REVIEW

A Paradigm Shift in the Management Approaches of Proliferative Diabetic Retinopathy: Role of Anti-VEGF Therapy

Rajiv Raman [1], Kim Ramasamy [2], Utkarsh Shah [3]

[1]Shri Bhagwan Mahavir Vitreoretinal Services, Chennai, Tamil Nadu, India; [2]Aravind Eye Hospital, Madurai, Tamil Nadu, India; [3]Novartis Healthcare Private Limited, Mumbai, India

Correspondence: Rajiv Raman, Shri Bhagwan Mahavir Vitreoretinal Services, Chennai, Tamil Nadu, India, Tel +91-9444288708, Email rajivpgraman@gmail.com

Abstract: Diabetic retinopathy (DR) is considered one of the leading causes of vision loss globally. It principally causes upregulation of pro-angiogenic, proinflammatory, and vascular permeability factors such as vascular endothelial growth factor (VEGF), leading to neovascularisation. The advanced stage of DR or proliferative diabetic retinopathy (PDR) is of more concern, as it leads to vitreous haemorrhage and traction retinal detachment. Various risk factors associated with PDR include hyperglycemia, hypertension, neuropathy, dyslipidemia, anaemia, nephropathy, and retinal complications of drugs used for diabetes. Current management approaches for PDR have been stratified and involve pan-retinal photocoagulation, vitrectomy, and anti-VEGF agents. Given the emerging role of anti-VEGF agents as a favourable adjunct or alternative therapy, they have a critical role in the management of PDR. The review emphasises current management approaches for PDR focusing on anti-VEGF therapy. The review also highlights the risk/benefit evaluation of the various approaches employed for PDR management in various clinical scenarios.

Keywords: neovascularisation, diabetic retinopathy, pan-retinal photocoagulation, vitrectomy, anti-VEGF, PDR in India

Introduction

Diabetes mellitus (DM) is one of the most common noncommunicable diseases in the world.[1] According to International Diabetes Federation Atlas 2021, it was estimated that approximately 537 million individuals in the world had diabetes (types 1 and 2), aged between 20 and 79 years representing 10.5% of the world population. India ranks second in terms of disease burden globally with around 74.2 million individuals having diabetes.[2] The national survey conducted in India establishes the prevalence of DM to be 11.2%.[3] It was established that diabetic retinopathy (DR) is one of the major diabetes-related complication having vision loss as a global concern, leading to substantial financial implications.[4] The global prevalence of DR was observed to be ranging between 22% and 35% in patients with diabetes as reported in different studies.[5–7] In 2020, the individuals affected with DR is estimated to be 103.12 million which is projected to increase to 160.50 million by 2045.[6] However, a disproportionate representation of DR is observed across geography where maximum prevalence is observed in Middle East and North Africa and the Western Pacific.[6] Additionally, no significant inter-gender difference was observed in the DR prevalence (females: 25.93%; males: 28.95%).[7] Sight-threatening DR or vision-threatening DR is defined as "presence of severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) and/or macular oedema in at least one eye".[8] The incidence of sight-threatening DR is more in type 1 when compared with type 2 DM.[9]

Advanced DR or PDR represents angiogenic response of the retina to extensive ischaemia from capillary closure.[10] The characteristics of PDR include retinal neovascularisation (NV), serum leakage, haemorrhage, and fibrovascular proliferation in the vitreous retinal interface. The characteristic clinical feature of PDR is growth of new vessels arising at the interface of perfused or nonperfused retina, viz. new vessels on the disc (NVD) or new vessels elsewhere (NVE). All these characteristics ultimately lead to vitreous haemorrhage (VH) and traction retinal detachment (TRD).[11] In some

instances, new vessels on the iris (NVI) and iridocorneal angle (NVA) also develop owing to advanced posterior segment ischaemic changes.[12]

Experimentally, it has been observed that elevated levels of vascular endothelial growth factor (VEGF) induce NV in mouse models and also that large amounts of miR-410 efficiently downregulates vascular endothelial growth factor expression, suppressing retinal NV.[13] Additionally, inhibition of intraocular VEGF was noted to prevent NVI in nonhuman primates.[14] It has also been reported that elevated levels of VEGF are found in the vitreous humour of patients with PDR.[15] Elevated levels of angiogenic factors are associated with endothelial cell proliferation and migration and disruption of tight junctions, which lead to new vessel formation and increased vascular permeability. Molecular studies have shown that VEGF-A encourages the process of vascular permeability and angiogenesis.[16,17]

Current management approaches for PDR include pan-retinal photocoagulation therapy (PRP), vitrectomy, and anti-VEGF agents.[18] Data from the Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study (DRS) advocate pan-retinal photocoagulation (PRP) as the gold standard for the management of PDR.[18,19] However, surgical intervention was noted to help in achieving increasingly better outcomes in a select group of patients with advanced PDR.[11] The ongoing attempts to modify the treatment landscape of PDR have led to researches where intravitreal injection of human mesenchymal stem cells has demonstrated a decline in progression of diabetic retinopathy.[20]

It has been noted that glycosylated haemoglobin (Hb1Ac) is an important biomarker to monitor the level of glucose in diabetic patients. An elevation in the level of Hb1Ac is an indicator of increased risk of developing diabetes associated retinal complications and negatively influences the visual outcomes of anti-VEGF therapy. Patients with lower HbA1c level tend to have an improvement in visual outcomes post treatment suggesting the role of blood sugar control in the management of PDR.[21,22] Patients with diabetes having higher Hb1Ac variability demonstrated increased risk of PDR requiring laser therapy, particularly in type 1 diabetes.[23]

For the majority of PDR cases, the mainstay treatment remains laser; however, there is growing evidence on the benefits offered by anti-VEGF injections regardless of Diabetic Macula Oedema (DME) presence or absence.[16,18] As the treatment landscape for PDR is evolving, this narrative review aims to combine currently available knowledge on anti-VEGF agents and their role in the management of PDR. It emphasises the risk-benefit evaluation of various approaches employed for PDR management and discusses consensus statements for managing a few clinical scenarios in the context of PDR.

Screening of Patients for DR

Sight-threatening DR (STDR) is an important cause of visual impairment in patients with diabetes and one of the most common causes of avoidable blindness. Regular dilated fundus examination is the first step in the identification and management of STDR.[24] Patients with no DR and mild NPDR are considered non-referable, whereas patients with or above moderate NPDR with or without macular oedema are considered referable DR Identification of DR in the early stages not only helps in preventing blindness but is also cost-effective for patients (expenses for treatment). The main aim of screening for DR is timely detection of STDR.[25]

Management of PDR

There are various treatment approaches to PDR with specific goals to halt or regress neovascular activity in the retina.

