Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

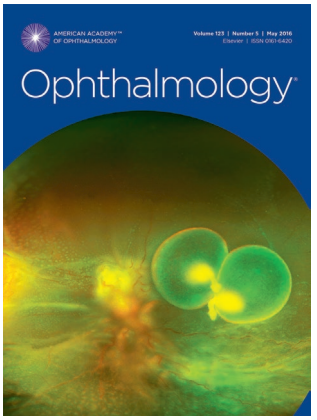
Ophthalmology

AMD in a Multi-Ethnic U.S. Population

June 2016

Fisher et al. described the incidence of age-related macular degeneration (AMD) and the effect of risk factors among 4 racial/ethnic groups residing in the United States—white, black, Hispanic, and Chinese. They found substantial variation of AMD incidence among these groups, with whites having the highest rate and blacks having the lowest.

In this prospective cohort study, the researchers examined 3,811 participants from the Multi-Ethnic Study of Atherosclerosis who ranged in age from 46 to 86. Fundus photography was performed on each participant twice, on average, at an interval of 8 years. The photos were graded at a central reading facility according to the Wisconsin Age-Related Maculopathy Grading System. The images were assessed for early and late AMD based on drusen size, type, and area; increased retinal pigment; retinal pigment epithelial depigmentation; neovascular lesions; and geographic atrophy. Demographic, clinical, and laboratory measures were included in multivariable regression models to determine their impact on the variation in AMD incidence among racial and ethnic groups.



The overall 8-year age- and sex-standardized incidence of early and late AMD was 4.1% and 2.3%, respectively. The incidence of early and late AMD, respectively, was highest in whites (5.3% and 4.1%); intermediate in Chinese individuals (4.5% and 2.2%) and Hispanics (3.3% and 0.8%); and lowest in blacks (1.6% and 0.4%). After adjustment for age and gender, black individuals had a 70% lower risk of developing early AMD than did whites; after multivariable adjustment, this finding decreased only slightly to 67%.

When adjustments were made for age, gender, and race/ethnicity, hyperopia and astigmatism were associated with early AMD; myopia was not. Age, race/ethnicity, current smoking, hyperopia, and AMD candidate gene variants *CFH* RS1061170 and *ARMS2* RS3793917 were independently associated with incident early AMD in multivariable models for the combined sample. However, increasing age was the only statistically significant factor consistently associated with incident early AMD across the 4 racial/ethnic groups.

Although earlier reports have hypothesized that the presence or absence of certain gene alleles may be responsible for the differences, in this study, the genetic, clinical, and environmental factors assessed did not account for racial/ethnic differences seen in AMD incidence.

Latanoprostene Bunod Versus Timolol Maleate in Open-Angle Glaucoma

May 2016

Latanoprostene bunod (LBN) is a novel monotherapy with the pharmacologic activity of both a prostaglandin F2α analogue and the physiologic signaling mediator nitric oxide. **Weinreb et al.** compared the diurnal intraocular pressure (IOP)-lowering effect of LBN ophthalmic solution 0.024% once every evening (qPM) with timolol maleate 0.5% twice daily (BID) among patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The study was a multicenter phase 3 randomized controlled double-masked parallel-group trial. Of the 420 randomized subjects, 387 completed the study: 264 who took LBN 0.024% and 123 who took timolol 0.5%. All participants were aged 18 or older and had been diagnosed with OAG or OHT in 1 or both eyes. The 3-month regimen included LBN qPM (plus a placebo drop in the morning to maintain masking) or 1 timolol drop BID. IOP was measured at 8 a.m., 12 p.m., and 4 p.m. at each postrandomization visit (week 2, week 6, and month 3).

The primary efficacy end point was IOP at each of the 9 assessment time points. Secondary end points were the proportion of patients with an IOP of

≤18 mm Hg consistently at all 9 time points and the proportion of patients with an IOP reduction ≥25% consistently at all 9 time points.

