

Journal Highlights

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

Ophthalmology

Anti-Inflammatory Agent CF101 in Dry Eye Syndrome

July's *Ophthalmology*

CF101 is an A3 adenosine receptor agonist that functions as an anti-inflammatory agent. Researchers have demonstrated its therapeutic potential to suppress inflammation and prevent tissue damage in experimental animal models of arthritis, inflammatory bowel disease, osteoarthritis and septic peritonitis. Phase 2a clinical studies in patients with rheumatoid arthritis have demonstrated that the drug was apparently safe and well-tolerated and helped improve disease signs and symptoms.

In this study, Avni et al. explored the effect of CF101 on moderate-to-severe dry eye syndrome. Thirty-three patients with moderate-to-severe dry eye syndrome were given 1-mg CF101 pills twice daily for 12 weeks; 35 patients received a placebo. Patients were then followed for two weeks. Results showed that CF101 given orally resulted in a statistically significant improvement in the corneal staining, tear break-up time and tear meniscus height compared with placebo. It was also well-tolerated with an excellent safety profile.

The authors conclude that these results support further evaluation of CF101 for dry eye disease.

Incision Size in Clear Corneal and Scleral Tunnel Incision Cataract Surgery

July's *Ophthalmology*

Hayashi et al. compared corneal shape and astigmatism changes after clear corneal incision cataract surgery and scleral tunnel incision cataract surgery.

The authors randomized 90 patients to 3- or 2-mm clear corneal surgery in one eye and 3- or 2-mm scleral tunnel surgery in the fellow eye. The researchers showed that corneal shape changes after 3-mm clear corneal surgery were greater than those after 3-mm scleral tunnel surgery. Yet the changes in shape after 2-mm clear corneal surgery and scleral tunnel surgery were virtually the same. In addition, postoperative corneal astigmatism and surgically-induced astigmatism were greater after clear corneal surgery than after scleral tunnel surgery when the incision width was 3 mm. However, when the incision width was 2 mm, there was no significant difference in either postoperative corneal astigmatism or

in induced astigmatism between the two techniques.

Topical Anti-Inflammatory Drugs Prior to Trabeculectomy

July's *Ophthalmology*

Several studies have provided evidence that long-term use of IOP-lowering medication has been linked to subclinical conjunctival inflammation. Breusegem et al. conducted a study to determine whether a preoperative, one-month treatment with anti-inflammatory medication improves outcomes following trabeculectomy.

The authors randomized 61 consecutive medically uncontrolled glaucoma patients scheduled for first-time trabeculectomy to one of three topical medical groups: a nonsteroidal anti-inflammatory drug (ketorolac), a steroid (fluorometholone) or placebo (artificial tears). Patients instilled one drop four times daily for one month prior to the procedure.

Significantly fewer postoperative needlings were required within the first year in the ketorolac (6 percent) and fluorometholone (5 percent) groups than the placebo group (41 percent). In addition, the percentage of patients who needed IOP-lowering medication to reach the target IOP at one year was 24 percent in the placebo group and 18 percent in the ketorolac group. No patients in the fluo-



rometholone group needed medication to reach the target.

These results support the authors' hypothesis that topical anti-inflammatory medication could provide clinical benefit in patients undergoing trabeculectomy.

Intraarterial Fibrinolysis Not Recommended for CRAO

July's *Ophthalmology*

Schmidt et al. compared local intra-arterial fibrinolysis (LIF) using recombinant tissue plasminogen activator with conservative standard treatment (CST) for management of acute nonarteritic central retinal artery occlusion (CRAO). They found that LIF and CST yielded similar visual results, but LIF was associated with a higher rate of adverse reactions.

The study involved 82 patients. CST treatment included isovolemic hemodilution but no anterior chamber paracentesis. Results showed a significant visual improvement of 0.443 logMAR in the CST group and 0.447 logMAR in the LIF group after one month. Two LIF patients experienced serious adverse reactions within the first 24 hours after treatment, including cerebral and cerebellar hemorrhage with paresis that resolved by the end of the study. One CST patient experienced a right hemiparesis and reduced consciousness after treatment, with incomplete recovery.

