Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Home Monitoring to Detect Rapid Visual Field Decline

December 2017

Recent technologic advancements have allowed patients to monitor their central visual field (VF) at home with portable devices. **Anderson et al.** investigated whether the greater test frequency afforded by home monitoring improves early detection of rapid VF loss in patients with glaucoma. They found it beneficial for this purpose, even if patient compliance is imperfect.

This computer simulation study included 43 patients who were being treated for glaucoma (open- or closed-angle), had ocular hypertension, or had suspected glaucoma. Series of VFs (n = 100,000) were simulated for those patients with stable glaucoma and for those with progressing glaucoma for 2 in-clinic schedules (yearly and every 6 months) and 3 home-monitoring schedules (monthly, fortnightly, and weekly), each lasting 5 years.

To simulate reduced compliance, the researchers randomly omitted varying percentages of home-monitored fields and manipulated the variability of the home-monitored VFs. Previously published variability characteristics were used for perimetry, and their appropriateness for home monitoring was confirmed by measuring the device's retest variability at 2 months among the study group. The criterion for determining progression was a significant slope of the ordinary least-squares regression of a simulated patient's mean deviation data.

In the clinic, sensitivity of 0.8 for rapid VF loss was achieved by 2.5 years of semiannual testing, while the same level of sensitivity was attained by 0.9 years with weekly home monitoring, despite only moderate compliance (63%) with the schedule. The superiority of weekly home monitoring over in-clinic testing every 6 months remained even when home monitoring was assumed to produce more variable test results or to be associated with low patient compliance.

Although the cost-benefit of home monitoring was not evaluated, this approach likely would reduce health resource utilization by decreasing the frequency of in-clinic testing, the researchers said.

OCT Predictors of Progression to Dry Atrophic AMD

December 2017

Certain patterns on spectral-domain optical coherence tomography (SD-OCT) have been linked to subsequent atrophy on color photography images from patients with age-related macular degeneration (AMD). Using SD-OCT findings from a previous study, **Sleiman et al.** sought to determine risk factors for new-onset geographic atrophy (GA) and central GA. They found that abnormal thinning volume of the retinal pigment epithelium (RPE) drusen complex was a strong predictor, as were atrophy or absence of the RPE layer.

For this prospective longitudinal study, the researchers evaluated a subset of patients from the Age-Related Eye Disease Study 2 (AREDS2). All 317 patients (317 eyes) in the study had bilateral large drusen or noncentral GA and at least 1 eye without advanced AMD. Baseline qualitative and quantitative SD-OCT variables were captured using standardized grading and semi-automated segmentation, respectively. Up to 7 years later, annual outcomes were extracted and were analyzed to fit multivariate logistic regression models, from which a risk calculator was derived.

Among 292 eyes with no advanced disease on baseline color photography, 46 (15.8%) developed central GA during the follow-up period (median, 4.0 years). Age-adjusted predictors determined from SD-OCT findings were abnormal thinning of the RPE drusen complex volume, intraretinal fluid or cystoid spaces, hyperreflective foci, and atrophy or absence of the RPE layer. Among the 265 eyes with no evidence of GA on baseline photography, 70 (26.4%) developed new-onset GA during follow-up (median, 4.1

years). Independent predictors were hyperreflective foci, RPE layer atrophy/absence, choroid thickness in the absence of subretinal drusenoid deposits, photoreceptor outer segment loss, volume of the RPE drusen complex, and abnormal thinning of the volume of this complex. The models yielded a calculator capable of computing risk probability of new-onset and central GA within 1 to 5 years.

The authors concluded that this risk-assessment model may simplify SD-OCT grading and, with future validation, could become a clinical prognostic tool. An online version of their calculator is available and will be updated as appropriate.