The researchers reported that at all 9 time points, the mean IOP in the study eye was significantly lower in the LBN group (range, 17.8-18.7 mm Hg) than in the timolol group (range, 19.1-19.8 mm Hg). In addition, the percentage of subjects with mean IOP ≤18 mm Hg was significantly higher in the LBN group compared with the timolol group (22.9% vs. 11.3%), as was the percentage of subjects with IOP reduction ≥25% (34.9% vs. 19.5%). The incidence of treatment-related adverse events—chiefly ocular irritation and conjunctival hyperemia—was low and occurred at similar rates between the 2 groups.

Topical Corticosteroids in Conjunction With Antiamoebic Therapy

May 2016

Many cornea specialists are uncertain about the risk-benefit balance of topical steroid use in the treatment of *Acanthamoeba* keratitis (AK). **Carnt et al.** performed a cohort study on the effect of topical corticosteroids administered after initiation of antiamoebic therapy (AAT). They found that use of steroids in this setting was not associated with worse outcomes and may provide benefits.

The study included 196 patients (1 eye each) diagnosed with AK at Moorfields Eye Hospital in London between January 1991 and April 2012. After exclusion of patients who had coexisting scleritis or hypopyon, outcomes for 129 patients were analyzed: 74 who received topical steroids after the start of AAT and 55 who received AAT but no steroids. (However, some patients in both groups had received steroids before diagnosis of AK.) The main outcome measure was a suboptimal outcome, which was defined as a final visual acuity of ≤20/80, corneal perforation, or the need for keratoplasty.

After multivariable analysis, the researchers found that topical corticosteroids started after initiation of AAT were not associated with a worse outcome (odds ratio [OR], 1.08); however, topical corticosteroid use before the start of AAT was a significant risk factor (OR, 3.85) for worse outcome, as were the presence a corneal ring infiltrate (OR, 5.89) and age 33 years or older at the start of ATT (OR, 4.02).

The authors concluded that clinicians and patients can be reassured that steroid use initiated after AAT is not associated with a worse outcome and, further, that it has several potential benefits, including reducing pain, corneal vascularization, and severe corneal stromal inflammation.

American Journal of Ophthalmology

Persistent Exogenous Bacterial Endophthalmitis

May 2016

Leung et al. performed a consecutive case series to investigate the characteristics and outcomes of persistently vitreous culture–positive bacterial exogenous endophthalmitis. They found that despite antibiotic therapy, visual outcomes were generally poor, with no statistically significant improvement in visual acuity (VA) between the initial and final examinations.

The 36 participants in this series were patients with exogenous endophthalmitis who were treated at the same tertiary care center between 1981 and 2015 and in whom vitreous culture identified the same bacteria on 2 or more visits (most common organisms, gram-positive *Staphylococcus* and *Streptococcus*). By comparison, over the same time period at the same institution, there were 1,189 patients with bacterial endophthalmitis who had only 1 positive culture. In the 36 patients with persistently positive cultures, 50% had developed endophthalmitis after cataract surgery, 31% after trabeculectomy, and the rest after other procedures or trauma. On presentation, mean VA was 2.16 ± 0.77 logMAR (Snellen equivalent approximately 20/2,900).

On the day of endophthalmitis diagnosis, all patients received intravitreal vancomycin and adjunctive topical antibiotics, 92% received an added intravitreal antibiotic, and 36% received systemic antibiotics. In 94%, topical steroids were used within 24 hours after initiation of antibiotics. In addition to these medications, 78% of patients had a vitreous tap, while 22% had a pars plana vitrectomy. Patients received further therapy if they were not improving. Ultimately, 92% of patients had a vitrectomy.

After a mean follow-up of 26.5 months, the mean final BCVA was 2.08 ± 0.97 logMAR (Snellen approximately 20/2,400). Of the 36 patients, 33% had a final VA of 20/200 or better, while 31% had no light perception or were enucleated.

