One-Year Outcomes of Low-Dose Bevacizumab for ROP
October 2022

Intravitreal bevacizumab at low or very low doses has been described as an effective short-term treatment for type 1 retinopathy of prematurity (ROP). Freedman et al., for the Pediatric Eye Disease Investigator Group, described the one-year outcomes for small doses of bevacizumab to manage ROP, including reactivation rates and the need for more treatment. They found that low and very low doses resulted in good retinal structure at one year—but that many eyes required further treatment. Reactivation of severe ROP tended to occur sooner if the bevacizumab dose was very low.

This multicenter, masked, dose de-escalation study included infants who were born prematurely and were diagnosed as having type 1 ROP. Low-dose bevacizumab was defined as \(0.25, 0.125, 0.063, \) or \(0.031 \text{ mg}\). Very low-dose treatment was defined as \(0.016, 0.008, 0.004, \) or \(0.002 \text{ mg}\). Treatments were administered to the study eye. If the fellow eye also exhibited type 1 ROP, researchers administered a dose that was one level higher than that given to the study eye. After the initial treatment, continuation or modification of treatment was at the investigator’s discretion. Main outcome measures were reactivation of severe ROP by six months’ corrected age, need for additional treatment, health of ocular structures, and refractive error at 12 months’ corrected age.

Altogether, 62 (55%) of 113 study eyes and 55 (56%) of 98 fellow eyes received additional treatment. In 31 (27%) of the study eyes, this consisted of further ROP therapy (six for failure of initial treatment, four for reactivation within four weeks, and 21 for reactivation later). Thirty-one infants required prophylactic laser treatment for persistent avascular retina. The need for additional treatment was unrelated to the initial bevacizumab dose, but reactivation occurred earlier if the dose was very low (mean, 76.4 days vs. 85.7 days for a low dose). By 12 months, 3% of the study population had a poor retinal outcome, and 5% had an anterior segment abnormality. Complications included macular ectopia and stage 5 retinal detachment. Optic atrophy was observed in 10% of the infants, and strabismus was present in 29%. The median refraction at 12 months’ corrected age was mildly myopic (\(-0.31 \text{ D}\)).

These data are consistent with previously reported rates of reactivation, said the authors. (For more on bevacizumab for ROP, see “A New Field Guide to ROP: ICROP-3,” page 28.)

Reticular Pseudodrusen Is a Key Risk Factor for Late AMD
October 2022

In a post hoc analysis of findings from the Age-Related Eye Disease Study (AREDS) and AREDS2, Agrón et al. explored reticular pseudodrusen (RPD) as a potential independent risk factor for progression to late age-related macular degeneration (AMD). They found RPD to be a substantial risk factor for late AMD, particularly for geographic atrophy. As a result, they recommend that RPD be incorporated into AMD clinical trials and classification systems, including risk stratification.

For this study, the authors analyzed images for eyes that had no evidence of late AMD at baseline in AREDS (6,959 eyes; 3,780 patients) or AREDS2 (3,355 eyes; 2,056 patients). They collected and graded color fundus photographs from the patients’ annual visits. The images were examined for soft drusen, pigment abnormalities, and late AMD. The presence of RPD was determined from deep-learning grading of the fundus photographs (in AREDS) and by grading fundus autofluorescence images (in AREDS2). Proportional hazards regression analyses were conducted, which accounted simultaneously for the AREDS AMD severity scales (modified simplified and 9-step)
and the presence of RPD. The main outcome measure was progression to late AMD, geographic atrophy, and neovascular AMD.

In AREDS, the analysis by person according to the simplified severity scale showed that the presence of RPD was linked to high risk of progression to late AMD (hazard ratio [HR], 2.15). However, the degree of risk differed by disease severity: the HRs for levels 0/1 through 4 were 3.23, 3.81, 2.28, and 1.64, respectively. According to the 9-step scale, RPD also carried a high risk for late AMD (HR, 2.54; 95% confidence interval [CI], 2.38-6.10). In the AREDS2 analysis, presence of RPD did not indicate an elevated risk for late AMD (HR, 1.18). In the 9-step analysis, the HR was 1.57 (95% CI, 1.31-1.89).

In both AREDS cohorts, RPD was associated with a higher risk for geographic atrophy than for neovascular AMD.

Based on these findings, “RPD status must be considered in combination with the traditional features for an accurate understanding of progression risk and subtype predictions,” said the authors.

Computer Vision Syndrome: Current Management Is Inadequate
October 2022

Singh et al. investigated interventions to treat eyestrain related to use of digital devices, often dubbed “computer vision syndrome” (CVS). Among the therapies that have been used for CVS, none showed high evidence of efficacy, but low-level evidence suggests that oral supplementation with omega-3 fatty acids may be somewhat helpful.

