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Diabetic Retinopathy

Roy MS, Janal MN. High Caloric and Sodium Intakes as Risk Factors for Progression of Retinopathy in Type 1 Diabetes Mellitus. *Arch Ophthalmol* 2010; 128:33-39.

Summary: In 469 African American patients with type 1 diabetes observed over six years, high caloric intake was a significant and independent risk factor for progression to proliferative diabetic retinopathy. Sodium intake was an independent risk factor for macular edema. Dietary recommendations of low caloric and sodium intakes may be beneficial in relation to the development of DR.

Gene Transfer

Simonelli F, et al. Gene Therapy for Leber's Congenital Amaurosis is Safe and Effective Through 1.5 Years After Vector Administration. *Mol Ther* 2009; Epub (From Pubmed)

Summary: The safety and efficacy of gene therapy for inherited retinal diseases is being tested in humans affected with Leber's congenital amaurosis (LCA), an autosomal recessive blinding disease. Three independent studies have provided evidence that the subretinal administration of adeno-associated viral (AAV) vectors encoding RPE65 in patients affected with LCA2 due to mutations in the RPE65 gene, is safe and, in some cases, results in efficacy. We evaluated the long-term safety and efficacy (global effects on retinal/visual function) resulting from subretinal administration of AAV2-hRPE65v2. Both the safety and the efficacy noted at early timepoints persist through at least 1.5 years after injection in the three LCA2 patients enrolled in the low dose cohort of our trial. A transient rise in neutralizing antibodies to AAV capsid was observed but there was no humoral response to RPE65 protein. The persistence of functional amelioration suggests that AAV-mediated gene transfer to the human retina does not elicit immunological responses which cause significant loss of transduced cells. The persistence of physiologic effect supports the possibility that gene therapy may influence LCA2 disease progression. The safety of the intervention and the stability of the improvement in visual and retinal function in these subjects support the use of AAV-mediated gene augmentation therapy for treatment of inherited retinal diseases.

Genetics of Eye Disease

See update at eyeGENEinfo@nei.nih.gov

Aged Related Macular Degeneration

1) Dadgostar H, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology* 2009; 116:1740-1747

Summary: Retrospective, interventional case series. On average, it took 3.0 injections and 3.5 months to achieve a "dry" or "flat" macula on OCT after initiating treatment. Resolution of intra- and subretinal fluid on OCT did not correlate with the degree of vision improvement. Eyes receiving more frequent injections (defined as <2 months mean inter-injection interval) gained more vision (+2.3 lines at 6 months) than eyes receiving injections less frequently (+0.46 lines at 6 months; P = 0.012). At 6 months, 3.1% of those in the more frequent injection group lost >3 lines of vision compared with 15.9% in the >2 months interval group (P = 0.011).

Treatment with ranibizumab on a strictly as-needed basis may result in undertreatment and significantly less visual gain when compared to patients treated with injections less than 2 months apart.

2) Engelbert M, et al. "Treat and Extend" Dosing of Intravitreal Antivascular Endothelial Growth Factor Therapy for Type 3 Neovascularization/Retinal Angiomatous Proliferation. *Retina* 2009; 29:1424-1431.

Summary: This was a retrospective analysis of visual acuity and optical coherence tomography data of 11 eyes of 10 consecutive patients with newly diagnosed neovascularization/retinal angiomatous proliferation treated with intravitreal bevacizumab and/or ranibizumab with at least a 12-month follow-up. Three monthly injections were followed by continued treatment at intervals increasing by 2 weeks per visit, to a maximum of 10 weeks, unless clinical or optical coherence tomography evidence of persistent or recurrent fluid was present. The mean number of injections was seven in the first year, six in the second year, and seven in the third year. Acuity improved and remained stable and OCT measurements remained consistent throughout the period of observation.

3) Kuhli-Hattenbach C, et al. Subretinal Hemorrhages Associated with Age-Related Macular Degeneration in Patients Receiving Anticoagulation or Antiplatelet Therapy. *Am J Ophthalmol* 2010; 149: 316-321.

Summary: Retrospective review of 71 consecutive patients with acute subretinal hemorrhages complicating age-related macular degeneration. Anticoagulants and antiplatelet agents are strongly associated with the development of large subretinal hemorrhages in AMD patients. Arterial hypertension is a strong risk factor for large subretinal hemorrhages in AMD patients receiving anticoagulants or antiplatelet agents. Physicians should be aware of an increased risk of extensive subretinal hemorrhage in AMD patients when deciding on the initiation and duration of anticoagulant and antiplatelet therapy.