The researchers could not identify any statistically significant associations between outcomes and initial vitreous tap vs. vitrectomy, use of steroids, type of bacteria, or timing of second treatment. The only group that experienced significant improvement in VA after treatment was patients with a history of uncomplicated phacoemulsification. Also, patients whose vision was hand motions or better at diagnosis were more likely to recover 20/200 or better vision at the final visit.

Intravitreal Aflibercept and Ranibizumab Injections for PCV

May 2016

In a study conducted in South Korea, **Cho et al.** compared the effectiveness of intravitreal aflibercept and ranibizumab in patients with polypoidal choroidal vasculopathy (PCV). They found no significant difference between the treatments in visual acuity (VA) results but observed that aflibercept caused more polyp regression.

Participants in this chart review study were 98 patients aged 50 years or older with angiography-confirmed PCV who were treated with either aflibercept or ranibizumab alone. The main outcome measure was mean change in VA at 3, 6, 9, and 12 months; the secondary outcome was mean change in central foveal thickness (CFT) at those same time points. All patients received a loading dose of 1 intravitreal injection of the study drug every month for 3 months; subsequent

injections were made on an as-needed basis.

The aflibercept group had a VA improvement from 20/85 (Snellen equivalent) at baseline to 20/55 at 12 months, while the ranibizumab group improved from 20/91 to 20/61 at the same points. In the aflibercept group, CFT was reduced from 396 ± 167 µm at baseline to 212 ± 144 µm at 12 months; in the ranibizumab group, CFT was reduced from 402 ± 198 µm to 240 ± 183 µm. Although the within-group improvements were significant, there was no statistically significant difference between the groups.

The only statistically significant difference between groups was in polyp regression: 39.5% of the aflibercept group experienced polyp regression compared with 21.7% of the ranibizumab group. The reason for this difference is unclear, although the authors said that some experts have posited that it is due to aflibercept's ability to bind VEGF-B and placental growth factor in addition to VEGF-A, the target for ranibizumab.

JAMA Ophthalmology

Characteristics of Medicare Beneficiaries With Glaucoma

April 2016

To better understand the effect of glaucoma on nonglaucomatous medical conditions and resultant secondary health care costs, **Prager et al.** assessed self-reported medical conditions, the use of medical services, and total health care costs among Medicare beneficiaries with glaucoma. The researchers found that patients with glaucoma had higher health care costs and use of health aides and services.

In this longitudinal observational study, self-reported health status, use of health care services, adjusted mean annual total health care costs per person, and adjusted mean annual nonoutpatient costs per person were extracted from the Medicare Current Beneficiary Survey for 72,587 Medicare beneficiaries. Participants were 65 years or older with (n = 4,441) or without (n = 68,146) a glaucoma diagnosis in the year before collection of survey data from 2004 to 2009. Their mean age was 76.9 years, and 43.2% were men. Patients with glaucoma who responded to survey questions on visual disability were stratified into those with (n = 1,748) and without (n = 2,639) self-reported visual disability.

The authors found that Medicare beneficiaries with glaucoma had higher adjusted odds of inpatient hospitalizations (odds ratio [OR], 1.27; 95% CI, 1.17-1.39) and home health aide visits (OR, 1.27; 95% CI, 1.13-1.43) compared with Medicare beneficiaries without glaucoma. Furthermore, patients with glaucoma who had self-reported visual disability were more likely to report depression (OR, 1.47; 95% CI, 1.26-1.71), falls (OR, 1.34; 95% CI, 1.09-1.66), and difficulty walking (OR, 1.22; 95% CI, 1.02-1.45) compared with those who did not report visual disability. In the risk-adjusted model, Medicare beneficiaries with glaucoma incurred an additional $2,903 (95% CI, $2,247-$3,558) in annual total health care costs and $2,599 (95% CI, $1,985-$3,212) in costs for nonoutpatient services than those without glaucoma.

