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Decision Making in Proliferative Diabetic Retinopathy Treatment

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Abstract

Purpose of Review—The goal of this paper is to provide a comprehensive review of the recent advances in the management options for proliferative diabetic retinopathy.

Recent Findings—For many years cases of proliferative diabetic retinopathy (PDR) have been managed by pan retinal photocoagulation (PRP). The advent of anti-vascular endothelial growth factor (anti-VEGF) agents has changed the future of PDR management and has provided an alternative to PRP.

Summary—Management of PDR requires the identification of high risk characteristics for PDR and the decision regarding the most appropriate treatment modality. The risk to benefit ratio for each treatment modality must be considered in determining the appropriate choice between surgical intervention (PRP) versus medical intervention with anti-VEGF.

Keywords

Proliferative diabetic retinopathy; vascular endothelial growth factor; anti-VEGF; pan retinal photocoagulation; intravitreal injection; ranibizumab; bevacizumab; aflibercept

Introduction

Diabetes mellitus (DM) along with the resulting obesity epidemic has become a major global health concern. The biochemical and physiologic changes caused by exposure to hyperglycemia lead to significant endothelial damage causing a selective loss of pericytes which leads to microaneurysm formation, basement membrane thickening, capillary bed closure, dilatation of adjacent capillaries, shunt formation, and permeability alterations. In

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Conflict of Interest

Mary B. Kansora and Raquel Goldhardt declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

essence, the findings seen in non-proliferative diabetic retinopathy (NPDR) and diabetic macular edema (DME). The natural progression to proliferative diabetic retinopathy (PDR) with ensuing arteriolar closure, areas of vascular non-perfusion as well neovascularization and more hemorrhage contribute to the increase in morbidity and mortality, as well as causing a large economic impact around the world.

In 2010, one-third of the world's population with diabetes had signs of diabetic retinopathy. As well, one-third of those with diabetic retinopathy had vision threatening diabetic retinopathy defined as severe NPDR, PDR or the presence of DME. PDR is the most common vision threatening entity in patients with type 1 diabetes.¹

The Diabetic Retinopathy Study (DRS) reported that without treatment, 50% of patients with high-risk PDR would experience vision loss within 5 years.² There are several hematologic and biochemical factors that correlate and favor the appearance of retinal ischemia and worsening of the diabetic retinopathy. These include increased platelet adhesiveness and erythrocyte aggregation, abnormal serum lipid and growth hormone levels, defective fibrinolysis, abnormal serum and whole blood viscosity, local and systemic inflammation and upregulation of vascular endothelial growth factor (VEGF).³⁻⁶ The pro-angiogenic cytokine VEGF is considered the primary factor involved in neovascularization in PDR. Increased levels of VEGF have been reported in the vitreous humour in eyes with anterior hyaloidal fibrovascular proliferation and PDR.⁷ VEGF activates two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. These receptors regulate physiological and pathological angiogenesis. VEGFR-2 is expressed mostly on vascular endothelial cells. Activation of VEGFR-2 stimulates endothelial cell proliferation, migration, and survival, as well as angiogenesis and microvascular permeability as in PDR.⁸

Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

Prevention is the key word in the management of diabetic retinopathy. The development of drugs that prevent or delay the appearance of diabetic retinopathy is a fundamental goal in current research. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) found that intensive glycemic control was associated with decreased risk of diabetic retinopathy and decreased risk of progression of existing retinopathy.^{9,10}

The objective in treatment of PDR is to control ischemia and reduce VEGF levels with resultant regression of neovascularization. Photocoagulation of the peripheral retina has been accepted and advocated for treatment of PDR for many years.¹¹⁻¹⁸

