NOTES FROM THE 46TH ANNUAL ARDS MEETING

Rounding out our coverage of the 46th Annual Aspen Retinal Detachment Society (ARDS) meeting are summaries of presentations by Carl D. Regillo, MD, and Antonio Capone, MD.

Kimberly Tran, MD, provides an overview of Dr. Regillo's presentation, Optimizing Long-Term Visual Outcomes in Wet Age-Related Macular Degeneration. *Dr. Regillo spoke about what has been learned over the past 12 years since the advent of anti-VEGF therapy.*

Also covered is Dr. Capone's talk, Management of Retinal Detachment in Retinopathy of Prematurity Following Anti-VEGF Treatment, *summarized below by Neepa Shah, MD. Dr. Capone spoke about the unique nature of retinal detachments that occur after initial treatment with anti-VEGF therapy in these tiny patients.*

—Timothy G. Murray, MD, MBA

OPTIMIZING LONG-TERM VISUAL OUTCOMES IN WET AGE-RELATED MACULAR DEGENERATION

Presentation by Carl D. Regillo, MD
Summarized by Kimberly Tran, MD

Anti-VEGF therapy has been available to retina specialists for more than a decade. Carl D. Regillo, MD, spoke to ARDS attendees about the available evidence for its efficacy in maintaining or improving VA and the challenge of maintaining VA gains over the long term.

DISEASE CONTROL

According to Dr. Regillo, most physicians administer two or three monthly anti-VEGF injections during the induction phase of treatment for wet age-related macular degeneration (AMD). During the maintenance phase, when maintaining the dry status of the macula and preserving upfront vision gains long-term is the primary goal, a considerable amount of variability in treatment strategies exists.

The most common management strategies for wet AMD are continuation of fixed interval anti-VEGF injections, prn injections, or a treat-and-extend (TAE) protocol, with some overlap among strategies. Responses to American Society of Retina Specialists surveys from 2012 and 2014 indicated that most US providers use a TAE approach while international treatment strategies vary widely by country.

Fixed Dosing

The visual benefits of fixed frequent dosing through 2 years of follow-up were established with the pivotal studies MARINA, ANCHOR, VIEW 1 and 2, and IVAN.[1-5] In the FIDO study, in which patients received long-term fixed dosing every 4 to 8 weeks, with a mean 10.5 injections per year, 43% of patients maintained ≥ 20/40 vision at 7 years; only 7% of patients lost more than 3 lines.[6] Geographic atrophy (GA) did not influence the outcomes in this study.

There are some arguments against monthly fixed dosing, Dr. Regillo noted. Wet AMD is a heterogeneous disease with variable natural history and pharmacologic response, and most patients do not require monthly therapy. VEGF suppression studies have demonstrated individual variability of response to treatment; intravitreal ranibizumab (Lucentis, Genentech) can suppress VEGF levels anywhere from 26 days to 3 months in any given patient.[7-9]

The prn arm of the HARBOR study demonstrated extreme variability in the numbers of 0.5 mg ranibizumab injections needed over 2 years.[10] The median was 14 treatments (eight in the first year, six in the second year), but the range of injections needed varied from three to 24.

Dr. Regillo pointed out that monthly treatment of all patients would result in some degree of overtreatment, as well as excessive expense, inconvenience, and a cumulative increased risk of infection, ocular hypertension, and glaucoma, in addition to possible GA and/or systemic adverse events.[11,12]

PRN Dosing

To avoid overtreatment, prn and TAE dosing strategies can be used, with the goals of suppressing choroidal neovascularization (CNV) growth and secondary exudation. The prn treatment strategy was effective in CATT and IVAN, especially through the first year.[4,5] However, in CATT at year 2, the prn treatment strategy was not noninferior to continuous fixed dosing treatment.

In the HARBOR trial, little difference between the prn treatment and the monthly fixed dosing treatment arms was seen at 24 months, demonstrating that, using monthly monitoring with spectral domain OCT, one can achieve and maintain visual gains reasonably well with the prn approach, at least through 2 years.

Photo courtesy of Kevin Caldwell.

Carl D. Regillo, MD, speaking at the 46th annual ARDS meeting.