Pan-Retinal Photocoagulation Therapy (PRP)

According to the Diabetic Retinopathy Study Research group (DRS), PRP was the first line of treatment for PDR in past decades.[18] It is a category of laser treatment employed to preserve existing vision and prevent any further possible visual impairment. The conversion of hypoxic regions to anoxic areas leads to a decrease in oxygen consumption, causing a reduction in angiogenic stimuli, thus regressing NV. Elevated levels of VEGF were observed more in patients with PDR in comparison with patients with NPDR; however, the level decreased significantly after PRP treatment.[26,27] Early treatment with PRP is recommended to prevent progression of disease processes and any further complications.[26–28] A decrease in arteriolar branching angle in patients with non-progression of PDR from baseline to 6 months of follow-up has also been observed with the PRP.[29] A decline in large foveal avascular zone area and in deep capillary plexus

vascular density in perifoveal region in patients with NPDR was also established with PRP.[30] Regression of PDR was also evident with PRP therapy with maximum regression in mild PDR (75%).[31]

It has been observed that PRP has the potential to reduce the incidence of severe vision loss in PDR by 50%. According to ICO 2017 guidelines, the typical initial settings on the Argon laser would be a 500-μm spot size, 0.1-second exposure, and 250–270-mW power. However, the power is gradually increased until a whitish reaction is obtained in the retina. A total of 1600–3000 burns are placed in one or more sittings. There is recent evidence of development in laser therapy, wherein several laser spots are delivered simultaneous, eg, patterned scanning laser, conventional laser, and navigated laser delivery system, eg, Navilas® (OD-OS, Germany). It has been noted that PRP provides long-lasting effects and is a highly cost-effective method and once off therapy.[26–28] The macular vessel density at the superficial, deep, and choriocapillaris levels significantly increased from baseline to 6 months of follow-up after PRP treatment. Foveal avascular zone area also improved from baseline to 6 months of follow-up (0.56 ± 0.27 vs 0.46 ± 0.21).[32] Additionally, macular thickness also increased significantly ($p<0.05$) after PRP therapy at 6 months of follow-up.[33] A decrease in amplitude and increase in latency of pattern-reversal visual evoked potentials was observed in patients with PDR post completion of PRP session. However, a partial recovery of these parameters were observed after 1.5 months of the therapy.[34]

However, as with other treatment methods, there are adverse effects and/or risks associated with PRP: laser scars, incidence of transient choroidal and exudative retinal detachments, diminished acuity and scotopic vision, reduction in visual field, and aggravation in macular oedema. Additionally, loss of colour vision, macular burn, pain during the sessions in some cases, rupture of the Bruch membrane might be unavoidable. The possibility of retreatment is present if there is incomplete regression. Furthermore, marginal improvement in mean and binocular visual acuity from baseline in certain cases, development of VH, ocular inflammation, cataract extraction, neovascular glaucoma, elevation in intraocular pressure were also observed in a few PRP-treated eyes.[27,35] The electroretinogram findings over the course of multiple PRP sessions demonstrated decreased retinal function after each session that partially recovers by 6 weeks after the completion of therapy.[36] However, the complications associated with PRP are mostly attributable to inadequate PRP and could be minimised by conducting multiple PRP sessions rather than one session. The risk factors are further aggravated due to the use of short duration and high-intensity burns.[35]

Apart from PRP, focal laser is another laser therapy that is being applied on limited area of the posterior pole to minimise the macular oedema. It is expected to obstruct the leaking microaneurysms in the retina and stimulation of cytokine production. This leads to the restoration of retinal pigment epithelium and fluid reabsorption in the macula.[37] Subthreshold micropulse laser treatment is also used that leaves the retinal cells intact. In this technique, micropulse mode of different wavelengths is available in conventional laser and releases short repetitive impulses allowing cooling of the retinal tissues. It reduces the diffusion of heat in the surrounding tissues and increases the production of heat shock proteins and a reduction in VEGF level.[38,39] It was established in a prospective randomised pilot trial that subthreshold microsecond laser could be used as an alternative to PRP in early PDR to avoid complications associated with PRP.[40]

Surgical Intervention

Surgical intervention is required in advanced stages of PDR. The goal of the intervention (Pars Plana vitrectomy; PPV) is to relieve traction (tangential and/or antero-posterior) and clear significant vitreous opacities, thus facilitating early visual rehabilitation in patients. The two most common conditions where surgical intervention is mandatory are non-clearing VH and TRD involving the macula.[41–43] In a randomised trial, 616 eyes with severe VH reducing visual acuity to 5/200 or less were randomly assigned to either early vitrectomy or deferral of vitrectomy for 1 year. After 2 years of follow-up, eyes receiving early vitrectomy showed improved visual acuity in comparison to deferred eyes,[44] thereby necessitating early intervention for better visual outcomes in these patients. Nevertheless, PPV is associated with certain limitations, including recurrent VH, vision loss, and infectious endophthalmitis.[43] In a retrospective case study series, 116 eyes of 92 patients who underwent PPV for PDR were followed up for 24 months in the young (18–44 years) and senior (>45 years) patient groups. A TRD secondary to PDR was observed in 62.1% and 12.1% of the eyes in the young and senior patient groups, respectively. There were certain postoperative complications detected, viz. VH, retinal detachment, neovascular glaucoma (NVG), and cataract.[43–46]

Anti-VEGF Therapy

A significant causal relationship has been established between the development and progression of PDR and VEGF.[13,14,17] Hence, the need to overcome the effect and influence of VEGF in PDR could be handled by anti-VEGF agents such as ranibizumab and aflibercept.[15,16,18]

The multicenter Phase II PRIDE study (ClinicalTrials.gov study identifier: NCT01594281) of 12 months' duration was conducted to evaluate the efficacy and safety of intravitreal ranibizumab (IVR) with or without PRP in comparison to PRP alone in the management of PDR. A total of 106 patients with PDR and without DME were randomised to receive different therapeutic regimens (IVR 0.5 mg monotherapy to 35 patients, PRP alone to 35 patients, combined ranibizumab 0.5 mg and PRP to 36 patients). The primary endpoint of the study was to determine the area of retinal NV, while the secondary endpoints were complete regression of leakage and best-corrected visual acuity (BCVA). The results obtained favoured IVR monotherapy since it exhibited superior effects in comparison to PRP alone. At 12 months, a statistically significant difference of -2.83 mm^2 in the mean change in NV between IVR monotherapy and PRP was observed, favouring IVR therapy. Around 67% and 28% complete regression of NV were also observed with IVR monotherapy in 3 months and 12 months, respectively.[47] The combination of PRP and anti-VEGF therapy has also demonstrated improvement in BCVA (reduction in units of logMAR of -0.23) and in mean neovascularisation on the disc (-28.41) as established from a meta-analysis.[48]

Protocol T shows a significant improvement in diabetic retinopathy severity score (DRSS) in the aflibercept group over a period of 12 months.[49,50] It was also reported to have a longer duration of action in comparison to other anti-VEGF agents.[51]

The Pan-American Collaborative Retina Study Group (PACORES), which is a collaborative research consortium, studied the clinical outcomes of intravitreal bevacizumab (IVB) for PDR management. Based on the results, the group recommended that in patients with prior PRP, IVB can control the retinal NV up to 70%. Additionally, improvement in BCVA was also observed. Moreover, it was evident that IVB, if administered prior to PPV, was associated with a 3.5% lower risk of developing TRD. However, a dose greater than 2.5 mg of bevacizumab was found to increase the risk of TRD progression.[52]

Advantages of Using Anti-VEGF Therapy in PDR

These agents are advantageous in cases where delivering PRP is difficult, such as VH and dense cataract or when PRP cannot prevent PDR progression.[45,53] Ranibizumab has demonstrated a potentially protective effect in eyes with DME in terms of progression to PDR in the RIDE/RISE trials (NCT00473382, NCT00473330). Similarly, the role of aflibercept in PDR has been studied in VIVID/VISTA trials (INCT01331681/NCT01363440).[39,40] In the RIDE/RISE Phase III clinical trials, which evaluated the efficacy and safety of ranibizumab for DME, monthly IVR delayed progression to PDR.[54,55] In a post hoc analysis of the RISE and RIDE trials, IVR treatment groups demonstrated clinically significant improvement from baseline.[54] There are other various pivotal global studies that established the effectiveness of anti-VEGF therapy.[56–58] Preoperative anti-VEGF injections have also been shown to decrease surgical time required, as well as being associated with reduced intraoperative bleeding. An IVB also helps in overcoming the complications of VH by minimising the need for PPV and decreasing vitreous clear-up time.[59] In a meta-analysis conducted by Gao et al to compare anti-VEGF therapy with PRP for PDR, anti-VEGF therapy was associated with superior visual acuity and reduced PDR-associated complications, although results showing recurrence of new vessels was lower for PRP mono-therapy. It was observed from trial data that anti-VEGF therapy is instrumental in ameliorating worsening of PDR and preventing regression of retinopathy. Additionally, it has been reported to improve visual acuity even in subjects with satisfactory vision and without DME.[53,59]

