

Issue 296

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug Treatment

J Fr Ophtalmol. 2016 Sep 5. [Epub ahead of print] [Article in French]

[Ranibizumab and exudative age-related macular degeneration: 5-year multicentric functional and anatomical results in real-life practice].

Boulanger-Scemama E, Sayag D, Ha Chau Tran T, Quaranta-El Maftouhi M, Rumen F, Creuzot-Garcher C, Blanco Garavito R, Jung C, Souied E.

PURPOSE: The goal of this study was to evaluate five year functional and anatomical outcomes of wet AMD patients treated with ranibizumab according to a pro re nata (PRN) regimen in real-life practice.

METHODS: A retrospective, multicentric chart review of 201 eyes of 201 patients who underwent their first ranibizumab intravitreal injection (IVT) between January 1, 2007 and December 31, 2008 was performed. Best-corrected visual acuity (BCVA), central macular thickness (CMT) on SD-OCT, number of IVT and follow-up visits were collected at baseline and during the entire follow-up period of 5 years.

RESULTS: Mean BCVA at baseline was 52.3 ± 16.5 letters. Mean BCVA change from baseline was respectively +2.8, +2.5, +1.8, -0.6 at 1, 2, 3, 4 years of follow-up. At year 5, 43% of eyes had a stable or improved letter score (≥ 0 letter gain), whereas 29% declined by 15 letters or more, with an overall significant mean decline of 2.8 letters ($P < 0.05$). No correlation was observed between final visual outcome and age, baseline BCVA, type of neovascularization, naive status, number of IVT or number of follow-up visits. On SD-OCT, mean CMT was $293 \pm 96 \mu\text{m}$ at baseline and was significantly reduced compared to baseline at each year end-point ($P < 0.005$). The mean number of IVT was 15 ± 10.4 at year 5, with 55% of eyes still being under active treatment.

CONCLUSION: PRN ranibizumab in real-life practice improved or stabilized visual acuity over 4 years. During the 5th year, progressive decline of visual acuity was observed.

PMID: 27609025

Vestn Oftalmol. 2016 Jul-Aug;132(4):35-42. [Article in Russian]

[Effectiveness of diffuse diabetic macular edema treatment in relation to structural changes in macular region].

Fursova AZh, Chubar' NV, Tarasov MS, Saifullina IF, Pustovaya GG.

AIM: to describe baseline functional and anatomical parameters of the macular region and how they

change under ranibizumab therapy depending on the type of diabetic macular edema (DME) determined with optical coherence tomography (OCT).

MATERIAL AND METHODS: The study included 100 patients (100 eyes) with diabetes mellitus and DME (38 men and 62 women) aged 61.9 ± 5.6 years with the mean disease duration of 8.48 years. Basing on OCT findings, 4 groups (25 patients each) were formed: sponge-like DME, cystoid DME, DME with serous neuroepithelium detachment (NED), and mixed DME (cystoid DME and serous NED). All patients received 3 consecutive monthly injections of 0.5 mg ranibizumab. The relationship between anatomical, functional, and clinical parameters was analyzed.

RESULTS: The lowest visual acuity (VA) at baseline was found in patients with mixed DME ($p < 0.05$). The greatest increase in VA after the 3 injections was noted in patients with sponge-like DME - 0.34 ± 0.18 . Retinal thickness was significantly lower ($p < 0.05$) in sponge-like DME as compared to other groups both at baseline and after the treatment. Foveolar thickness decreased after the treatment in all groups, the effect being the most pronounced (the edema got reduced by 42.4%, $p < 0.05$) in cystoid DME. The most significant reduction in macular volume (by 2.7 mm³) as well as its lowest absolute post-treatment values were reported for patients with cystoid edema (9.01 mm³, $p < 0.05$ as compared to sponge-like and mixed DME). Correlation analysis revealed an evident relationship between the improvement in VA (Δ VA) and the decrease in macular volume ($p < 0.05$). Of clinical parameters, only diabetes duration correlated with the extent of VA improvement ($r = -0.3$; $p < 0.05$).

CONCLUSION: The effectiveness of intravitreal ranibizumab therapy for diffuse DME depends on the morphological type of macular edema by OCT. Moreover, it correlates with diabetes duration.

PMID: 27600893

Acta Diabetol. 2016 Sep 6. [Epub ahead of print]

Dynamic functionality and static changes of retinal vessels in diabetic patients treated with intravitreal ranibizumab.

Benatti L, Corvi F, Tomasso L, Darvizeh F, La Spina C, Querques L, Bandello F, Querques G.

AIMS: To investigate the short-term effects of intravitreal ranibizumab on retinal vessel functionality in patients with diabetic macular edema (DME) by Dynamic Vessel Analyzer (DVA).

METHODS: Patients presenting with DME were enrolled in the study. All patients underwent a complete ophthalmic evaluation, including optical coherence tomography and dynamic and static vessel analysis, using the DVA before (baseline), 1 week and 1 month after administration of intravitreal ranibizumab. DME subject were compared with diabetic retinopathy (DR) without DME subjects, and with normal non diabetic subjects (controls) matched for age and sex.

RESULTS: A total of 45 eyes of 45 subjects (15 eyes for each group) were included in the analysis. In DME patients, dynamic analysis showed a significant decrease in mean arterial dilation from baseline to 1 week. Mean central retinal artery equivalent (CRAE) of DR patients without DME was significantly different from baseline and week 1 of DME eyes. In healthy control subjects, CRAE was significantly different from CRAE at baseline and 1 week on DME patients, but not significantly different from DR patients without DME.

