Intravitreal Bevacizumab in Diabetic Retinopathy. Recommendations from the Pan-American Collaborative Retina Study Group (PACORES): The 2016 Knobloch Lecture

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Abstract: The advent of intravitreal anti–vascular endothelial growth factor (anti-VEGF) medications has revolutionized the treatment of diabetic eye diseases. Herein, we report the outcomes of clinical studies carried out by the Pan-American Collaborative Retina Study Group (PACORES), with a specific focus on the efficacy of intravitreal bevacizumab in the management of diabetic macular edema and proliferative diabetic retinopathy. We will also discuss the use of intravitreal bevacizumab as a preoperative, adjuvant therapy before vitrectomy for proliferative diabetic retinopathy.

Key Words: intravitreal injections, bevacizumab, proliferative diabetic retinopathy, diabetic macular edema, tractional retinal detachment

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Diabetic retinopathy is a major cause of blindness in the world, especially in developing countries.[1] Vision loss due to diabetes mellitus is primarily caused by 2 mechanisms: diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). Diabetic macular edema within 1 disk diameter of the fovea, leading to central vision loss, is present in about 9% of the diabetic population.[2] Proliferative diabetic retinopathy is present in about 1.5% of adults with diabetes,[3] and PDR can lead to vision loss by various mechanisms, such as retinal neovascularization, vitreous hemorrhage, neovascular glaucoma, and tractional retinal detachment (TRD).

It has been shown that vision loss secondary to proliferative changes is more common in patients with type 1 diabetes, whereas vision loss secondary to DME is more common in patients with type 2 diabetes.[4]

Vascular endothelial growth factor (VEGF) is a major driving force in the development of PDR and DME,[5–9] and in recent years, intravitreal injection of anti-VEGF medications, such as bevacizumab (Avastin, Genentech Inc, San Francisco, CA), ranibizumab (Lucentis, Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany), has emerged as an important treatment modality, either as primary or adjuvant therapy for DME and PDR.

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The purpose of this review article is to summarize results of clinical studies carried out by the Pan-American Collaborative Retina Study Group (PACORES), with a specific focus on the treatment of DME and PDR with intravitreal bevacizumab. The PACORES is a collaborative research consortium, currently involving 19 centers in 13 countries across Latin America and Spain.

INTRAVITREAL BEVACIZUMAB FOR THE TREATMENT OF DME

In 2016, we published our 5-year results on the treatment of DME with intravitreal bevacizumab.[10] It was a retrospective study, involving 12 centers across 10 countries. In total, 201 consecutive patients (296 eyes) with center-involving DME and vision loss were included. All patients met the following criteria: (1) no other possible causes of decreased vision; (2) no prior treatment for DME such as macular laser photocoagulation, intravitreal triamcinolone, micropulse laser, or pars plana vitrectomy; (3) no evidence of vitreomacular traction on optical coherence tomography (OCT); (4) no evidence of macular ischemia on fluorescein angiography (FA); (5) at least 5 years of follow-up; and (6) no evidence of intraocular inflammation, uncontrolled intraocular pressure, or cataract surgery within the previous 6 months. Patients were treated monthly with 1.25 mg of intravitreal bevacizumab until the edema was stabilized, then they returned to clinic and were treated on an as-needed regimen at the discretion of the treating physician, based on best corrected visual acuity (BCVA) and OCT. The main outcome measures were changes in BCVA and central macular thickness (CMT) at the 60-month follow-up visit.

The mean number of intravitreal bevacizumab injections per eye was 8.4 ± 7.1. The mean baseline BCVA was Snellen 20/100 and the mean final BCVA at month 60 was Snellen 20/100, which was not statistically different ($P = 0.387$) despite statistically significant vision gain during the first 3 years. Subgroup analysis showed that at month 60 BCVA improved by 2 or more lines, remained stable, and decreased by 2 or more lines in 29%, 43.6%, and 27.4% of eyes, respectively. The mean baseline CMT was 403.5 μm. Significant decrease in CMT was seen by month 6 and the reduction in CMT was generally maintained throughout the remainder of the study period. At month 60, the mean CMT was 313.7 μm, which was significantly lower than that of baseline ($P \leq 0.0001$).

