Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

Intravitreal Injections and Dry Eye

May 2023

What effects do serial intravitreal injections of anti-VEGF agents have on the ocular surface of patients with age-related macular degeneration (AMD)? **Malmin et al.** set out to investigate this issue. Surprisingly, they found that repeated intravitreal injections, along with preinjection application of povidone-iodine, was associated with reduced meibomian gland (MG) loss, increased tear volume, and reduced signs of inflammation, suggesting that the regimen may have a beneficial effect on the ocular surface.

For this retrospective study, the researchers evaluated 90 patients with neovascular AMD (age range, 54-95 years). The participants received unilateral injections with anti-VEGF drugs, and their untreated fellow eyes served as controls. They all received povidone-iodine prior to the injections. Tear film and ocular surface examinations took place on a single occasion at a minimum of four weeks after an injection. Main outcome measures were MG atrophy, tear meniscus height (TMH), bulbar redness (BR) score, noninvasive tear breakup time, tear film osmolarity, Schirmer test, corneal staining, fluorescein tear film breakup time, MG expressibility, and meibum quality.

The median number of intravitreal injections in treated eyes was 19.5 (range, 2-132 injections). Ocular surface outcomes were as follows:
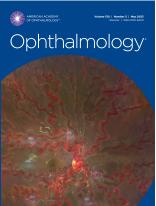
- **MG loss.** In the upper eyelid, mean MG loss was 19.1% ± 11.3% in treated eyes and 25.5% ± 14.6% in untreated fellow eyes. For the lower eyelid, median MG loss was 17.4% in treated eyes and 24.5% in fellow eyes.
- **Bulbar redness.** The mean BR was 1.32 ± .46 in treated eyes and 1.44 ± .45 in fellow eyes.
- **Tear meniscus height.** Median TMH was .36 in treated eyes and .32 in fellow eyes.
- **Other measures.** There were no significant differences between treated and fellow eyes with regard to the other measures.

The underlying mechanism contributing to these results may be the povidone-iodine protocol, which has antibacterial properties that can be protective against ocular surface damage associated with eyelid margin diseases, the researchers noted. Alternatively, the anti-inflammatory role of VEGF inhibition may have a positive effect on dry eye, they wrote, and they encouraged further research.

Adverse Events After Nd:YAG Capsulotomy

May 2023

Dot et al. estimated the incidence of and risk factors for three adverse events (AEs) within 12 months after Nd:YAG capsulotomy (Nd:YAG-caps). Of the three AEs of interest—ocular hypertension (OHT), macular edema (ME), and retinal detachments (RDs)—they found that OHT and ME were most likely to occur. They also found that patients who had diabetes and underwent Nd:YAG-caps between one and two years after their cataract surgery were more likely to experience an AE.

For this observational cohort study, known as the French YAG 2 Study, the researchers used a national claims database to identify patients who had Nd:YAG-caps between 2014 and 2017. The rates of all AEs, including OHT/glaucoma and ME, were assessed quarterly during 12 months of follow-up, with follow-up extended to 18 months for RDs.

All told, 6,210 patients were included in the study population, representing 7,958 procedures. Nearly two-thirds (65.3%) were women, and the mean age was 75 ± 10.3 years. The Nd:YAG-caps procedures were categorized as very early (within one year of cataract surgery; 8.7% of participants), early (between the first and second years after cataract surgery; 23.3%), and late (two or more years after cataract surgery; 68%).

Three-month and 12-month rates

for the AEs of interest were 8.6% and 13.3%, respectively. At the 12-month mark, OHT/glaucoma was the most frequent AE, with a rate of 9.6%. In comparison, the rate for ME was 6.4% during the same time period. RDs were rare, occurring at a rate of less than 1% at any time during follow-up.

Diabetes emerged as a contributing factor, with affected patients at greater risk of OHT (hazard ratio [HR], 1.233; p = .0448) and ME (HR, 1.810; p < .0001) than those without diabetes. Early Nd: YAG-caps also emerged as a risk factor, with those who underwent the procedure within one to two years after cataract surgery more likely to develop OHT than those who had it later on (HR, 1.429; p = .0002).

Risk of Ocular Trauma From Gel Pellets
May 2023

Lin et al. characterized the ocular injuries experienced by patients who had been hit with gel pellets. Despite the perception that gel blaster guns are safer than paintball and air guns, the researchers observed significant anterior and posterior segment complications, including uncontrolled IOP in the setting of hyphema. They recommend eye protection similar to that worn for play with paintball guns for any individuals who play with or are near those who use gel blaster guns.

