LONG-TERM EFFICACY OF PANRETINAL LASER PHOTOCOAGULATION AND INTRAVITREAL ANTI-VEGF THERAPY IN PROLIFERATIVE DIABETIC RETINOPATHY: A COMPARATIVE EVIDENCE REVIEW

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ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) threatens vision through pathological retinal neovascularization, vitreous hemorrhage and tractional retinal detachment. Panretinal photocoagulation (PRP) provides a durable treatment effect, whereas intravitreal anti–vascular endothelial growth factor (anti-VEGF) drugs rapidly suppress neovascular activity. Objective: To assess the comparative long-term effectiveness of PRP and anti-VEGF therapy and examine the clinical rationale for combined treatment. Methods: A focused narrative review of randomized trials, extended follow-up analyses, meta-analyses and recent ophthalmology guidance available through November 2026. Results: In DRCR Retina Network Protocol S, visual outcomes after five years were generally favorable in eyes completing follow-up with either ranibizumab or PRP, although the anti-VEGF arm required more visits. The CLARITY trial supported aflibercept efficacy through one year. In the 12-month PROTEUS trial, neovascular regression occurred more frequently with ranibizumab plus PRP than with PRP alone (92.7% vs 70.5%); however, definitive long-term superiority of combination therapy remains unproven. Conclusions: PRP and anti-VEGF are complementary, evidence-

supported options. Individualized treatment depends on neovascular activity, macular edema, complications, ability to return for visits and cost. No new patient-level data are reported.

Keywords: proliferative diabetic retinopathy; panretinal photocoagulation; anti-VEGF; ranibizumab; aflibercept; combination therapy; neovascularization; long-term outcomes; treatment adherence.

INTRODUCTION

Diabetic retinopathy is a microvascular complication of diabetes that progresses from early retinal vascular abnormalities to ischemia-driven formation of abnormal new vessels. The proliferative stage can cause recurrent vitreous hemorrhage, fibrovascular traction and retinal detachment. Protecting vision in PDR therefore requires both suppression of active neovascularization and prevention of late complications, together with systemic management of hyperglycemia, blood pressure and dyslipidemia [7].

For decades, panretinal photocoagulation (PRP) has been a standard treatment for high-risk PDR. By reducing ischemic retinal demand, PRP produces a persistent biological effect and lowers the likelihood of severe vision loss. Its limitations include possible reduction of peripheral visual field sensitivity, impaired night vision and aggravation of macular edema. Intravitreal anti-VEGF treatment, in contrast, can produce rapid regression of new vessels and is particularly relevant when diabetic macular edema (DME) coexists, but control is dependent on injections and scheduled reviews [1, 2, 7].

Combination therapy is attractive because it may unite the faster action of anti-VEGF with the more sustained protection of PRP. However, data supporting the two individual approaches over five years must not be confused with direct evidence for five-year outcomes of the combined regimen. Long-term efficacy also includes safety, disease recurrence, visual function and feasibility outside clinical trials [2, 4–8].

AIM OF THE ARTICLE

To analyze functional and anatomical outcomes, complication rates, follow-up demands and practical limitations of PRP, intravitreal anti-VEGF monotherapy and their combined use for PDR, with particular attention to how short-term neovascular regression relates to long-term clinical effectiveness.

MATERIALS AND METHODS

This article is a targeted narrative evidence review rather than an original clinical experiment or a registered systematic review. The source base comprises peer-reviewed randomized clinical trials (Protocol S, CLARITY and PROTEUS), the five-year Protocol S report, recent systematic reviews/meta-analyses, observational follow-up research and the American Diabetes Association 2026 Standards of Care [1–10]. Clinical evidence published up to November 2026 was considered.

The comparison addressed: (1) best-corrected visual acuity (BCVA, ETDRS letters); (2) regression or recurrence of neovascularization; (3) DME and ocular complication outcomes; (4) injection/visit burden and long-term adherence; and (5) certainty and duration of evidence. Because study inclusion criteria, treatment algorithms and follow-up intervals differ, trial-specific numerical results are interpreted within their own designs and not pooled into a new statistical estimate.