The authors concluded that glaucoma is associated with greater use of inpatient and home health aide services and with higher annual total and nonoutpatient medical costs. Self-reported visual disability among patients with glaucoma may be associated with depression, falls, and difficulty walking. Reducing the prevalence and severity of glaucoma may result in improvements in associated nonglaucomatous medical conditions and a reduction in health care costs.

Automated Quantification of Capillary Nonperfusion From OCT Angiography

April 2016

Macular ischemia is recognized as a key feature of diabetic retinopathy (DR). **Hwang et al.** studied the feasibility of using automated quantification of capillary nonperfusion via optical coherence tomography (OCT) angiography as a potential biomarker for DR.

In an observational study conducted in a tertiary subspecialty academic practice, the researchers evaluated macular nonperfusion with 6 × 6-mm OCT angiography obtained with commercially available 70-kHz OCT versus fluorescein angiography (FA) from Jan. 22 to Sept. 18, 2014. Participants included 12 individuals with normal vision (mean age, 54.2 years) serving as controls and 12 patients with various levels of DR (mean age, 55.1 years). Preplanned primary measures were parafoveal and perifoveal vessel density, total avascular area, and foveal avascular zone as detected with 6 × 6-mm OCT angiography and analyzed using an automated algorithm. Secondary measures included the agreement of the avascular area between the OCT angiogram and FA.

Compared with the 12 healthy controls, the 12 DR patients had parafoveal and perifoveal vessel density that was reduced by 12.6% (95% CI, 7.7%-17.5%) and 10.4% (95% CI, 6.8%-14.1%), respectively. Total avascular area and foveal avascular zone area, respectively, were greater in eyes with DR by 0.82 mm^2 (95% CI, 0.65-0.99 mm^2) and 0.16 mm^2 (95% CI, 0.05-0.28 mm^2). The agreement between the vascular areas in the OCT angiogram and FA had a κ value of 0.45 (95% CI, 0.21-0.70). Total avascular area in the central 5.5-mm-diameter area distinguished eyes with DR from control eyes with 100% sensitivity and specificity.

The authors concluded that avascular area analysis with an automated algorithm using OCT angiography, although not equivalent to FA, detected DR reliably in this small pilot study. Further study is needed to determine the usefulness of the automated quantification in clinical practice.

Risk for Cataract After Treatment of Childhood Cancer

April 2016

Few studies have been published on the association of the radiotherapy (RT) dose applied to the eyes for childhood cancer and the risk for later cataract; thus, **Allodji et al.** investigated the risk for cataract after treatment of nonretinoblastoma solid cancer in childhood.

They found a significantly increased risk of cataract in patients who had received RT, especially at higher doses.

The study used data from the Euro-2K cohort that includes 4,389 5-year survivors of solid tumors treated from Jan. 1, 1945, to Dec. 31, 1985. In this group 3,172 patients had been treated in France and were sent a self-reported questionnaire starting on Sept. 1, 2005; the response period ended Dec. 31, 2012, when follow-up was considered complete.

From the French patients, 1,833 questionnaires were analyzed (the rest of the patients had died, had retinoblastoma or enucleation, could not be located, or did not return the questionnaire or consent form). Among the 1,833 patients, 52.4% were men, and the mean (SD) age was 37.0 (8.5) years.

Radiation doses in both eyes were estimated for all patients who had received RT. The role of the radiation dose in cataract risk was investigated using the Cox proportional hazard regression model and the excess relative or the absolute risk model. The role of cytotoxic chemotherapy was also investigated.

After a mean follow-up of 32 years, 33 patients with unilateral or bilateral cataract were identified, for a total of 47 cataract events. The 47 events were validated by medical record review and by contacting the patients and their medical physician or ophthalmologist to obtain copies of diagnostic examinations or surgical reports.

