Chapter

Treatment Algorithm in Proliferative Diabetic Retinopathy. From Protocols to the Real World

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Abstract

Diabetes mellitus is a global epidemic that leads to multiple macrovascular and microvascular complications. The complex interrelated pathophysiological mechanisms triggered by hyperglycemia underlie the development of diabetic retinopathy (DR). Proliferative diabetic retinopathy (PDR) is a microvascular complication, considered the main cause of irreversible blindness in patients of productive age in the world. On the other hand, diabetic macular edema (DME) remains the clinical feature most closely associated with vision loss. In general, both manifestations are due to an increase in inflammatory factors, such as specific pro-inflammatory prostaglandins, interleukins and angiogenic substances including vascular endothelial growth factor (VEGF). Laser photocoagulation and VEGF inhibitors have been shown to be effective in the treatment of PDR and DME. Currently, randomized protocols suggest that VEGF inhibitors therapy could displace laser photocoagulation in the treatment of PDR with and without the presence of DME. The ongoing discussion still prevails about the different treatment modalities for both retinal manifestations in real-world settings.

Keywords: proliferative diabetic retinopathy, diabetic macular edema, treatment algorithm, treatment guidelines, panretinal photocoagulation, antiangiogenic therapy

1. Introduction

Diabetic retinopathy (DR) is characterized by progressive damage to retinal capillaries causing retinal ischemia. In severe cases, it leads to DR, which threatens vision induced by angiogenesis [1]. Vascular endothelial growth factor (VEGF) is an important agent in the development and progression of DR and diabetic macular edema (DME) [2, 3].

The Early Treatment of DR (ETDRS) study showed that focal photocoagulation of "clinically significant" DME reduces the risk of visual loss and increases the chances of visual improvement, decreases the frequency of persistent DME, and causes minor visual field losses [4]. Panretinal photocoagulation (PFC) has been the

standard treatment for proliferative diabetic retinopathy (PDR) since the DR study (DRS) demonstrated its benefit more than 40 years ago [5]. PFC has demonstrated permanent peripheral visual field loss and decreased night vision. On the other hand, it can exacerbate existing DME or increase its incidence. Different treatment alternatives in PDR should be considered [6].

DME can affect the macular center considering it as "with center-involving" (CI-DME) or it can respect the same, considering it as "non-center-involving" (NCI-DME). Anti-angiogenic (anti-VEGF) therapy in DME, has shown superior visual acuity results and acceptable risks compared to focal, grid, or untreated laser, and has also led to the observation that DR lesions can be reversed during treatment [7–14]. Anti-VEGF therapy is currently considered the first-line treatment for DME.

The objective of this chapter is to describe an algorithm in the treatment of PDR based on current publications that could be used in real-world scenarios and different practice settings.

2. Current treatments in DME and PDR

According to the results of the DRCR.net Protocol S, at two years of follow-up, intravitreal ranibizumab (RBZ) achieved the result of non-inferiority in the change of best-corrected visual acuity (BCVA), which was no worse than in the PFC group treatment for PDR [15]. There were no statistically significant differences in BCVA between the RBZ and PFC groups, with the recognition that 53% of the PFC group received additional RBZ injections to treat DME and only 6% of the RBZ group required PFC. There was greater peripheral visual field loss (95% CI for difference, 213–531 dB) and more vitrectomies (PPV) were performed (95% CI for one difference, 4% -15%) in the PFC group compared to the RBZ group. In addition, RBZ-treated eyes were less likely to develop CI-DME causing visual impairment of 20/32 or worse, similar to the 1-year results with aflibercept (AFB) in the CLARITY randomized clinical trial [16]. In the DRCR.net Protocol S, a greater number of patients in the PFC group developed DME (28 vs. 9). At 5-year results, the mean number of injections in the PFC group was 7.9 and 19.2 in the RBZ group. The mean final BCVA in both groups was 20/25. Despite the fact that at 2 years the PFC group presented a greater visual field loss, the decrease in the peripheral visual field progressed in both groups during the following 5 years of follow-up [17].

