

# News in Review

COMMENTARY AND PERSPECTIVE

## MICROBIOME

### AMD Risk May Lie in the Gut

**THANKS TO THE AGE-RELATED EYE Disease Studies (AREDS),** we now know that certain nutrients protect the retina from age-related macular degeneration (AMD). But the processes responsible for protective effects of nutrients on vision remain mysterious. Mechanistically, how is it that nutrients ingested orally translate into a healthier retina?

The answers appear to be more complicated than a certain vitamin or micronutrient entering the circulation and somehow acting directly on ocular tissue. Instead, evidence (most of it pre-clinical) increasingly points to another contributor to retinal health: molecular signals from gut microorganisms.

**Gut-retina axis.** Just as a dysregulated gut-brain axis has been implicated in the risk for Alzheimer disease,<sup>1</sup> a separate gut-retina axis appears to play a crucial but undefined role in maintaining the retina, researchers say.<sup>2-4</sup>

**Evidence from mice.** This summer, a group from Tufts University in Boston reported on the results of feeding mice high-glycemic and low-glycemic diets, in combination with antibiotics to kill off their normal gut bacteria.<sup>5</sup>

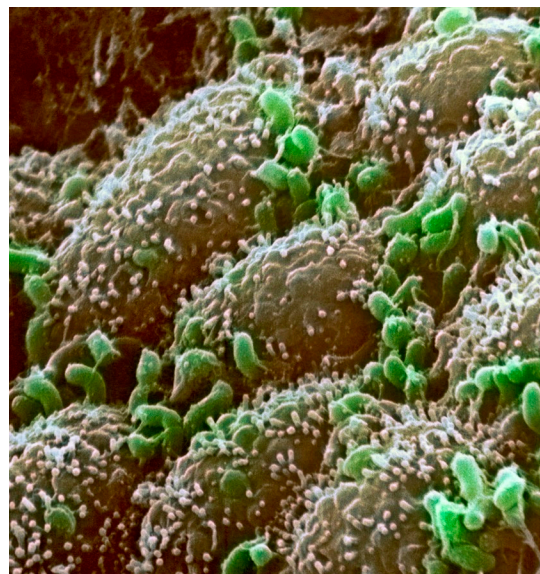
Earlier research, without antibiotics, showed that mice eating a high-glycemic diet developed retinal disease resembling AMD, but the low-glycemic group did not, said coauthor Sheldon Rowan, PhD. His group's working hypothesis is that commensal gut microbes or

their metabolites, possibly serotonin and tryptophan, interact with the immune system to protect retinal cells in response to a low-glycemic diet—and, perhaps, also exert a direct neuroprotective effect, Dr. Rowan said.

In this most recent Tufts study, most of the mice in the antibiotic-treated, high-glycemic group quickly died; the low-glycemic group survived but, lacking normal gut bacteria, had abnormal retinal findings despite their diets, Dr. Rowan said. He suggested that the antibiotic-treated animals fed the low-glycemic diet could not reap the ocular benefits of the diet without the normal gut bacteria. "There may be ongoing signals from the gut microbiome to the eye, which were impacted by the antibiotics, and that can't be completely resolved by changing diet, because you've killed off all the bacteria that would be responding to that diet."

**What about people?** Although data on the gut-retina axis in people are limited, the outlines of the emerging story are becoming clear and have been buttressed by early clinical studies, said coauthor Allen Taylor, PhD, also at Tufts.

"Our preclinical studies clearly establish a correlation between gut microbiota, diet, and ophthalmologic status of animals. In separate clinical studies, we found that diet is related to ophthalmologic status in large cohorts of humans," Dr. Taylor said. "Putting the dots together, there is reason to



**GUT-RETINA AXIS?** What role do normal gut bacteria (in green) play in protecting the retina?

think that in humans, as in mice, diet will be related to microbial status."

**Next steps.** One of the next steps will be to study patients with AMD and controls to look for specific microbial signatures associated with disease—and then to determine how these populations are affected by diet and nutritional intake, including AREDS supplementation. "We predict that, in the next couple of years, researchers will figure out whether the AREDS supplements themselves could be affecting the gut microbiome and whether that effect is mediating some of protection," Dr. Rowan said. —Linda Roach

1 Ghaisas S et al. *Pharmacol Ther.* 2016;58:52-62.

2 Rowan S et al. *Proc Natl Acad Sci USA.* 2017; 114(22):E4472-E4481.

3 Rinninella E et al. *Nutrients.* 2018;10(11). pii:E1677.

4 Weikel KA et al. *Mol Aspects Med.* 2012;33(4): 318-375.

5 Smith K et al. *Curr Dev Nutr.* 2019;3(Suppl 1).

Relevant financial disclosures—Drs. Rowan and Taylor: None.