Choroidal neovascularization

1) Wu PC, Chen WJ. Intravitreal injection of bevacizumab for myopic choroidal neovascularization: 1-year follow-up. *Eye* 2009; 23: 2042–2045.

Summary: Eight eyes of consecutive patients with myopic CNV without earlier treatment were treated with intravitreal injection of bevacizumab (2.5 mg). The follow-up period ranged from 13 to 17 months (mean, 14.9 months). The mean VA significantly improved from the baseline value 20/82 to 20/25 ($P=0.017$). At the 12-month follow-up, vision had improved in all eyes by three or more lines.

Intravitreal injection of 2.5 mg bevacizumab (Avastin) seems to be effective and safe in patients with myopic CNV.

2) Ehrlich R, et al. Intravitreal Bevacizumab for Choroidal Neovascularization Secondary To Presumed Ocular Histoplasmosis Syndrome. *Retina* 2009; 29:1418-1423.

Summary: Retrospective consecutive case series in which intravitreal bevacizumab (1.25 mg) (Avasin) was injected into 24 eyes with choroidal neovascularization resulting from presumed ocular histoplasmosis syndrome. mean follow-up was 31.8 weeks (standard deviation, 20.79 weeks). The average number of bevacizumab injections was 6.8 injections/year. After 12 months, visual acuity improved from mean logMAR 0.86 ± 0.35 (Snellen equivalent of 20/150) to mean logMAR 0.34 ± 0.33 (Snellen equivalent of 20/45) ($P = 0.006$, paired t test; $n = 9$). Fourteen (58.3%) eyes had final visual acuity of 20/40 or better compared with 5 (20.8%) eyes at baseline ($P = 0.003$, McNemar test). Ten patients (41.6%) had visual acuity of 20/200 or worse at baseline compared with 5 (20.8%) eyes at the final visit ($P = 0.059$, McNemar test).

Intravitreal injection of bevacizumab seems to be an effective treatment for choroidal neovascularization resulting from presumed ocular histoplasmosis syndrome.

Central serous chorioretinopathy

1) Reibaldi M, et al. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. *Am J Ophthalmol* 2010; 149:307-315.

Summary: Prospective, multi-center, masked, nonrandomized clinical trial. Forty-two eyes (42 patients) with chronic central serous chorioretinopathy were enrolled: 9 eyes received indocyanine green angiography-guided standard-fluence PDT (50 J/cm²); and 23 eyes received indocyanine green angiography-guided low-fluence PDT (25 J/cm²).

In both groups, most eyes showed improved visual acuity with complete subretinal fluid reabsorption. No significant difference was found between both groups, except choroidal hypoperfusion related to PDT could be reduced by low-fluence PDT.

2) Lim SJ, et al. Intravitreal bevacizumab injection for central serous chorioretinopathy. *Retina* 2010; 30; 100-106.

Summary: Retrospective study of 6 patients followed for an average of 9 months. Leakage on fluorescein angiography and hyperpermeability on indocyanine green angiography decreased in conjunction with improvement in central macular thickness observed by optical coherence tomography.

Intravitreal bevacizumab (Aavstin) injection for central serous chorioretinopathy resulted in improved visual acuity and anatomical results at 3 months.

Cystoid macular edema

Arevalo JF, et al. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. *Ophthalmology* 2009; 116:1481-1487.

Summary: Retrospective multicenter study of 36 eyes of 31 patients study treated with at least 1 IVT injection of 1.25 or 2.5 mg bevacizumab. Patients were followed up for 12 months. The mean number of injections was 2.7 (range, 1-6), and the mean interval between injections was 15.1 weeks (range, 4-45 weeks). Twenty-six eyes (72.2%) demonstrated improvement of best corrected acuity (\geq 2 Early Treatment Diabetic Retinopathy Study [ETDRS] lines), and no eye experienced worsening of visual acuity (\geq 2 ETDRS lines).

Short-term results suggest that IVT bevacizumab is well tolerated in patients with refractory pseudophakic CME. Treated eyes had a significant improvement in BCVA and decrease in macular thickness by OCT at 12 months. No ocular or systemic adverse events were observed.