In a post hoc analysis of the DRCR.net Protocol T [18], after 2 years of follow-up, an improvement in DR severity was demonstrated by approximately 25% for AFB, 22% for bevacizumab (BVZ) and 31% for RBZ in patients without proliferative-DR (NPDR) at baseline. This analysis also suggests a secondary benefit of DME after intravitreal AFB with respect to improvement in DR severity among patients who had PDR from baseline. Anti-VEGF therapy for DME improves the score of the DR severity scale (DRSS), evaluated in color fundus photos and can reduce the deterioration of the edema. Other randomized trials comparing anti-VEGF therapy and PFC in PDR, have demonstrated the non-inferiority of anti-VEGF over PFC in preventing PDR complications, at least during the first 2 years [19, 20]. Similar studies using ultra-wide-field (UWF) photographs and comparing them with ultra-wide-field fluorescein angiography (UWF-FAG) or wide field swept source optical coherent tomography (WF-SS-OCTA) in eyes with DR and DME [21, 22], conclude that after injections with anti-VEGF, improvement in the DRSS score can occur without vessel reperfusion or retinal capillary in UWF-FAG or WF-SS-OCTA. Therefore, the strong correlation between the number of lesions in DR and the areas of non-perfusion, established before any treatment, could no longer be relevant after anti-VEGF therapy. These results should be taken into account in future

studies, in order to demonstrate an improvement in peripheral retinal perfusion in DR after anti-VEGF therapy.

3. Changing paradigms in the treatment of PDR

Taking into account specific scenarios of PDR proposed by Sun JK et al. [23], based on the results of the DRCR.net Protocol S [15] in addition to considering the different advantages of each treatment modality, we describe a treatment algorithm that could be used in real-world scenarios and in different practice settings.

3.1 PDR without DME

Both PFC and anti-VEGF therapy are feasible therapeutic options. Anti-VEGF therapy is effective in reversing retinal neovascularization (NV) and reducing the risk of developing DME. However, it may not be cost effective overall [24].

A. If starting PFC.

- Add anti-VEGF only in case NV significantly worsens (**Table 1**) and/or DME develops (**Table 2**).

B. If starting anti-VEGF, it is suggested to perform it according to the treatment algorithm proposed by Protocol S (**Table 1**).

- If NV worsens significantly, adding PFC should be considered.

- If NV does not require further anti-VEGF and during the "sustain stability" period DME develops, add focal macular laser or anti-VEGF (**Table 2**).

The advantages and disadvantages of treatment options should be considered, as well as the individual conditions of the patient.

3.2 PDR with NCI-DME

Anti-VEGF therapy has been accepted as a first-line treatment in DME, displacing laser as a second-line therapy. Although some authors suggest the application of laser in NCI-DME [25–27], there are reports where the addition of conventional, subthreshold or micropulse laser does not add benefits to pharmacological monotherapy in any form of presentation [28–30].

1	Start with 6 monthly anti-VEGF injections (only with one exception), If the NV resolves after 4 or 5 injections, the injections may be postponed.
2	After 6 months, continue the anti-VEGF injections if NV continues to progress or continues to improve; but defer injections if NV is stable at current visit and last 2 visits ("sustained stability").
3	Resume anti-VEGF injections monthly if NV worsens after stopping injections. If "sustained stability" is achieved again, the injections can be postponed once more, but this requires at least 3 consecutive anti-VEGF injections again; one administered for the initial state of progressive NV and 2 more if the NV remains stable.

PFC is given only if NV is substantially worse despite anti-VEGF. Onset or worsening of preretinal or vitreous hemorrhage is not necessarily classified as worsening of NV, unless bleeding precludes evaluation of NV.

Table 1.
Algorithm for the treatment of PDR according to DRCR.net protocol S.

1	Start with 3 monthly ant-VEGF injections or until you achieve maximum improvement (loading phase).
2	After the loading phase, continue injecting according to reactive (Treat and Observe or Pro Re Nata) or proactive (Treat and Extend) behavior.

Table 2.
Algorithm for the treatment of DME.

A. If starting focal macular laser and PFC.

- Add anti-VEGF in case DME worsens (**Table 2**) and/or there is significant progression of NV (**Table 1**).

B. If starting anti-VEGF for DME (**Table 2**). *PFC can be deferred since the same anti-VEGF may control both (DME and PDR).*

- If DME does not require further anti-VEGF, NV status should be re-evaluated.

- If NV worsens significantly, it is suggested to decide on therapy according to Section 3.1 B (PDR without DME).

- In case of new DME activity, it is suggested to reactivate anti-VEGF therapy.

C. In the event that the DME has a poor or no response, several options should be considered (switching anti-VEGF, focal macular laser, dexamethasone implant, etc.).

Advantages and disadvantages of treatment options should be considered, as well as the individual conditions of the patient.

