

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Durability of DR Improvement With As-Needed Ranibizumab

May 2019

In this open-label extension of the RIDE and RISE studies, Sun et al. looked at the durability of improvement of diabetic retinopathy (DR) after patients were switched from monthly ranibizumab to pro re nata (PRN) dosing. They found that the DR improvements attained with monthly ranibizumab were maintained in more than 70% of patients after the switch to PRN dosing.

The extension study was a pooled analysis of data for patients with DR and diabetic macular edema (DME) who participated in RIDE or RISE for 36 months. In those studies, patients were assigned randomly (1:1:1) to receive ranibizumab 0.3 mg/month, ranibizumab 0.5 mg/month, or a monthly sham injection. After 24 months, the sham group received ranibizumab 0.5 mg/month.

After 36 months in the core studies, patients in the open-label extension (n = 500) could receive ranibizumab 0.5 mg PRN. DR severity was assessed photographically, using the scale from the Early Treatment Diabetic Retinopathy Study. The primary outcome of the extension study was the change in DR severity from months 36 to 48,

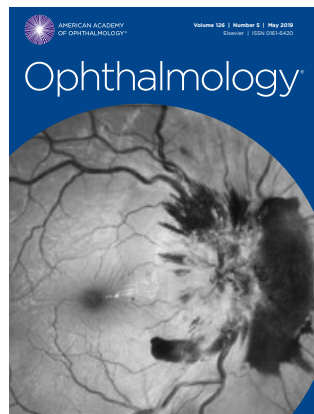
according to retreatment status.

Among patients in the open-label extension, 121 (24%) did not require further ranibizumab treatment. DR was evaluable for 367 patients at months 36 and 48. When comparing all three study groups (sham/crossover, ranibizumab 0.3 mg, and ranibizumab 0.5 mg), of the 279 patients who required continuation of ranibizumab, 84% to 94% experienced stability of DR (0- to 1-step change), and 2% had improvement of 2 steps or more. However, 3% to 14% had worsening of at least 2 steps between months 36 and 48. In general,

visual improvement was maintained throughout the extension study, regardless of changes in DR severity.

The authors recommend that careful monitoring be part of the long-term management of DR, particularly because the condition

often worsens. They added that their findings suggest the possibility of a paradigm shift in DR treatment—that is, focusing on early treatment to reduce DR severity and prevent vision-threatening complications, rather than using a wait-and-watch approach in which treatment is reserved only for advanced eye disease. (Also see related commentary by Robert N. Frank, MD, in the same issue.)



Can Patient-Reported Outcomes Serve as Endpoints in Trials?

May 2019

On behalf of the United Kingdom Glaucoma Treatment Study (UKGTS) investigators, Jones et al. gathered and compared self-reported outcomes for UKGTS participants. In the flagship trial, patients with open-angle glaucoma (OAG) had been assigned to receive latanoprost or placebo drops, and visual field progression was the outcome of interest. Eligible for the subsequent study were patients from UKGTS with newly diagnosed OAG and self-reported outcome measures at both baseline and study completion. Because the average changes in patient-reported outcome measures (PROMs) for health- and vision-related quality of life were found to be similar for the placebo and active-treatment groups, the researchers surmised that PROMs may not be sensitive enough to function as primary endpoints in clinical trials of early-stage glaucoma.

The PROM study included 182 patients who received latanoprost and 168 placebo recipients. At baseline and trial exit, participants completed general health PROMs (European Quality of Life in 5 Dimensions [EQ-5D] and 36-item Short Form [SF-36]) as well as glaucoma-specific PROMs (15-item Glaucoma Quality of Life [GQL-15] and 9-item Glaucoma Activity Limitation [GAL-9]). The percentage change between PROM values was calculated for each patient and compared between treatment arms. Also compared were

differences between patients whose glaucoma remained stable and those who experienced progression (determined by visual field changes).

The average percentage change in PROMs was similar for the placebo and latanoprost groups, with no significant between-group difference for any measure (EQ-5D overall, $p = .98$; EQ-5D visual analog scale, $p = .88$; SF-36, $p = .94$; GQL-15, $p = .66$; GAL-9, $p = .87$). As expected, there were significant differences in glaucoma-related PROMs between patients with and without progressing glaucoma (GQL-15, $p = .02$; GAL-9, $p = .02$), and the differences in general health PROMs were similar for these subgroups (EQ-5D, $p = .62$; EQ-5D visual analog scale, $p = 0.23$; SF-36, $p = .65$).