Major Reviews

Curcio C, et al. Aging, Age-Related Macular Degeneration, and the Response-to-Retention of Apolipoprotein B-Containing Lipoproteins. *Progress in Retinal and Eye Research* 2009; 28:393-422.

A prominent age-related change in the human retina is the accumulation of histochemically detectable neutral lipid in normal Bruch's membrane throughout adulthood. This change has the potential to have a major impact on physiology of the retinal pigment epithelium (RPE). It occurs in the same compartment as drusen and basal linear deposit, the pathognomonic extracellular, lipid-containing lesions of ARMD. This deposition can be accounted for by esterified cholesterol-rich, apolipoprotein B-containing lipoprotein particles produced by the RPE.

AMD lesions and sequelae may be considered a response to the retention of a sub-endothelial apolipoprotein B lipoprotein, similar to a widely accepted model of atherosclerotic coronary artery disease. This approach provides a foundation for the development of new model systems with potential benefit of AMD patients.

Laude A, et al. Polypoidal Choroidal Vasculopathy and Neovascular Age-Related Macular Degeneration: Same or Different Disease?

Progress in Retinal and Eye Research 2010; 29:19-29.

Summary: Polypoidal choroidal vasculopathy (PCV) has been described as a separate clinical entity differing from AMD and other macular diseases associated with subretinal neovascularization. It remains controversial as to whether or not PCV represents a sub-type of AMD. This article summarizes the current literature on the clinical and pathophysiological features and treatment responses of PCV and compares this condition to AMD. Patients with PCV are younger and more likely Asians. Eyes with PCV lack drusen and often present with serosanguinous maculopathy or hemorrhagic pigment epithelial detachment, and have differing responses to photodynamic therapy and anti-vascular endothelial growth factor agents. There are also significant differences in angiographic, optical coherence tomography and pathological features. Data suggests common genetic factors involving the complement pathway and environmental risk factors (e.g. smoking).

Refractive Surgery

Llovet F, et al. Infectious Keratitis in 204,586 LASIK Procedures. *Ophthalmology* 2010; 117: 232-238.

Summary: Retrospective study. The medical records of post-LASIK patients (204,586 eyes) were reviewed to identify cases of infectious keratitis. Post-LASIK infectious keratitis was diagnosed in 72 eyes from 63 patients (0.035%). Onset of infection was early (within 7 days after surgery) in 62.5% of cases. Cultures were positive in 21 of 54 cases in which samples were taken. The most frequently isolated microorganism was *Staphylococcus epidermidis* (9 cases). Final best spectacle-corrected visual acuity was less than 20/40 in 5 cases (6.94%).

Branch Retinal Vein Update: Overview

The SCORE Study Research Group. A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Standard Care to Treat Vision Loss Associated With Macular Edema Secondary to Branch Retinal Vein Occlusion: The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 6. Arch Ophthalmol 2009; 127:1115-1128.

Summary: Randomized trial of 411 participants, comparing standard laser photocoagulation to 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone for treatment of branch vein occlusion with macular edema. There was no difference identified in visual acuity at 12 months for the standard care group compared with the triamcinolone groups. However, patients who received either dosage of corticosteroid medication were more likely to develop a cataract or have an increase in eye pressure requiring medication than patients who received laser treatment. Between one and two years after treatment was begun, patients who received the 4 milligram dosage were also more likely to undergo cataract surgery.

Central Retinal Vein Occlusion Update: Overview

The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study

The SCORE Study Research Group. A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Observation to Treat Vision Loss Associated With Macular Edema Secondary to Central Retinal Vein Occlusion. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5. Arch Ophthalmol. 2009; 127:1101-1114.

Summary: The SCORE study is a randomized trial to compare the safety and effectiveness of standard care observation with two different dosages of triamcinolone: 1 milligram and 4 milligrams. Study participants included 271 people with CRVO who were an average of 68 years old. Patients in the treatment group could receive a maximum of three corticosteroid injections every year for up to three years, based on the state of their disease.

At one year, patients who received either dose of the corticosteroid medication were five times more likely than those who did not receive treatment to experience a substantial visual gain of three or more lines on a vision chart—equivalent to identifying letters that were half as small as they could read before treatment. However, patients in the 1.0 mg group had fewer side effects related to increased eye pressure and cataract formation than those in the 4.0 mg group.

Park D, Kim I. Long-Term Effects of Vitrectomy and Internal Limiting Membrane Peeling for Macular Edema Secondary To Central Retinal Vein Occlusion and Hemiretinal Vein Occlusion. Retina 2010; 30:117-124.