For this retrospective consecutive case series, researchers at six centers pooled data on 19 patients (19 eyes). The patients' average age was 17.8 years (range, 11-48 years), and 17 were male. On presentation, the average VA was 20/79, the median VA was 20/30, and the average IOP was 21.8 mm Hg.

Of the 19 eyes, 12 received an ocular trauma score (OTS) of 100, five had an OTS of 89 or 90, and two had an OTS of 60 to 70. The two most common injuries were hyphema (12 eyes) and corneal epithelial defect (eight eyes). Three eyes had commotio retinae, one had a macula-sparing retinal detachment, and one eye had a nonclearing vitreous hemorrhage at presentation.

Treatment included corticosteroid and cyclopegic drops in 16 eyes and ocular hypertensive drops in seven. Invasive procedures were needed in seven eyes; these included anterior chamber washout or paracentesis (six eyes), orphan trabeculectomy (three eyes), pars plana vitrectomy (two eyes), and cataract removal and IOL implantation (two eyes). At last follow-up, the mean VA was approximately 20/41, median VA was 20/20, and two eyes showed count fingers and hand motion vision.

Once reconstituted, gel pellets are 6 mm to 8 mm in diameter and are somewhat soft and pliable. However, as the authors noted, the pellets travel at a high velocity (at least 200 to 300 feet per second), and their force is concentrated onto a small surface area. As a result, they said, high-quality protective eye wear is essential for all who are in the area when gel blaster guns are being fired. —*Summaries by Jean Shaw*

Ophthalmology Retina
Selected by Andrew P. Schachat, MD

Meta-Analysis of Preoperative OCT Features in RDs
May 2023

Murtaza et al. set out to evaluate the prognostic relationship between preoperative features of retinal detachments (RDs) as noted on OCT scans and postoperative visual outcomes. They found that four features—greater height of retinal detachment (HRD), disruption of the ellipsoid zone (EZ) and/or the external limiting membrane (ELM), presence of intraretinal cystic cavities (ICCs), and macular detachment—were associated with poor visual recovery and post-op VA, although the quality of the evidence was low. They also proposed a standardized nomenclature for reporting preoperative RD OCT features for future studies.

For this meta-analysis, the researchers extracted data from 29 studies. All told, 1,670 patients (1,671 eyes) were included in the analysis. The primary outcome was the association between six preoperative OCT findings in RDs and postoperative VA. The participants' average age was 55 ± 6.42 years. At baseline, 89.4% of eyes had a macula-off RD, and 80.3% had a primary RD.

The average duration of detachment was 15.1 ± 9.9 days, and the average duration of follow-up after surgery was 15.4 ± 9.8 months (range, 1-30 months). Most eyes (62%) underwent pars plana vitrectomy.

Two features—outer retinal corrugations and central macular thickness (CMT)—had no bearing on post-op VA. A greater HRD at the fovea was only weakly associated with a poorer postoperative VA. Preoperative disruption of the EZ and/or ELM, the presence of ICCs, and the presence of macular detachment were significantly associated with poor post-op VA, ranging from a difference of 2 to 3 Snellen lines. All associations had a low quality of evidence, with CMT being of very low quality.

Because of inconsistencies in the literature regarding the classification and measurement of OCT features, the authors also proposed a nomenclature and classification system for common pre-op features seen on OCT in RDs. This system is meant to "guide and promote consistency in future studies," the authors wrote.
—*Summary by Jean Shaw*

Ophthalmology Science
Selected by Emily Y. Chew, MD

Using AI to Improve Ophthalmology Triage
March 2023

Tanya et al. evaluated a cloud-based triage system for on-call ophthalmology consults. They found that their clinical decision support system (CDSS) is accurate, standardizes information collection, and is superior to paper-based consults.

For this prospective comparative cohort study, the researchers used current practice guidelines and expert opinion to develop an artificial intelligence (AI)–based decision tree for referrals. Their CDSS collected specific information on patients' ophthalmic symptoms, produced a provisional diagnosis, and sent an electronic referral to two community-based ophthalmology clinics in Canada.

Data were collected between November 2020 and December 2021. Ten categories of new-onset symptoms were developed, along with 10 categories covering previous ophthalmic diagnoses and seven levels of referral urgency. Primary outcome measures included the category, diagnosis, and level of urgency for the referring provider, the CDSS, and the on-call clinician. The CDSS provided multiple options to communicate directly with the on-call ophthalmologist if needed, and the clinician's final diagnosis and assessment of urgency, based on a complete ophthalmic examination, served as the ground truth.