The low sensitivity of PROMs may render these tools inadequate as primary endpoints in trials of early-stage glaucoma. Although sensitivity to clinical meaningfulness is a common criterion for outcomes selection, quality of life is important as well. Even if PROMs cannot capture the disease-modifying effects of treatment, these tools may help to assess other consequences of therapy, such as side effects and dosing convenience. (Also see related commentary by Scott Wallace, MD, and Jane Edmond, MD, in the same issue.)

Cyclosporine A Cationic Emulsion for Pediatric Vernal Keratoconjunctivitis

May 2019

Leonardi et al. evaluated the efficacy and safety of an investigational therapy for severe vernal keratoconjunctivitis (VKC) in children: cyclosporine A (CsA) cationic emulsion (CE). Compared with conventional CsA formulation, the new product (an oil-in-water emulsion) demonstrated better bioavailability. This research indicates that high-dose CsA CE is safe and improves keratitis, its symptoms, and quality of life (QoL) for children with severe VKC.

This phase 3 trial involved 169 pediatric patients with active severe VKC (grade 3 or 4 on the Bonini severity scale) and severe keratitis (corneal fluorescein staining score of 4 or 5 on

the modified Oxford scale).

During the four-month study, patients were assigned randomly to receive high-dose treatment (CsA CE 0.1% eyedrops, four times daily), low-dose treatment (CsA CE 0.1% twice daily plus vehicle twice daily), or vehicle four times daily. The primary endpoint was a mean composite score reflecting corneal fluorescein staining, use of rescue medication (dexamethasone 0.1% four times daily), and corneal ulceration. QoL was assessed by a visual analog scale and questionnaire.

For the primary endpoint, differences in least-squares means versus vehicle were significant for the high dose of CsA CE (0.76; $p = .007$) as well as the low dose (0.67; $p = .010$); treatment effect was driven mainly by corneal fluorescein staining score. Compared with low-dose CsA CE, the higher dose resulted in larger improvements in photophobia and mucous discharge and much greater improvement in both QoL domains. The need for rescue medication differed significantly between the vehicle group and each active-treatment arm. VKC symptoms and QoL improved in all three groups, and improvement was significant for high-dose treatment versus vehicle.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Using Multicolor Imaging to Detect Polypoidal Choroidal Vasculopathy

May 2019

Multicolor imaging is a novel technology that can be used to visualize pathology in the posterior pole. Images are produced separately from three color wavelengths and can be combined to produce a composite image. Tan et al. evaluated the ability of multicolor imaging to discern features of polypoidal choroidal vasculopathy (PCV) and compared those results with those seen on standard color fundus photography and indocyanine green (ICG) angiography, the gold standard. They found that multicolor imaging could detect features suggestive of PCV, making it

a useful noninvasive imaging option, particularly if ICG angiography is not available.

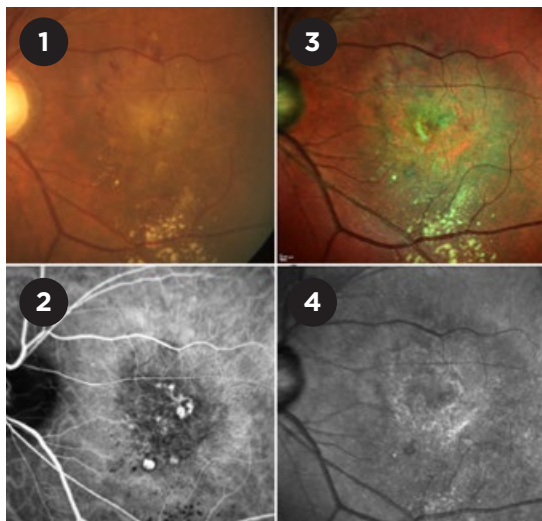
For this cross-sectional study, the researchers assessed 50 consecutive treatment-naïve patients (50 eyes) with PCV. Patients were evaluated with multiple imaging technologies, including multicolor imaging, fluorescein and ICG angiography, and color fundus photography. Each patient underwent all imaging modalities on the same day. One eye was selected for analysis. The color fundus and ICG angiography images were independently graded by retina specialists to identify the presence of polyps and distinguish lesion components.