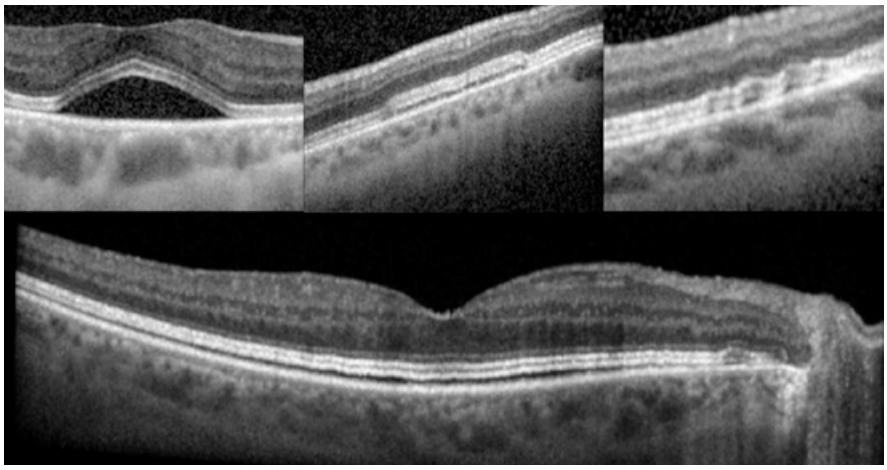
Ocular Side Effects of MEK Inhibitors: Fluid Foci

December 2017

Francis et al. studied the characteristics of serous retinal disturbances in patients who receive the class of drugs known as mitogen-activated protein kinase (MEK) inhibitors. They found that certain features distinguish these disturbances from those noted in central serous chorioretinopathy (CSC), even though the conditions have been considered analogous by some researchers.

For this retrospective single-center study, the researchers included 313 fluid foci from a total of 25 patients (50 eyes) who were receiving MEK inhibitors to treat metastatic cancer. All eyes had evidence of serous retinal detachment, confirmed by optical coherence tomography (OCT). The researchers assessed the presence or absence of subretinal fluid via clinical examination and OCT, and they evaluated the morphology, distribution, and location of fluid foci serially for each eye.

Two independent observers measured choroidal thickness at 3 time points (baseline, fluid accumulation, and fluid resolution). Statistical analysis was used to correlate interobserver findings and to compare choroidal thickness and visual acuity at each time point. OCT characteristics of retinal anomalies at baseline were compared with those at fluid accumulation.



FLUID FOCI CONFIGURATIONS. *Domes (upper left) appear as dome-shaped fluid accumulation between the RPE and the interdigitation zone. Caterpillar foci (upper middle) appear as straight or plateaued low-lying accumulations. Wavy foci (upper right) present as a linear collection of tiny domes and displace the interdigitation zone in a wave-like pattern. Splitting foci (lower) appear as a broad, low-lying accumulation of fluid between the RPE and the interdigitation zone.*

Most patients (92%) had bilateral fluid foci, which is less common in CSC. Most fluid foci in this study (77%) were multifocal, with at least 1 focus involving the fovea (83%). All fluid foci occurred between the interdigitation zone and an intact retinal pigment epithelium (RPE). Regarding morphology, the 313 fluid foci were classified as follows: dome (n = 231; 73.8%), caterpillar (n = 36; 11.5%), wavy (n = 31; 9.9%), and splitting (n = 15; 4.8%). Best-corrected visual acuity at fluid resolution did not differ significantly from that at baseline, and no eye lost more than 2 Snellen lines from baseline to fluid accumulation.

Choroidal thickness was similar at the 3 time points. Interobserver correlations were strong for choroidal thickness measurements and morphology grading. Contrary to typical CSC findings, the retinal pigment epithelium and choroid remained normal during MEK inhibition. There was no irreversible loss of vision and no serious eye damage.

The authors concluded that the subretinal fluid foci caused by MEK inhibition appear clinically and morphologically unique, and they noted that large prospective studies with greater imaging frequency are needed to draw firm conclusions.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Use Straylight to Plan Cataract Surgery in Retinal Dystrophy Patients

November/December 2017

The presence of cataracts often aggravates the visual disability experienced by patients with retinal dystrophies such as retinitis pigmentosa (RP). However, the question of whether to proceed with cataract surgery in these patients has not had a clear answer; evidence has suggested that although they may report improved visual function following cataract surgery, their postoperative visual acuity does not necessarily improve.