The Diabetic Retinopathy Study (DRS) determined that the indication for panretinal photocoagulation (PRP) in diabetes was the presence of high risk PDR. High risk PDR was defined by the DRS as mild neovascularization of the disc with vitreous hemorrhage, moderate to severe neovascularization of the disc with or without vitreous hemorrhage, or moderate neovascularization elsewhere with vitreous hemorrhage.² (Figure 1). From the DRS and the Early Treatment Diabetic Retinopathy Study (ETDRS), full PRP consists of at least 1200 laser spots of 500 microns in diameter using either argon green or blue-green

laser applied to the peripheral retina.^{2,19} Pattern scan laser (Pascal) PRP ablation has also been shown to have favorable PDR regression rates and minimal burn expansion over 18 months.²⁰

The success of PRP for PDR can be attributed to many possible factors. First, the destruction of ischemic retina can reduce VEGF levels. In addition, photocoagulation can effectively debride sick or fatigued RPE cells, thereby improving the blood-outer retinal barrier. Destruction of photoreceptors can lead to improved inner retinal oxygenation and compensatory vasoconstriction with decreased blood flow and decreased vascular leakage. As well, an increase in oxygen tension is seen in the remainder of the eye due to decreased consumption in the treated retina and increased diffusion from the choroid at the photocoagulation scar.^{21,22} Finally, photocoagulation can stimulate vascular endothelial proliferation resulting in restoration of the inner blood-retinal barrier.^{23,24}

Despite the success of PRP for PDR and the fact that it has been the standard of care for many years, functional deficits and anatomic complications can be seen. PRP results in permanent visual field loss, decreased night vision, decreased color vision, decreased contrast sensitivity, and pupil dilation.^{2,19} In addition, PRP may lead to worsening of DME.^{25–27} Anatomic complications include development of sub retinal neovascularization, sub retinal/sub macular fibrosis, serous macular detachment, ciliochoroidal detachment and enlargement of the photocoagulation scars.^{28–36}

Medical Treatment Options

- Corticosteroids

Corticosteroids have antipermeability, antiangiogenic and antifibrotic effects that stabilize the blood retinal barrier, downregulate inflammatory factors and increase absorption of fluid.³⁷ Corticosteroid has been useful in the treatment of cystoid macular edema.³⁸ In contrast, the use of intravitreal corticosteroid for PDR was first reported in 1979 by Machemer and was not successful.³⁹

- Anti-Vascular Endothelial Growth Factor

Anti-VEGFs sparked a dramatic shift in the treatment paradigm for diabetic retinopathy in 2006. Their usefulness was demonstrated for PDR in eyes with persistent new vessels despite adequate PRP, eyes with recurrent vitreous hemorrhage after PRP without traction or pars plana vitrectomy, preoperatively to decrease vessel size before pars plana vitrectomy as well as for eyes with neovascularization of the iris.^{40,41}

In November 2015, the DRCR.net published Protocol S: Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy.⁴² Protocol S was a multicenter randomized clinical trial at 55 sites in the United States. The study population included 305 adults with Type 1 or Type 2 diabetes mellitus and proliferative diabetic retinopathy. All study eyes were without previous PRP and were with or without DME. Patients were randomly assigned to PRP alone allowing for intravitreal injection of ranibizumab as needed for DME or intravitreal ranibizumab alone allowing for PRP for treatment failure. At the two-year follow-up, the mean change in visual acuity from baseline

(the primary outcome for Protocol S) was determined to be +2.8 in the ranibizumab group and +0.2 in the PRP group which met the non-inferiority criterion. Secondary outcomes were determined at the two-year follow-up as well. The mean change in visual acuity score (the area under the curve) was +4.5 for the ranibizumab group and -0.3 for the PRP group. The difference between these groups was greater at one year than at two years. In addition, the percentage of eyes with a 15-letter improvement, as well as the percentage of eyes with a 10-letter worsening or more, were similar between groups. At two years, the binocular outcomes were better in the ranibizumab group than the PRP group. Finally, eyes without active/regressed neovascularization of the disc or elsewhere on fundus photograph were similar (35% ranibizumab group vs 30% PRP group). Due to the fact that intravitreal ranibizumab met the non-inferiority outcome for visual acuity at the two-year mark, intravitreal ranibizumab has been considered no worse than PRP for treatment of PDR. Interestingly, the ranibizumab group had better visual acuity at 2 years while the PRP group had a higher rate of peripheral visual field loss, development of diabetic macular edema, and need for vitrectomy. The visual acuity between the ranibizumab group and the PRP group at two years was not statistically significant.

