Journal Highlights

Ophthalmology

Selected by Stephen D. McLeod, MD

Incidence of Macular Atrophy With Anti-VEGF Protocols

December 2020

Spooner et al. looked at the development and growth of macular atrophy in patients with neovascular age-related macular degeneration (AMD) who were receiving anti-VEGF therapy in pro re nata (PRN) and treat-

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and-extend (T&E) regimens. During the four-year study, the authors found no difference in the incidence or progression of macular atrophy by treatment regimen. They noted that the T&E approach produced better visual outcomes but required more injections.

This multicenter review included 264 consecutively treated patients (264 eyes) with AMD who were receiving anti-VEGF therapy.

Each year, patients underwent fundus autofluorescence (FAF) and optical coherence tomography (OCT) imaging. Two masked graders reviewed serial FAF and OCT images to establish the presence of macular atrophy and measure changes in atrophic area over four years. Incident macular atrophy was defined as a well-demarcated region or regions of marked hypoautofluorescence from an absence of the retinal pigment epithelium measuring at least 0.02 mm². In the T&E group (n = 163), macular atrophy was present in 24% (39/ 163) of eyes at baseline and 27% (34/ 124) at four years. In the PRN group (n = 101), the rates of macular atrophy were 20% (20/101) at baseline and 25% (20/81) at four years.

According to regression analysis, the risk of new macular atrophy did not differ by treatment regimen. Atrophic growth was similar in the two groups (approximately 0.4 mm²/year). In multi-



significant baseline predictors of atrophic progression were older age, poorer visual acuity (VA), and the presence of retinal angiomatous proliferation. By year 4, eyes in the T&E group had received significantly more injections (29.3 vs. 15.7) and VA

was similar to baseline values, but acuity in the PRN group had declined from baseline.

These findings suggest that the T&E and PRN protocols are indistinguishable in terms of macular atrophy occurrence and expansion in patients with AMD. Although T&E involved more injections over four years, it improved functional outcomes significantly without accelerating atrophic progression. Thus, it may be preferable overall to PRN, said the authors.

Low-Dose Atropine Reduces Elongation of Axial Length December 2020

Use of low-concentration atropine eyedrops is intended to slow myopia progression. Li et al. looked at changes in ocular biometrics among patients who received placebo or 0.05%, 0.025%, or 0.01% atropine. They observed antimyopia effects with low-dose atropine, including significant reductions in axial length (AL) elongation. However, no clinical effects on corneal or lens power were noted.

For this double-masked, randomized, placebo-controlled study, 383 children (age, 4 to 12 years) were recruited from the earlier LAMP study. All had myopic refraction of at least –1.0 D in both eyes and astigmatism of less than 2.5 D. Atropine or placebo was administered to both eyes once a day. Participants were assigned randomly to one of the four study groups. Lens power was calculated using measurements from both eyes, including cycloplegic spherical equivalent (SE), AL, corneal curvature (K), and anterior chamber depth (ACD).

The degree of response was found to be concentration dependent. Throughout the year, the changes in AL were 0.20 ± 0.25 mm, 0.29 ± 0.20 mm, 0.36 ± 0.29 mm, and 0.41 ± 0.22 mm with 0.05% atropine, 0.025% atropine, 0.01%atropine, and placebo, respectively (p < .001). The average K remained stable with all dosages of atropine. Although corneal astigmatism worsened in all atropine groups, the degree of change was similar for the three concentrations.



Lens power declined over time and ACD deepened in each group, with no discernible differences between concentrations. AL elongation was the greatest contributing factor to myopia progression, accounting for more than 70% of the progression. Contributions to SE progression from ocular biometric changes, adjusted for age and gender, were statistically similar for the four groups.

These findings suggest that low-dose atropine exerts antimyopia effects mainly by delaying AL elongation, which potentially could decrease the risk of subsequent myopia complications.