During the study period, 96 referrals that represented 59 unique diagnoses were processed. The most frequent referring categories were vitreoretinal pathology (37.5%), traumatic pathology (16.7%), and unspecified (14.6%).

Results showed that the CDSS performed as well as referring providers did in determining a disease category and better than they did in determining a diagnosis. With regard to assessing urgency, the CDSS correctly assigned 66 cases (68.8%), matching the ophthalmologist's assessment. Among the other 30 cases, the system assigned 15 a lower level of urgency and eight a higher level of urgency than did the ophthalmologist. The remaining seven were of unspecified urgency and represented instances of "tree failure," as information was unavailable for the initial data collection.

Future research directions include broadening the scope of clinical scenarios by increasing the number of decision trees, the authors wrote, with the goal of improving the system's diagnostic accuracy.

—*Summary by Jean Shaw*

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

Tracking the Cataract Surgery Learning Curve
May 2023

By 2050, an estimated 50 million or more Americans will develop cataracts.

As demand for cataract surgery grows, the need for competent surgeons will intensify. To better understand the early cataract learning curve among residents, **Balas et al.** tracked resident progress over the course of cataract surgery training by measuring procedural speed and the frequency of specific actions as a surrogate for competency and skill progression. They found that a basic level of surgical competency was achieved after 80 cases—but that advancement toward surgical finesse occurs after 300 cases.

For this longitudinal panel study, the researchers collected video recordings of 100 cataract surgeries performed by the same resident between 2021 and 2022. The videos ranged from the resident's sixth to 760th case. The start and end times of 19 distinct operative phases of cataract surgery were manually labeled by a trained annotator. For each action throughout the resident's first year of training, time series analysis was used to measure the direction and magnitude of trends in the resident's surgical speed.

The median total time for each video was 11.6 minutes (interquartile range [IQR], 10.1-14.4 minutes), with the overall speed increasing at a rate of 43.4 seconds for every 10 videos (95% CI, 35.1 to 52.7 seconds). The time for nine operative phases decreased significantly throughout the training. The greatest improvements in speed relative to average procedural times occurred during phacoemulsification and hydrodissection. On average, 26.9 distinct operative actions (not including idle periods) took place in each video.

According to the authors, this is the first effort to derive cataract surgery learning curves for all relevant operative actions. They noted that the 80 case milestone for basic cataract surgery competency is consistent with the findings of previous investigations.

Cup-to-Disc Ratio and Brain Changes
May 2023

Loss of brain volume is linked with normal aging as well as neurodegenerative disease. Because the optic nerve shares neuropathophysiology with the brain, **Wang et al.** sought to investigate the relationship between optic nerve cupping measurements and total and regional brain volumes. They found that in women 65 years of age and older, large cup-to-disc ratio (CDR)—defined as .6 or greater in either eye—was associated with lower relative total brain volume and decreased absolute regional volume in the frontal and occipital lobes.

Previously, using measurements from the Women's Health Initiative Sight Examination (WHISE) study, the authors found that women 65 years and older who did not have glaucoma but did have a large CDR had lower cognitive function than those who did not have a large CDR.

To determine whether large CDR was associated with changes in brain volumes, the researchers performed a secondary analysis of data from two randomized clinical trials. The authors included measurements from 471 women aged 65 to 79 without glaucoma who participated in WHISE and for whom MRI data on regional brain volumes were available from a second study, the WHI Memory Study (WHIMS).

All told, 34 women (7.2%) had large CDR. When the researchers controlled for total brain volume and for demographic and clinical characteristics, lateral ventricle volume was 3.01 cm^3 larger for subjects with large CDR than for those without large CDR (95% CI, .02 to 5.99; p = .048). However, frontal lobe volume was 4.78 cm^3 lower for subjects with large CDR compared to those without (95% CI, −8.71 to −.84; p = .02), and occipital lobe volume was 1.86 cm^3 lower for those with large CDR compared to those without (95% CI, −3.39 to −.3; p = .02).

According to the authors, this is the first epidemiologic analysis that demonstrates a relationship between large CDR and decreased brain volumes in individuals without glaucoma. They concluded that large CDR in women without glaucoma may be a sign of optic nerve and brain aging, but they noted that more longitudinal data are needed.

In addition, in their conclusion, the

authors pointed out that while they used "a large, well-characterized cohort" of women from studies (WHISE and WHIMS) that enrolled people from a "variety of racial backgrounds," most participants (93.8%) were White. Future investigations of CDR and brain volumes should represent multiple racial groups and genders to expand the scope of this study, they wrote.