In July 2018, five-year data for Protocol S was published.⁴³ Visual acuity (the primary outcome) continued to be good without statistically significant differences identified between the ranibizumab group versus the PRP group. At this time, several additional questions were asked regarding the two groups. No major modifications to treatment were made since the original 2-year trial. Only 240 eyes (61%) completed the 5-year visit. With regard to whether the absence of PRP in the ranibizumab group increased the development of neovascular glaucoma (NVG) or neovascularization of the iris (NVI), only 3% of eyes in the ranibizumab group and 4% in the PRP group progressed to NVG. For NVI, only 3% eyes in the ranibizumab group and 1% in the PRP group progressed. Table 1.

The rate of retinal detachment was increased in the PRP group (15%) as compared to the ranibizumab group (6%); however, most retinal detachments did not involve the center of the macula, were not vision threatening and did not require surgery. Table 1. Visual field loss at two years was higher in the PRP group; however, at five years, visual field loss was unexpectedly found to have progressed in both groups. Vitreous hemorrhage was seen in both groups with near equal frequency (48% in the ranibizumab group and 46% in the PRP group) Table 1.; however, 41% of eyes in the PRP group underwent vitrectomy whereas only 22% of eyes in the ranibizumab group had surgery.

For ranibizumab, the data revealed important information regarding the frequency of injection and systemic safety over the five-year period. In year one, eyes in the ranibizumab group received a mean of 7 injections for neovascularization or DME. In years two through five, eyes in the ranibizumab group received an average of three injections, an overall reduction in the number of injections per year. Despite the reduction in treatment, the mean visual acuity change from baseline remained constant through year five. Table 2. The number of injections beyond two years to maintain a quiescent PDR is unknown which means a possibility of lifelong monitoring to a much greater extent than those treated with PRP.

Regarding systemic safety, interim four-year data analysis suggested a possible increase in Antiplatelet Trialists' Collaboration events; however, the rates of such events were within the range of variability seen in previous studies.⁴⁴ Also, five-year data did not show a statistically significant increase in events between treatment groups.

The recently published PROTEUS study compared the use of intravitreal ranibizumab combined with PRP to PRP monotherapy.⁴⁵ Ranibizumab with PRP was found to be more effective than PRP monotherapy with a total reduction in neovascularization seen in 92.7% of eyes in the combined group and 70.5% in the PRP monotherapy group at month 12.

Despite aggressive anti-VEGF treatment in more recent randomized clinical trials, proliferative retinopathy still progresses. The analysis of RIDE/RISE showed that up to 5% of patients progressed to PDR over 24 month period⁴⁶, and in Protocol I, 31% progressed despite of a significant number of injections.⁴⁷

Rapid development or progression of a tractional retinal detachment (TRD) can occur after anti-VEGF injection in patient with severe PDR due to worsening of the fibrosis and traction, but is rare.⁴⁸

Cost analysis of the 2-year Protocol S trial data expressed as incremental cost- effectiveness ratios of ranibizumab versus PRP were \$55,568 per quality-adjusted life-year (QALY) for patients with DME and \$662,978 per QALY for patients without DME. Therefore, if ranibizumab is given for PDR and DME it appears to be more cost-effective than giving ranibizumab for DME in a patient who will also receive PRP for PDR.⁴⁹

Finally, the cost and cost utility of early pars plana vitrectomy (PPV) compared with PRP and intravitreal ranibizumab for PDR without diabetic macular edema was evaluated. Early PPV has cost utility similar to management with PRP. Moreover, early PPV has more favorable cost utility as compared to ranibizumab.⁵⁰