3.3 RDP with CI-DME

Anti-VEGF is considered first- line treatment in CI-DME. RBZ and AFB were highly effective in treating PDR [15, 16].

A. Anti-VEGF is recommended as first-line treatment in CI-DME (**Table 2**). *PFC can be deferred since the same anti-VEGF may control both (DME and PDR).*

- If DME does not require further anti-VEGF, NV status should be re-evaluated.

- If NV worsens significantly, it is suggested to decide on therapy according to Section 3.1 B (PDR without DME).

- In case of new DME activity, it is suggested to reactivate anti-VEGF therapy.

B. In the event that the DME has a poor or no response, several options should be considered (switching anti-VEGF, focal macular laser, dexamethasone implant, etc.).

Advantages and disadvantages of treatment options should be considered, as well as the individual conditions of the patient.

3.4 High-risk PDR with or without vision- impairing DME

Eyes with high-risk PDR (i.e., ≥ ETDRS level 71) face the greatest risk of severe vision loss without intervention [4, 5]. Eyes with the most advanced forms of PDR have the largest relative benefit of RBZ compared with PRP when managing PDR. Also, RBZ was superior to PRP with respect to change in visual acuity over 2 years and prevention of vision-impairing CI-DME over 2 years, regardless of baseline characteristics [31]. On the other hand, combined therapy has shown benefits in the management of high-risk PDR.

- Anti-VEGF should be considered as monotherapy (**Table 1**).
- If NV worsens significantly, it is suggested to decide on therapy according to Section 3.1 B (PDR without DME).

Although anti-VEGF may be recommended as monotherapy in eyes with high-risk PDR, complete PRP within the effective period of anti- VEGF agents might be recommended. Advantages and disadvantages of treatment options should be considered, as well as the individual conditions of the patient.

3.5 Worsening PDR

Worse baseline levels of DR severity (ETDRS scale) were associated with increased risk of worsening PDR (e.g., vitreous hemorrhage (VH), retinal detachment (RD), angle neovascularization (ANV), or neovascular glaucoma (NVG)), regardless of treatment with PRP or RBZ. There were generally fewer PDR-worsening events (e.g., VH, RD, ANV, or NVG) in eyes treated with RBZ versus PRP for PDR. Through 2-year, the cumulative probability of worsening PDR was 42% for PRP versus 34% for RBZ. The 2-year cumulative probability of VH was 39% for the PRP group and 30% for the RBZ group. The 2-year cumulative probability of RD was low in each treatment group at 11% for the PRP group and 5% for the RBZ group [20]. The fact that worsening PDR events were at higher rates in the PRP group, suggests that at least during the first two years of follow-up:

- Anti-VEGF should be considered as monotherapy (**Table 1**).
- If NV worsens significantly, it is suggested to decide on therapy according to Section 3.1 B (PDR without DME).

As in the eyes with high-risk PDR, complete PRP within the effective period of anti- VEGF agents might be recommended. Advantages and disadvantages of treatment options should be considered, as well as the individual conditions of the patient.

3.6 Vitrectomy for PDR

Eyes in both groups (RBZ or PRP) had visual loss associated with VH, being more severe in the PRP group. The protocol required investigators to wait at least 8 weeks for a nonclearing VH before proceeding to vitrectomy (in the absence of known RD, iris NV, or ANV). VH was the primary indication for most PPV, 24 (80%) procedures in the PRP group and 6 (75%) procedures in the RBZ group. Endolaser or indirect ophthalmoscopic laser during PPV were applied in 80% of procedures in the PRP group and in all procedures in the RBZ group. Only 1 eye in

the RBZ group received PRP independent of PPV. Possibly for convenience, the not masked investigators, decided to continue observing VH before proceeding to PPV in the RBZ group. The authors note that because VH, only 13% (7/52) in the RBZ group compared to 42% (29/69) in the PRP group underwent PPV at the end of 2 years. Therefore, because VH was the main indication for surgery in both groups, the reduced incidence of VH in the RBZ group and the potential difference in VH severity may explain the finding that eyes in the PRP group were more likely to undergo vitrectomy [20]. Although several studies do not support the hypothesis that anti-VEGF administered to an eye with PDR, with or without high-risk features (but without macular-threatening traction at baseline), causes tractional RD (TRD) more often than eyes with PRP [7, 28, 32], we must consider the possibility of additional PPV in these patients.