TAE Dosing

Several retrospective and prospective studies from 2009 to 2015 that evaluated the TAE approach achieved consistent results, averaging eight injections in year 1 and six injections per year thereafter, with visual gains maintained fairly well with follow-up of 1 to 3 years.[13-19]

More recent retrospective and prospective studies have also evaluated the efficacy of the TAE approach:

- In a Wills Eye retrospective, long-term TAE study, over 3 years, patients treated with ranibizumab or bevacizumab (Avastin, Genentech) for neovascular AMD gained 10.7 to 13.6 letters with a mean 7.6 injections in the first year, 5.7 in the second year, and 5.8 in the third year.[20]
- In the ATLAS prospective study, using aflibercept (Eylea, Regeneron) in a TAE approach, visual gains were maintained fairly well at 2-year follow-up, with a few outliers due to GA. The mean treatment interval at 2 years was 9 weeks, with 75% of patients treated at an interval of 8 or more weeks and 38% of patients extended to treatment every 12 or more weeks.[21]
- The Fight Retinal Blindness Study demonstrated that using aflibercept TAE resulted in ≥ 20/40 vision in 58% of patients over 2 years with a mean number of 7.8 treatments in the first year and 5.7 in the second year.[22]

Other prospective studies have compared TAE with monthly dosing:

- In the TREX-AMD Study, patients were randomly assigned to monthly ranibizumab or TAE after three initial monthly loading doses. This study demonstrated noninferiority for TAE over 2 years, with 10 treatments in year 1 and eight in year 2.[23,24] The mean extension in this study was 8.5 weeks, with a wide range: 33% of participants required monthly injections, and 37% of participants were extended to 11 to 12 weeks between treatments.
- TREND was a large European prospective multicenter study comparing monthly and TAE ranibizumab. The study followed 650 patients for 1 year and demonstrated noninferiority of the TAE approach in maintenance of vision and anatomic outcomes. The mean number of injections for the TAE approach was 8.7.[25]
- In the 2-year CANTREAT prospective Canadian study, 580 patients were randomly assigned to monthly ranibizumab or TAE. The study, presented by Peter Kertes at Euretina 2017, found TAE to be noninferior to monthly dosing at 12 and 24 months. The mean number of treatments was 9.4 in the first year and 8.6 in the second year.

LONG-TERM MAINTENANCE

Dr. Regillo noted that, in the 5-year follow-up results of the CATT, a surprising finding was the amount of vision loss as a result of GA (41% of patients), ongoing neovascular activity (>50% of patients), and, potentially, undertreatment, with four to five injections per year during years 2 to 5.[26] At 5-year follow-up, only 50% of patients had VA of 20/40 or better.

Other trials with long-term follow-up have shown better results. The Fight Retinal Blindness Study, an Australian registration-based observational study, reported that visual gains were well maintained up to year 6, with approximately five injections per year after the second year, but with some decline in VA at year 6 due to GA.[27]

In a retrospective long-term Norwegian TAE study, the mean number of injections was 6.1 ± 2.8 in the first year, followed by 5.6 ± 3.6 injections during year 7 and 5.4 ± 3.5 injections during year 8, respectively. VA was maintained up to year 5; a drop in VA occurred in years 6 through 8, due mostly due to GA.[18]

No study has demonstrated clinically meaningful differences in efficacy or durability among the three anti-VEGF drugs.[3-5,28] In a 12-month observational study that compared ranibizumab with aflibercept, the mean number of injections and VA gains were not statistically significantly different between agents.[28]

EARLY DETECTION

The ANCHOR, MARINA, HARBOR, and CATT data provided evidence indicating that, when neovascular lesions were small at baseline, patients experienced better VA gains.[29-31] In the CATT study, baseline VA was predictive of VA results after 1 year of anti-VEGF therapy.[31] In the Wills Eye TAE study, 75% of patients with VA of 20/40 or better at baseline maintained their VA through 2 years of followup.[32] In the Fight Retinal Blindness Study, over 90% of eyes with VA of 20/40 or better at baseline maintained this level of VA at 2 years.[22] Thus, Dr. Regillo concluded, early detection and early initiation of treatment appear to be associated with better visual outcomes.

Dr. Regillo's Recap

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THE FUTURE

Dr. Regillo said that optimizing long-term outcomes in neovascular AMD requires a combination of disease control, early detection, and minimizing the growth and exudation of CNV over many years. He said that providers should aim to minimize undertreatment and maximize early detection, when CNV is small and VA is good. Providers should also aim to prevent recurrences. In the future, he said, this may be aided by more durable anti-VEGF agents such as brolucizumab (Novartis), abicipar pegol (Allergan), and dual-target therapies targeting Ang2 and tissue factor.