Given the similar therapeutic outcomes but higher rate of adverse reactions associated with LIF, the authors recommend not using LIF to treat acute CRAO.

Low Vision Patients Benefit From Distance Refraction

July's *Ophthalmology*

Ophthalmologists may not necessarily consider performing distance refraction in low vision patients given the probability that the cause of the vision problem is not refractive but rather due to underlying ocular disease. However, there may be a subgroup of patients who can benefit

from distance refraction.

Sunness and El Annan conducted a retrospective, cross-sectional study to determine the proportion of 739 patients seeking low vision evaluation who benefited from distance refraction.

The authors found that 11 percent of patients improved by two or more lines of visual acuity with refraction. Improvement was experienced in patients with a variety of diagnoses and range of presenting visual acuities. In five patients, the eye that was one or more lines worse than the fellow eye at presentation became the eye that was one or more lines better than the fellow eye after refraction.

The authors conclude that clinicians may want to consider distance refraction in some of their low vision patients.

American Journal of Ophthalmology

Classification of Sensory Monofixation in Intermittent Exotropia

July's *AJO*

Hatt et al. hypothesized that the course of intermittent exotropia and response to surgery may depend on whether there is underlying monofixation.

In this retrospective study, they report on the prevalence of sensory monofixation in intermittent exotropia using different stereotests and determined the risk of misclassifying monofixation based on a single administration of each test.

The researchers identified 44 children with intermittent exotropia for whom Preschool Randot, Frisby and Titmus stereoacuity were measured at a single examination. Ninety-two children were identified with near stereoacuity measured on two sequential visits.

Monofixation was defined as stereoacuity less than published age-referenced normal thresholds; bifixation was defined as at least 40 arc seconds; and uncertain was defined as within normal range for age but worse than 40 arc seconds. In children measured by all three tests on the same visit,

sensory monofixation occurred in 36 percent using Preschool Randot, in 48 percent using Titmus and in 55 percent using Frisby. There was poor agreement between Frisby and Preschool Randot when classifying monofixation in individual patients.

In children measured on sequential visits, misclassification occurred in 5 percent with Preschool Randot, in 13 percent with Titmus and in 23 percent with Frisby (Preschool Randot vs. Frisby).

The authors conclude that classification of monofixation depends on the stereotest used. Regardless of the stereotest, there is a risk of misclassifying monofixation on a single assessment. This potential misclassification needs to be considered in clinical practice and when designing studies.

RNAi-Based Treatment for AMD

July's *AJO*

Kaiser et al. assessed the safety, tolerability, pharmacokinetics and dose-limiting toxicity of a single intravitreal injection of Sirna-027—a small interfering RNA-targeting vascular endothelial growth factor receptor-1—in patients with choroidal neovascularization resulting from neovascular age-related macular degeneration. Secondary objectives included assessment of anatomic changes in retinal thickness, size of choroidal neovascularization and changes in visual acuity.

In this prospective study, the authors examined 26 eyes of 26 patients with a median age of 82 years and choroidal neovascularization resulting from AMD who had previous treatments with other therapies. The patients were treated with a single dose of Sirna-027 (100, 200, 400, 800, 1,200 or 1,600 µg/eye). Blood was sampled for pharmacokinetic analysis at one, four and 24 hours after injection and on day 7. The main outcome measures were adverse reactions and dose-limiting toxicities.

Intravitreal injection of a single dose of Sirna-027 from 100 to 1,600 µg was well tolerated in patients with

AMD with no dose-limiting toxicity found. Adverse events were mild to moderate in severity. Adjusted mean foveal thickness decreased within two weeks after study treatment. The decrease was most pronounced in the 100- and 200- μ g doses.

The authors of the study conclude that a single intravitreal dose of

Sirna-027 up to 1,600 μ g/eye was well tolerated in patients with choroidal neovascularization resulting from AMD that had been refractory to other therapies. Stabilization or improvement in visual acuity and foveal thickness was observed. No dose-response or dose-limiting effects were noted.