Overall, the researchers found that the location and shape of lesions detected with multicolor imaging correlated well with those seen on color fundus photography and ICG angiography. Multicolor imaging was able to detect polyps in 49 of the 50 eyes (98%). Other clinical features detected via multicolor imaging included branching vascular network (BVN, seen in 60% of eyes), drusen (seen in 66% of eyes), and subretinal hemorrhages (seen in 40% of eyes). On the multicolor composite images, the polyps appeared as dark green oval lesions. When infrared reflectance imaging was used, the polyps appeared as dark grey oval lesions with distinct margins. Subretinal hemorrhages appeared red on the multicolor composite images, while BVNs typically appeared as an area of mottling.

The authors noted that optical coherence tomography (OCT) and

Ophthalmology Retina Now in PubMed

The Academy is pleased to announce that *Ophthalmology Retina* has been accepted by the National Library of Medicine for inclusion in Medline/PubMed, making the publication the first monthly, print U.S. ophthalmology journal to be accepted in more than 12 years. Indexing is expected to begin this month (May).



PCV WITH HEMORRHAGE. In this image set, the color fundus photograph (1) shows areas of sub-retinal hemorrhage with retinal edema and hard exudates. The ICG angiogram (2) illustrates polyps with a small BVN. On the multicolor composite image (3), the polyps are dark green and oval, the BVN appears as a mottled green area, and the hemorrhages are red. On the infrared reflectance image (4), the polyps appear as dark grey round lesions.

OCT angiography were not used in this study, which opens the door to follow-up research on whether the combination of OCT and multimodal imaging would increase diagnostic accuracy. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

CRAO-Associated Vascular Ischemic Events on the Rise

April 2019

Central retinal artery occlusion (CRAO) confers a high risk of acute vascular ischemic events, including myocardial infarction (MI) and stroke. Understanding the burden and risk-factor profile of ischemic events can help ophthalmologists in managing and referring patients. Mir et al. performed a nationwide cross-sectional study to determine the incidence and predictors of in-hospital ischemic events among inpatients with a diagnosis of CRAO in the United States. They found that the incidence of stroke nearly doubled

from 2003 to 2014. They also identified the following predictive factors: female sex, hypertension, carotid artery stenosis, aortic valve disease, smoking, and alcohol dependence/abuse.

During the 12-year study period, the estimated number of CRAO inpatient admissions was 17,117. The mean age was 68.4 years, and 53% were female. The overall incidence of in-hospital stroke and acute MI was 12.9% and 3.7%, respectively. The incidence of stroke increased significantly over time, from 7.7% in 2003 to 15.3% in 2014. Among this CRAO population, the combined risk of stroke, transient ischemic attack, and acute MI (or mortality) was 19%.

This research shows that the burden of vascular risk in this patient population is sizable and growing.

At present, there are no options to significantly improve visual outcomes in patients with CRAO; therefore, clinical management involves preventing vascular ischemic events. Because stroke risk is highest at the time of occlusion, prompt clinical evaluation is warranted, along with timely execution of stroke prevention measures.

To the authors' knowledge, their study is the largest of its kind to date. The findings confirm that CRAO is an important marker for subsequent vascular ischemic events. As the incidence of CRAO-associated stroke continues to rise, it would be prudent to have an adjunctive risk-prediction model to assist in triaging and referral, the authors said. This would optimize early evaluation of patients with the highest risk for ischemic events.

New Questionnaires to Assess Functional Vision and QOL in Children With Eye Disease

April 2019

In previous research based on interviews, Hatt et al. identified children's

concerns about functional vision and eye-related quality of life (ER-QOL). In a new study, these authors applied the patient-derived concerns to a different cohort of patients, with the goal of developing FDA-compliant questionnaires and testing their validity. This approach proved effective for devising questionnaires that separately assess the domains of functional vision and ER-QOL in children of any age, with any eye condition. (In subsequent research, the authors will test the reliability, construct validity, and responsiveness of these tools.)

The researchers' goal was to create short forms that represent individual, analysis-driven, unidimensional domains within the separate constructs of functional vision and ER-QOL, for use in any clinical setting. The researchers enrolled 444 children (0 to <18 years of age) from two centers, with the children representing 10 diagnostic categories.

Parents filled out a master questionnaire and proxy questionnaires for their children. Younger children had questions read to them; older children were given forms to fill out. Factor analysis was applied to identify unidimensional domains, and Rasch analyses (differential item functioning, targeting, fit) were performed to reduce the number of items. Rasch lookup tables were used for scoring, and the data were analyzed separately by age group and for each factor.