It has been evident that high levels of VEGF are the primary cause of retinal/macular ischaemia in PDR and is represented as disease severity and progression. Anti-VEGF therapy was observed to be safe in macular ischaemia at baseline since it did not cause macular perfusion index aggravation. Vessel density and FAZ area also remained statistically unaltered during short term as evaluated using optical coherence tomography angiography (OCTA).[60,61] Certain studies have also established stable or improved macular perfusion post anti-VEGF treatment using fluorescein

angiography and OCTA.[62,63] Studies have demonstrated no change in macular non-perfusion based on the findings from fundus fluorescein angiography and OCTA in patients with PDR after anti-VEGF treatment.[61]

On comparing the PRP and anti-VEGF therapy, it was seen that patients receiving the anti-VEGF therapy did not show a significant change in macular vessel density. However, in patients who received PRP therapy, vessel density increased upon treatment which is significantly related to the impairment in visual acuity.[64] Currently, a trial is being undertaken to evaluate the macular perfusion changes in patients with PDR following anti-VEGF therapy versus PRP using OCTA (NCT04674254).[65]

Limitations of Anti-VEGF Agents in PDR

There are certain limitations associated with the use of anti-VEGF agents. There are local and systemic adverse effects associated with the use of anti-VEGF therapy, including TRD, rise in intraocular pressure (IOP), foveal avascular zone (FAZ) enlargement, macular hole. Further, anti-VEGF agents have a short-term effect on abnormal vessels and the risk of endophthalmitis. They might also cause thromboembolic events and intraocular inflammation.[66] There have also been studies demonstrating increased fibrosis in patients with PDR receiving IVB before PRP.[67] Further, the relatively limited half-life poses an escalating treatment burden. The increased treatment burden, along with the increased number of hospital visits, gives rise to patient noncompliance. Monotherapy with anti-VEGF is not suggested for advanced PDR with macular traction. Such cases would see the use of individualised treatment regimens using selective anti-VEGF in combination with PRP or vitrectomy.[57] The use of intravitreal anti-VEGF also leads to an infrequent complication termed "crunch syndrome", which is characterised by the sudden loss of vision within 1–6 weeks of anti-VEGF injection due to new or progressing TRD, especially bevacizumab.[68] Further, anti-VEGF is associated with the problem of microdosing: research findings reveal that giving half the dose is suitable to prevent bleeding during PPV. A similar approach was envisaged in patients with tractional components not involving the macula, where a reduced dose of anti-VEGF injection is administered to patients a few days prior to PRP.[53]

In a prospective cohort study, patients with PDR and incomplete response to PRP were followed monthly and administered IVB to determine regression of new vessels. However, the therapy was not considered successful due to the occurrence of certain events (NV in three eyes), traction development in five eyes, dense VH in six eyes.[57] In certain rare scenarios, protein aggregation has been observed after IVB injection in the American Academy of Ophthalmology survey. This might be attributable to the other ingredients present in the injection besides the active ingredients.[69]

Effect of Anti-VEGF on Tractional Component

Anti-VEGF agents have been noted to play a significant role when the tractional component of PDR is considered. A TRD is associated with multiplication of fibrous tissue or neovascular growth arising from retinal vasculature.[70] Excessive tractional component occasionally leads bleeding of intricate new vessels into the vitreous or preretinal space, leading to vitreous/subhyaloid haemorrhage and retinal detachment.[71] If PRP is performed before the development of serious PDR complications, including TRD, the incidence of severe vision loss is reduced by 50%.[26,72] Additionally, patients with extramacular TRD would require additional PRP to halt the extension of detachment to the macula.[26,28] In patients affected by PDR with TRD, bevacizumab was injected to prepare prior to surgical intervention. It was noted that in the 38 eyes with PDR that received preoperative bevacizumab, two eyes suffered worsening retinal tractional within 1.5–2 months.[73] In a separate series, worsening of tractional component within 3–31 days (13 days mean) of bevacizumab injection suggested a cause–effect relationship. Studies have thus proved that anti-VEGF agents can lead to worsening of TRD conditions in affected patients or might cause combined rhegmatogenous and tractional detachment.[74]

Safety Evaluation Studies

Interim safety outcomes generated from the 2-year follow-up of Protocol S where intravitreal ranibizumab (IVR) was compared with PRP in PDR patients, suggested the noninferior characteristics of IVR in terms of mean visual acuity from the baseline over 2 years. Additionally, the secondary outcomes showed better outcomes with IVR therapy as an alternative to PRP, since 2-year data did not indicate any systemic safety concerns.[69,75] In a post hoc analysis of Protocol S, NV status through 2 years was measured. The results obtained confirmed that at 2 years, 43% had NV resolution, 5%

showed improvement, 23% were stable, and 27% deteriorated since the last visit.[76] Moreover, the 5-year results of Protocol S also question the long-term benefits derived from anti-VEGF therapy, since dramatic visual field loss was significant in a few patients.[77] However, there was decreased incidence of vision-impairing DME and PDR-associated severe complications.[76] As per studies, the effectiveness of 1.25 mg dose of bevacizumab in regressing NV exhibits level of evidence IV.[53] However, certain research groups did not demonstrate significant changes in the extent of NV at different doses of IVB, yet hypothesised that higher doses might yield a longer duration of effect.[72,77] Even so, higher doses of IVB (2.5 mg) have raised concerns of FAZ, which needs to be studied further.[73,78] All anti-VEGF agents have established potential outcomes in the regression of NV but are limited by their short duration of action. A level of evidence II was established after validating the average rate of retinal NV after 6 weeks and recurrence at 16 weeks post-IVR in patients with PDR.[46,66] Although IVB do not affect the mid-term electrophysiological retinal function; however, patients treated with IVB demonstrated transient alterations of electroretinogram measures. This might be attributable to short-term disruption of the retinal equilibrium because of the injection used.[79]

Pivotal Trials Related to Use of Anti-VEGF Therapy in PDR

Protocol S and the CLARITY study formed the basis for the use of anti-VEGF therapy in PDR; hence, the study results along with the follow-up trial results are described in detail.