—*Summaries by Mary Brophy Marcus*

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

Perfluorohexyloctane Eyedrops for Meibomian Gland Disease
April 2023

Perfluorohexyloctane, a preservative-free lipophilic compound, is marketed in Europe as an eyedrop for dry eye disease (DED). **Tian et al.** evaluated the compound's efficacy and safety in Chinese patients who had DED associated with meibomian gland disease (MGD). They found that the perfluorhexyloctane eyedrops quickly relieved the signs and symptoms of MGD-associated DED and were safe and well-tolerated.

For this double-masked phase 3 clinical trial, the researchers recruited patients from 15 hospital ophthalmology departments in China. All participants (N = 312) were 18 years or older. They also had the following: symptoms of DED for six months or longer at screening, an ocular surface disease index (OSDI) score of ≥25, tear film breakup time (TBUT) of ≤5 seconds, Schirmer 1 test of ≥5 mm at 5 minutes, total corneal fluorescein score (tCFS) of 4 to 11 on the 15-point NEI scale, and an MGD score of ≥3.

The participants were randomly assigned 1:1 to receive either perfluorohexyloctane eyedrops or .6% saline eyedrops four times a day for nearly two months. The primary endpoints were the changes from baseline to tCFS and eye dryness scores at day 57. Results were as follows:
- **tCFS.** This score decreased by –3.8 in the treatment group, versus –2.7 in controls.
- **Eye dryness score.** This dropped by

–38.6 in the treatment group and by –28.3 in controls.
- **OSDI.** This decreased by –29.9 in the treatment group, versus –23.9 in controls.
- **Other measures.** No significant changes in MGD, TBUT, or Schirmer 1 outcomes were noted in either group. However, those in the treatment group reported improvement in symptoms such as burning, foreign body sensation, and blurred vision.
- **Adverse events.** Treatment-related adverse events were noted in 34 of those who received the perfluorohexyloctane drops and in 40 of those in the control group. Perfluorohexyloctane's safety and tolerability profile may be due to the absence of additives such as phosphates and preservatives that may negatively affect the ocular surface, the researchers wrote.

The results support the use of perfluorohexyloctane eyedrops if these findings "can be confirmed independently and over longer time periods," the authors concluded. *(Also see related commentary by Gerami D. Seitzman, MD, and Thomas M. Lietman, MD, in the same issue.)*

Pediatric Lensectomy and Glaucoma-Related AEs
April 2023

After lensectomy, how do children with pediatric cataracts fare with regard to glaucoma-related adverse events (AEs)? In a report for the Pediatric Eye Disease Investigator Group (PEDIG), **Bothun et al.** set out to answer this question. They found that glaucoma-related AEs were common in aphakic eyes within five years of lensectomy—and that children with pseudophakia, who tended to be older at the time of surgery, were less likely to develop a glaucoma-related AE.

For this prospective longitudinal study, the PEDIG researchers collected data on children who were 12 years old or younger at the time they underwent unilateral or bilateral lensectomy. This analysis comprised 810 children (1,049 eyes) who had at least one follow-up examination within 5.5 years following their initial surgery.

Median age at first lens surgery was

.21 years in aphakic eyes and 5.32 years in pseudophakic eyes. The five-year cumulative incidence of glaucoma-related AEs was 29% in 443 eyes with aphakia and 7% in 606 eyes with pseudophakia. In addition, 7% of aphakic eyes and 3% of pseudophakic eyes were diagnosed as glaucoma suspect.

Among children with aphakia, the risk of a glaucoma-related AE was higher in those who were 3 months or younger at the time of surgery, had an abnormal anterior segment, experienced intraoperative complications, and had bilateral aphakia.

Glaucoma surgery was performed in 7% of aphakic eyes and in .5% of pseudophakic eyes. VA at the five-year mark varied according to subgroup: for instance, in those who developed glaucoma, median VA was 20/80 for the 41 eyes with bilateral aphakia and 20/50 for the 17 eyes with unilateral aphakia. In those who had no glaucoma or ocular complications, median VA was 20/63 in 109 eyes with bilateral aphakia and 20/200 in 85 eyes with unilateral aphakia.

All told, the researchers wrote, the findings suggest that ongoing monitoring for the development of glaucoma is needed after lensectomy at any age. *(Also see related commentary by Eric Crouch, MD, in the same issue.)*

Diagnostic Accuracy of the Amsler Grid for AMD
April 2023

In a systematic review and meta-analysis, **Bjerager et al.** reviewed data on the diagnostic accuracy of the Amsler grid test when used by patients for self-assessment of signs of age-related macular degeneration (AMD). They found low sensitivity and moderate specificity.