RESULTS AND DISCUSSION

1. Panretinal photocoagulation: durable control and treatment trade-offs

PRP reduces the risk of severe vision loss in high-risk PDR and remains strongly recommended for appropriate cases in contemporary clinical guidance [7]. Its clinical advantage is that treatment is not dependent on indefinitely repeated intravitreal injections. Nevertheless, adequate initial coverage, possible supplementary laser and continuing surveillance may still be necessary. PRP does not eliminate all risk of recurrent neovascularization or vitreous hemorrhage, and treatment planning should take peripheral visual field effects and pre-existing DME into account [1, 2].

The 2015 Protocol S randomized trial included 394 study eyes from 305 participants, comparing PRP with a structured ranibizumab treatment protocol; both groups could receive ranibizumab for DME. At two years, mean BCVA improvements were +0.2 letters with PRP and +2.8 letters with ranibizumab, meeting the prespecified noninferiority criterion for ranibizumab. Because over half of PRP eyes received ranibizumab for coexisting or incident DME, the trial should not be interpreted as a pure laser-only versus injection-only comparison in every eye [1].

2. Five-year evidence: Protocol S and comparative durability

The five-year Protocol S analysis found that most eyes completing follow-up maintained good visual acuity with either strategy, and serious PDR complications were uncommon. Among eyes without DME at baseline, the cumulative probability of vision-impairing DME by five years was approximately 22% in the ranibizumab group and 38% in the PRP group [2]. These outcomes indicate a macular benefit with anti-VEGF under an organized follow-up regimen, rather than a universal advantage for every patient.

Treatment burden differed substantially. Among unilateral study-eye participants completing five-year follow-up, the median number of visits was 43 in the ranibizumab group versus 21 in the PRP group. The mean cumulative number of ranibizumab injections among completers was 19.2 over five years. Importantly, the five-year visit was completed for only about 61% of enrolled study eyes, limiting certainty about outcomes for those who did not return. Differences in adherence and access to care can therefore change which treatment is safer and more sustainable in routine practice [2].

CLARITY, an independent 52-week randomized trial, also supports anti-VEGF as an effective alternative for selected PDR patients. Aflibercept achieved a mean adjusted BCVA benefit of 3.9 ETDRS letters compared with standard PRP in the modified intention-to-treat analysis, while satisfying the trial’s noninferiority criterion [3]. Its one-year design does not establish five-year durability, nor does it test a fixed PRP-plus-aflibercept combination.

3. Combination treatment: neovascular regression and shorter-term outcomes

In the PROTEUS randomized study of high-risk PDR, adjunctive ranibizumab plus PRP was compared with PRP alone. At 12 months, total neovascularization reduction was observed in 92.7% of combination-treated participants versus 70.5% of PRP-only participants (P = 0.009). Complete regression rates were numerically higher with combination therapy (43.9% vs 25.0%) but did not reach conventional statistical significance (P = 0.066). Mean BCVA at month 12 also did not differ significantly. These results favor combination therapy for the studied regression endpoint but do not demonstrate definitively superior long-term vision outcomes [4].

A 2025 systematic review and meta-analysis incorporating 19 studies (1,788 eyes) found that combination treatment was associated with a mean 4.06-letter BCVA advantage over PRP alone at 12 months (95% confidence interval 0.26–7.86). However, heterogeneity in disease severity, injection protocols and outcome reporting limits extrapolation across settings; its authors called for longer-term randomized comparisons [5]. A separate 2023 meta-analysis of eight studies (375 eyes) suggested reductions in central macular thickness and need for vitrectomy with combination treatment but did not identify a clear difference in BCVA change [6].

Additional retrospective evidence from 2025 found less new-onset DME over 12 months with combined anti-VEGF/PRP than with PRP alone, while vitreous hemorrhage incidence was similar in the two groups. The nonrandomized design and modest sample restrict causal interpretation [9]. Taken together, current studies support a reasonable role for adjunctive injections in selected eyes with marked neovascular activity, associated DME or the need for rapid vessel regression; they do not justify routinely labeling combination therapy as superior in all PDR cases.