Topical Antibiotics Lower Infection Risk After Periocular Surgery

December 2020

Topical antibiotics are commonly used after routine oculofacial plastic surgery. Considering the overall low infection rates for clean and clean-contaminated wounds, along with concerns about antibiotic resistance, drug-related adverse events, and health care costs, Ashraf et al. questioned whether topical antibiotics make a significant difference after oculofacial plastic surgery. They found that patients who used an antibiotic ointment had a much lower risk of surgical site infection (SSI).

For this randomized, placebocontrolled study, 401 adults were recruited from a clinic population undergoing periocular surgery. Patients were assigned randomly to receive a post-op antibiotic or placebo. Within the antibiotic group (n = 208), treatments were chosen randomly and consisted of 0.5% erythromycin ophthalmic ointment, bacitracin zinc ophthalmic ointment, or bacitracin zinc plus polymyxin B sulfate. The placebo group (n = 193)received one of four ophthalmic lubricant ointments consisting only of mineral oil and petrolatum. All participants were instructed to apply their ointment four times daily for seven days. The primary outcome measure was the frequency of SSI (superficial or deep) at the first post-op visit, which took place seven to 14 days after the surgery. The incidence of allergic contact dermatitis

was a secondary outcome.

The most common procedures in both study arms were blepharoplasty; repair of ptosis/ectropion/entropion; reconstruction after Mohs surgery; and eyelid lesion removal or biopsy (or both).

A modestly higher rate of infection was observed for the placebo group (2.7% vs. 0% for the antibiotic group), but the difference between groups was significant (p = .025). Contact dermatitis was rare, occurring in only one patient of each group.

The authors acknowledged that their study was limited by the lack of SSI in the active-treatment group, which precluded any subanalyses. (*Also see related commentary by Jeremiah P. Tao, MD, in the same issue.*)

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Detecting Glaucoma Progression: Trend-Based Analysis or the Rule of 5

November/December 2020

To evaluate glaucomatous progression, many clinicians use the "rule of 5" to gauge the rate of change in the retinal nerve fiber layer (RNFL), as seen on spectral-domain optical coherence tomography (SD-OCT). That is, a loss of 5 µm of global RNFL is considered to be evidence of progression when a follow-up scan is compared with baseline scanning results. Thompson et al. compared results derived from use of the rule of 5 with the results of trend-based analysis of SD-OCT scans. They found that trend-based analysis outperformed the rule of 5 for identifying progression in glaucomatous eyes.

For this prospective study, the researchers evaluated 300 eyes of 210 patients. The patients were followed for an average of 5.4 ± 1.5 years and were examined during a median of 11 visits (range, 7-14). All participants completed at least five SD-OCT tests during a two-year period.

Using trend-based analysis, eyes were considered to have progressed if

the slope was negative and statistically significantly different from zero (p < .05). The specificity of trend-based analysis was matched to that of the rule of 5 to allow meaningful comparison of the hit rate (the proportion of glaucoma eyes categorized as progressing at each time point). The main outcome measure was the comparison between hit rates of trend analysis versus the rule of 5 when results were matched for the same specificity.

When the two methods were matched, hit rates obtained for the trend-based analysis were greater than those for the rule of 5. By comparing the two methods, the researchers determined that trend-based analysis was able to detect progression in 18.5% to 26.3% more eyes than the rule of 5 during each year of the study.

The authors acknowledge limitations in the study, including their use of global average RNFL rather than sectorial measurements to assess progression. Nonetheless, they said, trend-based analysis was superior to the rule of 5 for identifying progression and should be preferred as a method for longitudinal assessment of global SD-OCT RNFL change over time.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Genotype and Phenotype of Geography Atrophy Subgroups December 2020

Biarnés et al. set out to examine whether subgroups of patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) can be defined by their genotype and phenotype. They identified three GA subgroups that differed mostly by genotype; atrophy location and drusen type were the most relevant phenotypic features.