As a result, **van Bree et al.** set out to investigate factors that may predict visual outcomes in patients with RP and other retinal dystrophies who undergo cataract surgery. They found that straylight (disability glare) was the only parameter whose preoperative value could be used to support and thus improve the chance of a beneficial postoperative outcome.

For this prospective study, the researchers evaluated 16 patients (25 eyes) with retinal dystrophy and cataract. The patients' average age was 50 years (range, 28-71 years), and 10 of the

16 had RP. As for cataract type, posterior subcapsular cataracts dominated, observed in 20 of the 25 eyes.

The patients' corrected distance visual acuity (CDVA), spatial contrast sensitivity, and straylight were assessed pre- and postoperatively, and straylight values were compared with reference values derived from studies of healthy young eyes. Retinal function was assessed with Goldmann visual field and temporal contrast sensitivity testing, and central retinal structure was assessed with optical coherence tomography and fundus autofluorescence. Patients also completed questionnaires on visual function before and after surgery.

Straylight improvement was found in 72% of eyes postoperatively. The average straylight value was 1.75 preoperatively and 1.45 postoperatively —7.1 and 3.5 times higher than values observed in healthy young eyes, respectively.

In contrast, postoperative CDVA improved in only 20% of eyes. The postoperative CDVA measurements could not be explained by the postoperative presence or progression of maculopathy, as macular structure and function remained stable, the authors reported. They concluded that cataract surgery in patients with retinal dystrophy and early cataract may be beneficial because it significantly reduces glare disability, despite its more limited benefits with regard to CDVA. In addition, they recommended that a cut-off value for straylight of log(s) ≥ 1.66 be used as an indication criterion for cataract surgery. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Uveitis and Blau Syndrome: Preliminary Findings

December 2017

Blau syndrome, a rare autoinflammatory disease that can be debilitating, usually presents as a triad of uveitis, arthritis, and dermatitis. **Sarens et al.** are studying the course of Blau syndrome in a prospective multicenter interventional case series. Preliminary findings of their international 5-year study showed that many patients experience severe ocular morbidity despite continuous immunomodulatory therapy.

Preliminary findings were reported for 49 patients (75 eyes), each with follow-up for 1-3 years. Ophthalmic data were obtained at baseline and annual visits.

The median age at onset of Blau syndrome was 60 months, and the duration of eye disease at baseline was 145 months. In addition, 38 patients (78%) had uveitis at baseline, with 37 of the 38 experiencing bilateral involvement. Eighteen of 66 eyes (the number for which information was available) had moderate or severe visual impairment at baseline, and panuveitis was found in 38 of the 75 eyes (51%). The most common signs of optic nerve involvement were optic disc pallor (9 eyes; 12%) and peripapillary nodules (9 eyes; 12%). Of the 49 patients, 31 (63%) manifested all 3 classic features of Blau syndrome.

Active anterior chamber inflammation was observed in 30 of the 75 eyes (40%). Panuveitis was associated with longer duration of disease. At baseline, 56 of all eyes (75%) were on topical corticosteroids. Twenty-six patients received a combination of systemic corticosteroids and immunomodulatory therapy. Despite prolonged treatment in all patients, there was no significant decrease of inflammatory activity from baseline to the yearly exams; at year 3, active inflammation was evident in 11 of 18 eyes (61%).

These findings emphasize the need for frequent ophthalmologic surveillance and effective treatments in affected patients, the authors said. Greater understanding of the downstream effects of NOD2 mutations may be instrumental in the development of targeted therapies. *(Also see related commentary in the same issue by Gary N. Holland, MD.)*

