

The Anti-VEGF Arsenal in the Fight Against Diabetic Retinopathy

A brief look at the role of pharmacologic agents commonly used to treat patients with diabetic eye disease.

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Diabetic retinopathy (DR) is a common microvascular complication of type 1 and type 2 diabetes mellitus (DM). More than 60% of people with type 2 DM and more than 90% of patients with type 1 DM develop DR within the first 20 years after diagnosis.¹ Duration of DM and control of hyperglycemia are the two greatest risk factors for developing DR.²

Clinically, DR is characterized by increasing intraretinal hemorrhages and lipid exudates, microaneurysms, areas of retinal ischemia, intraretinal microvascular abnormalities, retinal neovascularization, tractional retinal detachment, and vitreous hemorrhage, all leading to reduction in vision. The severity of DR can be seen to progress through stages, starting with mild nonproliferative DR (NPDR) and ending with severe proliferative DR (PDR). DR is classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) group classification as mild, moderate, severe, or very severe NPDR or early versus high risk for PDR.^{3,4} Approximately 50% of patients with very severe NPDR progress to PDR within 1 year.⁵

EARLY APPROACHES TO DR TREATMENT

The landmark Diabetic Retinopathy Study first showed the benefit of laser photocoagulation or panretinal photocoagulation (PRP) in the treatment of DR.⁶⁻⁸ Since the time of this trial, PRP has become a mainstay in the treatment of DR, specifically high-risk PDR. Patients who received PRP in this study had a greater than 50% decrease in the rate of severe visual acuity loss.⁹

Adverse effects associated with PRP can include pain during treatment, nyctalopia, loss of peripheral field of vision, worsening of macular edema, uveal effusion, vitreous hemorrhage, and loss of central vision. Additionally,

the presence of media opacities can make performing PRP difficult or impossible. Given these limitations, clinicians have searched for other therapeutic modalities with potentially less destructive tissue effects and the possibility of reducing risk of progression to PDR and severe visual acuity loss. Pharmacotherapy—in the form of anti-VEGF agents—has shown promise in the treatment of DR, much as it has already been shown to be effective in treating diabetic macular edema (DME). Other agents, such as candesartan, cilexetil, and intravitreal corticosteroids, have also demonstrated some efficacy against DR progression; however, these agents are not discussed in this article.¹⁰⁻¹²

ANTI-VEGF DRUGS: THE BIG PICTURE

VEGF is considered to be a key player in the process of neovascularization in PDR.¹³ VEGF activates VEGFR-1 and VEGFR-2, both tyrosine kinase receptors involved in the regulation of angiogenesis. VEGFR-2 is expressed mainly on vascular endothelial cells, and, when activated,

At a Glance

- Shown to be effective in the treatment of DME, anti-VEGF pharmacotherapy has also shown promise in the treatment of DR.
- Anti-VEGF therapy's value in treating DR without active DME is still under review, but it is promising.
- Results from the DRCR.net Protocol S phase 3 study comparing prompt PRP with ranibizumab with deferred PRP for patients with PDR will add value to the existing data.

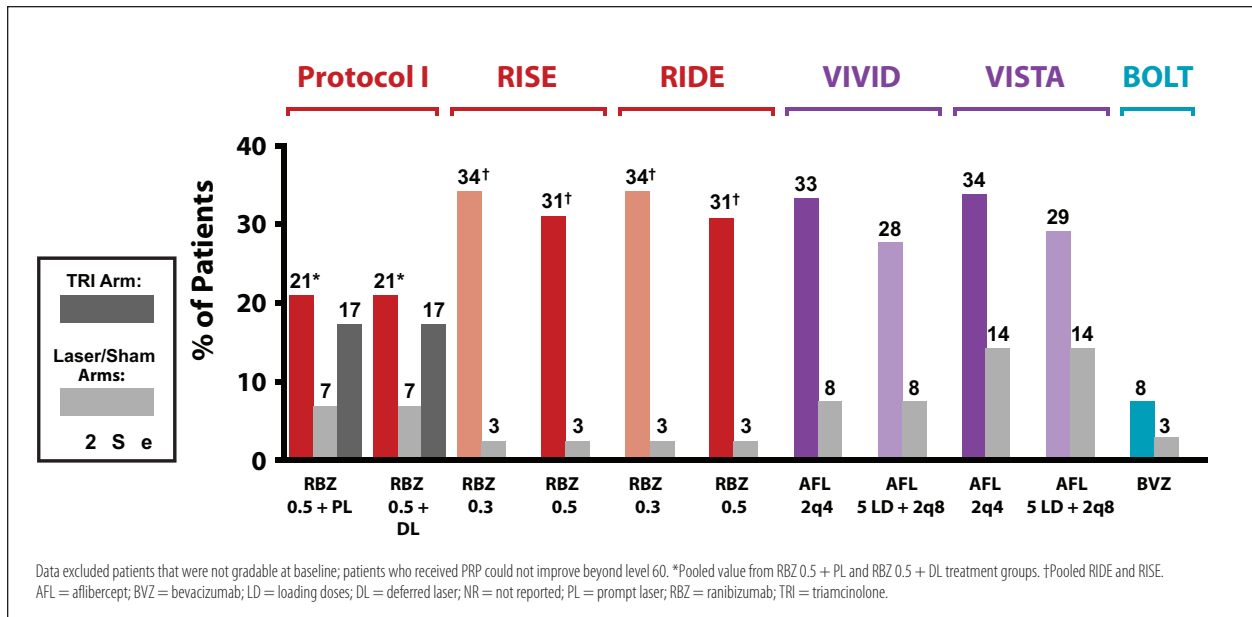


Figure. Year 1 improvement in DR. Treatment with anti-VEGF therapy significantly improved DRSS compared with laser/sham treatment.