For this retrospective analysis, the researchers evaluated 188 eyes of 188 patients. The mean age of the participants was 82.4 years (range, 56.9-97), and 121 (61.7%) were female.

Participants were graded for the presence of six fundus features: large

soft drusen, reticular pseudodrusen, refractile drusen, hyperpigmentation, location of atrophy, and multifocal lesions. Genetic risk scores (GRSs) were based on five major risk alleles-and if this genetic information was available for a participant, the person's GRS was calculated for three different pathways previously associated with AMD: the complement pathway, lipid metabolism, and extracellular matrix remodeling. The researchers used hierarchical cluster analysis to identify subgroups; they then determined the discriminative ability of genotype, phenotype, or both for each subgroup.

Three GA subgroups were identified: Subgroup 1 (n = 115; 61.2%) was characterized by a high median GRS for the complement pathway. A high median GRS was found for the lipid pathway, and participants were more likely to have foveal atrophy and large soft drusen.

Subgroup 2 (n = 21; 11.2%) had low to moderate values for all GRSs, less foveal atrophy, and few drusen of any type.

• Subgroup 3 (n = 52; 27.7%) had the highest GRSs for extracellular matrix remodeling and the ARMS2 gene, and participants were more likely to have reticular pseudodrusen and extrafoveal lesions.

These subgroups may provide new insights into GA pathogenesis and could contribute to developing therapies that target subgroup-specific disease pathways, the authors said. (Also see related commentary by Tiarnán Keenan, MD, PhD, in the same issue.) -Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Real-World Outcomes of DMEK in the Netherlands

December 2020

Dunker et al. looked at practice patterns, graft survival, and other outcomes of Descemet membrane endothelial keratoplasty (DMEK). Their findings support the effectiveness of DMEK for restoring vision in patients with

Fuchs endothelial dystrophy (FED). Graft survival improved with surgeon experience, and the degree of endothelial cell loss was acceptable.

For this prospective registry study, the authors gathered data on 752 DMEKs performed from October 2011 through May 2018 that were registered in the Netherlands Organ Transplant Registry. The surgeries were performed at 10 corneal clinics in the Netherlands. The leading indication for DMEK was FED (90% of cases), followed by graft failure (5%) and pseudophakic bullous keratopathy (3%). The main outcome measure was graft survival. Secondary outcomes included best spectaclecorrected visual acuity (BSCVA), endothelial cell density, hyperopic shift, and rates of rebubbling.

According to the analysis, the proportion of DMEKs increased significantly over time (p < .001), with the greatest increase occurring between 2015 and 2016. In contrast, the frequency of Descemet stripping automated endothelial keratoplasty and penetrating keratoplasty decreased after 2015. Among the 468 DMEK procedures analyzed for graft survival (after excluding fellow eyes, non-FED indications, and cases with missing data), the graft survival rate was 87% at three months, 85% at six months and one year, and 78% at two years. The rate was significantly better for surgeries performed after 2015 (p < .001). Graft rejection occurred in two patients within six months and was reversible in both.

At three months, the mean hyperopic shift was +0.36 D; endothelial cell loss was 33% at this point and stabilized thereafter. BSCVA improved markedly from pretreatment through at least two years post-DMEK. By 12 months following DMEK, Snellen BSCVA $\geq 20/25$ was achieved in 67% and $\geq 20/20$ in 28%. The most common complication was rebubbling, which occurred in 19%.

Although studies have shown that immunologic rejection is less common with DMEK than with other keratoplasty techniques, the authors noted that lengthier follow-up is needed to determine long-term outcomes.

