

Journal Highlights

NEW FINDINGS FROM *OPHTHALMOLOGY*, *AJO*, AND *JAMA OPHTHALMOLOGY*

Ophthalmology

Use of SD-OCT to Identify Glaucoma Progression

Ophthalmology

Published online March 7, 2013

Using spectral-domain optical coherence tomography (SD-OCT), Na et al. compared the longitudinal changes in three parameters—circumpapillary retinal nerve fiber layer (cRNFL), macular volume and thickness, and optic nerve head—between eyes with progressing and nonprogressing glaucoma. The authors discovered that serial measurements in all three areas can help identify progression in glaucomatous eyes.

This study included 279 eyes of 162 glaucoma patients who were classified as progressors or nonprogressors based on visual field progression analysis and photographic assessment of the optic disc and cRNFL. The authors used linear mixed-effects models to evaluate the overall rate of change of the three parameters, adjusting for age, spherical equivalent, signal strength, and baseline SD-OCT measurements.

They identified 63 eyes (22.6 percent) of 52 patients as progressors. Optic nerve head rim area as well as average, inferior-quadrant, and 6- and 7-o'clock sector cRNFL thickness decreased faster in progressors than in nonprogressors. Macular cube volume and the thickness of temporal outer

and inferior inner macular sectors also decreased faster in progressors. Average and vertical cup-to-disc ratio, however, increased faster in progressors than in nonprogressors.

Although the study was limited by the short follow-up period (2.2 years) and retrospective review, the authors concluded that the parameters measured by SD-OCT represent viable tools to detect progression in glaucomatous eyes.

Omega-3 Fatty Acids Associated With Reduced Risk of Geographic Atrophy Progression

Ophthalmology

Published online March 7, 2013

Reynolds et al. investigated the impact of specific types of fats on geographic atrophy (GA) and whether their intake could affect disease progression. They found that increased self-reported intake of omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid is associated with a reduced risk of GA and that this dietary intake may modify genetic susceptibility for progression to GA.

The authors evaluated 2,531 patients from the Age-Related Eye Disease Study for progression to GA. Patients with advanced age-related



macular degeneration at baseline were excluded from the analysis. The Database of Genotypes and Phenotypes and food frequency questionnaires were used to collect dietary and behavioral data, including smoking and body mass index measurements.

The authors also geno-

typed eight single-nucleotide polymorphisms in seven genes (*CFH*, *ARMS2/HTRA1*, *CFB*, *C2*, *C3*, *CFI*, and *LIPC*). Cox proportional hazard models were then used to test for associations between incident GA and intake of dietary lipids and interaction effects between dietary fat intake and genetic variation on the risk of GA.

Given their findings, the authors suggested that eating one or more servings of fish high in omega-3 fatty acids on a weekly basis might reduce risk of progression to GA.

Three-Year Results of Gene Therapy for Leber Congenital Amaurosis Type 2

Ophthalmology

Published online March 7, 2013

Testa et al. evaluated the progress of five patients with Leber congenital amaurosis type 2 and *RPE65* gene mutations who had undergone a single subretinal injection of the adeno-associated virus AAV2-hRPE65v2 vector. Results showed improvement in visual

and retinal function within a few months after the injection. Maximum improvement was achieved within six months after treatment, and visual improvement was stable for up to three years.

In this long-term clinical trial, the investigators selected the eye with worse visual function for gene therapy treatment. Patients underwent complete ophthalmic evaluation before and after surgery. Treatment efficacy was determined using best-corrected visual acuity (BCVA), kinetic visual field, nystagmus testing, and pupillary light reflex.

All treated eyes showed a statistically significant improvement in BCVA between baseline and three-year follow-up. The investigators also reported an enlargement of visual field area and a reduction of nystagmus frequency. Furthermore, a statistically significant difference was observed in the pupillary constriction of the treated eye compared with the untreated eye in three patients at one- and three-year follow-up. No patient experienced serious adverse events related to the vector during the follow-up period.

American Journal of Ophthalmology

Intravitreal Bevacizumab for Treatment of Retinal Arterial Macroaneurysm

May *AJO*

Cho et al. evaluated the therapeutic effect of intravitreal bevacizumab for symptomatic retinal arterial macroaneurysm and found that the drug likely hastens resolution of macular edema and hemorrhage secondary to the aneurysm.