Other sustained delivery approaches may optimize long-term outcomes in wet AMD; these include a Port Delivery System (Genentech) that is currently in phase 2 clinical trials, polymers and microparticles that are in phase 1 trials, and gene therapies that are in phase 1 trials.

Additionally, home-based OCT may augment our ability to monitor for disease activity in asymptomatic patients. ■

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431.
2. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444.
3. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
4. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398.
5. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382(9900):1258-1267.
6. Peden MC, Suñer IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. *Ophthalmology*. 2015;122(4):803-808.
7. Muether PS, Hermann MM, Viebahn U, Kirchhof B, Fauser S. Vascular endothelial growth factor in patients with exudative age-related macular degeneration treated with ranibizumab. *Ophthalmology*. 2012;119(10):2082-2086.
8. Muether PS, Hermann MM, Dröge K, Kirchhof B, Fauser S. Long-term stability of vascular endothelial growth factor suppression time under ranibizumab treatment in age-related macular degeneration. *Am J Ophthalmol*. 2013;156(5):989-993.e2.
9. Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. *Am J Ophthalmol*. 2014;158(3):532-536.
10. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(11):2181-2192.
11. Dedania VS, Bakri SJ. Sustained elevation of intraocular pressure after intravitreal anti-VEGF agents: what is the evidence? *Retina*. 2015;35(5):841-858.
12. Grunwald JE, Pistilli M, Ying GS, Maguire MG, Daniel E, Martin DF; Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Growth of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2015;122(4):809-816.
13. Engelbert M, Zweifel SA, Freund KB. "Treat and extend" dosing of intravitreal antivascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. *Retina*. 2009;29(10):1424-1431.
14. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified "treat and extend" dosing regimen of intravitreal antivascular endothelial growth factor therapy. *Retina*. 2010;30(9):1368-1375.
15. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. *Retina*. 2013;33(7):1351-1358.
16. Abedi F, Wickremasinghe S, Islam AF, Inglis KM, Guymer RH. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. *Retina*. 2014;34(8):1531-1538.
17. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*. 2015;122(1):146-152.
18. Berg K, Roald AB, Navaratnam J, Bragadóttir R. An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration. *Acta Ophthalmol*. 2017;95(8):796-802.
19. Arnold JJ, Campain A, Barthelmes D, et al. Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. *Ophthalmology*. 2015;122(6):1212-1219.
20. Rayess N, Houston SK, Gupta OP, Ho AC, Regillo CD. Treatment outcomes after 3 years in neovascular age-related macular degeneration using a treat-and-extend regimen. *Am J Ophthalmol*. 2015;159(1):3-8.e1.
21. DeCroos FC, Reed D, Adam MK, et al. Treat-and-extend therapy using aflibercept for neovascular age-related macular degeneration: a prospective clinical trial. *Am J Ophthalmol*. 2017;180:142-150.
22. Barthelmes D, Nguyen V, Daien V, et al. Two year outcomes of "treat and extend" intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. *Retina*. 2018;38(1):20-28.
23. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122(12):2514-2522.
24. Wykoff CC, Ou WC, Croft DE, et al. Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. *Br J Ophthalmol*. 2018;102(4):460-464.
25. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J; TREND study group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND Study. *Ophthalmology*. 2018;125(1):57-65.
26. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751-1761.
27. Gillies MC, Campain A, Barthelmes D, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2015;122(9):1837-1845.
28. Gillies MC, Nguyen V, Daien V, Arnold JJ, Morlet N, Barthelmes D. Twelve-month outcomes of ranibizumab vs. aflibercept for neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2016;123(12):2545-2553.
29. Ho AC, Albini TA, Brown DM, Boyer DS, Regillo CD, Heier JS. The potential importance of detection of neovascular age-related macular degeneration when visual acuity is relatively good. *JAMA Ophthalmol*. 2017;135(3):268-273.
30. Regillo CD, Busbee BG, Ho AC, Ding B, Haskova Z. Baseline predictors of 12-month treatment response to ranibizumab in patients with wet age-related macular degeneration. *Am J Ophthalmol*. 2015;160(5):1014-1023.e2.
31. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(1):122-129.
32. Rahimy E, Rayess N, Ho AC, Regillo CD. Treatment outcomes for neovascular age-related macular degeneration patients with initial vision better than 20/40 using a treat-and-extend regimen. *Retina*. 2016;36(5):875-880.