—Summary by Lynda Seminara

Checkpoint Inhibitors for Ophthalmic Sebaceous Carcinoma December 2020

Immune checkpoint inhibitors (ICIs), which block the programmed death 1 (PD-1) receptor and its ligands, PD-L1 and PD-L2, are not routinely used for ocular adnexal malignancies. However, a handful of recent reports have described the successful use of ICIs in patients with advanced ocular adnexal sebaceous carcinoma (OASC). Wolkow et al. set out to evaluate the expression of PD-L1 and PD-L2 in patients with OASC and to assess whether the results support the use of ICIs. They confirmed that PD-L1 and PD-L2 are expressed in a high percentage of OASC cases, and they noted that the results support the premise that ICIs hold therapeutic promise for these patients.

For this retrospective study, the researchers immunostained 20 cases of primary OASC for PD-L1, PD-L2, and the lymphocyte CD8. They used the combined positive score (CPS) and the tumor proportion score (TPS) to grade PD-L1 and PD-L2 expression, and they graded CD8 expression on a 0-3 scale. They then compared the results with those of similar recent investigations.

For the 20 cases, mean expression of PD-L1 with the CPS was 29.7 (range, 0-101.5) and 12.2 with the TPS (range, 0-95.8). Mean expression of PD-L2 was 7.9 with the CPS (range, 0-37.3) and 1.9 with the TPS (range, 0-12.9). Histologic results indicated that 19 (95%) and 17 (85%) of the samples expressed some degree of PD-L1 with the CPS and TPS, respectively. In contrast, 13 (65%) and four (20%) of the samples expressed some degree of PD-L2 with the CPS and TPS, respectively. All 20 cases had CD8-positive T lymphocytic infiltrates, with a mean \pm standard deviation of 1.75 ± 0.72 , and significant correlations were observed between tissue expression of PD-L1, PD-L2, and CD8.

In analyzing four other studies, the researchers found similar results. They also summarized reported positive outcomes of OASC patients treated with ICIs. As a result, they conclude, "there is now a pressing and inescapable



rationale for the implementation of ICI drugs in clinical trials, particularly at advanced stages of OASC."

—Summary by Jean Shaw

JAMA Ophthalmology

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

Is It Time to Reconsider Cornea Donation Guidelines?

November 2020

Concern about the risk of HIV transmission via corneal transplantation prompted North American authorities to ban cornea donation from men who had sex with other men (MSM) during the preceding 12 months (Canada) or five years (the United States). **Puente et al.** assessed the consequences of these rules and found that in 2018 alone, up to 3,217 corneas could have been added to the transplantation supply if the ban had not existed.

For this study, the investigators conducted a telephone survey of the 65 eye banks in North America to estimate the number of corneas disqualified due to the MSM restrictions. For banks whose initial screening process was handled by a partner organ-procurement facility, the authors contacted the partner firm to obtain the data. Eye banks that did not log MSM-related disqualifications were excluded.

In addition, the authors obtained a separate estimate by reviewing and combining published population-based data on sexual behavior and orientation for the two countries.

Of the 54 (83%) eye banks that responded, 24 maintained the relevant records. Among these 24 banks, 360 referrals were denied in 2018 because of MSM status, which would equate to 720 corneas. The same 24 eye banks accounted for 46.2% of cornea donations in the United States and Canada in 2018. Assuming that those banks also represented 46.2% of total North American MSM donor deferrals, the overall number of corneas denied on this basis in 2018 would be 1,558. The separate estimate of published demographics indicated that up to 3,217 corneas intended for donation

may have been disqualified in 2018 by the MSM policies.

In light of modern virologic testing that is reliable within days of HIV exposure, coupled with the ongoing need for cornea tissue, the authors urge reevaluation of MSM-related policies. (Also see related commentary by Alan Sugar, MD, and Woodford S. Van Meter, MD, in the same issue.)

Pupillary Light Reflex Metrics and Concussions in Teen Athletes November 2020

Master et al. investigated the utility of pupillary light reflex (PLR) data as potential physiological biomarkers for concussion in teen athletes and found that nearly all PLR metrics examined were much higher in those who sustained concussion than in healthy controls.