Conclusion and real-world application

Cost, compliance and practicality are mandatory consideration when individualizing and selecting the treatment for your patient. From Protocol S, clinical practice may be influenced by the fact that PRP has the potential to be completed in one visit and has no risk of endophthalmitis or systemic anti-VEGF exposure. However, in the presence of DME and planned use of anti-VEGF, PRP may be postponed or unnecessary if compliance is not an issue. The problem is that patients with PDR treated only with anti-VEGF require lifelong monitoring to a much greater degree than patients treated with PRP only. The reality of loss to follow-up in the diabetic population was highlighted by the 5-year analysis where the completion rate was only 61% in both groups. Finally, Protocol S suggested that intravitreal ranibizumab may be superior to PRP for mean visual outcome over two years with less visual field loss and fewer eyes developing DME or needing pars plana vitrectomy. However, at five years, there was no statistical difference between the two groups for mean visual acuity and visual field loss was found in both groups without any meaningful difference. What it did not reveal was whether the sustained therapeutic benefit of anti-VEGF alone is as durable as Protocol I demonstrated that it was for DME with fewer

injections in the later years. Another issue is that ranibizumab is not FDA-approved for PDR treatment and physicians might not be able to be reimbursed favoring the use of off label bevacizumab. Anti-VEGF therapy is certainly useful for certain patients and there is no question that initial anti-VEGF is key when centered DME or vitreous hemorrhage with significant media opacity is present.

While we wait for additional data on longer follow-up, ophthalmologists should be vigilant and engage patients as vigilant partners in this marathon. Ultimate visual outcomes might be worse in patients who are initially lost to follow-up and received anti-VEGF only.

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References

1. Lee R, Wong T, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis.* 2015 9 30; 2:17
2. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology.* 1981; 88(7):583–600. [PubMed: 7196564]
3. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med.* 2012; 366(13):1227–1239 [PubMed: 22455417]
4. Ashton N Studies of the retinal capillaries in relation to diabetic and other retinopathies. *Br J Ophthalmol* 1963; 47:521–38. [PubMed: 14189723]
5. Cogan DG, Kuwabara T. Capillary shunts in the pathogenesis of diabetic retinopathy. *Diabetes* 1963; 12:293–300. [PubMed: 14081839]
6. Cogan DG, Toussaint D, Kuwabara T. Retinal vascular patterns. IV. Diabetic retinopathy. *Arch Ophthalmol* 1961; 66:366–78. [PubMed: 13694291]
7. Kobayashi et al. Vitreous levels of vascular endothelial growth factor in eyes with anterior hyaloidal fibrovascular proliferation. *Clinical Ophthalmology* 2010;4 1043–1046. [PubMed: 20922040]
8. Gupta N, Mansoor S, Sharma A et al. Diabetic Retinopathy and VEGF. *Open Ophthalmol J.* 2013; 7:4–10. [PubMed: 23459241]
9. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993; 329(14):977–986. [PubMed: 8366922]
10. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J.* 1998; 317(7160):703–713. [PubMed: 9732337]
11. Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976; 81:383–96. [PubMed: 944535]
12. Hamilton AM. Management of diabetic retinopathy. *Trans Ophthalmol Soc UK* 1977; 97:494–6. [PubMed: 281779]
13. Hercules BL, Gayed II, Lucas SB, et al. Peripheral retinal ablation in the treatment of proliferative diabetic retinopathy: a three-year interim report of a randomised, controlled study using the argon laser. *Br J Ophthalmol* 1977; 61:555–63. [PubMed: 336079]
14. Meyers SM. Macular edema after scatter laser photocoagulation for proliferative diabetic retinopathy. *Am J Ophthalmol* 1980; 90:210–6. [PubMed: 6158867]