The authors began this work by identifying appropriate randomized controlled trials (RCTs) from multiple registries. For the analysis, interventions were grouped by the following categories: optical aids, complementary medicine and nutritional supplements, artificial tears, environmental modification, ergonomic adjustment, visual hygiene, binocular vision training, and other. Complementary medicine and nutritional supplements were further subclassified as oral berry extract, polyunsaturated fatty-acid supplements, antioxidant supplements, traditional medicine, combination supplements, or other interventions. The studies were appraised for risk of bias and evidence of certainty; the latter was judged according to the Grading of Recommendations, Assessment, Development, and Evaluation system.

Forty-five RCTs were included, representing nearly 4,500 participants. The analyses showed that multifocal lenses were no better than single-vision lenses for reducing visual fatigue, with low-level certainty at best. Low-certainty evidence also indicated that blue-blocking spectacles did not help to alleviate eyestrain. Compared with placebo, oral supplementation with berry extract did not improve visual fatigue or dry eye symptoms, nor did it have a significant effect on critical flicker-fusion frequency (CFF) or accommodative amplitude. Relative to placebo, low-certainty evidence suggested that dry eye symptoms improve with 45 to 90 days of oral omega-3 supplements. Oral carotenoid supplementation improved CFF in comparison to placebo, but whether this finding is significant is unclear, said the authors.

None of the evidence was of sufficient quality to support routine use of any of the reported interventions as treatment for CVS, said the authors, who also noted that methodology varied widely among the studies.

Ophthalmology Glaucoma
Selected by Henry D. Jampel, MD, MHS

Corneal Hysteresis and Rates of Neuroretinal Rim Change
September/October 2022

Jammal and Medeiros set out to evaluate the impact of corneal hysteresis (CH) as a risk factor for progressive neuroretinal rim loss in glaucoma, using spectral-domain OCT of Bruch membrane opening minimum rim width (MRW). They found that lower CH measurements were associated with faster loss of the neuroretinal rim. In addition, they found that the predictive ability of CH was superior to that of central corneal thickness (CCT).

For this prospective observational cohort study, the researchers assessed 70 participants (118 eyes) with glaucoma, all of whom had open angles on gonioscopy. The patients’ mean age at baseline was 71.2 ± 10 years. Thirty-two (46%) were women, and 25 (36%) were Black. Participants were evaluated at baseline and at six-month intervals, for an average follow-up time of 3.9 ± 1.3 years. Linear mixed models were used to investigate the relationship between the rates of MRW loss and baseline CH. Multivariable analyses were used to adjust for IOP, CCT, age, race, and baseline disease severity.

At baseline, global MRW was 194 ± 60.3 µm. The average rate of MRW change was –.33 µm per year. A lower CH was significantly associated with MRW change: after adjustment for confounders, each 1-mm Hg lower measurement of CH was associated with a faster MRW loss of –.38 µm per year (p = .019). With regard to mean IOP, each 1-mm Hg higher reading in pressure was correlated with a –.35 µm per year faster change in MRW (p < .001). In the analysis of predictive strength, the mean IOP was the strongest predictive factor (R² = 23%), followed by CH (R² = 14%) and baseline disease severity (R² = 6%). CCT explained only 3% of the variability in slopes of change in global MRW.

These results suggest that a clinical assessment of CH may contribute to the understanding of a patient’s risk of glaucoma progression, with CH proving to be a more important predictive factor than CCT, the authors said.

Ophthalmology Retina
Selected by Andrew P. Schachat, MD

Initial Observation for Idiopathic Vitreomacular Traction
October 2022

Patel et al. reviewed the clinical course and outcomes of patients with idiopathic vitreomacular traction (VMT) who are managed initially by observation. They found that VMT follows a generally stable clinical course when
managed in this manner. Stable VMT grade was the most frequent outcome, and eyes with grade 1 VMT were more likely to undergo spontaneous release than eyes with grade 2 or 3.

For this retrospective chart review, the researchers assessed the outcomes of 317 patients (436 eyes) who were evaluated between Jan. 1, 2015, and Feb. 15, 2021. Patients’ mean age was 72.2 ± 8.9 years at the initial visit, and the mean follow-up time was 34 ± 19.2 months. The authors ascribed VMT severity grade to each patient using previously published grading criteria. The main outcome measures were the rate of spontaneous release, grade at baseline compared with grade at final follow-up, and outcomes of any interventions performed.