## RETINA

# AREDS: Aspirin Safe for Patients With AMD

**PATIENTS WITH AGE-RELATED MACULAR degeneration (AMD)** should not worry that taking aspirin after a heart attack could increase their disease progression. That's the conclusion of the 19th report culled from the two Age-Related Eye Disease Studies (AREDS).<sup>1</sup>

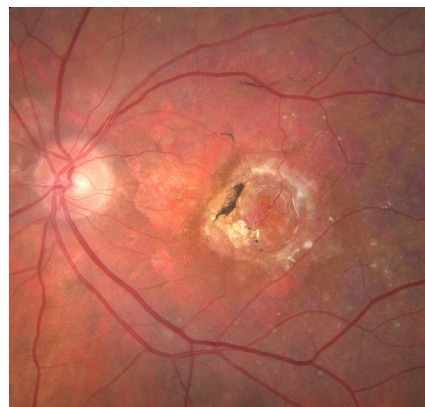
"We found that taking aspirin was not associated with an increased risk of developing AMD, either the wet or the dry form," said Emily Y. Chew, MD, at the NEI.

The literature has been mixed on the association between aspirin, an established therapy for the secondary

prevention of cardiovascular events, and the risk of progression to late AMD. However, Dr. Chew said the robust nature of the AREDS and AREDS2 data gives more credence to this study's findings than any earlier conflicting cross-sectional and population-based studies. Among the strengths are long follow-up—10 years for AREDS and five for AREDS2—plus a sufficiently large sample size of persons with AMD.

This study's statistical methodology attempts to level the playing field by matching the patients to focus on the effect of aspirin. In addition, two previous randomized trials also showed no increased risk of AMD progression with aspirin use.<sup>2,3</sup>

**Caution: Not the last word.** "The obvious limitation of our study is that it is not a clinical trial," Dr. Chew said. "It is still an association study, so we cannot prove cause and effect." For



**PROGRESSION.** The AREDS results indicate that aspirin does not affect progression of either dry or wet AMD (shown here).

that, she is looking to ASPREE (Aspirin in Reducing Events in the Elderly), which set out to investigate whether the daily use of 100 mg of enteric-coated aspirin would prolong the healthy

## CATARACT

# Dislocated IOLs: Outcomes Equal With Two Techniques

**WHEN IT COMES TO FIXING LATE IN-THE-BAG DISLOCATIONS** of IOLs, Norwegian researchers found equivalent visual outcomes at two years after surgery with both scleral suturing of the existing lens and IOL exchange using a retropupillary iris-claw lens.<sup>1</sup>

"An important implication of this trial is that patients with late in-the-bag IOL dislocation have an overall good visual prognosis when treated surgically, and the degree of dislocation at baseline (grade 1-3) did not affect the long-term visual outcome," the researchers reported.<sup>1</sup>

Retrospective studies have found long-term vision-threatening complications after IOL dislocation surgery, the researchers noted. But the results from this prospective, randomized trial found this not to be the case.

The study was well-designed, according to Samuel Masket, MD. "The key message is that the surgical methods are equivalent and that both can have a place in our armamentarium," said Dr. Masket, in practice in Los Angeles. "Unfortunately, the Artisan [iris-claw] IOL is not available in the United States at this time. However, an FDA trial is underway, and hopefully the device will receive approval in the foreseeable future."

**Study specifics.** The Norwegian trial randomly assigned 104 older patients to have their dislocated IOLs either sutured in place or replaced with an iris-claw lens (Verisyse VRSA54, Johnson & Johnson). Of the

104 patients, 66 (mean age, 79.6 ± 7.6 years) completed two years of follow-up. No statistically significant differences in postoperative complications or visual acuity were noted between eyes in the two groups.

**Adverse outcomes.** Cystoid macular edema occurred in four scleral-fixation eyes and five iris-claw eyes. In addition, there was one re-dislocated IOL in each group. No retinal detachments occurred.

**Visual acuity.** The mean corrected distance visual acuity (CDVA) was logMAR 0.20 ± 0.29 SD (range: -0.18 to 1.10) in the scleral-fixation eyes and 0.22 ± 0.30 SD (range: -0.10 to 1.22) in the iris-claw group. Four patients in each group had a worse CDVA after surgery compared to baseline.

**Unanswered questions.** Dr. Masket said the study does not clarify the relative values of other methods of stabilizing a dislocated IOL. "There are a host of other methods that were not considered," including intrascleral haptic fixation, anterior chamber IOLs, and scleral suture fixation of IOLs (with eyelets) that are specifically designed for that purpose, he said.

"Perhaps large-scaled, multicentered randomized trials for all of these methods will be designed and performed to determine if there is a superior choice," Dr. Masket said. "In the interim, surgeons can be comfortable with either of the methods considered in the Norwegian study." —Linda Roach

1 Dalby M et al. *Am J Ophthalmol*. Published online June 10, 2019.

**Relevant financial disclosures**—Dr. Masket: None.

life span of older adults. Although the parent ASPREE trial concluded in January 2018, a five-year randomized substudy, ASPREE-AMD, will assess the effect of daily aspirin on the course of AMD in 5,000 subjects age 70 and older.