Protocol S

A randomised clinical trial (Protocol S)[76] was conducted wherein ranibizumab was compared with PRP in eyes with PDR (ClinicalTrials.gov study identifier: NCT01489189). Of note, 305 patients with PDR were recruited; both eyes of 89 patients were included, thus totalling to 394 eyes for a final follow-up of 2 years. The intervention consisted of IVR (0.5 mg) in 191 eyes followed by PRP if treatment failed, ranibizumab in case of DME development, PRP in 203 eyes, and ranibizumab in case of DME development. There was a more significant improvement in visual acuity in the ranibizumab group (+2.8) when compared to the PRP group (+0.2),[73] although the findings warrant long-term evaluation. However, Protocol S was associated with certain limitations. The possibility of ascertainment biases was present since IVR group had more frequent visits in comparison to PRP group. Additionally, the interpretation of safety findings was difficult, since a large proportion of patients in the PRP group received IVR as well. Though participants who completed the 2-year visit showed slightly better baseline visual acuity, no visual acuity differences between treatment groups were apparent. Moreover, participant retention through 2 years was a challenge and lower than desired. The nature of the treatments precluded masking participants and clinicians.[76,80] In a follow-up trial, patient-centred outcomes with both ranibizumab and PRP were analysed in 216 patients with one eye with PDR, out of the previous 305 patients. Conclusions were drawn based on predetermined subscale scores of the National Eye Institute Visual Function Questionnaire-25, University of Alabama Low Luminance Questionnaire, Work Productivity and Activity Impairment Questionnaire. The ranibizumab group had more beneficial outcomes in some areas in comparison to the PRP group in the context of work productivity and driving-related issues.[81] Furthermore, it was evident from 2-year follow-up results that ranibizumab led to less worsening PDR than PRP, especially in cases where PDR is not in conjunction with centre-involved diabetic macular oedema (CI-DME). However, more frequent follow-up visit schedules were inevitable in the case of anti-VEGF therapy.[82] Additionally, over a period of 2 years, the incremental cost–effectiveness ratio of ranibizumab compared with PRP could not be overruled in patients with PDR and vision-impairing DME, in whom it ranged from $55,000 to $150,000/quality-adjusted life-year, whereas it was $662,978/quality-adjusted life-year for PRP.[83] Similar cost-effective results were reciprocated in a 5-year study as well for ranibizumab and PRP therapy.[84] It was also discerned from the post hoc analysis of NV status through 2 years from IVR that 43% of the total eyes (66 of 154) had complete NV with 5% (7 of 154) showing improvement.[85] Moreover, IVR caused a decrease in the thickness of the retinal nerve fibre layer in comparison to PRP, ascribed to a decrease in oedema by IVR.[86] Further, IVR was superior to PRP with respect to change in visual acuity and development of CI-DME over a period of 2 years (15 out of 147 eyes, ie, 10% in IVR-treated eyes, and 42 out of 155 eyes, ie, 27% of PRP eyes, developed vision-threatening CI-DME), especially in patients with enhanced arterial pressure, without prior focal/grid laser, with NVD or NVE, and with advanced PDR.[87] Again, in a post hoc retrospective analysis of 2-year outcomes in Phase 3 of Protocol S, approximately 47 eyes receiving IVR as per the protocol showed at least a 4-step DR severity improvement on the DRSS along with improvement in visual acuity.[88]

Clarity

A phase 2b, single-blinded trial (CLARITY) was conducted in the UK, wherein 232 adults aged ≥18 years with type 1 or 2 diabetes were recruited who were either untreated or had PDR even post-laser treatment (ISRCTN registry number 32207582). The patients were randomly assigned to repeated intravitreal aflibercept (2 mg/0.05 mL at initial dose, 4 weeks and 8 weeks; and post-12 weeks, the patients were reviewed every 8 weeks, the injection was administered as and when needed) or PRP (where either single or multisport laser was performed, and post-12 weeks, the patients were reviewed every 8 weeks and PRP was done as and when required) for a duration of 52 weeks. The findings proved that aflibercept was superior with improved visual outcomes and had no additional safety concerns in comparison to PRP for PDR.[84,89] The CLARITY study was the first randomised clinical trial of intravitreal aflibercept for PDR and its use over PRP in PDR management.[90,91] In the post hoc analysis of the CLARITY study, 120 treatment-naïve patients with PDR were randomly assigned to intravitreal aflibercept (2 mg/0.05 mL at baseline, 4 weeks, 8 weeks, and as needed from 12 weeks onwards) or PRP (conducted in initial fractionated sessions and reviewed every 8 weeks followed by PRP again if required). The investigation was undertaken to establish the outcome of aflibercept and PRP on NV in PDR by examining the topological response. The results showed the increased effect of aflibercept over PRP in treating NVE. However, it was observed that NVD was rare, although more resistant to available treatment regimens.[84,90]

Selecting a Patient with PDR for Anti-VEGF Therapy

Anti-VEGFs can be used in the management of PDR in select groups of patients with active PDR in which despite good PRP there is persistence of new vessels and when there is difficulty in performing PRP (such as VH and dense cataract)[53]:

1. Preoperatively before a diabetic vitrectomy to reduce the risk of intraoperative bleeding.
2. Anterior segment NV when the view is compromised to perform PRP.
3. DME with PDR.
4. As an adjunct to PRP in the absence of foveal traction.

According to ICO guidelines, in case of stable or treated PDR, follow-up between 6 and 12 months is required.[91] Loss to follow-up (LTFU) is often evident based on factors such as type of procedure, age, and race. Anti-VEGF therapies generally follow intensive treatment plans, when compared with PRP. Hence, compliance with follow-up is crucial in such patients, depending on the patient's general health status, social network, available conveyance to the clinic, along with the patient's intrinsic motivational drive.[92] A patient with multiple systemic diseases might not be able to attend all scheduled visits; hence, such patients are not ideal candidates for anti-VEGF therapy. Additionally, patients who had a recent stroke or heart attack (within 2 months) were also not included in clinical trials using anti-VEGF therapy for DR.[92]

It was also observed in the 5-year follow-up trial of Protocol S that LTFU was relatively higher in the anti-VEGF treatment group.[93] In the prospective cohort study conducted by Abdelmotaal et al, causes of LTFU were determined post-PRP and intravitreal anti-VEGF therapy. The various reasons causing LTFU, as studied based on the questionnaire, were trust and satisfaction concerns with the therapy, loss of corrected visual activity, affordability, age, devoid of social support, and frequency of anti-VEGF injections.[94] The study by Obeid et al also highlighted a few other causes for LTFU, such as type of procedure, race of the patient, distance from the clinic, associated complications as DME, and pain level perceived by the patient with the respective therapy.[95] Thus, LTFU could be minimised by addressing patient-centric problems at the initiation of the concerned therapy.

A Few Clinical Scenarios for PDR Management

Scenario 1: PDR with Single NVE

Janssin et al in their retrospective series found that 40% of the eyes with PDR had a single NVE. It is important to access the extent of non-perfusion in these eyes. A wider extent of non-perfusion would warrant closer follow-up. Presence of

NVE is an indication of PRP. However, in a select group of patients with no tractional element and those who have demonstrated good compliance with regular follow-up, intravitreal anti-VEGFs can be tried. Although, intravitreal anti-VEGFs have shown to improve severity of diabetic retinopathy over time, studies based on FFA and OCTA analysis have shown no significant change in macular ischaemia on follow-up.[61] PRP on the other hand has been noted to have significant improvement in vessel density of superficial and deep capillary plexuses for fovea and para foveal retina and constriction of FAZ on OCTA.[32] PDR with single NVE is presented in Figure 1A.

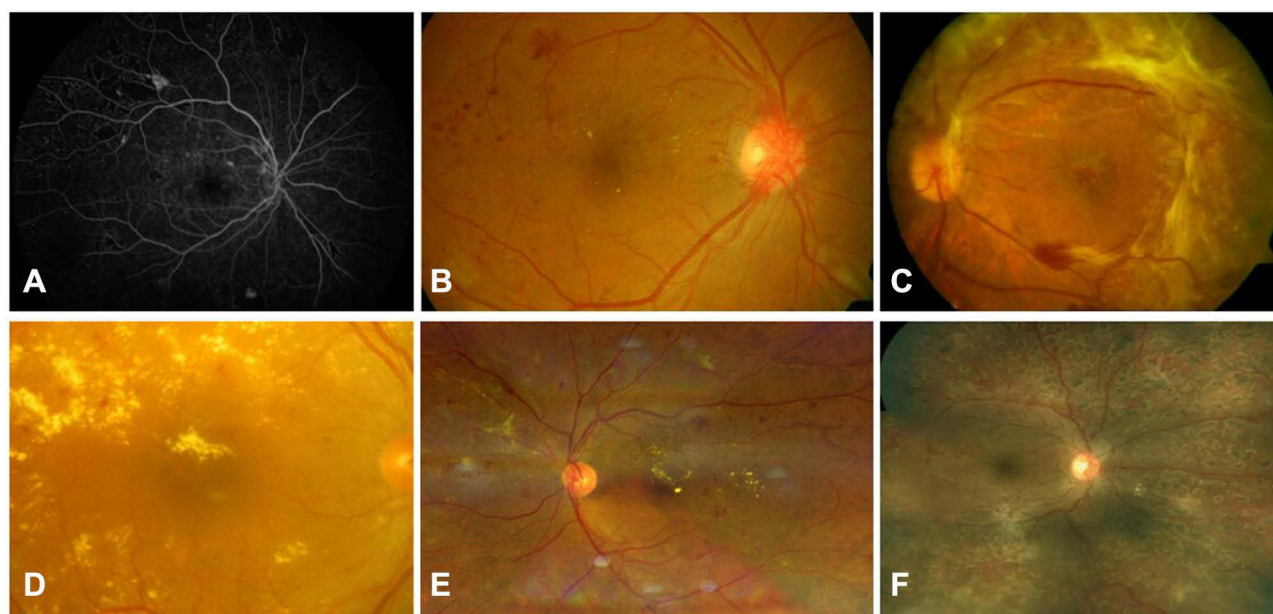## Scenario 2: PDR with No Traction and Patient with Good Compliance