At baseline, the patients’ mean BCVA was 20/40. Baseline OCT demonstrated grade 1 VMT in 212 eyes (48.6%), grade 2 in 172 (39.4%), and grade 3 in 52 (11.9%). Outcomes by grade were as follows:

- Eyes initially grade 1. Of these eyes, 25% had spontaneous release of VMT (median, 290 days), 50.9% remained stable, and 10.4% worsened.
- Eyes initially grade 2. Of these eyes, 14.5% had spontaneous release of VMT (median, 570 days), 55.2% remained stable, 4.7% improved, and 2.3% worsened.
- Eyes initially grade 3. Of these eyes, 5.8% had spontaneous release of VMT (median, 790 days), 28.8% remained stable, and 5.8% improved.

All told, development of macular holes occurred in 42 (9.6%) of the 436 eyes. Pars plana vitrectomy (PPV) was performed in 94 eyes (21.6%). The mean BCVA in these treated eyes was 20/78 prior to PPV and 20/55 at final follow-up. —Summary by Jean Shaw

**American Journal of Ophthalmology**
Selected by Richard K. Parrish II, MD

**New Tool to Detect Glaucoma in Eyes With High Axial Myopia**
October 2022

Bowd et al. looked at the diagnostic accuracy of a new en face OCT method aimed at differentiating glaucomatous from nonglaucomatous eyes among adults with high axial myopia. Their comparison of eyes with primary open-angle glaucoma (POAG) and control eyes showed that the new method, which requires segmentation of only one retinal layer, can distinguish glaucomatous eyes from unaffected eyes. This method also was diagnostically superior to standard OCT thickness measurements.

For this research, the authors recruited participants of the Diagnostics Innovations in Glaucoma Study, enrolling adults with high axial length myopia (axial length >26 mm), BCVA of 20/40 or better, and open anterior chamber angles. They explained that the en face method was developed from the SALSA-Texture model and produces a visual pattern reflecting spatial arrangement of an image’s pixel intensities; it can capture the granularity and repetitive patterns of object surfaces. In the study, they generated OCT en face images from 70-μm slabs just below the vitreal border of the inner limiting membrane. The data used for the comparative analysis included areas under the receiver operating characteristic curves (AUROCs) and areas under the precision recall curves (AUPRCs), which were adjusted for both eyes, participant age, axial length, disc area, and image quality.

There were 92 eyes in the POAG cohort and 44 in the control group. The best parameter-adjusted AUROC for differentiating glaucomatous from nonglaucomatous eyes in patients with high myopia was .92 for en face texture images, compared with 0.88 for thickness of the retinal nerve fiber layer (RNFL), .87 for thickness of the ganglion cell–inner plexiform layer, and .87 for thickness of the ganglion cell complex. In eyes with highly advanced myopia (axial length ≥27 mm), the best parameter-adjusted AUROC also was .92 for en face images, whereas thickness-measurement AUROCs were .84 for the RNFL and .86 for each of the other layers. AUPRC values also were superior for the new method.

The authors believe that this novel texture-based analysis can exceed the diagnostic accuracy of standard OCT measurements and avoid the challenges of multiple-layer segmentation.

**Racial Disparities in Glaucoma Severity and Monitoring**
October 2022

Glaucoma prevalence varies widely by race and ethnicity, and the disease is more common in Blacks and Hispanics than in Whites. However, the rate of glaucoma diagnosis in higher-risk populations is lower than expected, suggesting underdiagnosis. Many studies have shown that Black people have earlier onset, greater severity, and poorer visual outcomes of glaucoma, but less is known about racial differences in functional measures of glaucoma severity, progression, or visual field (VF) loss. Halawa et al. used VF and demographic data to explore VF testing frequency and disease severity by race and ethnicity. They found that severe disease at the time of diagnosis was more common in Black, Asian, and Hispanic patients and that Blacks had less frequent monitoring and greater likelihood of progression.

This retrospective cohort study included patients who had VF testing at a tertiary eye care center in Boston from 1998 to 2020. Collected data included clinical parameters as well as self-identified race, ethnicity, and preferred language. Outcome measures were VF mean deviation (MD), progression rate, and testing frequency. Multivariable and longitudinal missed-effects models were used in the analyses.