Prevalence of Macular Telangiectasia Type 2

July's *AJO*

Klein et al. examined the prevalence of macular telangiectasia type 2 and the lesions characterizing it. In this cohort study, 4,790 people had their stereoscopic fundus

FOCUS ON OPHTHALMOLOGY

New Treatment for Diabetic Macular Edema

June's *Ophthalmology*

The standard of care for diabetic macular edema—focal/grid laser—may need to be rethought. The **Diabetic Retinopathy Clinical Research Network (DRCR.net) Writing Committee** reports that adding injections of ranibizumab (Lucentis) to either prompt or deferred laser treatment produced greater improvements in vision than did laser alone through at least one year of follow-up. Prompt treatment was defined as laser three to 10 days after injection, and deferred treatment was laser 24 weeks or more after injection.

The study involved 854 eyes of 691 people who had either type 1 or type 2 diabetes and DME involving the fovea in at least one eye. On average, the participants were in their early 60s; their BCVA ranged from 20/32 to 20/320. They were randomly assigned to one of four groups: 1) sham injection plus prompt laser, 2) 0.5 mg ranibizumab plus prompt laser, 3) 0.5 mg ranibizumab plus deferred laser or 4) 4 mg triamcinolone (Trivaris) plus prompt laser.

After one year, participants in the two ranibizumab groups experienced the greatest improvement, gaining an average of 2 lines, with almost 50 percent gaining 2 or more lines and less than 5 percent losing 2 or more lines. Those who received either laser alone or triamcinolone plus laser gained an average of 1 line, with approximately 30 percent gaining 2 or more lines and almost 15 percent losing 2 or more lines.

With regard to safety outcomes, adverse effects during the first year included three cases of injection-related endophthalmitis and one case of a traction retinal detachment in the ranibizumab groups; increases in IOP and cataract surgery were more frequent in the triamcinolone plus laser group.

Preliminary two-year outcomes were similar to the one-year outcomes, the investigators report. The DRCR.net investigators will follow all study participants for at least three years to obtain longer-term follow-up.

VALUE TO CLINICAL PRACTICE: “It’s rare to have a published study that can have as much potential impact on patient care as this one,” said Carl D. Regillo, MD, professor of ophthalmology at Wills Eye Institute in Philadelphia. “This clearly will shift more clinicians in the direction of using anti-VEGF therapy to treat clinically significant DME involving the fovea.”

Neil M. Bressler, MD, chair of the DRCR.net and professor of ophthalmology at the Wilmer Eye Institute in Baltimore, said, “While there is no uniform definition of ‘diffuse’ DME, the study shows that intravitreal ranibizumab was superior to laser across a wide range of retinal thicknesses, a wide range of visual acuities and a wide range of edema classifications. This suggests that intravitreal ranibizumab with deferred or prompt focal/grid laser is superior to prompt focal/grid laser alone for all types of edema involving the center of the macula, including ‘diffuse’ edema.”

Dr. Bressler also noted that the results “show a benefit of intravitreal ranibizumab over focal/grid laser for people who had DME and prior macular laser in eyes in which the ophthalmologist believed maximal focal/grid laser had not been applied.”

A clinician choosing to adopt this approach will need to pay attention to several key issues, said J. Fernando Arevalo, MD, professor of ophthalmology at the Universidad de los Andes in Mérida, Venezuela. “Practicing ophthalmologists should keep in mind that the characteristics of their patients should be similar to those included in the study, and the follow-up and re-treatment protocol should be similar as well.”

The re-treatment protocol is a significant concern given its complexity, as *Ophthalmology* editor Andrew P. Schachat, MD, noted in his accompanying editorial.¹ Dr. Schachat also raised the issue of cost, with regard to the cost of the drug itself as well as the need for more frequent patient visits mandated by the re-treatment protocol.

—Jean Shaw

1 Schachat, A. P. *Ophthalmology* 2010;117(6):1059–1060.

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photographs graded to measure for macular telangiectasia type 2. The condition was present at baseline in 0.1 percent of the population.

The frequencies of specific macular telangiectasia type 2 lesions in those patients without macular telangiectasia type 2 were low, varying from 0.06 percent for retinal telangiectatic vessels to 1.2 percent for lamellar holes. Retinal blunted vessels, retinal crystalline deposits and lamellar holes were more likely to be bilateral than unilateral when present.