15. Meyer-Schwickerath GRE, Schott K. Diabetic retinopathy and photocoagulation. *Am J Ophthalmol* 1968; 66:597–603. [PubMed: 5729579]
16. Okun E, Cibis PA. The role of photocoagulation in the therapy of proliferative diabetic retinopathy. *Arch Ophthalmol* 1966; 75:337–52. [PubMed: 5903819]
17. Patz A, Schatz H, Ryan SJ. Argon laser photocoagulation for treatment of advanced diabetic retinopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1972; 76:984–9. [PubMed: 4677398]
18. Plumb AP, Swan AV, Chignell AH, et al. A comparative trial of xenon arc and argon laser photocoagulation in the treatment of proliferative diabetic retinopathy. *Br J Ophthalmol* 1982; 66:213–8. [PubMed: 6175340]
19. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology*. 1991;98(5 suppl):766–785 [PubMed: 2062512]
20. Mugit M, Marcellino G, Henson D et al. Pascal panretinal laser and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study Report 4. *Eye (Lond)*. 2011 11; 25(11):1447–1456. [PubMed: 21818132]
21. Mendrinos E, Mangioris G, Papadopoulou DN, et al. Retinal vessel analyzer measurements of the effect of panretinal photocoagulation on the retinal arteriolar diameter in diabetic retinopathy. *Retina*. 2010 4;30(4):555–61. [PubMed: 20010452]
22. Funatsu H1, Hori S, Yamashita H, Kitano S. [Effective mechanisms of laser photocoagulation for neovascularization in diabetic retinopathy]. *Nippon Ganka Gakkai Zasshi*. 1996 5;100(5):339–49. [PubMed: 8651051]
23. Marshall J, Clover G, Rothery S. Some new findings on retinal irradiation by krypton and argon lasers. *Doc Ophthalmol Proc Ser* 1984; 36: 21–37
24. Adamis AP, Miller JW, Bernal M-T. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994; 118:445–50. [PubMed: 7943121]
25. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: EARLY Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol*. 1985;103(12):1796–1806. [PubMed: 2866759]
26. Brucker AJ, Qin H, Antoszyk AN, et al.; Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol*. 2009;127(2):132–140. [PubMed: 19204228]
27. Googe J, Brucker AJ, Bressler NM, et al.; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina*. 2011;31(6):1009–1027. [PubMed: 21394052]
28. Berger AR, Boniuk I. Bilateral subretinal neovascularization after focal argon laser photocoagulation for diabetic macular edema. *Am J Ophthalmol* 1989; 108:88–90.
29. Lewis H, Schachat AP, Haimann MH. Choroidal neovascularization after laser photocoagulation for diabetic macular edema. *Ophthalmology* 1990; 97:503–11. [PubMed: 1691477]
30. Varley MP, Frank E, Purnell EW. Subretinal neovascularization after focal argon laser for diabetic macular edema. *Ophthalmology* 1988; 95:567–73. [PubMed: 2459645]
31. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. *Am J Ophthalmol* 1992; 113:652–6. [PubMed: 1376019]
32. Han DP, Mieler WF, Burton TC. Submacular fibrosis after photocoagulation for diabetic macular edema. *Am J Ophthalmol* 1992; 113:513–21. [PubMed: 1575225]
33. Rutledge BK, Wallow IHL, Poulsen GL. Sub-pigment epithelial membranes after photocoagulation for diabetic macular edema. *Arch Ophthalmol* 1993; 111:608–13. [PubMed: 8489438]
34. Wallow IHL, Bindley CD. Focal photocoagulation of diabetic macular edema; a clinicopathologic case report. *Retina* 1988; 8:261–9. [PubMed: 3231918]
35. Elliott A, Flanagan D. Macular detachment following laser treatment for proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 1990; 228:438–41. [PubMed: 2227487]

