MANAGING DR IN PATIENTS WITH GOOD VISION

The DRCR Retina Network sheds light on the optimal treatment approaches.

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Anti-VEGF medications have transformed the treatment landscape for diabetic macular edema (DME). Approximately 90% of eligible eyes with DME receive anti-VEGF therapy, which is employed as the first-line treatment in nearly 80% of cases.[1] Thus, many studies have explored the most effective agents and the optimal treatment timing, particularly in patients presenting with good visual acuity (VA). Here, we examine the literature shaping how clinicians make informed decisions regarding the management of DME in patients with good baseline VA.

CHOOSING THE RIGHT AGENT

In 2013, the Medicare reimbursement cost for a single intravitreal injection was approximately $1,950 for 2 mg aflibercept (Eylea, Regeneron), $1,200 for ranibizumab (Lucentis, Genentech/Roche), and $50 for bevacizumab (Avastin, Genentech/Roche).[2] This stark cost difference led the Diabetic Retinopathy Clinical Research (DRCR) Retina Network to investigate the efficacy and safety of these agents in Protocol T.[2]

AT A GLANCE

- DRCR Retina Network's Protocol T demonstrated that, for patients with diabetic macular edema (DME) and good baseline visual acuity, 2 mg aflibercept (Eylea, Regeneron), ranibizumab (Lucentis, Genentech/Roche), and bevacizumab (Avastin, Genentech/Roche) were equally effective.
- Protocol V found no significant difference in visual acuity loss at 2 years for patients with DME treated with immediate anti-VEGF therapy, observation with deferred anti-VEGF therapy, or initial focal laser with deferred anti-VEGF therapy.
- Opting for initial observation or laser therapy over immediate anti-VEGF treatment could result in substantial long-term cost savings.

Patients were randomly assigned to receive aflibercept, bevacizumab, or ranibizumab.[2] At the 1-year mark, aflibercept showed superior vision improvement compared with the other agents, but only in patients with a baseline VA of 20/50 or worse. Among patients with a VA between 20/32 and 20/40, the differences between treatments were not statistically significant.[2]

At 2 years, the results were similar: No significant differences were observed among patients with an initial VA of 20/32 to 20/40. However, among those with a VA worse than 20/50, aflibercept showed a significant advantage over bevacizumab but not over ranibizumab (Figure).[3] Thus, Protocol T concluded that, for patients with good baseline VA, the three agents were equally effective. This provided clinicians with strong evidence to consider more cost-effective options, thereby reducing the financial burden on patients and the health care system. With this information, attention shifted to the next question: When should treatment begin for patients with good initial VA?

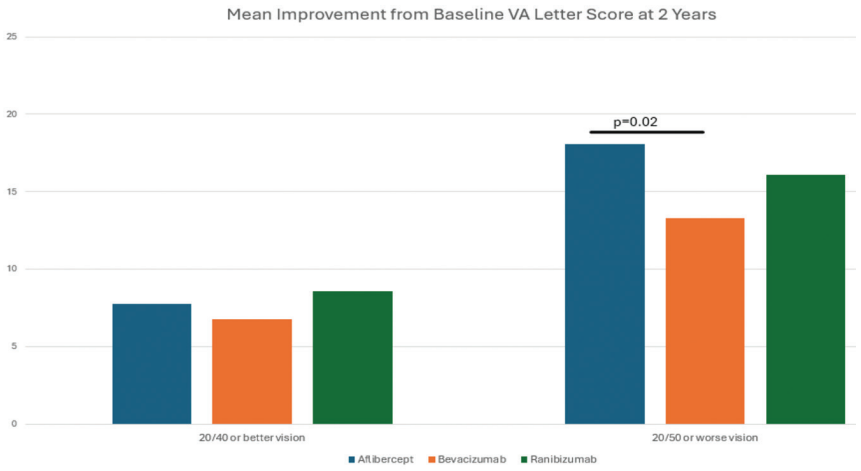

Figure. In Protocol T, the mean improvement from baseline at 2 years was only statistically significant in patients with a baseline VA worse than 20/50 who were treated with bevacizumab compared with those treated with aflibercept.[3]

DRCR Retina Network's Protocol V then compared the benefits of three treatment approaches: immediate anti-VEGF therapy, observation with anti-VEGF therapy if VA worsened, or initial focal laser with deferred anti-VEGF therapy.[4] Study patients had a baseline VA of 20/25 or better. The study found no significant difference in VA loss at 2 years—mean VA remained 20/20 across all groups.[4]

DOES COST MATTER?

