Week 4, however, 7 patients (63%) had undergone focal/grid laser, which may well have influenced CSFT results thereafter.

No significant change in IOP was observed in patients included in the present study, which is consistent with other studies using anti-VEGF for DME.[11,22,23] In addition, no ocular adverse events related to intravitreal ranibizumab, such as retinal detachment or endophthalmitis, were observed during the 12-week study period.

Limitations of the present study include the small number of patients included, limited follow-up duration, and lack of a control group. Despite these limitations, to the best of our knowledge and based on a PubMed search, this study is the first to describe the perioperative use of ranibizumab in patients with DME undergoing cataract surgery and suggests that this anti-VEGF agent does not contribute to CSFT reduction postoperatively. Further investigation of a larger number of patients with longer follow-up is necessary to confirm these preliminary findings. Maybe, in these future larger studies, a significant reduction in CSFT will be observed, consistent with other studies of anti-VEGF therapy in patients with DME.[11,18,23]

Key words: cataract surgery, diabetic macular edema, diabetic retinopathy, ranibizumab, VEGF.

References

1. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1–9.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–1474.
3. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007;114:881–889.
4. Chung J, Kim MY, Kim HS, et al. Effect of cataract surgery on the progression of diabetic retinopathy. J Cataract Refract Surg 2002;28:626–630.
5. Gupta A, Gupta V. Diabetic maculopathy and cataract surgery. Ophthalmol Clin North Am 2001;14:625–637.
6. Miyake K, Masuda K, Shirato S, et al. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: a multicentered prospective trial. Jpn J Ophthalmol 2000;44:58–67.
7. Matsunaga N, Ozeki H, Hirabayashi Y, et al. Histopathologic evaluation of the internal limiting membrane surgically excised from eyes with diabetic maculopathy. Retina 2005; 25:311–316.
8. Cunha-Vaz J, Bernardes R. Nonproliferative retinopathy in diabetes type 2. Initial stages and characterization of phenotypes. Prog Retin Eye Res 2005;24:355–377.
9. Menchini U, Cappelli S, Virgili G. Cataract surgery and diabetic retinopathy. Semin Ophthalmol 2003;18:103–108.
10. EDTRS. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1985;103:1796–1806.
11. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–1077.
12. Chylack LT Jr, Wolfe JK, Singer DM, et al. The lens opacities classification system III. The longitudinal study of cataract study group. Arch Ophthalmol 1993;111:831–836.
13. Costa RA, Calucci D, Skaf M, et al. Optical coherence tomography 3: automatic delineation of the outer neural retinal boundary and its influence on retinal thickness measurements. Invest Ophthalmol Vis Sci 2004;45:2399–2406.
14. Goebel W, Franke R. Retinal thickness in diabetic retinopathy: comparison of optical coherence tomography, the retinal thickness analyzer, and fundus photography. Retina 2006;26:49–57.
15. Kim SJ, Belair ML, Bressler NM, et al. A method of reporting macular edema after cataract surgery using optical coherence tomography. Retina 2008;28:870–876.
16. Ribeiro JAS, Messias A, Scott IU, Jorge R. Alternative technique for reducing compound waste during intravitreal injections. Arq Bras Oftalmol 2009;72:641–644.
17. Cheema RA, Al-Mubarak MM, Amin YM, Cheema MA. Role of combined cataract surgery and intravitreal bevacizumab injection in preventing progression of diabetic retinopathy: prospective randomized study. J Cataract Refract Surg 2009;35:18–25.
18. Takamura Y, Kubo E, Akagi Y. Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. Ophthalmology 2009;116:1151–1157.
19. Chen CH, Liu YC, Wu PC. The combination of intravitreal bevacizumab and phacoemulsification surgery in patients with cataract and coexisting diabetic macular edema. J Ocul Pharmacol Ther 2009;25:83–89.
20. Akinci A, Batman C, Ozkilic E, Altinsoy A. Phacoemulsification with intravitreal bevacizumab injection in diabetic patients with macular edema and cataract. Retina 2009;29:1432–1435.
21. Funatsu H, Yamashita H. Pathophysiology of diabetic retinopathy. Drug News Perspect 2002;15:633–639.
22. Paccola L, Costa RA, Folgosa MS, et al. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol 2008;92:76–80.
23. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 2010;117:1078–1086.