The number of items per questionnaire/proxy ranges from 29 to 42. The form for the youngest children (0-4 years) consists of three domains: functional vision, bothered by eyes/vision, and social. For ages 5-11 and ages 12-17, the forms include four unidimensional domains: functional vision, bothered by eyes/vision, social, and frustration/worry.

For parents, the master questionnaire includes four domains: impact on parent/family, worry about child's eye condition, worry about child's self-perception and interactions, and worry about child's visual function. The number of domains on parental proxy forms vary according to the age of the child.

Next steps include testing the reliability and validity of the new questionnaires in another cohort of patients.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Trends in Eye Care Use and Spectacle Affordability

April 2019

In an analysis of data from the U.S. National Health Interview Survey (2008–2016), Varadaraj et al. looked at trends in eye care use and the affordability of eyeglasses. They found that those least likely to use eye care or to be able to afford eyeglasses were women, racial/ethnic minorities, and visually impaired people, regardless of study year. Since 2014, spectacles were deemed more affordable than in previous years, which may relate to economic recovery and/or health care reform.

Survey participants were adults 18 years and older. They were grouped into nine annual cross-sectional population-based samples, ranging from 21,781 to 36,697 people. Visual impairment was defined as self-reported difficulty with seeing despite wearing eyeglasses. Outcome measures included visits to eye care professionals and the inability to afford eyeglasses if deemed needed in the preceding year. Survey logistic regression, with adjustment for demographics and other factors, was used to detect associations between survey years and eye care outcomes.

Compared with the first year of the survey, the final year was associated with higher proportions of Asians, Hispanics, and older adults in the U.S. population. Throughout the study period, substantial trends were observed for both outcomes. The fully adjusted models showed that people were less likely to use eye care in 2016 than in 2008 (odds ratio [OR], 0.90; $p < .001$). Compared with 2008, spectacle affordability was easier from 2014 onward (2014 OR, 0.82; $p < .001$; 2015 OR, 0.81; $p < .001$; 2016 OR, 0.70; $p < .001$). After adjustment for all covariates, including survey year, visually impaired

people were more likely than nonimpaired individuals to use eye care (OR, 1.54; $p < .001$), but they had greater difficulty affording eyeglasses (OR, 3.86; $p < .001$). Overall, women were more likely than men to use eye care (OR, 1.42; $p < .001$) and to have difficulty affording eyeglasses (OR, 1.68; $p < .001$). Compared with non-Hispanic whites, those who are Hispanic, Asian, or black were less likely to use eye care, and Asians and blacks were more able to afford eyeglasses.

Why Children Do—and Don't—Wear Their Eyeglasses

April 2019

Nearly 13 million children worldwide have visual impairment resulting from uncorrected refractive errors. Although eyeglasses are a simple and cost-effective solution, low adherence to spectacle wear can occur in any income setting. Morjaria et al. looked at predictors of spectacle adherence among students aged 11 to 15 years. They found that the greatest predictors of spectacle wear were “poorer presenting visual acuity [VA]” and “greater improvement in VA with correction.” The main reason for nonwear was bullying or teasing by peers. The predictors of adherence support using prescribing guidelines such as those in this study.

The study was a planned analysis of secondary objectives from a non-inferiority study among students who fulfilled eligibility criteria, including correction improvement of at least 2 lines in the better eye. Participants were recruited from government schools in Bangalore, India. Masked observers documented the rate of compliance to spectacle wear during unannounced visits to the schools several months after the spectacles had been distributed.

Of the 460 participants, follow-up information was available on 362 (78.7%). At that time, 92 (25.4%) were not wearing their eyeglasses. The main reason for nonwear was teasing or bullying by peers (48.9%), followed by lost, forgotten, or stolen spectacles (26.1%). Headaches and parental disapproval also had an impact, with headaches and discomfort reported by

more boys than girls (10.4% vs. 4.5%, respectively), and parental disapproval directed more at girls than boys (11.4% vs. 4.2%, respectively).