Discussion

To our knowledge, this study provides one of the longest-term follow-up datasets on the efficacy of anti-VEGF treatments in DME. Specifically, we believe that no other studies have reported the 5-year results of intravitreal bevacizumab for

center-involving DME. The major weaknesses of this study include its retrospective nature and likely undertreatment of the involved patients. In our study, the average number of injections was 8.4 over 5 years in each eye, with an average of 3.3 injections given during the first year, which was significantly lower than that reported in other randomized, prospective studies. For example, in the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I Study, the median number of intravitreal injections over 5 years was 13 and 17 in the ranibizumab plus prompt laser and ranibizumab plus deferred laser groups, respectively.[11] In the DRCR.net Protocol T Study, the median number of injections over 2 years was 15, 16, and 15 in the aflibercept, bevacizumab, and ranibizumab groups, respectively.[12] In the BOLT Study, the bevacizumab arm received a median number of 13 injections over 2 years.[13] In the phase 3 trials RISE and RIDE, the treatment arm received monthly ranibizumab injections.[14]

It is interesting to note that in our study, though the mean CMT remained fairly stable between year 1 and 5, the mean BCVA steadily decreased from year 1 onwards, such that by year 4 the initial vision gain had ceased to be statistically significant. This suggests that undertreatment of DME and chronic fluid in the macula can lead to relatively limited improvements in vision despite anatomic response, an observation that is corroborated by the outcomes in the sham crossover group in the RISE and RIDE trials.[14] Despite the design limitation of our study, we believe that our results provide valuable real-world data that reflects real-world practice patterns. The treatment regimen employed in clinical trials is difficult to replicate in most countries, especially in the long-term and in developing countries due to various factors, such as access to care and costs. Our data can be used as a reasonably reliable framework with which to counsel patients. For example, a typical patient with center-involving DME in a developing country will have a roughly 70% chance of stabilized or improved vision with intravitreal bevacizumab treatment over a time course of 5 years.

INTRAVITREAL BEVACIZUMAB FOR THE TREATMENT OF PDR

In 2017, we published our 2-year results on the treatment of PDR with intravitreal bevacizumab.[15] It was a retrospective, multicenter study involving 5 institutions. In total, 81 consecutive patients (97 eyes) with PDR were included. Major exclusion criteria were any previous anti-VEGF treatment and scatter photocoagulation, focal/grid laser photocoagulation, or previous intravitreal triamcinolone injection within the past 6 months. Patients were treated with an initial intravitreal injection of 1.25 mg of bevacizumab. Patients were examined at 1 week, 2 weeks, and 1 month after the first injection and monthly thereafter. An assessment for retreatment with bevacizumab, retreatment with laser, or initiation of panretinal photocoagulation (PRP) occurred at each visit, and treatments were performed at the discretion of the treating physician. Reinjections of bevacizumab were performed if retinal neovascularization had not totally resolved on ophthalmic examination or FA, or if there had been a recurrence of neovascular activity. The main outcome measures were change in retinal neovascularization, defined as the change in the area of leakage from retinal neovascularization in the late phase of FA, and changes in BCVA with assessment of CMT measured by OCT.

The mean number of intravitreal bevacizumab injections per eye was 4 ± 2.5, and the mean interval between injections was 3 ± 7 months. The mean baseline BCVA was Snellen 20/125, whereas the mean final BCVA at month 24 was Snellen 20/60. The improvement was statistically significant ($P < 0.0005$). Subgroup analysis showed that at month 24 BCVA improved by 2 or more lines, remained stable, and decreased by 2 or more lines in 43.3%, 50.5%, and 6.2% of eyes, respectively. The mean baseline CMT was 359.9 μm, whereas the mean final CMT at month 24 was 311.7 μm. The decrease was statistically significant ($P < 0.0001$).

At month 24, 59.7%, 17.7%, and 22.6% of eyes showed complete, partial, and no regression of retinal neovascularization, respectively. Subgroup analysis showed that at month 24, within the group of patients who had prior PRP (61.9% of total patients), 73.3%, 15.1%, and 11.6% of eyes showed complete, partial, and no regression of retinal neovascularization, respectively. Within the group of patients who had no prior PRP (38.1% of total patients), 37.9%, 21.6%, and 40.5% of eyes showed complete, partial, and no regression of retinal neovascularization, respectively. In terms of treatment received over the study period, within the group of patients who had prior PRP, 68.3%, 16.6%, and 15% of eyes received bevacizumab alone, bevacizumab plus immediate laser treatment, and bevacizumab plus deferred laser treatment, respectively. Within the group of patients who had no prior PRP, 32.4%, 48.6%, and 18.9% of eyes received bevacizumab alone, bevacizumab plus immediate laser treatment, and bevacizumab plus deferred laser treatment, respectively.