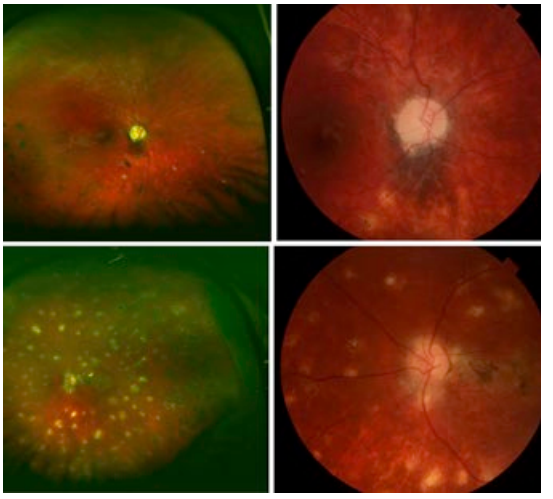
Tocilizumab for Noninfectious Uveitis: 6-Month Outcomes of STOP-Uveitis

December 2017

Sepah et al. reported 6-month safety and efficacy outcomes for 2 doses of intravenous (IV) tocilizumab administered to patients with noninfectious intermediate uveitis (NIU). Both doses were efficacious and well tolerated.

STOP-Uveitis is a randomized open-label trial of the safety, efficacy, and bioactivity of tocilizumab that is currently underway at 5 centers in the United States. Thirty-seven patients with NIU were assigned to receive an IV infusion of tocilizumab 4 mg/kg (group 1) or 8 mg/kg (group 2). Infusions were given every 4 weeks through month 6. Main outcome measures were the incidence and severity of systemic and ocular adverse events from baseline through month 6. Secondary outcomes were mean changes in visual acuity (VA), vitreous haze (VH), and central macular thickness (CMT) during the same period.

Of the patients with potential for a 2-step decrease in VH, a mean of 44%



BLAU SYNDROME UVEITIS. *Widefield fundus (left set) and optic disc fundus (right set) images from 2 patients with Blau syndrome uveitis. In the first patient, chorioretinal scars are evident in the inferior retina (top left photograph), and the pale optic disc has a nodular border (top right). Images from the second patient show multiple chorioretinal scars (bottom left) as well as peripapillary nodules around the border of the optic disc and a macular scar (bottom right).*

achieved this by 6 months (40% in group 1; 46% in group 2). By month 6, the mean change in CMT was –83.88 ± 136.1 µm (–131.5 ± 41.56 µm in group 1; –38.92 ± 13.7 µm in group 2). The mean change in VA was 8.22 ± 11.83 ETDRS letters (10.9 ± 14.6 in group 1; 5.5 ± 7.8 in group 2). There were no significant differences in efficacy or safety between the doses. The safety profile of IV tocilizumab was similar to that in other studies, and no new safety signals were detected. The higher dose was associated with 2 cases of neutropenia. (The neutropenia resolved subsequently in 1 patient, who was continued on the study medication.)

The authors concluded that both doses of IV tocilizumab (4 mg/kg and 8 mg/kg) are safe and effective in patients with NIU, and they noted that the drug may help achieve the overall goal of preventing recurrence or attaining quiescence.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Time Spent by Ophthalmologists on EHRs

November 2017

Although electronic health records (EHRs) have multiple advantages in clinical practice, many physicians see them as an obstacle to productivity. In a study of EHR use among ophthalmologists, **Read-Brown et al.** found that a substantial portion of time spent with patients is indeed devoted to EHRs.

This study entailed 2 types of research: time motion and data analytics. In the time-motion phase, manual observation was used to compare time spent on the EHR with that spent on patient conversation and examination. In the data analytics phase, EHR time stamps were used for large-scale determination of the time spent on EHRs both during and after patient visits. All 27 participating ophthalmologists (10 women, 17 men) had a standard clinical practice at the Casey Eye Institute of Oregon Health & Science University in Portland.

The mean total time spent during each patient encounter was 11.2 minutes (standard deviation [SD], 6.3 minutes). Of that, 3 minutes were devoted to EHR use (27% of the visit time), 4.7 minutes to conversation with the patient (42%), and 3.5 minutes to the examination (31%). The ophthalmologists' mean total per-encounter EHR time was 10.8 minutes (SD, 5.0 minutes; range, 5.8-28.6 minutes). Overall, 3.7 hours of each full clinic day was spent on EHRs (2.1 hours during the encounter, 1.6 hours at other times). Linear mixed-effects models demonstrated a positive correlation between EHR use and billing level and a negative correlation between per-encounter EHR use and clinic volume.