After a search of 12 databases, the researchers found 10 studies eligible for their review. The studies were clinic-based and took place between 2003 and 2015, and they collectively included 425 eyes with neovascular AMD, 1,262 eyes with dry AMD, and 203 healthy control eyes. Participants' age ranged from 62 to 83 years. Main outcomes were sensitivity and specific-

ity of the Amsler grid for detecting neovascular AMD, with comparators being either healthy control eyes or eyes with dry AMD.

Sensitivity and specificity to diagnose neovascular AMD were 67% and 99%, respectively, when compared to healthy control participants—and were 71% and 63%, respectively, when compared to eyes with dry AMD.

These findings indicate that the Amsler grid test should be used with caution for detecting neovascular AMD, the researchers wrote. They acknowledged that the test continues to appeal to patients, as it is inexpensive, readily available, easy to use, and does not require any electronics or devices. However, they wrote, "Although the Amsler grid may perform well in some cases, it may also provide a false sense of security in others." As a result, they said, patients should be encouraged to have regular ophthalmic exams, regardless of their self-assessment results.

—*Summaries by Jean Shaw*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Visual Recovery After Ethambutol-Induced Optic Neuropathy
Clinical Ophthalmology
2023;17:545-554

Ethambutol-induced optic neuropathy (EON) is an uncommon but well-recognized adverse event in patients who take the antituberculosis drug ethambutol. Although some researchers have found that patients recover vision after immediate discontinuation of ethambutol, others have reported irreparable damage. **Srithawatpong et al.** set out to study visual recovery and identify the factors that may contribute to it in patients with EON. They found that EON damage was not always reversible—and that initial VA was the only factor that appeared to correlate with visual recovery.

For this retrospective observational study, the researchers evaluated the charts of patients who were diagnosed with tuberculosis and treated with ethambutol between 2012 and 2021

in a tertiary eye center. The primary outcome was visual recovery, which was defined as experiencing improvement from the initial VA assessment and achieving a final BCVA of 20/50 or better once the drug was discontinued.

Of 5,394 patients diagnosed with tuberculosis during the 10-year study period, 23 (.43%) were diagnosed with EON. All 23 developed impaired vision in both eyes. After ethambutol was discontinued, good visual recovery was achieved in nine (39.13%) of the 23 patients, while poor visual recovery was noted in the remaining 14 (60.87%). The mean daily dose of ethambutol was slightly higher in those who achieved good visual recovery, but this did not reach statistical significance (p = .55). Similarly, no statistically significant differences were noted between the two groups of patients with regard to age, body weight, mean duration of ethambutol treatment, or cumulative dose of ethambutol.

After adjustment with multivariate analysis, initial VA was found to be the only significant factor associated with visual recovery: specifically, only those eyes with initial BCVA of 20/200 or better at presentation recovered vision.

In their discussion, the authors recommend that ophthalmologists regularly screen patients who are taking ethambutol. Ophthalmologists and pulmonologists should work together to minimize the risk of EON—and if it is discovered, ethambutol should be immediately discontinued.

Predicting DMEK Graft Rejection
Translational Vision Science & Technology
2023;12(2):22

Using endothelial cell images, **Joseph et al.** investigated the ability of machine learning (ML) to predict future episodes of graft rejection in patients who underwent Descemet membrane endothelial keratoplasty (DMEK). They found that ML classifiers—algorithms that sort data into one or more categories—predicted future graft rejections one to 24 months before the rejections became clinically apparent.

For this study, the researchers ob-

tained endothelial cell images from 44 patients (44 eyes) who had undergone DMEK. Of these, half experienced graft rejection. The images were acquired via specular microscopy at multiple time points following surgery (range, 1-123 months). ML was used for segmentation of images from the patients' last and second-to-last imaging visits. A bank of 432 features—which represented cellular and image intensity distribution, texture, and shape parameters—was developed; after highly correlated features were removed, the initial 432 features were reduced by approximately 50%. Random forest and logistic regression models were trained to predict the likelihood of future graft rejection.

The results showed that the novel ML classifiers used in this study outperformed those trained in traditional morphometrics, such as measuring endothelial cell density. Features most indicative of graft rejection were cell-graph spatial arrangement, intensity, and shape.

In their discussion, the authors wrote that this study "introduces the potential benefits of two alterations to the standard practice of care for post-keratoplasty patients: consistent and frequent specular microscopy imaging and machine learning models trained on novel quantitative features" outlined in the study. They added that their ML application could help clinicians "identify patients at risk for graft rejection."

—*Summaries by Jean Shaw*

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