Students with poorer presenting VA and greater correction of VA were more likely to be wearing their eyeglasses: Those whose uncorrected VA was less than 6/18 (20/60) in the better eye were nearly three times more likely to be wearing their spectacles than were those whose VA ranged from less than 6/9 to 6/12 (20/30 to 20/40; adjusted odds ratio [OR], 2.84). Compared with correction resulting in improvement of 3 lines or less, correction of 3 to 6 lines was associated with an adjusted OR of 2.31, and correction of at least 6 lines had an adjusted OR of 2.57.

The fact that most students were wearing their eyeglasses at follow-up supports the use of prescribing guidelines in this study. (Spectacles are provided for students who require correction of at least 2 lines in the better eye.)

The authors emphasized the importance of interventions to reduce teasing and bullying. However, they also acknowledged that it would be difficult to address the issues underlying parental disapproval. (Also see related commentary by Vivian Manh, OD, MS, in the same issue.)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Early Detection of HCQ Retinopathy With OCT

British Journal of Ophthalmology
Published online Feb. 28, 2019

Early detection of hydroxychloroquine (HCQ) retinopathy is crucial because the drug may cause severe irreversible vision loss, even after discontinuation. Garrity et al. evaluated optical coherence tomography (OCT) findings of patients who had taken HCQ for many years and had also undergone Humphrey visual field (VF) testing. They found that OCT was able to detect HCQ-related abnormalities before they were picked up by VF testing.

For this retrospective, observational study, the researchers identified 10

patients (17 eyes) with HCQ-related abnormalities detected on spectral-domain OCT (SD-OCT) and normal VF results. The researchers conducted several ancillary tests—including color fundus photography, fundus autofluorescence, and microperimetry—as part of a comprehensive examination.

The mean duration of treatment with HCQ was 11 years (range, 3-26 years), and the mean dose of HCQ was 1,611 g (range, 730-3,796 g). (Of note, the recommended dosage is 5 mg/kg of actual—not ideal—body weight.) At baseline, all 10 patients had visual acuity between 20/20 and 20/30 in the eye(s) with HCQ retinopathy. Three of the patients reported no visual symptoms; the remainder reported blurry vision, floaters, or photopsia.

All 10 patients presented with normal 10-2 perimetry testing. However, features of early HCQ macular toxicity were evident on SD-OCT, including attenuation of the parafoveal ellipsoid zone (relative to the central ellipsoid band) and loss of a clearly identifiable continuous parafoveal interdigitation zone. These observations were bilateral in seven patients and unilateral in three. Six eyes eventually developed advanced HCQ retinopathy with characteristic paracentral VF defects and/or advanced outer retinal disruption.

Using Deep Learning to Evaluate Macular Thickening

Investigative Ophthalmology & Visual Science
2019;60(4):852-857

Arcadu et al. set out to determine whether deep learning could be used to predict optical coherence tomography—equivalent quantitative measures of diabetic macular thickening (MT), using color fundus photographs. They found that it could, and they suggested that, when used in this manner, deep learning models could significantly benefit teleophthalmology initiatives.

For this study, the authors obtained data from the phase 3 RIDE and RISE studies of diabetic macular edema (DME); nearly 18,000 color fundus images were included. Deep learning with a transfer-learning cascade was applied

to the photographs to predict time-domain optical coherence tomography (TD-OCT)—equivalent MT measures, including central subfield thickness (CST) and central foveal thickness (CFT). Two conventional TD-OCT cutoff points—250 μm and 400 μm —were used to identify abnormal MT. A deep learning regression model was created to quantify actual CST and CFT measurements from the fundus photographs. Four models of deep convolutional neural networks were analyzed (two each for CST and CFT).

The best deep learning model was able to predict CST $\geq 250 \mu\text{m}$ and CFT $\geq 250 \mu\text{m}$, with area under the curve (AUC) of 0.97 and 0.91, respectively. For CST and CFT predictions of $\geq 400 \mu\text{m}$, AUC of the best model was 0.94 and 0.96, respectively. The best neural network regression model to quantify CST and CFT had an R^2 of 0.74 and 0.54, respectively. The models were less accurate when images were of poor quality or if laser scars were present.

The researchers cautioned that their findings may not be generalizable to the overall population of patients with diabetes. In addition, it's possible that the deep learning model is not truly detecting macular thickening but rather retinal phenotypes. Although abnormal thickening does correlate with such phenotypes, the authors affirmed that the deep learning model can detect abnormal MT regardless of diabetic retinopathy severity or the presence of hard exudates. More research is needed to validate such models with real-world data. —*Summaries by Lynda Seminara*

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