In this interventional case series, the investigators randomized 23 eyes (23 patients) with symptomatic retinal arterial macroaneurysm into an intravitreal bevacizumab group (11 eyes) and an untreated group (12 eyes). Bevacizumab was injected at the initial visit, followed by as-needed monthly reinjection. The mean follow-up period for all subjects was 10.8 months, and the mean number of injections for

the treated group was 1.42. BCVA and central macular thickness were documented and analyzed between groups.

At the last follow-up, mean logMAR BCVA improved from baseline by 0.26 in the bevacizumab-treated group and by 0.34 in the untreated group. Average central macular thickness decreased from 384.4 ± 150.1 to 265.6 ± 112.5 μm in the bevacizumab-treated group and from 413.2 ± 155.2 to 236.3 ± 103.5 μm in the untreated group.

BCVA significantly improved from baseline after one month in the bevacizumab-treated group and after three months in the untreated group. However, there was no statistically significant difference between the two groups in BCVA improvement or central macular thickness improvement achieved at the last follow-up.

Anterior Chamber Paracentesis With Polymerase Chain Reaction for Diagnosing Anterior Uveitis

May *AJO*

Anwar et al. investigated the value of anterior chamber paracentesis with polymerase chain reaction (PCR) for patients with anterior uveitis. They found that the procedure had a relatively low diagnostic utility and resulted in few management changes for patients.

In this observational case series, the authors reviewed the records of 53 patients with a diagnosis of anterior uveitis who underwent anterior chamber paracentesis with PCR. The main outcome measures were diagnostic utility and frequency of management change.

Fifteen patients had acute anterior uveitis, and 35 patients had chronic anterior uveitis. PCR positivity of herpes simplex virus, cytomegalovirus, varicella zoster virus, and Epstein-Barr virus was 8 percent, 2 percent, 3 percent, and 6 percent, respectively. Overall, seven patients had a change in management because of PCR results from anterior chamber paracentesis. Four patients experienced paracentesis complications, one with long-term sequelae.

The authors concluded that anterior chamber paracentesis for suspected infectious anterior uveitis should be reserved for patients who fail empiric therapy with topical corticosteroids and oral acyclovir.

Tacrolimus Ointment for Inflammatory Ocular Surface Disease

May *AJO*

Lee et al. evaluated the therapeutic effects of topical tacrolimus ointment on refractory inflammatory ocular surface diseases. The authors found that the ointment successfully controlled the inflammation on the ocular surface such that it could assist in the tapering of steroids, and it suppressed the inflammatory relapse without any effect on intraocular pressure (IOP).

This interventional case series involved 12 patients with refractory inflammatory ocular surface diseases who had previously been treated with steroid therapy. Tacrolimus ointment (0.02 percent) was applied one to three times per day, depending on disease severity, for up to 31 months. Seven patients had chronic cicatrizing conjunctivitis, four had scleritis, and one had Mooren ulcer with corneal perforation.

The authors evaluated the therapeutic outcomes based on the following criteria: IOP, need for steroid therapy, and changes in clinical findings, such as decrease of hyperemia, ocular pain, epithelial defect, and pseudomembrane.

In all three groups, tacrolimus showed an immunosuppressive effect, especially on scleritis and Mooren ulcer. These effects included suppression of corneoscleral melting and reduction of hyperemia. In chronic cicatrizing conjunctivitis, combined topical tacrolimus and tapering of steroid therapy suppressed the inflammatory relapse. The elevated IOP in steroid responders recovered to normal range after successful tapering of steroid. No adverse side effects were noted after 1.5 to 31 months of continuous tacrolimus treatment.

JAMA Ophthalmology**Limbal Epithelial Transplantation in Pediatric Patients With Ocular Surface Burns**April *JAMA Ophthalmology*

The corneal epithelial surface is maintained in a transparent state by the corneal epithelial stem cells that are located at the basal layer of the limbal epithelium. Any physical, chemical, thermal, or immunological disturbance to the limbal region can result in permanent damage to the corneal epithelial stem cells, leading to limbal stem cell deficiency.

Sejpal et al. reported the outcomes of autologous ex vivo cultivated limbal epithelial transplantation (CLET) in pediatric patients with ocular trauma. The authors found that transplantation was successful in restoring the ocular surface and improving vision in almost half of the children blinded by ocular burns.