Until results from ASPREE-AMD are available, doctors may advise patients that aspirin is not likely to affect the progression of their AMD, Dr. Chew said. “We believe it is safe for patients who have AMD to take aspirin when indicated for other medical conditions.” —*Miriam Karmel*

1 Keenan TD et al. *Ophthalmology*. Published online June 26, 2019.

2 Christen WG et al. *Arch Ophthalmol*. 2001; 119(8):1143-1149.

3 Christen WG et al. *Ophthalmology*. 2009; 116(12):2386-2392.

Relevant financial disclosures—Dr. Chew: None.

## COMPREHENSIVE

# Checkpoint Inhibitors: Watch for AEs

**AS MORE OF THE TARGETED CANCER** drugs known as immune checkpoint inhibitors (ICIs) are introduced—and as the indications for their use expand—ophthalmologists are being challenged to keep up with their potential ocular adverse effects.

While the literature supports a multidisciplinary approach to dealing with such immune-related adverse events (AEs), it has offered no roadmap. Now, researchers at Johns Hopkins University in Baltimore have shown a way. They report a multidisciplinary collaboration in which oncologists, ophthalmologists, and other specialists successfully diagnosed and managed patients with immune-related AEs.<sup>1</sup> The team approach proved both feasible and useful, the researchers said.

“We are the first group to show that oncology providers deferred to team recommendations on immune-related AE diagnosis and management,” said oncologist and lead author Jarushka Naidoo, MBBCh.

**Multispecialty investigation.** The pilot collaboration involved eight oncologists, four oncology nurses, and an immune-related toxicity team of 21 medical specialists, including two ophthalmologists. They interacted through an electronic messaging forum where oncologists could seek diagnostic and management assistance from the medical specialists, who were to respond via e-mail within 24 hours. In all, 117 oncology consultations (involving 102 patients treated with ICIs) were made over eight months ending in March 2018.

**Ocular and other adverse events.** Pneumonitis topped the list of confirmed toxicities, followed by arthritis, dermatitis, and diarrhea/colitis. In the pilot program, the only ocular event, a case of bilateral anterior uveitis, resolved with topical steroids, per the advice of team ophthalmologist Meghan Berkenstock, MD.

Other researchers have found a broader range of ocular immune-related AEs, including corneal perforation, corneal punctate epithelial erosion, subconjunctival hemorrhage, uveitis, hypotony maculopathy, cystoid macular edema, retinal detachment, choroiditis, optic neuritis, melanoma-associated retinopathy, and visual field loss related to antiretinal and anti-

optic-nerve autoantibodies.<sup>2</sup>

**A growing concern.** The current evidence indicates that ophthalmic complications occur in approximately 1% of patients on ICIs.<sup>2</sup> But as Dr. Berkenstock pointed out, “These side effects will be more common in the future, given the expanding indications for use of these drugs.” (The checkpoint inhibitors are licensed for at least 13 cancer types.)

Thus, ophthalmologists need to watch for new symptoms in patients who have been treated with an ICI—even if the infusion took place several weeks prior to their ophthalmologic appointment.

And close collaboration with the patient’s oncologist and other specialists should be part of the ophthalmologist’s treatment plan, Dr. Berkenstock cautioned. “Hence, the need for a toxicity team to facilitate this communication.” —*Miriam Karmel*

1 Naidoo J et al. *J Natl Compr Netw*. 2019;17(6): 712-720.

2 Kim JM et al. *Ophthalmology*. 2019;126(7): 1058-1062.

Relevant financial disclosures—Dr. Berkenstock: None. Dr. Naidoo: AstraZeneca/MedImmune: C,L,S; Bristol-Myers Squibb: C,L; Calithera: S; Kyowa Hakko Kirin: S; Merck: S; Takeda: C.

## ICIs at a Glance

Primary use of ICIs that have been approved by the FDA. Other applications are under investigation.

Target	Drugs	Used to Treat
Inhibition of PD-1	Cemiplimab (Libtayo); pembrolizumab (Keytruda); nivolumab (Opdivo)	Melanoma of the skin; non-small cell lung cancer; kidney cancer; bladder cancer; head and neck cancers; Hodgkin lymphoma
Inhibition of PD-L1	Atezolizumab (Tecentriq); avelumab (Bavencio); durvalumab (Imfinzi)	Bladder cancer; non-small cell lung cancer; Merkel cell cancer
Inhibition of CTLA-4	Ipilimumab (Yervoy)	Melanoma of the skin

PD-1 = programmed cell death protein 1; PD-L = programmed death-ligand 1; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4.

**SOURCE:** American Cancer Society