4. Discussion

In clinical practice, treating PFC with one or more sessions may be sufficient to control PDR and no additional procedures are required. On the other hand, the cost of laser therapy is less expensive than anti-VEGF therapy and there is no risk of endophthalmitis or systemic adverse events [15]. The DRCR.net in a cost–benefit analysis regarding RBZ or PFC monotherapy for PDR, noted that it was more appropriate to start with PFC for patients with PDR without associated DME and RBZ for those with DME at the time of treatment detection [33]. Therefore, the relative benefits of treating PDR with anti-VEGF versus PFC could be considered in a patient presenting with DME, where anti-VEGF therapy is generally necessary, as long as the patient adheres to treatment and is able to access it. In Mexico, as in some countries, it is possible to adopt the algorithm suggested by the DRCR.net Protocol S; however, the circumstances of patients and environment could modify the scheme. Likewise, the advantages and disadvantages of treatment options should be considered, in addition to socioeconomic conditions, adherence to treatment, and access to "off-label" medications.

It is generally known that the pathogenesis and progression of DR involves changes in the vitreous structure and its relationship with the vitreoretinal interface [34–40]. A study whose objective was to evaluate the costs and usefulness of early PPV compared to PFC and intravitreal RBZ in PDR patients without DME, using a "decision analysis" based on the results of DRCR.net Protocol S at 2 years of treatment for each scenario, concluded that PPV as a treatment strategy demonstrates a similar cost utility to treatment with PFC and a more favorable cost utility compared to short-term intravitreal RBZ therapy [41]. This advantage over anti-VEGF is continuing when lifetime costs are considered. The safety of anti-VEGFs compared to primary PPV (without anti-VEGF) for persistent VH is being evaluated in the Protocol AB.

Currently, the PANORAMA study [42], a double-masked, randomized phase 3 trial, the objective of which is to evaluate the efficacy and safety of intravitreal injection of AFB compared to sham therapy in improving moderate-to-severe NPDR in the absence of CI-DME, demonstrate at week 24 that AFB improved the severity of DR in patients with moderately severe to severe NPDR and suggests that anti-VEGF can reverse disease progression in these patients.

In turn, there is interest if steroid therapy in the treatment of DME can delay the progression or even improve DR. Corticosteroids inhibit the inflammatory processes involved in DME, including the production of pro-inflammatory mediators, increased levels of VEGF, and the loss of endothelial tension-binding proteins [43, 44]. There are clinical trials that have shown some benefit of intravitreal steroids