Smoking was associated with pigment clumping, retinal pigment epithelial depigmentation, loss of retinal transparency and the presence of a yellow spot in the fovea, but it was not associated with presence of macular telangiectasia type 2.

The authors conclude that the prevalence of macular telangiectasia type 2 is higher than previously thought. These data are useful in estimating the burden of this macular condition in the population. The suggested role of smoking in the development of macular telangiectasia type 2 requires further study.

Archives of Ophthalmology

African/European Descent and the Optic Nerve

May's Archives

Girkin et al. published the baseline results for optic nerve imaging in normal patients enrolled in the African Descent and Glaucoma Evaluation Study.

The authors evaluated stereo photography, confocal scanning laser ophthalmoscopy and OCT from 648 subjects exhibiting no detectable ocular disease. They also compared the mean morphometric measurements of the optic nerve head, retinal nerve fiber layer and macula between individuals of African and European descent, and adjusted for differences in optic disc area and/or reference plane height where appropriate.

Individuals of African descent subjects had significantly greater optic

disc area with both ophthalmoscopy and OCT and a deeper cup depth with ophthalmoscopy than the European group. The Moorfields Regression Analysis and Glaucoma Probability Score correctly identified a similar proportion of subjects as normal in each group. Retinal nerve fiber layer thickness (as measured by OCT) was greater in the European group except within the temporal region where it was significantly thinner. Ophthalmoscopy central macular thickness and OCT macular volume were also less in the African group.

The authors conclude that most of the variations in optic nerve morphology between individuals of African and European ancestry are due to either differences in disc area or differences in reference plane height. However, small residual differences remain in ophthalmoscopy cup depth, OCT macular thickness and volume. The authors suggest that these differences should be considered in the determination of disease status.

Detection and Quantification of Pathogenic Bacteria and Fungi

May's Archives

Itahashi et al. detected and quantified the causative pathogens in patients with corneal ulcer using real-time polymerase chain reaction (PCR) by cycling probe.

The authors used bacterial culture and real-time PCR with the patient's corneal scrapings to examine 40 patients (40 eyes) suspected of corneal ulcer. For real-time PCR, probes and primers were designed to be pathogen specific for simultaneous detection of *Staphylococcus aureus*, *S. pneumoniae*, *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus*, *Candida* species and *Fusarium* species. Results by both methods were evaluated and compared.

Both bacterial culture and PCR detected pathogens in 20 of 40 eyes: *S. aureus* (three eyes), *S. pneumoniae* (five eyes), *P. aeruginosa* (eight eyes), methicillin-resistant *S. aureus* (one eye) and *Candida* species (three eyes).

Six eyes showed negative results. Results from the methods disagreed in 14 eyes; specifically, 11 eyes had positive PCR results only, two eyes had positive culture results only and one eye had positive results for different pathogens from each method.

The authors conclude that real-time PCR assay can simultaneously detect and quantify the causative bacterial and fungal pathogens in patients with corneal ulcer. Real-time PCR can be a fast diagnostic tool and may be useful as an adjunct to identify potential pathogens.

Vertical Rectus Surgery for Superior Oblique Muscle Paresis

May's Archives

In this retrospective review, **Burton J. Kushner** evaluated the efficacy of treating Knapp class 2 superior oblique muscle palsy using 7-mm nasal transposition of the ipsilateral inferior rectus muscle. He combined this technique with recession of the contralateral inferior rectus muscle when the primary position hypertropia is 10 prism diopters (PD) or less.

Eight consecutive patients with Knapp class 2 superior oblique muscle paresis were treated in the aforementioned manner. Mean preoperative hypertropia was 5 PD \pm 1.5 and 13.1 PD \pm 3.6 in the primary position and downgaze, respectively. After surgery, mean hypertropia was 1.25 PD \pm 1.0 and 3.25 PD \pm 1.3 in the primary position and downgaze, respectively. Mean subjective excyclotropia decreased from 6.6 degrees \pm 1.3 preoperatively to 0.5 \pm 0.9 after surgery, and there was a mean objective decrease in the excyclotropion of the paretic eye by 7.8 degrees \pm 1.4.

All patients were diplopic before surgery and all were asymptomatic after surgery.