Overall, in a multivariable Cox proportional hazard regression analysis, patients who had received RT had a 4.4-fold (95% CI, 1.5- to 13.0-fold) increased risk for cataract compared with patients who did not receive RT. Exposure to radiation doses of at least 10 Gy to the eyes increased the hazard ratio 39-fold (95% CI, 12.0- to 127.9-fold), relative to no radiation exposure. Treatment with melphalan hydrochloride was associated with a strong increase in cataract risk (hazard ratio, 26.3; 95% CI, 7.1-96.6), although this finding was based on few patients. The authors noted that these results could aid in developing guidelines for long-term follow-up for cataract.

OTHER JOURNALS

Tocilizumab for Induction and Maintenance of Remission in GCA

The Lancet
Published online March 4, 2016

Corticosteroids are the gold-standard treatment for giant cell arteritis (GCA), but they are associated with serious adverse events. **Villiger et al.** studied the safety and efficacy of tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, as a steroid-sparing therapy. They found that tocilizumab effectively induced and maintained remission in GCA.

This was a single-center phase 2 randomized double-blind placebo-controlled trial of tocilizumab in patients aged 50 years or older with GCA. Patients with new-onset or relapsing disease were randomly assigned (2:1) to receive either tocilizumab (8 mg/kg) or placebo intravenously. They received 13 infusions in 4-week intervals until week 52. Both groups also took oral prednisolone, starting at a dosage of 1 mg/kg per day and tapering to 0 mg according to a standard reduction scheme defined in the study protocol.

The primary outcome measure was complete clinical disease remission of GCA, along with normal erythrocyte sedimentation rate and C-reactive protein at a prednisolone dose of 0.1 mg/kg per day at week 12. Vision was not an outcome measure.

Complete remission was achieved in 85% of tocilizumab patients at 12 and 52 weeks. In the placebo group, 40% of patients achieved remission at 12 weeks, and that rate dropped to 20% at 52 weeks. Serious adverse events were numerically equal in the tocilizumab and placebo groups, with a preponderance of serious gastrointestinal adverse events in the tocilizumab group, and cardiovascular and metabolic complications in the placebo group.

The researchers noted that a number of case series and an open-label study had found positive results with tocilizumab. Now, this first randomized placebo-controlled trial confirms the efficacy of the drug in inducing and maintaining remission of GCA.

Visual Recovery After Retinal Detachment With Macula Off

British Journal of Ophthalmology
Published online February 11, 2016

Frings et al. investigated the clinical importance of lag time between the onset of central visual acuity (VA) loss and surgical intervention for macula-off retinal detachment. They found that eyes surgically repaired within the first 3 days had better visual outcomes than those with delayed surgery.

In this retrospective case series, the researchers reviewed all consecutively treated eyes with primary macula-off retinal detachment (1,727) treated at a university hospital in Germany from February 2010 to February 2015. Of this group, only 89 eyes met all inclusion criteria. Eyes were repaired with either pars plana vitrectomy alone, phacovitrectomy, or scleral buckling based on the extent of retinal detachment and lens status. The main outcome measure was final VA as a function of the symptom duration (defined as time from onset of central VA loss to surgery) of macula-off detachment. Secondary outcome measures were the effect of age and surgical technique.

The researchers found that eyes with a symptom duration of 3 days or less achieved the best final VA; within this 3-day window, there were no significant differences. Further, they concluded that after 10 days of central VA loss, the final visual outcome was clinically comparable to that of surgery delayed up to 30 days. Age and preoperative VA had no influence, but vitrectomized eyes had a better outcome than those treated with scleral buckling.

Ophthalmology summaries are written by Marianne Doran and edited by Susan M. MacDonald, MD. *American Journal of Ophthalmology* summaries are written by Peggy Denny and edited by Richard K. Parrish II, MD. *JAMA Ophthalmology* summaries are based on authors' abstracts, as edited by senior editor(s). *Other Journals* summaries are written by Marianne Doran and edited by Deepak P. Edward, MD.

EXTRA **MORE ONLINE.** See this article at www.aao.org/eyenet for an additional *AJO* summary.