The findings emphasize the importance of creating EHR systems that meet the needs of patients and physicians, the authors said. *(Also see related commentary by Michael V. Boland, MD, PhD, in the same issue.)*

Ranibizumab and Verteporfin Photodynamic Therapy for PCV

November 2017

Polypoidal choroidal vasculopathy (PCV) is a type of exudative age-related macular degeneration common to Asians. In the 2008 EVEREST study, ranibizumab plus verteporfin photodynamic therapy (vPDT) was more efficacious than ranibizumab monotherapy in diminishing polypoidal lesions within 6 months. In EVEREST II, **Koh et al.** investigated longer-term outcomes of these treatments in a large Asian population with PCV. They found that, at 12 months, combination therapy continued to be superior to ranibizumab monotherapy for improving vision and resolving polyps.

In this double-masked multicenter clinical trial, Asian adults with symptomatic macular PCV were assigned randomly to receive intravitreal ranibizumab 0.5 mg with either vPDT (n = 168) or sham PDT (n = 154). Demographic data were similar for the study groups. Ranibizumab injections were administered on day 1 and at months 1 and 2. vPDT or sham PDT (5% dextrose solution) was given on day 1. In both groups, treatments were followed by pro re nata regimens. Main outcome variables were changes in best-corrected visual acuity from baseline to 12 months and effects on polyp regression, as assessed by indocyanine green (ICG) angiography.

At 12 months, mean improvement from baseline to month 12 was 8.3 letters for patients on combination therapy and 5.1 letters for those on monotherapy (mean difference, 3.2 letters), denoting noninferiority as well as superiority of the combined therapy. Complete absence of a polypoidal lesion on ICG angiography by month 12 occurred in 69.3% of patients on dual therapy and only 34.7% of patients on ranibizumab alone. The median numbers of ranibizumab injections were 4 and 7, respectively. Safety profiles were comparable for the 2 study groups.

In conclusion, as ranibizumab plus vPDT was superior to ranibizumab monotherapy, the authors said that combination treatment warrants consideration for patients with PCV. Because dual therapy entails fewer injections overall, it has potential to reduce the costs and overall burden of treatment. *(Also see related commentary by David J. Browning, MD, PhD, in the same issue.)*

Opioid Prescribing Patterns of Ophthalmologists

November 2017

Drug overdose is a leading cause of death among American adults, and the abuse of prescription opioids is a growing public concern. **Patel and Sternberg** looked at the role of ophthalmologists in the opioid abuse epidemic. They found that most practicing ophthalmologists use discretion in prescribing opioids to their patients.

For this study, the researchers collected Medicare Part D prescriber data pertaining to opioid drugs for all participating ophthalmologists from 2013 to 2015. Documented details included the number of original prescriptions and refills, the number of days' supply, and prescribing rates. The mean annual number of opioid prescriptions written by ophthalmologists was calculated and

compared with the number of overall prescriptions issued. The researchers also noted the geographic distribution of the opioid prescriptions.

The number of ophthalmologists varied by study year from 19,587 to 19,712. Although most (88%-89%) issued 10 or fewer opioid prescriptions each year, approximately 1% wrote more than 100 such prescriptions annually (mean supply, 5 days); this remained constant for each year of the study. Nearly half of ophthalmologists did not issue any opioid prescription or refill during the study period (44% in 2013 to 49% in 2015). The mean number of opioid prescriptions written by ophthalmologists, including refills, was similar for the 3 years.

Among the ophthalmologists who wrote more than 10 opioid prescriptions each year, these drugs represented only 8% (mean) of their total annual prescriptions. Geographically, Alabama, Arkansas, Georgia, Oklahoma, Tennessee, and Texas had the highest volume of opioid prescriptions, while Alaska, Iowa, New Jersey, North Dakota, South Dakota, Vermont, and Wyoming had the lowest volume. The District of Columbia also was a low-volume location.