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

ROUNDUP OF OTHER JOURNALS

Hapten's Role Identified in Initiating AMD

Molecular Neurobiology
Published online Feb. 12, 2010

Previous research has provided evidence that inflammation may play a role in the pathology of age-related macular degeneration. Yet, what is the source of this inflammation? Hollyfield et al. demonstrated that a hapten generated by the oxidative fragmentation of docosahexaenoic acid can initiate an immunological response that with aging produces an AMD-like disorder.

C57BL/6J mice were immunized with mouse serum albumin adducted with carboxyethylpyrrole (CEP), a protein adduct found in drusen and in plasma of AMD patients at higher levels than controls. The immunized mice developed antibodies to CEP, accumulated drusen below the retinal pigment epithelium over time, demonstrated decreased a- and b-wave amplitudes in response to light and developed lesions in the retinal pigment epithelium similar to geographic atrophy.

While other inflammatory factors may be present in AMD, an immune response to a CEP-adducted self-protein may be enough to cause localized AMD-like lesions in mice.

Identifying Genes Involved in Central Corneal Thickness Determination

Molecular Vision
2010;16:562–569

The recognition of central corneal thickness (CCT) as a major risk factor for open-angle glaucoma (OAG) prompted Dimasi et al. to investigate the genetic factors involved in CCT determination.

The researchers began by selecting eight different CCT gene candidates and tagging single nucleotide polymorphisms (SNPs) selected from the HapMap database. They then geno-

typed the SNPs to include the majority of genetic variation within each gene, screened each SNP in a large, population-based cohort, and completed single SNP and haplotype analyses.

The investigators identified two potential SNPs involved in determining CCT: rs17352842 from fibrillin-1 (FBN1) and rs3026398 from paired box 6 (PAX6). Haplotype analysis demonstrated one haplotype within FBN1 and two haplotypes within PAX6.

The researchers conclude that since only one major gene, myocilin, has been identified in the search for a genetic component to OAG (and mutations in this gene are only responsible for 3 percent of cases), genetic characteristics of CCT in relationship to OAG should be explored. In addition, there could be a biological link between genes that regulate corneal thickness and the tissue properties involved in glaucoma pathogenesis, including the lamina cribrosa or trabecular meshwork. The identification of genes associated with normal CCT variation is a first step.

Hypoxemic Events and Severe Retinopathy of Prematurity

The Journal of Pediatrics
Published online March 22, 2010

Di Fiore et al. have shown a higher incidence of hypoxemic events in infants with severe retinopathy of prematurity (ROP) who required laser therapy than those infants having less severe or no ROP.

The investigators used high-resolution pulse oximetry to document the occurrence of intermittent hypoxemic events in 79 preterm infants during their first eight weeks of life. Severity of ROP was based on whether the infants did or did not require laser treatment. The researchers used a linear mixed model to study the link between the incidence of intermittent hypoxia and laser treatment of ROP, controlling for gestational age, sex, race,

initial illness severity and whether the mother had multiple births.

For all infants, hypoxemic events increased with postnatal age. Controlling for all covariates, a higher incidence of oxygen desaturation events was found in the infants undergoing laser therapy for ROP, males and infants of younger gestational age.

3D-OCT vs. Fluorescein Angiography in Detecting Cystoid Macular Edema

Investigative Ophthalmology and Visual Science

Published online March 31, 2010

Ouyang et al. have found that 3D-OCT is more sensitive and reproducible than fluorescein angiography for detecting cystoid macular edema (CME).

The study involved 413 eyes of 207 patients who underwent digital fluorescein angiography and horizontal raster 3D-OCT scans on the same day in a retina subspecialty clinic. The images were independently reviewed by four reading-center graders. These analyses were then adjudicated as a group to provide a single result for each eye and each device.

The researchers found that intergrader agreement was higher for 3D-OCT than for fluorescein angiography both before and after adjudication. In addition, the sensitivity for detection of definite CME was higher for 3D-OCT than for fluorescein angiography.

The investigators caution that because they chose to focus exclusively on CME for this study, these results should not be extrapolated to comparisons of noncystoid causes of leakage by fluorescein angiography and noncystoid edema by OCT. They conclude that these findings may prove useful in designing future trials involving diseases associated with CME.

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