Summary: In a retrospective study of 20 patients (20 eyes) carried over 5 years, pars plana vitrectomy with internal limiting membrane peeling (with indocyanine green) in eyes with macular edema secondary to CRVO and hemiretinal vein occlusion (HRVO) produces an anatomical improvement, which persists up to 5 years. Best-corrected visual acuity of the perfused CRVO and HRVO groups tended to improve in contrast to the ischemic CRVO group.

Prosthetic eye (Artificial Vision)

Nguyen P, et al. Applications of Nanobiotechnology in Ophthalmology - Part I. *Ophthalmic Res* 2010; 44:1-16

Abstract: Much progress has been achieved in the field of nanotechnology and its applications in ophthalmology. It is evident that drug delivery, gene therapy, implantable devices and regenerative medicine are some of the key areas of active research. To the best of our knowledge, there is limited review work on this subject area in the current literature. To assist the interested clinicians and scientists, this bipartite commentary will focus the discussion on emerging researches in nano-ophthalmology and other enabling technologies that soon may be available in the clinician's armamentarium to maintain and restore eyesight. This installment will focus on recent discoveries in drug delivery, gene therapy, imaging and visual prostheses; the second installment will discuss the impact of nanotechnology on artificial environment, cell-nanostructure interaction, other enabling nano-ophthalmic technologies, and safety and biocompatibility of nanostructures. We will take this opportunity to introduce some exciting nano-ophthalmic applications under investigation in our laboratory. The accomplishments by the scientific community are tremendous and the future prospects are wide open. Copyright © 2010 S. Karger AG, Basel.

Retinal Surgery

Shiragami C, et al. Displacement of the Retina after Standard Vitrectomy for Rhegmatogenous Retinal Detachment. *Ophthalmol* 2010; 117:86-92.

Summary: In a prospective study of 43 eyes with retinal detachment repaired by vitrectomy without buckling, 27 eyes showed evidence of inferior displacement of the retina. Of the 27, 59% showed 1-5 degrees of extorsion and 48% showed 1-4 degrees of vertical deviation. The extent of retinal detachment and the macular status (on or off) were significantly associated with postoperative displacement of the retina.

Kumagai K, et al. Incidence and Factors Related to Macular Hole Reopening. *Am J Ophthalmol* 2010; 149:127-132.

Summary: In a retrospective consecutive case series of 831 patients with macular hole, ILM peeling significantly decreased the incidence of the reopening of a macular hole over several years. The macular hole reopened in 2/514 eyes with excised ILM and 26/363 eyes with intact ILM. Although the pathogenesis of the reopening of macular holes is undetermined, myopia and intraoperative retinal tears may be related to the reopening.

Stem Cell Research

Seiler MJ, et al. Visual restoration and transplant connectivity in degenerate rats implanted with retinal progenitor sheets. *Eur J Neurosci* 2010 Jan 25. [Epub ahead of print] (from Pubmed)

Abstract The aim of this study was to determine whether retinal progenitor layer transplants form synaptic connections with the host and restore vision. Donor retinal sheets, isolated from embryonic day 19 rat fetuses expressing human placental alkaline phosphatase (hPAP), were transplanted to the subretinal space of 18 S334ter-3 rats with fast retinal degeneration at the age of 0.8-1.3 months. Recipients were killed at the age of 1.6-11.8 months. Frozen sections were analysed by confocal immunohistochemistry for the donor cell label hPAP and synaptic markers. Vibratome slices were stained for hPAP, and processed for electron microscopy. Visual responses were recorded by electrophysiology from the superior colliculus (SC) in 12 rats at the age of 5.3-11.8 months. All recorded transplanted rats had restored or preserved visual responses in the SC corresponding to the transplant location in the retina, with thresholds between -2.8 and -3.4 log cd/m². No such responses were found in age-matched S334ter-3 rats without transplants, or in those with sham surgery. Donor cells and processes were identified in the host by light and electron microscopy. Transplant processes penetrated the inner host retina in spite of occasional glial barriers between transplant and host. Labeled neuronal processes were found in the host inner plexiform layer, and formed apparent synapses with unlabeled cells, presumably of host origin. In conclusion, synaptic connections between graft and host cells, together with visual responses from corresponding locations in the brain, support the hypothesis that functional connections develop following transplantation of retinal layers into rodent models of retinal degeneration.