Discussion

Our data suggests that patients who have had prior PRP tend to have better overall control of retinal neovascularization over a 2-year period. This is supported by the higher rate of complete regression, 73%, versus 37.9% seen in the no prior PRP group. This observation is interesting, as a high percentage of patients (48.6%) within the no prior PRP group actually received immediate PRP in conjunction with initiation of intravitreal bevacizumab treatment. Yet, despite this, this particular group fared worse over a span of 2 years. One could argue that the rate of complete regression in both groups might be different had the patients been treated with intravitreal bevacizumab more frequently. Although it is true that our patients might be undertreated receiving a mean of 4 injections over 2 years, as compared with a median of 10 ranibizumab injections over 2 years in the ranibizumab without baseline DME group and a median of 14 ranibizumab injections over 2 years in the ranibizumab with baseline DME group in the DRCR.net Protocol S Study,[16] our study was not designed to answer the question of whether bevacizumab or PRP was a superior modality. Instead, the main purpose of this study was to reflect real-world experience in using intravitreal bevacizumab in the treatment of PDR and to explore the role of intravitreal bevacizumab as an adjuvant to PRP for future studies.

Our recommendation is that in a patient with prior PRP, intravitreal bevacizumab alone provides a reasonable chance of control of retinal neovascularization (close to 70%) even at a modest treatment frequency. However, in a patient without prior PRP, unless regular follow-up visits and timely repeated intravitreal anti-VEGF treatments can be ensured, immediate PRP in conjunction with anti-VEGF injections is more likely to provide long-term control of retinal neovascularization. Otherwise, more than 50% of patients will end up needing PRP or vitrectomy.

PREOPERATIVE INTRAVITREAL BEVACIZUMAB BEFORE PARS PLANA VITRECTOMY FOR MANAGEMENT OF PDR

We published a retrospective study in 2008[17] on the development or progression of TRD after preoperative intravitreal bevacizumab as an adjuvant to vitrectomy for management of PDR. Out of 211 eyes, 11 eyes (5.2%) developed or had progression of TRD. Seven out of these 11 eyes had localized TRDs before intravitreal bevacizumab. Within this group, the development or progression of TRD led to a statistically significant decline in vision from a mean BCVA of 20/125 to a mean BCVA of hand motions ($P < 0.0001$). The time from injection to TRD development or progression was a mean of 13 days (range, 3 to 31 days).

We published a follow-up study with a larger sample size in 2011,[18] involving 698 eyes. Out of the 698 eyes, 25 eyes (3.5%) developed or had progression of TRD after a preoperative intravitreal bevacizumab injection. A total of 626 of the 698 injections were 1.25 mg of bevacizumab. Nineteen out of these 626 eyes (3%) developed or had progression of TRD. Seventy-two of the 698 injections were 2.5 mg of bevacizumab. Six out of these 72 eyes (8.3%) developed or had progression of TRD. We further performed multivariate and bivariate analysis to identify risk factors for development or progression of TRD. These risk factors were found to be statistically significant: more than 15 years from diagnosis of diabetes mellitus ($P = 0.009$), more than 13 days from injection to vitrectomy ($P = 0.0001$), and the use of a higher dose (2.5 mg) of bevacizumab ($P = 0.022$).

Discussion

We believe that preoperative intravitreal bevacizumab is beneficial before vitrectomy for PDR, as it tends to decrease intraoperative bleeding, facilitate intraoperative fibroproliferative membrane dissection, and decrease postoperative bleeding. From our experience, intravitreal bevacizumab before vitrectomy is safe, with a low incidence (3.5%) of TRD development or progression. The chance of TRD development or progression can be further decreased with careful planning and patient selection. If intravitreal bevacizumab were to be given, it should be given no more than 2 weeks before surgery, given the mean number of days from injection to TRD development/progression was 13 days. Ideally, it should be given within 4 days of surgery, given that in our series TRD development/progression happened in more than 80% of cases 5 days or more after injection. In addition, we caution against using a higher dose (2.5 mg) of intravitreal bevacizumab, as it may lead to a higher chance of TRD development/progression.