Of the 29,891 patients with Humphrey VF measurements during the study period, 55.1% were female. With regard to race and ethnicity, 71% self-identified as White or Caucasian, 14% as Black, 7.4% as Asian, and 6.4% as Hispanic. English was the preferred language for 89%. At presentation, the mean VF MD was –9.3 ± 9.7 dB for Blacks, –6.2 ± 7.6 dB for Asians, and –8.3 ± 9.3 dB for Hispanics. For those who identified as White or non-Hispanic, it was –5.5 ± 7.3 dB (p < .001) and –6.2 ± 7.8 dB (p < .001), respectively. After controlling for age, gender, and English proficiency, disparities in dis-
ease severity at presentation were less pronounced, especially for Asians and Hispanics. The frequency of VF testing per person-year was lower for Blacks (1.07 ± 0.53) than for Whites (1.12 ± 0.52, p = .006). Disease progression was 0.43 dB/year faster for Blacks than for Whites (p < .001). VF monitoring occurred more frequently for Hispanics than non-Hispanics (1.18 ± 0.64 vs. 1.11 ± 0.52; p < .001), but there was no significant difference in the rate of disease progression for these cohorts.

—Summaries by Lynda Seminara

JAMA Ophthalmology
Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Ocular Adverse Events Related to Taxane-Based Drugs
September 2022

Sodhi et al. quantified the risk of three mutually exclusive ocular adverse events—epiphora, cystoid macular edema (CME), and optic neuropathy—with the use of docetaxel and paclitaxel. They found that these taxane-based drugs, which are used to treat women with breast cancer, were associated with an elevated risk of these adverse outcomes.

For this retrospective cohort study, the researchers used the PharMetrics Plus database, which captures information from more than 150 million enrollees in the United States. They created a cohort of women who were new users of taxanes and a control group of women who were new users of tamoxifen. (Tamoxifen was chosen as the reference drug because its method of action is different than that of taxanes.)

Results were as follows:
• Epiphora: The incidence was 55.6 per 10,000 person-years among taxane users, versus 7.9/10,000 for those taking tamoxifen. The adjusted hazard ratio (HR) was 5.15 (95% confidence interval [CI], 2.79-9.54). Of note, this category included stenosis of lacrimal canaliculi and obstruction of nasolacrimal ducts.
• CME: The incidence was 34.8/10,000 person-years for those taking a taxane, versus 16.8/10,000 person-years for those on tamoxifen. The adjusted HR was 1.33 (95% CI, 70-2.53).
• Optic neuropathy: The incidence was 10.6/10,000 person-years for taxane users, versus 1.2/10,000 person-years for those taking tamoxifen. The adjusted HR was 4.44 (95% CI, 1.04-18.87).

Of note, this category included both ischemic optic neuropathy and toxic optic neuropathy.

The researchers urge awareness of the potential for ocular adverse effects secondary to taxane-based chemotherapeutics, as early treatment may prevent complications and improve outcomes.

Metastasis-Free Survival in Uveal Melanoma
September 2022

Singh et al. set out to compare the predicted metastasis-free survival (MFS) with the observed MFS in patients with uveal melanoma and with those reported in published studies. They also explored the association of tumor variables, including tumor size, with the MFS in patients predicted to be at high risk of metastasis. They found the observed MFS did not differ from and was potentially better than the predicted MFS, and they noted that incorporating tumor size in the prediction model may enhance its accuracy.

For this study, the authors evaluated 347 patients from two academic centers who underwent prognostic fine-needle aspiration biopsy at the time of their treatment for uveal melanoma. They extracted the patients’ predicted MFS from a commercially available gene expression profiling (GEP) test report. The observed MFS was defined as time to metastasis. Cox proportional hazards models were fit to identify tumor variables impacting MFS in patients with class 2 tumors. The overall estimate of the published MFS was obtained by performing meta-analysis of data from published series.

The patients’ mean age at diagnosis was 59.4 years. There were 150 class 1A tumors (43%), 76 class 1B tumors (22%), and 121 class 2 tumors (35%). Through a follow-up interval of 38 months (range, 19-57 months), 48 patients developed metastatic disease; of these, five had class 1A, three had class 1B, and 40 had class 2 tumors.

The MFS for patients with class 1 tumors was 93% at three years and 87% at five years. For those with class 2 tumors, the three- and five-year outcomes were 67% and 47%, respectively. In the meta-analysis of the published studies for patients with class 2 tumors, the three- and five-year MFS outcomes were 62% and 40%, respectively. When compared to the predicted outcomes reported by the developer of the GEP test, these outcomes were similar for class 1 tumors and significantly better for class 2 tumors. (According to the GEP developer, the predicted MFS for class 2 tumors is 50% and 28% at three and five years, respectively.)

With regard to tumor size, within the group of patients with class 2 tumors, those who experienced metastasis had larger tumors, and an increasing tumor size was associated with increased hazard ratio (HR) of metastasis (HR, 1.16, 95% confidence interval, 1.06-1.27; p < .001). Incorporating tumor size in the prediction model may enhance its accuracy, the authors noted.