Based on these findings, researchers have noted the potential for significant cost implications with various treatment approaches.[5,6] One analysis took a deeper dive into these data to forecast cost savings from Protocol V.[6] The study reported that the per-person cost for the aflibercept group was $15,926 in 2019, $5,537 for the observation group, and $3,729 for the laser group. In the observation and laser groups, 80% and 64% of the costs, respectively, were associated with injection-related expenses due to worsening VA.[6]

The researchers subsequently conducted a 10-year population cost analysis to assess the economic effect of patients with center-involved DME and a VA of 20/25 or better undergoing the respective treatment options. The team found a total savings of $10.33 billion when starting with observation compared with initiating treatment with aflibercept and $11.35 billion when starting with laser therapy instead of aflibercept. Consequently, the authors concluded that, while individual circumstances may influence treatment decisions, opting for initial observation or laser therapy over immediate anti-VEGF treatment could result in substantial long-term cost savings.[6]

RECENT SHIFTS

Since the completion of Protocol V, the proportion of patients with type 2 diabetes on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has nearly doubled.[7] A large retrospective cohort study found that patients with diabetes (regardless of prior retinopathy) on monotherapy with GLP-1 RAs experienced significantly higher rates of new-onset DME at every follow-up interval and showed an increased risk of progression to proliferative diabetic retinopathy.[8] They also had a greater need for anti-VEGF therapy at 1 and 3 years after treatment initiation compared with patients receiving sodium-glucose co-transporter 2 inhibitor monotherapy.[8] Thus, patients on GLP-1 RAs may warrant closer observation and more in-depth discussions on when to initiate treatment for diabetic eye disease.

NEWER TREATMENT OPTIONS

One major issue with anti-VEGF therapy is the burden it places on patients—an issue newer therapies aim to address. In the PHOTON trial of 8 mg aflibercept (Eylea HD, Regeneron) for DME, researchers compared 8 mg aflibercept every 12 or 16 weeks after three monthly loading doses versus 2 mg aflibercept every 8 weeks after five monthly loading doses.[9] They found that adverse event rates and improvements in BCVA and anatomic outcomes were comparable between the groups.[9] Patients with baseline VA of 20/40 or better and those with 20/50 or worse saw gains in BCVA, with the greatest improvement in the latter group. Among patients with baseline VA better than 20/40, more were able to maintain longer dosing intervals.[10] Therefore, in patients with DME and good baseline VA, 8 mg aflibercept may be a viable option to reduce treatment burden.

In the YOSEMITE trial of faricimab (Vabysmo, Genentech/Roche), researchers compared three regimens for DME: faricimab every 6 weeks, faricimab using a treat-and-extend protocol, and 2 mg aflibercept every 8 weeks. The study

TABLE. SUMMARY OF STUDIES FOR TREATING DME

Protocol	Baseline VA	Treatment Arms	Summary of Findings
Protocol T	20/32 to 20/320	2 mg aflibercept vs bevacizumab vs ranibizumab	No significant difference in treatment outcomes in patients with baseline VA of 20/32 to 20/40
Protocol V	20/25 or better	Immediate anti-VEGF vs observation with deferred anti-VEGF vs initial focal laser with deferred anti-VEGF	No significant difference in long-term outcomes
PHOTON	20/50 or worse and 20/40 or better	2 mg aflibercept vs 8 mg aflibercept	Reduced treatment burden with similar outcomes
YOSEMITE	20/40 to 20/400	Faricimab every 6 weeks, faricimab treat-and-extend vs aflibercept every 8 weeks	Reduced treatment burden w/ similar VA outcomes and greater CST reduction in faricimab groups compared with aflibercept

included patients with baseline VA ranging from approximately 20/40 to 20/400.[11] At 2 years, improvements in BCVA were similar between groups. Notably, the treat-and-extend group achieved these results with an average of 10 injections versus 15 for the aflibercept group.[11] More faricimab-treated patients achieved central subfield thickness < 325 µm and absence of DME compared with the aflibercept group.[11] Although faricimab may be able to reduce treatment burden while maintaining efficacy, this trial did not include patients with a baseline BCVA better than 20/40.

In 2023, a smaller retrospective study assessed DME patients who were refractory to aflibercept and ranibizumab who were switched to a prn faricimab protocol. With a mean baseline VA of 20/40, these patients were able to extend their treatment intervals.[12] However, the study's small sample size and short follow-up limit its generalizability.[12]

New real-world data showed that among patients starting faricimab, 50% had VA of 20/40 or better. Moreover, injection frequency decreased 6 months after switching, indicating extended treatment intervals.[13] This supports the potential benefit of faricimab in DME patients with good baseline VA. Importantly, most eyes in these studies were previously treated with another anti-VEGF agent, so further research is needed to evaluate faricimab as initial therapy in treatment-naïve patients with good baseline VA.

PUTTING IT ALL TOGETHER

Deciding how to manage patients presenting with good VA is multifactorial and warrants individualized discussion, but numerous studies provide clinicians confidence in their recommendations (Table). Protocol T demonstrated that first-generation anti-VEGF agents achieve similar outcomes in patients with good baseline VA, allowing treatment choice to be guided by provider-patient discussions.

Protocol V explored whether to begin early treatment in patients with good VA. It found no increased risk of long-term vision loss when initial treatment was deferred, as observation or laser yielded comparable VA outcomes at 2 years.

Since Protocol V, the expanded use of GLP-1 RAs may merit closer monitoring, given a possible association with DME and proliferative diabetic retinopathy. Recently, next-generation anti-VEGF agents have been shown to reduce injection frequency while maintaining visual outcomes. However, further research is needed to understand the role of newer agents in patients with good baseline VA. ■

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