CONCLUSIONS

The advent of intravitreal anti-VEGF medications has revolutionized the treatment of diabetic eye diseases. Whereas ranibizumab and aflibercept are specifically formulated for intraocular uses, off-label use of bevacizumab remains popular and widespread in the world, especially in low-income and middle-income countries, given its lower cost, perceived effectiveness, and comparable safety profile.[19,20] Based on our experience, we recognize intravitreal bevacizumab to be an important tool in our armamentarium for treating the complications of diabetic retinopathy. For center-involving DME, our real-world data suggests that there is a roughly 70% chance of stabilized or improved vision with intravitreal bevacizumab treatments over a time course of 5 years. For PDR, intravitreal bevacizumab is a good adjuvant therapy for patients who have already received prior PRP treatment, and unless frequent follow-up visits and treatments can be ensured, treatment-naive patients will likely have better control of retinal neovascularization with prompt PRP in conjunction with initiation of intravitreal treatments. Lastly, preoperative intravitreal bevacizumab before vitrectomy is safe, with a low incidence (3.5%) of TRD development or progression. This risk can further be reduced by performing surgery within 4 days of injection and by avoiding the usage of a higher dose (2.5 mg) of bevacizumab. In terms of future research directions, our group recently carried out a prospective study on the utility of preoperative intravitreal bevacizumab before diabetic TRD repair, and currently the data is being analyzed.

REFERENCES

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature.* 2001;414:782–787.
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. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA.* 2010;304:649–656.
4. Richter B, Kohner E. Medical interventions for diabetic retinopathy. In: Wormald R, Smeeth L, Henshaw K, eds. *Evidence-Based Ophthalmology*. London: BMJ Books; 2004:331–340.
5. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol.* 1994;118:445–450.
6. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.* 1994;331:1480–1487.
7. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. *Arch Ophthalmol.* 1994;112:1476–1482.
8. Pe'er J, Shweiki D, Itin A, et al. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. *Lab Invest.* 1995;72:638–645.
9. Funatsu H, Yamashita H, Sakata K, et al. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. *Ophthalmology.* 2005;112:806–816.
10. Arevalo JF, Lasave AF, Wu L, et al. Intravitreal bevacizumab for diabetic macular oedema: 5-year results of the Pan-American Collaborative Retina Study group. *Br J Ophthalmol.* 2016;100:1605–1610.
11. Bressler SB, Glassman AR, Almukhtar T, et al. Five-year outcomes of ranibizumab with prompt or deferred laser versus laser or triamcinolone plus deferred ranibizumab for diabetic macular edema. *Am J Ophthalmol.* 2016;164:57–68.
12. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology.* 2016; 123:1351–1359.
13. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol.* 2012;130:972–979.
14. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of

ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology.* 2013;120:2013–2022.

15. Arevalo JF, Lasave AF, Wu L, et al. Intravitreal bevacizumab for proliferative diabetic retinopathy: results from the Pan-American Collaborative Retina Study Group (PACORES) at 24 months of follow-up. *Retina.* 2017;37:334–343.
16. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA.* 2015;314:2137–2146.
17. Arevalo JF, Maia M, Flynn HW Jr, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol.* 2008;92:213–216.
18. Arevalo JF, Sanchez JG, Saldarriaga L, et al. Retinal detachment after bevacizumab. *Ophthalmology.* 2011;118:2304, e2303–e2307.
19. Anothaisintawee T, Leelahavarong P, Ratanapakorn T, et al. The use of comparative effectiveness research to inform policy decisions on the inclusion of bevacizumab for the treatment of macular diseases in Thailand's pharmaceutical benefit package. *Clinicoecon Outcomes Res.* 2012;4:361–374.
20. Hutton D, Newman-Casey PA, Tavag M, et al. Switching to less expensive blindness drug could save medicare part B $18 billion over a ten-year period. *Health Aff (Millwood).* 2014;33:931–939.

APPENDIX

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