Association of Industry Payments With Glaucoma Eyedrop Prescribing Patterns
September 2022

What is the magnitude of the association between industry payments to U.S. eye care providers by makers of branded prostaglandin analog (PGA) eyedrops and the clinicians’ prescribing patterns? Nguyen et al. investigated this issue and found that recipients of even small amounts of transfers of value (TOV) were more likely to prescribe branded PGA drops than were those with no reported TOV.

For this retrospective cohort study, the researchers used a nationally representative 20% sample of 2018 Medicare Part D claims and TOV information reported by industry to the Open Payments program. Optometrists and ophthalmologists who had more than 10 claims for PGA eyedrops in the 20% sample were analyzed. Analyses included subgroup models for optometrists
Social Media’s Role for Ophthalmologists

Clinical Ophthalmology 2022;16:2263-2274

Use of social media by physicians skyrocketed during the COVID-19 pandemic, prompting He et al. to explore its role in networking, mentorship, and support among ophthalmology community. Findings of their cross-sectional survey showed that social media is a key tool to enhance professional and personal growth in ophthalmologists, especially women, trainees, and young surgeons.

The authors developed and distributed a 40-item questionnaire to active users of social media. All responses were anonymous. The survey addressed the domains of career planning/advancement, workplace dynamics, practice management, financial planning, work-life harmony, parenting, and mentorship. Collected demographics included gender, race, age, career stage, number of children, and marital status.

Of the 149 respondents, 67% were women, and 56% were 25 to 35 years of age. Women were more likely than men to report workplace discrimination (p < .005) and work-life imbalance (p < .05). Compared with men, women found social media more helpful for overcoming challenges related to workplace discrimination (p < .01), work-life disharmony (p < .001), parenting (p < .0001), and mentorship (p < .05).

Ophthalmologists under 45 years of age cited more challenges than older ophthalmologists in regard to practice management (p < .005) and more often turned to social media for guidance (p < .05). Trainees were more likely than seasoned ophthalmologists to experience difficulties in career development (p < .05), practice management (p < .0001), and financial planning (p < .05), and they found social media more beneficial for financial education (p < .05). Qualitative analysis of free-form responses revealed a mix of positive and negative attitudes toward ophthalmology-related social media.

This study suggests that social media is an important venue for community building and education in ophthalmology. The authors recommend exploring patterns of social media use among underrepresented individuals in ophthalmology to ensure inclusivity.

Drusen Characteristics As a Potential Genetic Marker for AMD

Investigative Ophthalmology & Visual Science 2022;63(8):17

Osterman et al. set out to identify genetic-risk loci for retinal traits in an Amish population and to compare findings with the known-risk loci of age-related macular degeneration (AMD). In their study of more than 1,000 participants, six single-nucleotide polymorphisms (SNPs) met the criteria for genome-wide significance, and 48 others were potentially significant.

For this research, the investigators recruited residents of Amish communities in Ohio, Indiana, and Pennsylvania. Eligible individuals were those over 50 years of age from families in which at least two members had early or intermediate AMD. The authors obtained a health history from each participant, conducted eye exams and genotyping, and applied genome-wide association analysis to determine the presence and degree of geographic atrophy (GA), drusen area, and drusen volume. The data were collected as part of the Amish Eye Study, which is designed to identify early predictors of progression to AMD in at-risk individuals. They compared their SNP findings with those of a previous genome-wide association study consisting mainly of individuals of European descent. They also applied a genetic risk score for AMD to predict the presence and quantity of the three retinal characteristics.

The final analysis set included 1,074 participants. After correction via the Benjamini-Hochberg model with a false discovery rate of 20%, the SNPs with a significant association with drusen area or volume were rs8125299, rs79746087, rs7028791, rs7850939, rs76316680, and rs17759824. The affected chromosomes were 2, 4, 9, 19, and 20. The SNP findings did not correlate strongly with the known-risk SNPs for AMD, and the genetic risk score for AMD was highly predictive of the retinal findings except for GA area.

The authors noted that “whole genome sequencing could allow for better detection of rare variants within the genome-wide significant loci, as the Amish may demonstrate variation that differs from a general European ancestry population.” The underlying genetic component of drusen may differ from that of AMD, they said. Given the relatively high heritability of AMD, it is plausible that drusen could be inherited in a similar manner, as suspected in previous studies. Further research may improve the understanding of drusen as a biomarker for genetic risk of AMD, said the authors, who concluded that building this knowledge could lead to better screening and treatment strategies for AMD.