The authors noted that advancements in ophthalmic surgery may contribute to the relatively fixed opioid prescribing rates in ophthalmology as opposed to the rising rates in other surgical specialties. Even so, they cautioned, "the current epidemic highlights the substantial risk of opioid dependency even with seemingly innocuous prescribing patterns."

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Optic Nerve Infiltration in Primary CNS Lymphoma: Presentation and Outcome

JAMA Neurology
Published online October 2, 2017

Optic nerve infiltration (ONI) is a rare presentation of primary central nervous system lymphoma (PCNSL). To better understand lymphomatous ONI, **Ahle et al.** retrospectively reviewed data for affected patients. They found that visual and systemic prognosis was poor, even if neuroimaging showed a response to chemotherapy.

The authors examined databases of 3 French hospitals for a 17-year period and identified 752 cases of PCNSL. Lymphomatous ONI was documented for 7 of them, and data were collected from medical records, including clinical presentation, neuroimaging results, and biological features. Treatment response was assessed clinically and by follow-up magnetic resonance imaging (MRI), utilizing response criteria of the International PCNSL Collaborative Group.

The median age at diagnosis was 65 years (range, 49-78 years). Five of the 7 patients were female. Two patients had ONI at initial diagnosis of PCNSL, and 5 experienced ONI during disease relapse after chemotherapy. In all 7 patients, ONI was characterized by subacute severe visual impairment that progressed rapidly. MRI scanning of the optic nerve showed contrast enhancement in all 7 patients and thickening in 3 of them. Additional lesions were observed in 4 patients. Lymphomatous meningitis was detected from cerebrospinal fluid in the 2 patients with ONI at initial presentation.

At follow-up (median, 13 months), 5 patients had persistent severe low visual acuity or vision loss, and 2 patients exhibited partial recovery. The median progression-free survival time after ONI identification was 11 months; the median overall survival period was 18 months.

In conclusion, lymphomatous ONI is a rare condition involving rapid severe visual loss and poor optic nerve function, even in patients whose disease responds to chemotherapy. Early diagnosis, which can be difficult in the absence of cerebral lesions or meningitis, along with prompt treatment can improve the visual prognosis.

Vision Screening in Young Children: Evidence Review

JAMA
2017;318(9):845-858

Untreated amblyopia, strabismus, and nonamblyopic refractive error can lead to bullying, poor academic performance, and reduced quality of life. In 2011, the U.S. Preventive Services Task Force recommended screening for these conditions and their risk factors in 3- to 5-year-olds. In an effort to provide updated information to the task force, **Jonas et al.** reviewed recent evidence on the effectiveness and safety of such screening in children aged 6 months to 5 years. They found that, although direct data are limited and inconclusive, indirect evidence supports testing of preschoolers at risk for vision problems.

The authors searched primary databases for English-language articles published from January 2009 through June 2016 and reviewed clinical trial registries. Among the 40 studies analyzed (34,709 children), 34 involved assessment of test accuracy. Positive likelihood ratios for amblyopia risk factors or refractive error were moderate (5-10) in most studies but higher (> 10) in studies involving multiple clinical tests. Test accuracy did not differ by age group. The most common difficulty related to screening was false-positive findings, with higher rates (usually > 75%) in studies with a low prevalence (< 10%) of vision abnormalities.

After 5-12 weeks of treatment, patching improved visual acuity by a mean of < 1 line on a standard chart in children with amblyopic risk factors who were pretreated with eyeglasses. Children who were patched were more likely to improve ≥ 2 lines than those who weren't (45% vs. 21%, respectively). By 1 year, compared with no treatment, patching plus eyeglasses improved visual acuity by approximately 1 line in children not pretreated with eyeglasses, whereas eyeglasses alone improved it < 1 line. None of the reviewed studies addressed the effects of treatment on school performance, functioning, long-term amblyopia, or quality of life, and none established whether vision screening in preschoolers is beneficial.

The authors acknowledged that inability to cooperate may limit the use of some tests in children who are younger than 3 years of age.

—Summaries by Lynda Seminara