MANAGEMENT OF RETINAL DETACHMENT IN RETINOPATHY OF PREMATURITY AFTER ANTI-VEGF TREATMENT

Presentation by Antonio Capone, MD
Summarized by Neepa Shah, MD

Antonio Capone, MD, spoke about the unique nature of retinal detachments (RDs) that can occur after initial treatment with anti-VEGF therapy in patients with retinopathy of prematurity (ROP). He noted that the use of anti-VEGF therapy in the treatment of ROP is increasing, and that the anatomy of RDs seen in patients with ROP who have received anti-VEGF therapy is different from that seen in patients with ROP treated with laser photocoagulation. There is a so-called *crunch phenomenon* in these eyes—a complication of anti-VEGF therapy that results from contraction of the vascular component of fibrovascular proliferation, which makes management of RDs more challenging.

Dr. Capone reviewed data from 35 infants with ROP who developed RD after treatment with anti-VEGF therapy. Progression was noted a

"With increasing use of anti-VEGF therapy in children with ROP, more peripheral vascular anomalies have been noted during their growth and development."

mean 70 days after anti-VEGF therapy, but with a wide range, from 4 days to almost 1 year. Three configurations of RDs were noted: acceleration of a typical funnel detachment, atypical crunch, and effusive.

About one-third of the children developed acceleration of a typical funnel RD. In addition, two types of atypical crunch were noted.

Peripheral crunch occurred in more anteriorly vascularized (zone 2) eyes. In this type of crunch, fibrosis and contracture of flat new vascularization created a tight circular annular RD with an exaggerated circumferential configuration compared with its anteroposterior component.

Generally, Dr. Capone said, with RDs in ROP eyes that are treated with laser or that are untreated, proliferation from the ridge toward the anterior part of the eye is predominant. In the anti-VEGF treated eyes, by contrast, the contraction was more intrinsic and posterior.

In the other variant, termed *peripapillary crunch*, hyaloid contraction occurred over or near the optic nerve head. This occurred primarily in patients who had posterior zone 1 disease. Dr. Capone noted that both forms of atypical crunch are amenable to surgical repair, though it may be tedious.

About half the children had bilateral RDs, and most of the time (90%) the bilateral RDs were simultaneous and highly symmetrical.

SURGICAL REPAIR

Dr. Capone shared surgical videos of RD repair. He said he places his trocars anteriorly, within 1 mm of the limbus, to make sure that he stays in the pars plana. There are multiple tissue planes that must be meticulously dissected, and Dr. Capone stated that he prefers a 27-gauge cutter for this task.

Dr. Capone presented some cases of focal contraction. In these eyes, delamination of the hyaloid off the retina is the surgical approach. Because the hyaloid is densely adherent and the retina is quite thin, Dr. Capone said, he uses ocriplasmin (Jetrea, ThromboGenics) to assist. Even with anatomic success, VA may remain poor.

PERSISTENT RETINAL AVASCULARITY

With increasing use of anti-VEGF therapy in children with ROP, more peripheral vascular anomalies have been noted during their growth and development. In many of these children the peripheral retina remains avascular, and there is a question whether this predisposes them to future retinal tears, detachments, or recurrence of ROP.

Dr. Capone said he tends to perform laser photocoagulation

Dr. Capone's Recap

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in children who have meaningful avascular retina after regression with or without anti-VEGF treatment. He showed an example of a grown premature boy who had never been treated and who now displayed lattice-like peripheral vascular changes. In high school, the boy developed an asymptomatic detachment in his better seeing eye that split his fovea. Fortunately, he did well with surgical repair, Dr. Capone said, but cases such as this stress the potential importance of early laser prophylaxis.

FUTURE DIRECTIONS

Ongoing prospective studies such as the RAINBOW trial (NCT02375971), Dr. Capone said, may bring a better understanding of the long-term effects of anti-VEGF therapy in ROP. Although anti-VEGF drugs are helpful in the acute phase of disease, long-term aspects of the therapy such as RD rates and surgical complexity remain under investigation. ■

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