These patients can be initiated on anti-VEGF treatment and observed for regression of NV. In case of worsening of PDR even after four–six injections, PRP can be performed. PDR with no traction is presented in Figure 1B.

Scenario 3: PDR with Traction Not Involving the Fovea

Extramacular/extrafoveal TRDs should be observed closely, as about 15% of them progress to the macula in 1 year, and 21–24% do so in 2 years. However, very close monitoring is important, as even transient macular detachments may result in permanent visual loss, and progression to combined tractional-rhegmatogenous retinal detachment will reduce surgical success rates and visual outcomes. In case of a predominantly fibrous proliferation or fibrovascular proliferation, PRP can be completed avoiding one DD (disc diameter) area from the TRD. If this condition is associated with DME, initial treatment with intravitreal anti-VEGF can be started and PRP added at follow-up visits. PDR with traction is presented in Figure 1C.

Scenario 4: PDR with CI-DME

CSME (Clinically significant macular oedema) can be categorised as CI-DME (centre involving-diabetic macular oedema) or NCI-DME (non-centre involving-diabetic macular oedema). Traditionally in CSME, the treatment involved completing the macular laser and nasal PRP and deferring the temporal retina for PRP as per ETDRS guidelines.[96,97] PRP is known to increase the macular oedema. This traditional protocol was thus to prevent worsening of any pre-existing macular oedema or precipitation of the same. However, currently in cases of PDR with CI-DME, complete PRP with intravitreal anti-VEGF can be done. However, one needs to assess the degree of tractional elements before planning intravitreal anti-VEGF. In

Figure 1 (**A**) PDR with single NVE, (**B**) PDR with no traction, (**C**) PDR with traction, (**D**) PDR with CI-DME, (**E**) PDR with non-centre involving DME, (**F**) Active PDR after pan-retinal photocoagulation.

a patient with good compliance, one can plan intravitreal anti-VEGF with deferred PRP. However, in cases with NCI-DME, PRP with focal laser can be considered as the primary course of action. PDR with CI-DME is exhibited in Figure 1D.

Scenario 5: Active PDR After Complete PRP

A stable NV requires active monitoring. If clinical examination reveals active proliferation and generation of newer vessels or associated haemorrhages even after comprehensive PRP, additional PRP can be planned to skip areas. In case of active neovascularisation after complete PRP, new vessels should be assessed. Mature neovessels in such cases, characterised by a wider diameter and less branching, can be observed. In the absence of traction, intravitreal anti-VEGF can be considered in patients with good compliance. PDR with non-centre involving DME is exhibited in Figure 1E.

Scenario 6: PDR with NVI

In these situations, immediate aggressive PRP to the extent possible facilitates iris vessel regression. The treating ophthalmologist should re-access regression in 2 weeks. In case of poor regression, intravitreal anti-VEGF can be tried. The IOP should be lowered by medical management before giving intravitreal injection. In cases where the IOP does not reduce, anterior chamber paracentesis can be considered during intravitreal injection. Intracameral anti-VEGF injections can also be considered in patients with barriers to PRP or intravitreal anti-VEGF injections and it has been considered as more effective for IOP control than the intravitreal route.[98]

Regular follow-up of patients with diabetic retinopathy is imperative to track the disease activity. Fundus fluorescein angiography (FFA) is an established tool used to detect vascular sequlae in diabetic retinopathy including non-perfusion areas, neovascularisation, leaking microaneurysms and enlargement of FAZ. However, FFA is a time-consuming and invasive technique. Of late, optical coherence tomography angiography (OCTA) has been increasingly used to detect progression and need for treatment. Retinal neovascularisation area measured by OCTA has been shown to be predictive of progression in PDR and to evaluate response to treatment following PRP.[99] Papayannis et al introduced an SS-OCTA cortical vitreous segmentation protocol that can be utilised for reproducible detection of neovascularisation and accurate detection of regression activity on follow-up.[100] Pereira et al conducted a comprehensive analysis of 248 studies of OCT and OCTA dine in diabetic retinopathy cases to review recent developments and potential implications of the modalities in clinical settings. They noted the accuracy of wide-field OCTA in detecting neovascular complexes and non-perfusion areas and the adequacy of currently available wide-field OCTA protocols provided the correct segmentation and scanning area is incorporated.[101] Active PDR after pan-retinal photocoagulation is exhibited in Figure 1F.

Conclusion

Since the prevalence of diabetes is high, PDR is a cause of concern, leading to sight-threatening conditions or even vision loss. The review provides a holistic overview across different aspects of treatment approaches for PDR in India in line with the standard guidelines. The review also highlights certain clinical scenarios encountered in a clinical setting on day-to-day basis and the necessary steps taken by the ophthalmologists to deal with them. Ophthalmologists need to be vigilant and carefully carry out the screening of patients to offer the best management approach for PDR. The current gold standard for PDR is PRP therapy, although certain ophthalmologists consider anti-VEGF therapy to be a more favourable option and as an alternative or adjunct therapy. The in-depth risk-benefit analysis of anti-VEGF including its advantages, limitations, and safety profile has been presented. Anti-VEGF therapy is beneficial in the regression of neovascularisation along with demonstrated efficacy with minimal adverse effects. Anti-VEGF therapy is currently being used for PDR without tractional component or with traction without fovea followed by supplemental PRP, while it is first-line therapy for PDR with CI-DME. Additionally, certain studies conducted for a duration of 5 years justify the safety profile of anti-VEGF therapy; yet such studies are scarce and typically have limited inclusion criteria. The review also highlights certain clinical scenarios encountered in a clinical setting on day-to-day basis and the necessary steps taken by the ophthalmologists to deal with them. Therefore, extensive studies are warranted to position anti-VEGF therapy as a safe and effective approach for PDR.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

Utkarsh Shah is an employee of Novartis Healthcare Private Limited. The other authors have no conflicts of interest to declare.