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it stimulates endothelial cell proliferation, migration, survival, and angiogenesis in PDR.¹⁴ Inhibition of VEGF, therefore, represents an important treatment strategy for retarding and potentially reversing DR. Intraocular levels of VEGF are correlated with the severity of DR.¹⁵ In addition, as VEGF levels increase in the eye, a positive feedback loop is created, further enhancing intraocular ischemia and thus promoting further VEGF release. Given this situation, a rational approach to halting this feedback loop would be to block VEGF release or VEGF receptor binding.

The introduction of anti-VEGF medications for treatment of DME has resulted in a paradigm shift in the treatment algorithm for this blinding condition. Several studies have demonstrated the superiority of anti-VEGF agents over macular laser photocoagulation for treatment of DME.¹⁶⁻¹⁹ A number of trials have also shown that, when DME is treated with anti-VEGF therapy, many patients exhibit a reduction in DR as a positive byproduct.¹⁸⁻²⁰

AVAILABLE ANTI-VEGF AGENTS

Four anti-VEGF agents have been approved by the US Food and Drug Administration (FDA) for various clinical indications: bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and pegaptanib (Macugen, Bausch + Lomb).

Because pegaptanib has limited data and use in the treatment of DR, it is not discussed in this article.

Bevacizumab

Approved by the FDA for the treatment of colorectal and other cancers, bevacizumab is used by ophthalmologists as an off-label medication in the treatment of various VEGF-mediated eye diseases including DME and DR. Although several trials support the drug's use in the treatment of DME, limited randomized, prospective data exist evaluating its effect in preventing DR progression.²¹⁻²⁶ The BOLT trial found suggestions of a small reduction in the progression of DR in treated patients.²⁵

Ranibizumab

Ranibizumab is a monoclonal antibody fragment derived from the same murine antibody as bevacizumab.²⁷ Based on the results of the RISE and RIDE studies, ranibizumab received FDA approval for the treatment of DME in 2012.^{5,28} Those two trials also evaluated the effect of ranibizumab dosed monthly versus sham treatment on the progression of DR over 2 years as secondary and exploratory analyses. Patients were graded based on the ETDRS severity scale (DRSS). In total, 759 patients were randomly assigned to sham or monthly ranibizumab treatments. In the sham group, the median DR level remained at moderately severe NPDR through the course of the study. In contrast, in the

ranibizumab group, the median DR level decreased from moderately severe to mild NPDR over the 24 months. Significantly fewer eyes in the ranibizumab group worsened by 2 or more steps on the DRSS from baseline to month 24 compared with the sham group (1.7-2.1% compared with 9.6%, respectively). Treated eyes also experienced less vitreous hemorrhage.²⁹ Ranibizumab received FDA approval in 2015 for treatment of DR in the presence of DME.

Aflibercept

A fusion protein composed of key domains of human VEGF 1 and 2 receptors fused to the Fc domain of human immunoglobulin G1, aflibercept binds and inhibits both VEGF-A and placental growth factor.³⁰ The efficacy of this drug as DME therapy is supported by two phase 3 trials, VIVID and VISTA, which also evaluated the effect of aflibercept on DR compared with laser control as a pre-specified secondary endpoint (ie, the proportion of eyes with a ≥ 2 -step improvement in the DRSS).¹⁹ A statistically greater proportion of eyes treated with aflibercept at both 4- and 8-week intervals had a 2-step or greater improvement in DRSS score in both VIVID (33.3% and 27.7% vs 7.5%, respectively; $P < .001$) and VISTA (33.8% and 29.1% vs 14.3%, respectively; $P < .01$). These results were the basis for the FDA's approval in 2015 of aflibercept for treatment of DR in the presence of DME.

THE FUTURE OF ANTI-VEGF TREATMENT FOR DR

The prevention of PDR as a result of the regression or stabilization of the level of DR was a welcome result from the pivotal phase 3 ranibizumab and aflibercept trials. The value of the application of anti-VEGF therapy for DR in clinical practice remains to be seen. Although data are currently limited to DR patients with concurrent DME, it seems fair to extrapolate these results to patients without active DME, given that VEGF has been shown to mediate more than just DME in DR.³¹

Furthermore, questions remain, such as how effective anti-VEGF therapy is in preventing DR progression when dosed in a less-than-fixed fashion (ie, with an as-needed or treat-and-extend strategy). In both the BOLT trial²⁵ and the Protocol I study³² by the Diabetic Retinopathy Clinical Research Network (DRCR.net), patients were dosed in a less-than-monthly fashion, and improvement in DR was demonstrated in the treatment groups, although not to the extent seen in the fixed-dosing treatment arms in RISE and RIDE or VIVID and VISTA (Figure).

Another unanswered question relates to how DR may progress in patients after discontinuation of anti-VEGF therapy. The ongoing DRCR.net Protocol S study is a phase 3 trial comparing prompt PRP with ranibi-

zumab with deferred PRP in patients with PDR. The results of this trial will be an interesting addition to the existing data on anti-VEGF use in DR. This study should also document and compare the extent of damage to peripheral vision resulting from laser, as visual fields will be obtained in many patients in both treatment arms.

CONCLUSION

The introduction of anti-VEGF agents to the list of treatment options has resulted in a fundamental change in the treatment algorithm for DME. The positive effects of anti-VEGF agents on levels of DR is an exciting finding, and the possibility of arresting or in some cases reversing the disease makes these agents welcome additions to existing treatment regimens. Soon, we may be deciding once again between laser and anti-VEGF therapy, but this time in the setting of proliferative or preproliferative disease. Could this be the end of PRP? We doubt it, but more customized care with combination approaches will likely become more widespread. ■

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