For this study, the researchers recruited athletes from a concussion program and a private suburban high school. All told, 98 athletes with a diagnosis of sport-related concussion (SRC) and 134 healthy controls participated. Participants were 12 to 18 years old, and 56% and 58% of the SRC and control groups were male, respectively. In the SRC group, PLR values were obtained at a median of 12 days following injury (interquartile range, 5-18 days). Main outcomes were the differences in PLR measurements between the study groups, including maximum and minimum pupillary diameter, peak and average constriction/dilation velocity, percentage of constriction, latency, and time to 75% pupillary redilation (T75).

Eight of the nine metrics examined were found to be significantly greater in the SRC group after Bonferroni correction, as follows: maximum pupil diameter (4.83 mm vs. 4.01 mm); minimum pupil diameter (2.96 mm vs. 2.63 mm); constriction percentage (38.23% vs. 33.66%); average constriction velocity (3.08 mm/s vs. 2.50 mm/s); peak constriction velocity (4.88 mm/s vs. 3.91 mm/s); average dilation velocity (1.32 mm/s vs. 1.22 mm/s); peak dilation velocity (1.83 mm/s vs. 1.64 mm/s); and T75 (1.81 seconds vs. 1.51 seconds). The only metric that did not differ substantially was latency, defined as the time to maximum constriction in response to the light stimulus. Exploratory analyses showed that girls with SRC had longer T75 than their male counterparts (1.96 seconds vs. 1.63 seconds). In healthy controls, some PLR metrics diminished after exercise, including pupil size, and there were no gender-related differences for any metric in this group.

The findings suggest that elevated PLR metrics may be physiologic biomarkers of acute concussion in teenagers. To better understand the utility of these metrics, the authors encourage multicenter studies, as well as multivariable modeling, to account for factors such as history of concussion. They also recommend more research on PLR metrics in girls, following exercise, and longitudinally after concussion. (*Also see related commentary by Wesley T. Beaulieu, PhD, and Adam R. Glassman, MS, in the same issue.*)

Timolol Eyedrops Ease Migraine Pain November 2020

Migraine is a debilitating condition and a leading cause of disability worldwide. Oral timolol maleate, a beta-blocker, is an FDA-approved drug for migraine prophylaxis. Although oral beta-blockers cannot ease migraine pain, topical preparations of these drugs have reduced pain in case reports and a small series of patients, warranting larger studies. In a double-masked randomized trial, Kurian et al. evaluated the short-term efficacy and safety of timolol maleate ophthalmic solution in the treatment of acute migraine pain. They found that these eyedrops were superior to placebo in lowering pain scores. No adverse events were noted.

For this single-center study, 50 patients with migraine were assigned randomly to receive either timolol eyedrops (0.5%) or placebo eyedrops. The participants were instructed to instill one drop of solution in each eye as soon as a migraine began. After three months on the initial regimen, there was a washout period of one month, followed by three months of the opposite regimen. Patients graded the pain of each migraine on a scale of 0-10, both before and after use of the eyedrops. The main outcome measure was reduction in pain score by four points (or to zero) 20 minutes after applying the drops.

During the study, there were 619 episodes of migraine. Of these, 284 (46%) were treated with timolol, 271 (44%) received placebo, and 64 (10%) occurred during the washout period. Seven patients withdrew after randomization. Of the timolol-treated migraines, 233 (82%) met the primary end point, compared with 38 (14%) of migraines that received placebo drops. A generalized estimating equation analysis showed that the mean reduction in pain score at 20 minutes was 4.63 points greater in the timolol group (p < .001). No adverse reactions or systemic adverse effects occurred during the study.

These findings indicate that topically applied beta-blockers can quickly alleviate migraine pain in many patients. The drops can, at least theoretically, abolish confounding factors such as high first-pass metabolism, said the authors. Thus, the drugs hold promise as a "welcome addition to existing medications for abortive pharmacotherapy of acute migraine."