This retrospective, interventional case series included children up to 15 years of age with limbal stem cell deficiency secondary to chemical or thermal injury who underwent CLET between 2001 and 2010. Following a biopsy from a healthy area of the limbus, the limbal epithelial cells were cultured on a denuded human amniotic membrane substrate using a xeno-free explant culture technique. The amniotic membrane and a monolayer of cultivated epithelial cells were transplanted onto the patient's affected eye after pannus excision. Ocular surface stability and visual improvement were the primary and secondary outcome measures. Surgical success was defined as a stable corneal epithelium without conjunctivalization.

Of the 107 eyes (107 patients) included in this study, 73 eyes (68 percent) and 34 eyes (32 percent) underwent one and two autologous CLET procedures, respectively. At a mean follow-up of 3.4 years, 50 eyes (46.7 percent) achieved completely epithelialized, avascular, and stable ocular surfaces. At the final visit, 58 eyes (54 percent) had improvement in visual acuity

of greater than 0.2 logMAR units.

The authors concluded that management of limbal stem cell deficiency in children remains challenging, with even poorer outcomes in adults. Timely intervention, visual rehabilitation, and amblyopia management are essential to achieve ocular surface stability and maximize outcomes.

Temporal Macular Thinning Associated With X-Linked Alport SyndromeApril *JAMA Ophthalmology*

Ahmed et al. assessed the ocular phenotypic findings and their corresponding genotypes for X-linked Alport syndrome (XLAS), a degenerative multisystem disease affecting both the kidneys and the eyes. They found that temporal macular thinning is a prominent sign associated with the disease, suggesting that optical coherence tomography (OCT) measurements are essential in both the diagnosis and prognosis of XLAS. The authors also noted that the L1649R mutation in the *COL4A5* collagen gene caused a relatively mild form of the disease compared with other *COL4A5* mutations.

Thirty-two patients with XLAS with confirmed mutations in *COL4A5* had eye examinations and retinal imaging with fundus photography and OCT. The authors calculated a temporal thinning index from macular OCT results to quantify the retinal changes, which were then compared with a published normative database.

Eleven unique *COL4A5* mutations were identified in the XLAS study population, a majority of which were missense. Severe pathological thinning of the temporal retina was a prominent feature that was much more common than lenticonus. Those patients with an L1649R mutation were characterized by later-onset renal failure and less-frequent severe temporal macular thinning relative to the other reported mutations in *COL4A5*.

The authors noted that the pathological basis for the retinal abnormalities seen in XLAS remains to be established.

Fibrin Membrane Combined With Solid Platelet-Rich Plasma in the Management of Perforated Corneal UlcersApril *JAMA Ophthalmology*

Corneal perforations can be the result of trauma or ulcerative disease of different sources. Alió et al. evaluated the use of autologous solid platelet-rich plasma in combination with an autologous fibrin membrane as a surgical alternative for wound closure in perforated corneal ulcers. They found that the combined therapy is a safe and effective alternative for closure of corneal perforations and can be considered as a temporary measure until the cornea's condition permits definitive intervention.

This study included 11 patients with perforated corneal ulcers treated with a combination of autologous fibrin membrane and platelet-rich plasma clot. All patients, except one, had experienced a central corneal perforation caused by a chronic corneal ulcerative disorder.

In all patients, the corneal perforation was sealed. The fibrin membrane was present over the corneal surface for the first three to five days and then gradually disappeared. The investigators detected no evidence of infection or inflammation. Digital tonometry confirmed acceptable levels of ocular tonus in all cases from day 2 after surgery. No patient reported pain, discomfort, or other symptoms, and no complications were observed. After three months of follow-up, there was no evidence of relapses or perforations. Corneal grafting was eventually performed in seven of the 11 cases.

Considering that the preparation for this combined therapy is possible in most hospitals, it deserves further study to confirm its role for emergency management of perforations related to chronic ulcerative corneal disorders.

Ophthalmology summaries are written by Lori Baker Schena, EdD, and edited by John Kerrison, MD. American Journal of Ophthalmology summaries are edited by Thomas J. Liesegang, MD. JAMA Ophthalmology summaries are written by the lead authors.