References

1. Disdier-Flores OM, Rodríguez-Lugo LA, Pérez-Perdomo R, Pérez-Cardona CM. The public health burden of diabetes: a comprehensive review. *P R Health Sci J*. 2001;20(2):123–130.
2. International Diabetes Federation. IDF diabetes atlas 10th Edition; 2021. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. Accessed September 2, 2022.
3. Vashist P, Senjam SS, Gupta V, et al. Prevalence of diabetic retinopathy in India: results from the National Survey 2015–19. *Indian J Ophthalmol*. 2021;69(11):3087–3094. doi:10.4103/ijo.IJO_1310_21
4. Cheloni R, Gandolfi SA, Signorelli C, Odone A. Global prevalence of diabetic retinopathy: protocol for a systematic review and meta-analysis. *BMJ Open*. 2019;9(3):e022188–e022188. doi:10.1136/bmjopen-2018-022188
5. International Diabetes Federation te. IDF diabetes atlas. Brussels; 2019. Available from: https://www.diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf. Accessed September 2, 2022.
6. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*. 2021;128(11):1580–1591. doi:10.1016/j.ophtha.2021.04.027
7. Hashemi H, Rezvan F, Pakzad R, et al. Global and regional prevalence of diabetic retinopathy; a comprehensive systematic review and meta-analysis. *Semin Ophthalmol*. 2022;37(3):291–306. doi:10.1080/08820538.2021.1962920
8. Sapkota R, Chen Z, Zheng D, Pardhan S. The profile of sight-threatening diabetic retinopathy in patients attending a specialist eye clinic in Hangzhou, China. *BMJ Open Ophthalmol*. 2019;4(1):e000236. doi:10.1136/bmjophth-2018-000236
9. Romero-Aroca P, Navarro-Gil R, Valls-Mateu A, Sagarra-Alamo R, Moreno-Ribas A, Soler N. Differences in incidence of diabetic retinopathy between type 1 and 2 diabetes mellitus: a nine-year follow-up study. *Br J Ophthalmol*. 2017;101(10):1346–1351. doi:10.1136/bjophthalmol-2016-310063
10. Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology*. 2018;125(10):1608–1622. doi:10.1016/j.ophtha.2018.04.007
11. Newman DK. Surgical management of the late complications of proliferative diabetic retinopathy. *Eye*. 2010;24(3):441–449. doi:10.1038/eye.2009.325
12. Rodrigues GB, Abe RY, Zangalli C, et al. Neovascular glaucoma: a review. *Int J Retina Vitreous*. 2016;2:26. doi:10.1186/s40942-016-0051-x
13. Chen N, Wang J, Hu Y, et al. MicroRNA-410 reduces the expression of vascular endothelial growth factor and inhibits oxygen-induced retinal neovascularization. *PLoS One*. 2014;9(4):e95665. doi:10.1371/journal.pone.0095665
14. Tolentino MJ, Miller JW, Gragoudas ES, Chatzistefanou K, Ferrara N, Adamis AP. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol*. 1996;114(8):964–970. doi:10.1001/archopht.1996.01100140172010
15. Wang X, Wang G, Wang Y. Intravitreous vascular endothelial growth factor and hypoxia-inducible factor 1a in patients with proliferative diabetic retinopathy. *Am J Ophthalmol*. 2009;148(6):883–889. doi:10.1016/j.ajo.2009.07.007
16. Zhao Y, Singh RP. The role of anti-vascular endothelial growth factor (anti-VEGF) in the management of proliferative diabetic retinopathy. *Drugs Context*. 2018;7:212532. doi:10.7573/dic.212532
17. Antonetti DA, Barber AJ, Hollinger LA, Wolpert EB, Gardner TW. Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden 1. A potential mechanism for vascular permeability in diabetic retinopathy and tumors. *J Biol Chem*. 1999;274(33):23463–23467. doi:10.1074/jbc.274.33.23463
18. El Rami H, Barham R, Sun JK, Silva PS. Evidence-based treatment of diabetic retinopathy. *Semin Ophthalmol*. 2017;32(1):67–74. doi:10.1080/08820538.2016.1228397

19. The 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.

20. Scalinci SZ, Scorolli L, Corradetti G, et al. Potential role of intravitreal human placental stem cell implants in inhibiting progression of diabetic retinopathy in type 2 diabetes: neuroprotective growth factors in the vitreous. *Clin Ophthalmol.* 2011;5:691–696. doi:10.2147/opth.S21161

21. Chen YP, Wu AL, Chuang CC, Chen SN. Factors influencing clinical outcomes in patients with diabetic macular edema treated with intravitreal ranibizumab: comparison between responder and non-responder cases. *Sci Rep.* 2019;9(1):10952. doi:10.1038/s41598-019-47241-1

22. Mjwara M, Khan M, Kruse CH, Sibanda W, Connolly C. Significance of HbA1c levels in diabetic retinopathy extremes in South Africa. *S Afr Med J.* 2021;111(9):886–890.

23. Hietala K, Wadén J, Forsblom C, et al. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. *Diabetologia.* 2013;56(4):737–745. doi:10.1007/s00125-012-2816-6

24. Rajalakshmi R, Behera UC, Bhattacharjee H, et al. Spectrum of eye disorders in diabetes (SPEED) in India. Report # 2. Diabetic retinopathy and risk factors for sight threatening diabetic retinopathy in people with type 2 diabetes in India. *Indian J Ophthalmol.* 2020;68(Suppl1):S21–S26. doi:10.4103/ijo.IJO_21_19

25. Raman R, Ramasamy K, Rajalakshmi R, Sivaprasad S, Natarajan S. Diabetic retinopathy screening guidelines in India: All India Ophthalmological Society diabetic retinopathy task force and Vitreoretinal Society of India Consensus Statement. *Indian J Ophthalmol.* 2021;69(3):678–688. doi:10.4103/ijo.IJO_667_20

26. Royle P, Mistry H, Auguste P, et al. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. *Health Technol Assess.* 2015;19(51):v–xxviii, 1–247. doi:10.3310/hta19510

27. Paulus YBM. Panretinal photocoagulation for treatment of proliferative diabetic retinopathy. Available from: https://www.aao.org/munnerlyn-laser-surgery-center/laser-treatment-of-proliferative-nonproliferative-?msclkid=6c919d58cee711ec9c955581b57ba257. Accessed September 2, 2022.

28. Saxena S, Jalali S, Meredith TA, Holekamp NM, Kumar D. Management of diabetic retinopathy. *Indian J Ophthalmol.* 2000;48(4):321–330.

29. Torp TL, Kawasaki R, Wong TY, Peto T, Grauslund J. Temporal changes in retinal vascular parameters associated with successful panretinal photocoagulation in proliferative diabetic retinopathy: a prospective clinical interventional study. *Acta Ophthalmol.* 2018;96(4):405–410. doi:10.1111/aos.13617

30. Sabaner MC, Dogan M, Akdogan M, Şimşek M. Panretinal laser photocoagulation decreases large foveal avascular zone area in non-proliferative diabetic retinopathy: a prospective OCTA study. *Photodiagnosis Photodyn Ther.* 2021;34:102298. doi:10.1016/j.pdpdt.2021.102298

31. Muqit MM, Marcellino GR, Henson DB, Young LB, Turner GS, Stanga PE. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study Report 4. *Eye.* 2011;25(11):1447–1456. doi:10.1038/eye.2011.188

32. Abdelhalim AS, Abdelkader M, Mahmoud MSE, Mohamed Mohamed AA. Macular vessel density before and after panretinal photocoagulation in patients with proliferative diabetic retinopathy. *Int J Retina Vitreous.* 2022;8(1):21. doi:10.1186/s40942-022-00369-1

33. Huang T, Li X, Xie J, et al. Long-term retinal neurovascular and choroidal changes after panretinal photocoagulation in diabetic retinopathy. *Front Med.* 2021;8:752538. doi:10.3389/fmed.2021.752538

34. Amini Vishte R, Mirzajani A, Khojasteh H. Visual evoked potentials after panretinal photocoagulation in patients with proliferative diabetic retinopathy. *Clin Ophthalmol.* 2019;13:1635–1640. doi:10.2147/opth.S213448

35. Reddy SV, Husain D. Panretinal photocoagulation: a review of complications. *Semin Ophthalmol.* 2018;33(1):83–88. doi:10.1080/08820538.2017.1353820

36. Khojasteh H, Amini Vishte R, Mirzajani A, et al. Electroretinogram changes following sequential panretinal photocoagulation for proliferative diabetic retinopathy. *Clin Ophthalmol.* 2020;14:967–975. doi:10.2147/opth.S248678