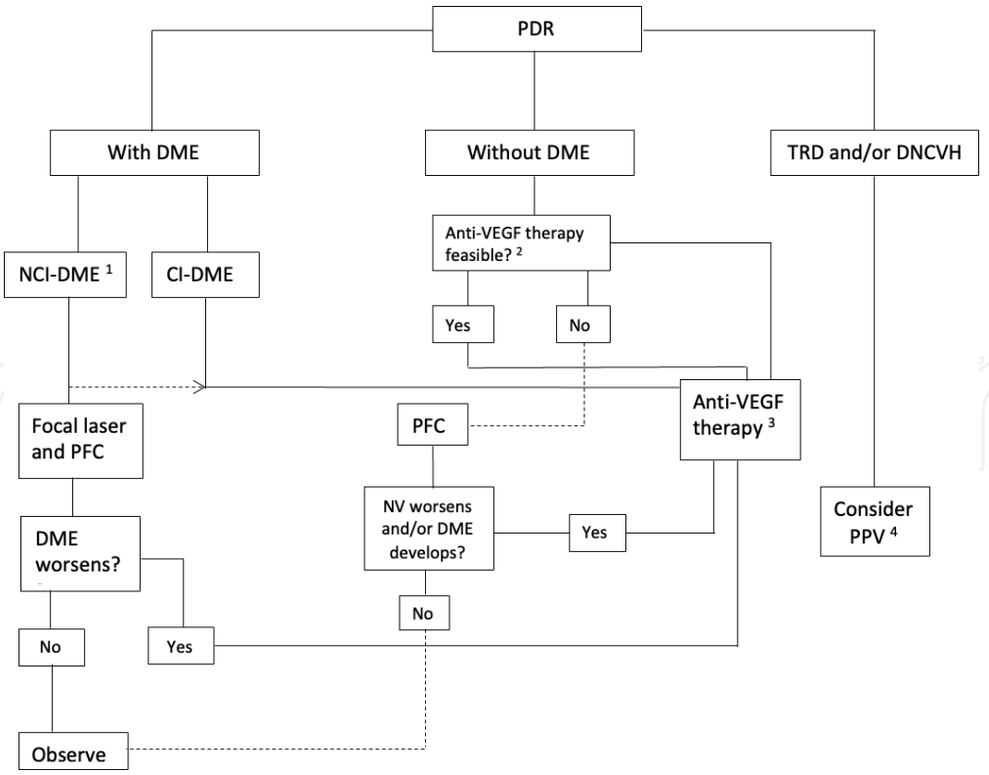

Figure 1.
Treatment flow-chart in different presenting PDR scenarios. DME: Diabetic macular edema; DNCVH: Dense non-clearing vitreous hemorrhage; CI-DME: Center-involving diabetic macular edema. NCI-DME: Non-center-involving diabetic macular edema; NV: New vessels; PDR: Proliferative diabetic retinopathy; PFC: Panretinal photocoagulation; TRD: Tractional retinal detachment threatening or involving macula; PPV: Pars plana vitrectomy. [1]If starting anti-VEGF for DME, PFC can be deferred since the same anti-VEGF may control both DME and PDR. [2]Consider factors such as risk of non-compliance, treatment cost, and treatment burden. [3]Cases with TRD should not receive only anti-VEGF therapy due to increased traction progression risk. [4]Anti-VEGF injection can be applied a few days before PPV is performed to decrease intraoperative and postoperative VH.

in the progression of DR. [12, 45] The "DR-Pro-Dex" study provides the first long-term evidence that the dexamethasone implant has the potential to not only delay the progression of DR and PDR but may also improve the severity of DR in 24 months [46]. On the other hand, the results of the "TRADITION" study conclude that the implantation of dexamethasone at the end of a PPV in patients with TRD improves the severity of PDR and reduces the detachment rates [47].

In the case of DME, the little or no response of the anti-VEGF used and its relationship with persistent peripheral retinal ischemia require modifications in treatment. Alternatives should be considered such as: switching from anti-VEGF, intravitreal dexamethasone implant, additional PFC (peripheral retina), PPV or combining treatments. Although anti-VEGF monotherapy achieves stabilization of NV in PDR, adding PFC could result in a lower frequency of intravitreal applications, resulting in lower risks and costs for the patient.

In **Figure 1**, a flow-chart of treatment modalities for different presenting PDR scenarios is shown.

5. Conclusion

In general, the objective to achieve success in the treatment of PDR and DME is the inhibition of VEGF and pro-inflammatory factors, a condition that seems to be obtained more efficiently with pharmacological therapy in relation to retinal ablation. Currently the indications for laser, intravitreal drug therapy (anti-VEGF's and

anti-inflammatory steroids) and PPV are increasingly clear. Based on the results previously mentioned, anti-VEGF therapy appears to be emerging as first-line therapy in PDR, as is currently suggested in the treatment of DME. Treatment regimens in patients with severe NPDR with or without DME, may be indifferent to those currently suggested in PDR patients with or without DME; including that early PPV is an alternative to prevent retinal complications of diabetic microvascular disease. This chapter suggests a treatment algorithm for PDR in different settings; however, we must not forget that both DME and PDR are different manifestations of DR and therefore must be assessed individually. Treatment decisions can be different for each manifestation and can be modified depending on its behavior. Several protocols are currently being developed to more accurately understand the behavior of PDR and DME in different settings and to provide a more solid foundation for an effective and timely treatment scheme.

6. Protocols in progress

1. **Protocol W:** Safety and efficacy of AFB vs. observation in severe NPDR and BCVA ≥20/25 without DME and without previous treatment, to assess the appearance of edema or progression of retinopathy.

2. **Protocol AA:** To evaluate lesions in the peripheral DR and their association with the progression of retinopathy in patients with NPDR, without DME or previous treatment, comparing UWF images vs. standard photographs of the seven fields (ETDRS) in order to determine if UWF photographs contribute more information than conventional ones.

3. **Protocol AB:** Treatment of early PPV versus ARB in vitreous secondary to PDR is compared by evaluating BCVA at 6 months of treatment.

4. **Protocol AD (PROMINENT):** To assess whether treatment with pemfibrate (0.2 mg / 12 h orally) compared with placebo reduces the rate of worsening of DR in patients with type 2 diabetes and NPDR.

5. **Protocol GEN:** Create a genetic material and information on the clinical phenotype, which allows evaluating genetic susceptibility or resistance in DR and determining variants on key biomarkers in the development of DME and NV.

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