ROUNDUP OF OTHER JOURNALS

Seven New Loci Linked to Age-Related Macular Degeneration

Nature Genetics

Published online March 3, 2013

The AMD Gene Consortium is composed of 18 research groups from around the world whose purpose is to accelerate the pace of discovery in age-related macular degeneration (AMD) genetics. The consortium, with support from the National Eye Institute, has discovered seven new loci associated with increased risk of AMD and confirmed 12 loci identified in previous studies.

This collaborative genome-wide association study included data from more than 17,000 individuals of European and Asian ancestry with the most advanced and severe forms of AMD and more than 60,000 individuals of similar ancestry without AMD. The consortium's meta-analysis evaluated evidence for association at 2,442,884 single-nucleotide polymorphisms.

The 19 identified loci were all associated at $P < 5 \times 10^{-8}$ and showed enrichment for genes involved in the regulation of complement activity, lipid metabolism, extracellular matrix remodeling, and angiogenesis. The seven new loci with associations reaching $P < 5 \times 10^{-8}$ were found near the genes *COL8A1-FILIP1L*, *IER3-DDR1*, *SLC16A8*, *TGFBRI*, *RAD51B*, *ADAMTS9*, and *B3GALT1*.

Increased Macular Volume in Patients With Multiple Sclerosis Taking Fingolimod

Neurology

2013;80(2):139-144

Previous research has shown that multiple sclerosis (MS) patients treated with fingolimod, an oral sphingosine-1-phosphate receptor modulator, experience less loss of brain volume than patients treated with placebo or once-weekly interferon- β -1a. Nolan et al. conducted an observation-

al study to determine if fingolimod is linked to increased retinal tissue volume in patients with MS. They found that this therapy is associated with a relatively rapid, but modest, increase in macular volume.

The authors used spectral-domain optical coherence tomography (SD-OCT) to compare macular volume changes in 30 patients with MS who had started fingolimod therapy and 30 MS patients who had never used the drug. Macular volume was evaluated using the paired *t* test, and the change in macular volume between groups was analyzed using multiple linear regression.

The authors found that 74 percent of eyes in the fingolimod-treated group showed an increase in macular volume compared with 37 percent of untreated eyes over a mean follow-up period of five months. In addition, only 9 percent of fingolimod-treated eyes showed a decline in macular volume compared with 42 percent of eyes in the untreated group.

Whether this small increase in macular volume represents a subclinical form of cystoid macular edema or an entirely different physiologic process remains to be determined. However, the authors recommended that clinicians visually monitor those patients who show increases in macular volume. Also, these increases should be taken into account when interpreting retinal SD-OCT findings in patients with MS.

Wireless Subretinal Electronic Implant Restores Some Visual Function in Blind Patients

Proceedings of the Royal Society B

Published online Feb. 20, 2013

Stingl et al. tested the alpha-IMS subretinal implant in nine blind patients with hereditary retinal disease. The authors found that the wirelessly powered artificial vision device restored useful vision in daily

life for at least two-thirds of the participants.

This study involved eight patients with retinitis pigmentosa and one patient with cone-rod dystrophy who were fitted with the alpha-IMS subretinal implant. The device uses light-sensitive detector arrays and amplifiers to convert light into signals that stimulate the bipolar cell neurons via tiny metal electrodes. The wireless power and signal transmission allowed the patients to use the implant at home or outdoors and provided a diamond-shaped visual field of 15 degrees. The participants underwent a series of efficacy tests, including standardized screen tasks, daily living activities, and letter recognition, and provided self-reports of the experience.

The subretinal implant restored some light perception, light localization, and motion detection in most of the patients. In addition, identification, localization, and discrimination of objects improved significantly throughout a nine-month period. In the near-vision range, patients reported recognizing facial characteristics and distinguishing objects such as telephones, cutlery, signs on doors, and red wine versus white wine. Three patients could read letters spontaneously. In the far-vision range, the most frequently reported perception was finding the line of the horizon and objects along the horizon, such as houses and trees.

The authors concluded that the implant, positioned in the subfoveal subretinal space, can restore useful vision for daily life for many blind patients. The multicenter phase of this clinical study has already begun in Europe and Asia and will address long-term stability and safety and the development of visual recognition abilities via learning effects.

Roundup of Other Journals is written by Lori Baker Schena, EdD, and edited by Deepak P. Edward, MD.