MANAGING DIABETIC EYE DISEASE WITH INTRAVITREAL ANTI-VEGF INJECTIONS

Key clinical trials compare the use of anti-VEGF agents alone and in conjunction with laser therapy.

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For decades, standard-of-care treatment for patients with diabetic retinopathy (DR) revolved around optimization of systemic well-being with glycemic control and blood pressure management. Diabetic macular edema (DME) was typically managed with focal and grid laser photocoagulation, and panretinal photocoagulation (PRP) was applied for cases of high-risk proliferative disease.¹-³

Although laser strategies are still used in managing diabetic eye disease, the paradigm is shifting toward use of serial intravitreal anti-VEGF injections, particularly for the treatment of patients with DME. As a result, retina specialists are now equipped with targeted therapies that have substantially improved their ability to combat blinding disease. This article explores the rationale in using anti-VEGF therapy and highlights recent insights gained for managing patients with diabetic eye disease.

THE VEGF CONNECTION TO DIABETIC EYE DISEASE

Microvascular damage caused by chronic hyperglycemia due to diabetes can lead to DR. Increased disease duration and worsening glycemic control represent major risk factors for initial development of DR and subsequent progression through advancing stages.⁴ Therefore, optimization of systemic well-being is fundamental in managing DR. The development of ocular neovascularization separates nonproliferative stages from proliferative DR (PDR).

Exact mechanisms of DR development are unknown, but structural and biochemical abnormalities are implicated. Loss of pericytes and endothelial cells are histopathological features of DR. These factors, which lead to breakdown of the blood-retina barrier along with vascular hyperpermeability of microaneurysms, is believed to contribute to the development of DME. Although many cytokines are implicated in the pathophysiology of DR, VEGF has a substantial role. In fact, VEGF was first called vascular permeability factor due to its property of increasing the permeability of blood vessels.⁵,⁶

VEGF is induced by hypoxia and is elevated in the vitreous of eyes undergoing vitrectomy for PDR.⁷,⁸ Anti-VEGF injections into the vitreous humor can induce regression of neovascularization and reduce vascular permeability, which are both beneficial effects for patients with DR.

ANTI-VEGF DRUGS VS. DIABETIC EYE DISEASE

The anti-VEGF molecules that have been extensively tested intravitreally for treatment of DR and DME include pegaptanib (Macugen, Bausch + Lomb); bevacizumab (Avastin, Genentech); ranibizumab (Lucentis, Genentech); and aflibercept (Eylea, Regeneron). At this time, bevacizumab is not approved by the US Food and Drug Administration for intravitreal indications; however, it is commonly used off label in this manner. Although inhibition of VEGF is common among these drugs, their pharmacologic profiles and

AT A GLANCE

- VEGF plays a substantial role in the pathophysiology of DR.
- Serial intravitreal anti-VEGF injections have become the standard of care in patients with center-involved DME.
- Evidence exists that serial intravitreal anti-VEGF injections can prevent PDR onset and may have durable effects.
Pharmaceutical charges vary by region, but, on average, 1.25 mg of bevacizumab costs approximately $70, 0.3 mg of ranibizumab costs around $1200, and 2.0 mg of aflibercept costs nearly $2000.

DME

DME is a leading cause of vision loss in people with DR. In the early 1980s, the ETDRS study defined the role of laser photocoagulation in reducing the risk of vision loss from swelling in the macula. However, substantial gains were rarely seen. Within the past 5 years, pivotal clinical trials have established the superior outcomes of serial intravitreal anti-VEGF injections compared with focal or grid laser photocoagulation, independent of the agent utilized. Specifically, the BOLT trial and the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study provide the best evidence for bevacizumab. The RISE and RIDE studies demonstrated the benefit of ranibizumab, and VIVID and VISTA evaluated aflibercept. As a result of these trials, serial intravitreal anti-VEGF injections have become the standard of care for individuals with center-involved DME and visual compromise.

With multiple drug options and substantial cost differences, the DRCR.net Protocol T study was developed to directly compare serial intravitreal injections of bevacizumab, ranibizumab, and aflibercept in 660 subjects with center-involved DME over 1 year. Treatment algorithms dictated therapy as determined by visual acuity and central retinal thickness on optical coherence tomography (OCT). Application of focal or grid laser was permitted beyond week 24 if DME was not improving. All three anti-VEGF agents demonstrated improvements in visual acuity (Figure, A). According to a prespecified subgroup analysis, individuals with worse initial visual acuity (≤ ETDRS 20/50) had a statistically significantly better response to the use of aflibercept in terms of visual acuity, OCT thickness, and frequency of laser application (Figure, B). This benefit of aflibercept was also clinically meaningful, with an increased likelihood of gaining 3 lines compared with bevacizumab or ranibizumab. Two-year outcomes will be examined to determine whether this effect is persistent and to help guide future clinical care.

PDR

With neovascularization comes increased risk of visual acuity loss from complications such as vitreous hemorrhage and tractional retinal detachment (TRD). Fifty percent of
Recent evidence suggests that serial intravitreal anti-VEGF injections can prevent PDR onset, and repeated use may have durable effects.
should always be applied to attached retina preoperatively when available due to the high likelihood of improvement with time and the benefit of retinectomy. 17,19 Complications of surgery include early and delayed recurrent vitreous hemorrhage due to persistent ocular neovascularization. Several studies have examined the role of perioperative anti-VEGF injections on surgical outcomes. Preoperative bevacizumab has been associated with decreased duration of surgery, fewer retinal breaks, less intraoperative bleeding, less endodiathermy application, and a lower likelihood of early postoperative recurrent vitreous hemorrhage. 25-32

CONCLUSION

Anti-VEGF treatment is a truly revolutionary breakthrough for managing complications of DR. The pendulum has already swung away from focal or grid laser, a standard of care for DME that had persisted for decades, in favor of intravitreal anti-VEGF injections. Furthermore, these injections provide superior outcomes when used to facilitate clearance of vitreous hemorrhage, when combined with PRP, and before vitrectomy. We may be on the cusp of a similar paradigm shift for treatment of PDR or uncomplicated DR. The temporary effect of intravitreal injections, combined with the unreliable nature of patient follow-up, mandates that caution be exercised in interpreting results of Protocol S. At this time, PRP should be considered standard of care due to its durable benefit, especially in circumstances in which patient compliance may be poor or financial limitations exist. Long-term data and real-world experience will fine-tune our ability to optimize the translation of these groundbreaking developments into clinical practice.


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