The authors recommend multicenter studies that involve assessments at later time points, including two and four hours after dosing. (*Also see related commentary by Bradley J. Katz, MD, PhD, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Long-Term Vision After Trabeculectomy

British Journal of Ophthalmology Published online Sept. 19, 2020

For many patients, the main goal of trabeculectomy is adequate vision for their remaining years. However, data on whether this goal is being achieved are lacking. To fill the gap, **Chen and King** quantified vision after trabeculectomy by documenting visual acuity (VA) and visual field status from surgery to the last follow-up visit. They found that in most patients, vision remained stable postoperatively. For the others, visual loss often was unrelated to glaucoma.

This study population underwent trabeculectomy performed by the same surgeon between October 2000 and November 2012. The authors collected demographic data as well as clinical measurements from surgery until patient death. Preoperative values served as baseline data for outcome comparisons.

Among the 659 patients who received trabeculectomy in the study period, 160 (24.3%) died before November 2018. Of these, 156 (196 eyes) had sufficient information for study inclusion. The most common disease type was primary open-angle glaucoma (69% of eyes). Fifty-eight percent of patients were male, and 86% were white. The mean age at surgery on the first eye was 76.5 years. The average life expectancy after trabeculectomy was 7.5 years (range, 0.1 to 17.2 years).

The mean individual change in VA, measured as LogMAR (standard deviation), was 0.32 (0.59). For patients with at least one year of follow-up (n = 144), the median visual field deviation was -0.44 dB/year (range, -5.98 to 3.9 dB/ year). Severe vision loss (≥ 10 letters) by end of life occurred in 78 eyes (40%); in 18 eyes (9%), the worsening VA resulted from glaucoma progression. At the last follow-up visit, 69 patients (44%) were using glaucoma drops. There was no link between socioeconomic status and preoperative mean deviation or change in mean deviation from baseline to last measurement.

These findings indicate that trabeculectomy slows or prevents glaucoma progression in most patients, regardless of the person's socioeconomic status. Those who lost vision generally were older and had poorer baseline VA and visual field status, and the functional decline was unrelated to glaucoma in most cases. With life expectancy continuing to increase, the authors recommend more research on the lifetime value of trabeculectomy.

Eplerenone or Placebo for Chronic Central Serous Chorioretinopathy Lancet

2020;395(10220):294-303

Many ophthalmologists now prescribe eplerenone as first-line treatment for central serous chorioretinopathy (CSCR), but research by **Lotery et al**. may cause them to reconsider this practice. Results of their study showed that by 12 months of treatment, eplerenone was no better than placebo for improving best-corrected visual acuity (BCVA), leading the authors to discourage the drug's use.

For this placebo-controlled study, adults with treatment-naive CSCR for at least four months were assigned randomly (1:1) to receive oral eplerenone (25 mg/day for one week, increasing to 50 mg/day for up to 12 months) or placebo, in addition to usual care for all. The primary study outcome was BCVA at 12 months.

Overall, 57 patients received eplerenone and 57 had placebo. All patients in the eplerenone group and 54 from the placebo group were included in the primary outcome analysis. The mean age at randomization was 48.7 years; 75% of patients were male, and 87% were white.

Modeled mean (standard deviation) BCVA at 12 months was 80.4 (4.6) letters in the eplerenone group and 79.5 (4.5) letters in the placebo group. No meaningful difference in BCVA was found between the groups at 12 months; the adjusted estimated mean difference was 1.73 letters (p = .24). Although central subfield retinal thickness (SRF) did not differ significantly between the two groups, a difference in SRF thickness was noted at 12 months, favoring placebo (p = .0066). Eight patients in each group experienced hyperkalemia. Three patients in the placebo group had a serious adverse nonophthalmic event.

The authors recommend that ophthalmologists discourage eplerenone use for CSCR and instead urge their patients to participate in clinical trials of other therapies.

—Summaries by Lynda Seminara