4. Evidence comparison and clinical interpretation

Table 1. Key evidence informing PDR treatment selection

Study / follow-up	Treatment comparison	Reported finding	Interpretation
Protocol S, 2 years [1]	Ranibizumab vs PRP (DME treatment permitted)	BCVA change +2.8 vs +0.2 letters	Anti-VEGF met visual-acuity noninferiority criterion
Protocol S, 5 years [2]	Ranibizumab vs PRP	Vision-impairing DME risk 22% vs 38% in eyes without baseline DME	Both viable among completers; higher anti-VEGF visit burden
CLARITY, 52 weeks [3]	Aflibercept vs PRP	Adjusted BCVA difference +3.9 letters	Supports aflibercept at 1 year, not long-term combination
PROTEUS, 12 months [4]	Ranibizumab + PRP vs PRP	Any total NV reduction 92.7% vs 70.5%	Combination improved this short-term NV endpoint
Meta-analysis, 2025 [5]	Anti-VEGF / combination vs PRP	Combination BCVA +4.06 letters at 12 months	Between-study variability; long-term trials needed

BCVA: best-corrected visual acuity; DME: diabetic macular edema; NV: neovascularization; PRP: panretinal photocoagulation. Results are from separate designs and must not be interpreted as direct long-term comparisons of all three strategies.

5. Follow-up reliability and risk of serious complications

An important determinant of real-world effectiveness is the patient's capacity to attend repeated visits. Anti-VEGF produces pharmacological suppression, which can diminish if injections are stopped. In an IRIS Registry analysis of patients who returned after more than one year without follow-up, new complications at return included vitreous hemorrhage in 8.4% and tractional retinal detachment in 3.3% of eyes. These figures describe a selected group with prolonged interruption and should not be generalized to all treated eyes [10].

Recent meta-analytic evidence found lower long-term rates of tractional retinal detachment with anti-VEGF than PRP in pooled data, but that conclusion relied on only two studies for longer-term outcomes, with incomplete grading of detachment severity [8]. Consequently, clinical choice must consider the risk of recurrent disease if future care is disrupted. PRP may be particularly valuable where sustained return visits are uncertain; anti-VEGF may be favored when coexisting vision-impairing DME and reliable follow-up support repeated treatment [2, 7, 8].

6. Individualized clinical approach and remaining research gaps

Baseline evaluation should document BCVA, dilated retinal findings, extent of neovascularization, vitreous hemorrhage, tractional changes and optical coherence tomography evidence of DME. PRP should be considered promptly in high-risk PDR; anti-VEGF can be selected as an alternative for suitable patients or as an adjunct when rapid regression, DME control or specific preoperative circumstances are important. Where significant tractional membranes are present, careful retinal-surgical assessment is essential before treatment decisions. Complications such as nonclearing vitreous hemorrhage or tractional retinal detachment may require pars plana vitrectomy rather than repeated injections alone [7].

Care plans should explicitly address appointment access, patient education, financial constraints and systemic diabetes control. Follow-up intervals must be individualized by the treating ophthalmologist and adapted to activity rather than inferred from outcomes of other trials. The unresolved scientific question is whether adding anti-VEGF to PRP yields superior long-term patient-important outcomes compared with well-executed PRP or anti-VEGF monotherapy under routine conditions. Future multicenter randomized studies should report five-year vision, visual fields, quality of life, cataract and tractional complications, total treatment cost and retention in care.

CONCLUSION

High-quality randomized evidence supports both PRP and intravitreal anti-VEGF therapy as viable treatments for PDR. Protocol S demonstrates favorable five-year visual

outcomes among patients who remain in follow-up, but anti-VEGF treatment requires considerably more clinical visits. Adjunctive anti-VEGF with PRP can accelerate regression of neovascularization and may improve selected short-term outcomes; however, evidence for its long-term superiority over either monotherapy remains limited. Treatment should be individualized according to disease severity, accompanying DME, risk of retinal complications, cost and expected adherence. Clinical monitoring and systemic metabolic management remain essential regardless of the local ocular treatment.

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