36. Schatz H, Madeira D, McDonald HR, et al. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. *Arch Ophthalmol* 1991;109: 1549–51. [PubMed: 1755735]
37. Silva PS, Sun JK, Aiello LP. Role of steroids in the management of diabetic macular edema and proliferative diabetic retinopathy. *Semin Ophthalmol* 2009; 24:93–9. [PubMed: 19373693]
38. Zacks DN, Johnson MW. Combined intravitreal injection of triamcinolone acetonide and panretinal photocoagulation for concomitant diabetic macular edema and proliferative diabetic retinopathy. *Retina* 2005; 25:135–40. [PubMed: 15689801]
39. Machemer R, Sugita G, Tano Y. Treatment of intraocular proliferations with intravitreal steroids. *Trans Am Ophthalmol Soc* 1979; 77:171–80. [PubMed: 545825]
40. Erdol H, Turk A, Akyol N, et al. The results of intravitreal bevacizumab injections for persistent neovascularizations in proliferative diabetic retinopathy after photocoagulation therapy. *Retina* 2010; 30:570–7. [PubMed: 20224478]
41. Yeh PT, Yang CM, Lin YC, et al. Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy. *Retina* 2009; 29:768–74. [PubMed: 19516117]
- 42•. Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314(20):2137–2146. [PubMed: 26565927] This study provides an in-depth comparison of the use of intravitreal ranibizumab vs PRP for the treatment of proliferative diabetic retinopathy.
- 43•. Gross JG, Glassman AR, Liu D, et al. Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2018 7 24. doi:10.1001/jamaophthalmol.2018.3255. [Epub ahead of print]. This follow up study allowed the reader to observe how the primary outcome seen at 2 years was upheld, as well as allowed the observation of additional outcome measures regarding the use of intravitreal ranibizumab vs PRP for PDR.
44. Gross JG, Glassman AR, Klein MJ, et al. Interim Safety Data Comparing Ranibizumab with Panretinal Photocoagulation Among Participants With Proliferative Diabetic Retinopathy. *JAMA Ophthalmol*. 2017 6 1;135(6):672–673. [PubMed: 28492921]
45. Figueira J, Fletcher E, Massin P, et al. Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study). *Ophthalmology* 2018 5; 125(5):691–700 [PubMed: 29395119]
46. DongNguyen Q, Brown D, Marcus D et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; 119:789–801. [PubMed: 22330964]
47. Bressler S, Odia I, Glassman A et al. Changes in diabetic retinopathy severity when treating diabetic macular edema with ranibizumab: DRCR.net Protocol I 5-year report. *Retina*. 2018 10;38(10):1896–1904. [PubMed: 30234859]
48. 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 2;92(2):213–6. [PubMed: 17965108]
- 49•. Hutton DW, Stein JD, Bressler NM et al. Cost-effectiveness of Intravitreal Ranibizumab Compared With Panretinal Photocoagulation for Proliferative Diabetic Retinopathy. *JAMA Ophthalmol*. 2017 6; 135(6): 576–584. [PubMed: 28492920] This study outlines the cost analysis of the 2-year Protocol S data in comparing the use of ranibizumab vs PRP for DME.
- 50•. Lin J, Chang JS, Yannuzzi NA, Smiddy WE. Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy. *Ophthalmology*. 2018 9;125(9):1393–1400. [PubMed: 29606379] This study suggests that the cost utility of PPV vs PRP is similar and that PPV has a more favorable cost utility as compared to ranibizumab.

Figure 1. High risk proliferative diabetic retinopathy with neovascularization elsewhere (arrow) with vitreous hemorrhage. *Photo Credit: Luis Bernhard, CRA*

Table 1.

Diabetic Retinopathy Markers of Progression

	Ranibizumab Group Number (%)	PRP Group Number (%)
Progression to NVG	6 (3)	9 (4)
Progression to NVI	5 (3)	3 (1)
Rate of Retinal Detachment	12 (6)	30 (15)
Vitreous Hemorrhage	91 (48)	93 (46)

NVG = neovascular glaucoma

NVI = neovascularization of the iris

Table 2.

Injection Frequency of Ranibizumab for PDR

	2-year Follow -Up Ranibizumab	5-year Follow-Up Ranibizumab
Baseline Mean Letter Score (Snellen Equivalent)	75.0 (20/32)	77.0(20/32)
Mean Change in Letter Score from baseline	+2.8	+3.1
Median Number of Injections at 1-year	7.1	
Median Number of Injections at 2-years	3.3	
Median Number of Injections 3-years		3.0
Median Number of Injections at 4-years		2.9
Median Number of Injections at 5-years		2.9