37. Everett LA, Paulus YM. Laser therapy in the treatment of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep.* 2021;21(9):35. doi:10.1007/s11892-021-01403-6

38. Gawęcki M. Micropulse laser treatment of retinal diseases. *J Clin Med.* 2019;8(2):242. doi:10.3390/jcm8020242

39. Scholz P, Altay L, Fauser S. A review of subthreshold micropulse laser for treatment of macular disorders. *Adv Ther.* 2017;34(7):1528–1555. doi:10.1007/s12325-017-0559-y

40. Jhingan M, Goud A, Peguda HK, Khodani M, Luttrull JK, Chhablani J. Subthreshold microsecond laser for proliferative diabetic retinopathy: a randomized pilot study. *Clin Ophthalmol.* 2018;12:141–145. doi:10.2147/opth.S143206

41. Sharma S, Hariprasad SM, Mahmoud TH. Surgical management of proliferative diabetic retinopathy. *Ophthalmic Surg Lasers Imaging Retina.* 2014;45(3):188–193. doi:10.3928/23258160-20140505-01

42. Cruz-Iñigo YJ, Acabá LA, Berrocal MH. Surgical management of retinal diseases: proliferative diabetic retinopathy and traction retinal detachment. *Dev Ophthalmol.* 2014;54:196–203. doi:10.1159/000360467

43. Gupta V, Arevalo JF. Surgical management of diabetic retinopathy. *Middle East Afr J Ophthalmol.* 2013;20(4):283–292. doi:10.4103/0974-9233.120003

44. The Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study report 2. *Arch Ophthalmol.* 1985;103(11):1644–1652. doi:10.1001/archopht.1985.01050110038020

45. Canan H, Sizmaz S, Altan-Yaycıoğlu R. Surgical results of combined pars plana vitrectomy and phacoemulsification for vitreous hemorrhage in PDR. *Clin Ophthalmol.* 2013;7:1597–1601. doi:10.2147/opth.S47780

46. Liao M, Wang X, Yu J, et al. Characteristics and outcomes of vitrectomy for proliferative diabetic retinopathy in young versus senior patients. *BMC Ophthalmol.* 2020;20(1):416. doi:10.1186/s12886-020-01688-3

47. Lang GE, Stahl A, Voegeler J, et al. Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy - The PRIDE study. *Acta Ophthalmol.* 2019. doi:10.1111/aos.14312

48. Zhang W, Geng J, Sang A. Effectiveness of panretinal photocoagulation plus intravitreal anti-VEGF treatment against PRP alone for diabetic retinopathy: a systematic review with meta-analysis. *Front Endocrinol.* 2022;13:807687. doi:10.3389/fendo.2022.807687

49. Bressler SB, Liu D, Glassman AR, et al. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol.* 2017;135(6):558–568. doi:10.1001/jamaophthalmol.2017.0821

50. Giuliari GP. Diabetic retinopathy: current and new treatment options. *Curr Diabetes Rev.* 2012;8(1):32–41. doi:10.2174/157339912798829188

51. Saeed MU, Gkaragkani E, Ali K. Emerging roles for antiangiogenesis factors in management of ocular disease. *Clin Ophthalmol*. 2013;6:533–543. doi:10.2147/opth.S31016

52. Arevalo JF, Liu TYA. Intravitreal bevacizumab in diabetic retinopathy. Recommendations from the Pan-American Collaborative Retina Study Group (PACORES): the 2016 Knobloch lecture. *Asia Pac J Ophthalmol*. 2018;7(1):36–39. doi:10.22608/apo.2017466

53. Osaadon P, Fagan XJ, Lifshitz T, Levy J. A review of anti-VEGF agents for proliferative diabetic retinopathy. *Eye*. 2014;28(5):510–520. doi:10.1038/eye.2014.13

54. Shah SM, Nguyen QD, Sy JP, Ianchulev T. The RIDE and RISE studies of the efficacy and safety of intravitreal ranibizumab (LUCENTIS®) in clinically significant macular edema with center involvement secondary to diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2008;49(13):1562.

55. Mitchell P, McAllister I, Larsen M, et al. Evaluating the impact of intravitreal aflibercept on diabetic retinopathy progression in the VIVID-DME and vista-DME studies. *Ophthalmol Retina*. 2018;2(10):988–996. doi:10.1016/j.oret.2018.02.011

56. Gao S, Lin Z, Shen X. Anti-vascular endothelial growth factor therapy as an alternative or adjunct to pan-retinal photocoagulation in treating proliferative diabetic retinopathy: meta-analysis of randomized trials. systematic review. *Front Pharmacol*. 2020;11. doi:10.3389/fphar.2020.00849

57. Mehanna CJ, Abdul Fattah M, Haddad S, Tamim H, Ghazi N, Salti H. Anti-VEGF therapy for persistent neovascularization after complete panretinal photocoagulation in proliferative diabetic retinopathy. *Ophthalmol Retina*. 2019;3(6):473–477. doi:10.1016/j.oret.2019.02.001

58. Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. *Cochrane Database Syst Rev*. 2015;2015(8):Cd008214. doi:10.1002/14651858.CD008214.pub3

59. Zhao XY, Xia S, Chen YX. Antivascular endothelial growth factor agents pretreatment before vitrectomy for complicated proliferative diabetic retinopathy: a meta-analysis of randomised controlled trials. *Br J Ophthalmol*. 2018;102(8):1077–1085. doi:10.1136/bjophthalmol-2017-311344

60. Zhu ZY, Meng YA, Yan B, Luo J. Effect of anti-VEGF treatment on nonperfusion areas in ischemic retinopathy. *Int J Ophthalmol*. 2021;14 (11):1647–1652. doi:10.18240/ijo.2021.11.01

61. Chatziralli I, Touhami S, Cicinelli MV, et al. Disentangling the association between retinal non-perfusion and anti-VEGF agents in diabetic retinopathy. *Eye*. 2022;36(4):692–703. doi:10.1038/s41433-021-01750-4

62. Elnahry AG, Elnahry GA, Cicinelli MV. Optical coherence tomography angiography of macular perfusion changes after anti-VEGF therapy for diabetic macular edema: a systematic review. *J Diabetes Res*. 2021;2021:6634637. doi:10.1155/2021/6634637

63. Elnahry AG, Abdel-Kader AA, Habib AE, Elnahry GA, Raafat KA, Elrakhawy K. Review on recent trials evaluating the effect of intravitreal injections of anti-VEGF agents on the macular perfusion of diabetic patients with diabetic macular edema. *Rev Recent Clin Trials*. 2020;15 (3):188–198. doi:10.2174/1574887115666200519073704

64. Lee MW, Baek SK, Lee KH, Lee SC, Kim JY, Lee YH. Comparison of retinal layer thickness and microvasculature changes in patients with diabetic retinopathy treated with intravitreous bevacizumab vs panretinal photocoagulation. *Sci Rep*. 2022;12(1):1570. doi:10.1038/s41598-022-05513-3

65. Elnahry AG. Macular perfusion changes after anti-VEGF versus targeted retinal photocoagulation in proliferative diabetic retinopathy (PROPER). ClinicalTrials.gov. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04674254. Accessed July 12, 2022.

66. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye*. 2013;27(7):787–794. doi:10.1038/eye.2013.107

67. Kuiper EJ, Van Nieuwenhoven FA, de Smet MD, et al. The angio-fibrotic switch of VEGF and CTGF in proliferative diabetic retinopathy. *PLoS One*. 2008;3(7):e2675. doi:10.1371/journal.pone.0002675

68. Tan Y, Fukutomi A, Sun MT, Durkin S, Gilhotra J, Chan WO. Anti-VEGF crunch syndrome in proliferative diabetic retinopathy: a review. *Surv Ophthalmol*. 2021;66(6):926–932. doi:10.1016/j.survophthal.2021.03.001

69. Schargus M, Frings A. Issues with intravitreal administration of anti-VEGF drugs. *Clin Ophthalmol*. 2020;14:897–904. doi:10.2147/opth.S207978

70. Zhang Q, Qi Y, Chen L, et al. The relationship between anti-vascular endothelial growth factor and fibrosis in proliferative retinopathy: clinical and laboratory evidence. *Br J Ophthalmol*. 2016;100(10):1443–1450. doi:10.1136/bjophthalmol-2015-308199

71. Stewart MW, Browning DJ, Landers MB. Current management of diabetic tractional retinal detachments. *Indian J Ophthalmol*. 2018;66 (12):1751–1762. doi:10.4103/ijo.IJO_1217_18

72. Patz A, Fine S, Finkelstein D. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology*. 1978;85(1):82–106. doi:10.1016/s0161-6420(78)35693-1

73. Moradian S, Ahmadieh H, Malihi M, Soheilian M, Dehghan MH, Azarmina M. Intravitreal bevacizumab in active progressive proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(12):1699–1705. doi:10.1007/s00417-008-0914-4

74. Arevalo JF, Maia M, Flynn HW, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol*. 2008;92(2):213–216. doi:10.1136/bjo.2007.127142

75. 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;135(6):672–673. doi:10.1001/jamaophthalmol.2017.0969

76. Sun JK, Glassman AR, Beaulieu WT, et al. Rationale and application of the protocol s anti-vascular endothelial growth factor algorithm for proliferative diabetic retinopathy. *Ophthalmology*. 2019;126(1):87–95. doi:10.1016/j.ophtha.2018.08.001

77. Arevalo JF, Sanchez JG, Wu L, et al. Primary intravitreal bevacizumab for diffuse diabetic macular edema: the Pan-American Collaborative Retina Study Group at 24 months. *Ophthalmology*. 2009;116(8):1488–97, 1497.e1. doi:10.1016/j.ophtha.2009.03.016

78. Lee SJ, Koh HJ. Enlargement of the foveal avascular zone in diabetic retinopathy after adjunctive intravitreal bevacizumab (avastin) with pars plana vitrectomy. *J Ocul Pharmacol Ther*. 2009;25(2):173–174. doi:10.1089/jop.2008.0092

79. Stahl A, Feltgen N, Fuchs A, Bach M. Electrophysiological evaluation of retinal photoreceptor function after repeated bevacizumab injections. *Doc Ophthalmol*. 2009;118(2):81–88. doi:10.1007/s10633-008-9136-7

80. Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015;314(20):2137–2146. doi:10.1001/jama.2015.15217

81. Beaulieu WT, Bressler NM, Melia M, et al. Panretinal photocoagulation versus ranibizumab for proliferative diabetic retinopathy: patient-centered outcomes from a randomized clinical trial. *Am J Ophthalmol*. 2016;170:206–213. doi:10.1016/j.ajo.2016.08.008

82. Bressler SB, Beaulieu WT, Glassman AR, et al. Factors associated with worsening proliferative diabetic retinopathy in eyes treated with panretinal photocoagulation or ranibizumab. *Ophthalmology*. 2017;124(4):431–439. doi:10.1016/j.ophtha.2016.12.005

83. Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: secondary analysis from a diabetic retinopathy clinical research network randomized clinical trial. *JAMA Ophthalmol*. 2017;135(6):576–584. doi:10.1001/jamaophthalmol.2017.0837

84. Hutton DW, Stein JD, Glassman AR, Bressler NM, Jampol LM, Sun JK. Five-year cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(12):1424–1432. doi:10.1001/jamaophthalmol.2019.4284

85. Bressler SB, Beaulieu WT, Glassman AR, et al. Panretinal photocoagulation versus ranibizumab for proliferative diabetic retinopathy: factors associated with vision and edema outcomes. *Ophthalmology*. 2018;125(11):1776–1783. doi:10.1016/j.ophtha.2018.04.039

86. Jampol LM, Odia I, Glassman AR, et al. Panretinal photocoagulation versus ranibizumab for proliferative diabetic retinopathy: comparison of peripapillary retinal nerve fiber layer thickness in a randomized clinical trial. *Retina*. 2019;39(1):69–78. doi:10.1097/iae.0000000000001909

87. Bressler SB, Beaulieu WT, Glassman AR, et al. Photocoagulation versus ranibizumab for proliferative diabetic retinopathy: should baseline characteristics affect choice of treatment? *Retina*. 2019;39(9):1646–1654. doi:10.1097/iae.0000000000002377

88. Chiang A, Garg SJ, Klufas MA, et al. Ultra-response to ranibizumab: improvement by 4 or more steps in diabetic retinopathy severity in diabetic retinopathy clinical research network protocol S. *Ophthalmol Retina*. 2021;5(3):251–260. doi:10.1016/j.oret.2020.07.009

89. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet*. 2017;389(10085):2193–2203. doi:10.1016/s0140-6736(17)31193-5

90. Halim S, Nugawela M, Chakravarthy U, et al. Topographical response of retinal neovascularization to aflibercept or panretinal photocoagulation in proliferative diabetic retinopathy: post hoc analysis of the CLARITY randomized clinical trial. *JAMA Ophthalmol*. 2021;139(5):501–507. doi:10.1001/jamaophthalmol.2021.0108

91. Ophthalmology ICo. Updated 2017 ICO guidelines for diabetic eye care. Available from: https://vrsp.org.ph/wp-content/uploads/2018/08/ICOGuidelinesforDiabeticEyeCare.pdf?msclkid=5fa83d16cf5a11ecbba51a6d9defb584. Accessed September 2, 2022.

92. Lim JI. Laser therapy vs anti-VEGF for diabetic retinopathy, patient compliance is a key factor in treatment choice. Available from: https://www.retinalphysician.com/issues/2019/october-2019/laser-therapy-vs-anti-vegf-for-diabetic-retinopath. Accessed September 2, 2022.

93. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(10):1138–1148. doi:10.1001/jamaophthalmol.2018.3255

94. Abdelmotaal H, Ibrahim W, Sharaf M, Abdelazeem K. Causes and clinical impact of loss to follow-up in patients with proliferative diabetic retinopathy. *J Ophthalmol*. 2020;2020:7691724. doi:10.1155/2020/7691724

95. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. *Ophthalmology*. 2019;126(3):407–413. doi:10.1016/j.ophtha.2018.07.027

96. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol*. 1985;103(12):1796–806.

97. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early treatment diabetic retinopathy study report number 2. *Ophthalmology*. 1987;94(7):761–774. doi:10.1016/S0161-6420(87)33527-4

98. Bhagat PR, Agrawal KU, Tandel D. Study of the effect of injection bevacizumab through various routes in neovascular glaucoma. *J Curr Glaucoma Pract*. 2016;10(2):39–48. doi:10.5005/jp-journals-10008-1200

99. Vergmann AS, Sørensen KT, Torp TL, et al. Optical coherence tomography angiography measured area of retinal neovascularization is predictive of treatment response and progression of disease in patients with proliferative diabetic retinopathy. *Int J Retina Vitreous*. 2020;6(1):49. doi:10.1186/s40942-020-00249-6

100. Papayannis A, Tsamis E, Stringa F, Iacono P, Battaglia Parodi M, Stanga PE. Swept-source optical coherence tomography angiography vitreo-retinal segmentation in proliferative diabetic retinopathy. *Eur J Ophthalmol*. 2021;31(4):1925–1932. doi:10.1177/1120672120944028

101. Vaz-Pereira S, Morais-Sarmento T, Engelbert M. Update on optical coherence tomography and optical coherence tomography angiography imaging in proliferative diabetic retinopathy. *Diagnostics*. 2021;11(10):1869. doi:10.3390/diagnostics11101869