CONCLUSIONS: Using DVA in patients with DME, dynamic analysis showed a significant decrease in mean arterial dilation from baseline to 1 week in DME eyes. A significant reduction in arterial vessels could be demonstrated in DME patients compared to DR patients without DME and controls.

PMID: 27600440

Klin Monbl Augenheilkd. 2016 Sep 6. [Epub ahead of print]

[Correction: Switching Therapy from Ranibizumab and/or Bevacizumab to Aflibercept in Neovascular Age-Related Macular Degeneration (AMD): One-Year Results].

[Article in German]

Pfau M, Fassnacht-Riederle HM, Freiberg FJ, Wons JB, Wirth M, Becker MD, Michels S.

PMID: 27599047

Am J Ophthalmol. 2016 Sep 1. pii: S0002-9394(16)30379-8. doi: 10.1016/j.ajo.2016.07.027. [Epub ahead of print]

Long-Term Results of Pro Re Nata Regimen of Aflibercept Treatment in Persistent Neovascular Age-Related Macular Degeneration.

Venkatesh R, Dave PA, Singh S, Gurav P, Gujral G.

PMID: 27594519

Other Treatment and Diagnosis

Int Ophthalmol. 2016 Sep 3. [Epub ahead of print]

Early deterioration in ellipsoid zone in eyes with non-neovascular age-related macular degeneration.

Toprak I, Yaylalı V, Yildirim C.

ABSTRACT: The purpose of this study was to investigate the early effects of soft drusen on retinal pigment epithelium (RPE), ellipsoid zone (EZ, photoreceptor inner segment/outer segment junction), and external limiting membrane (ELM) reflectivities using optical coherence tomography (OCT) image analysis. This retrospective comparative study comprised 47 patients with non-neovascular AMD (with intact RPE, EZ, and ELM bands on OCT) and 45 age- and sex-matched healthy controls with normal OCT. A single masked physician performed OCT image analysis using a medical image processing software. Reflectivities of RPE, EZ, and ELM; number of drusen; vertical and horizontal diameters of the largest druse; druse reflectivity; foveal involvement by a druse; and presence of ≥ 1 large druse (n) were evaluated based on the macular OCT scan. Forty-seven right eyes of 47 patients with non-neovascular AMD and 45 right eyes of 45 healthy subjects were recruited. In the non-neovascular AMD group, absolute EZ and RPE reflectivities were significantly lower compared to those of the control eyes ($P < 0.001$ and $P = 0.001$, respectively). Comparing relative reflectivity values, only relative EZ reflectivity (EZ/ELM reflectivity) remained to show a significant difference between the groups ($P < 0.001$). Correlation analyses revealed no significant relation between the reflectivity values and drusen characteristics ($P > 0.05$). In eyes with non-neovascular AMD, decreased RPE (only absolute) and EZ (both absolute and relative) reflectivities prior to the disruption of these layers on OCT might indicate early photoreceptor damage. However, lower reflectivity values appear to be independent of the drusen characteristics.

PMID: 27591785

Graefes Arch Clin Exp Ophthalmol. 2016 Sep 5. [Epub ahead of print]

Investigation of precursor lesions of polypoidal choroidal vasculopathy using contralateral eye findings.

Kang SW, Lee H, Bae K, Shin JY, Kim SJ, Kim JM; Korean Age-related Maculopathy Study (KARMS) Group.

PURPOSE: The purpose was to investigate precursor lesions of polypoidal choroidal vasculopathy (PCV).

METHODS: This cross-sectional study involved 276 unaffected contralateral eyes from unilateral PCV patients (Group 1), unilateral typical exudative age-related macular degeneration (AMD) patients (Group 2), and unilateral epiretinal membrane patients (Group 3) as age-matched controls. Grayish-yellow sub-retinal or sub-retinal-pigment-epithelial deposits larger than 63 μm in size with irregular but discrete margins were defined as drusen-like deposits (DLDs). The frequencies of DLDs, drusen, and pigmentary changes in each group were compared.

RESULTS: DLDs larger than 125 μm in size were found more frequently in Group 1 (19.5 %) than in Groups 2 (3.4 %) and 3 (3.2 %) ($p < 0.001$). Soft drusen were discovered more frequently in Group 2 eyes than in Groups 1 and 3 ($p < 0.001$). Pigmentary changes were found more frequently in Groups 1 and 2 compared to Group 3. Compared with the other groups, Group 1 manifested a higher frequency of choroidal vascular hyperpermeability ($p < 0.005$) and thicker choroid ($p < 0.001$).

CONCLUSIONS: The precursor lesions of PCV are different from those of exudative AMD. DLDs larger than 125 μm and pigmentary changes may be early preclinical markers of PCV. Long-term longitudinal studies are warranted for validation.

PMID: 27596850

Sci Rep. 2016 Sep 8;6:32548.

Proteomics-based identification and validation of novel plasma biomarkers phospholipid transfer protein and mannan-binding lectin serine protease-1 in age-related macular degeneration.

Kim HJ, Ahn SJ, Woo SJ, Hong HK, Suh EJ, Ahn J, Park JH, Ryoo NK, Lee JE, Kim KW, Park KH, Lee C.

ABSTRACT: Age-related macular degeneration (AMD) is a major cause of severe, progressive visual loss among the elderly. There are currently no established serological markers for the diagnosis of AMD. In this study, we carried out a large-scale quantitative proteomics analysis to identify plasma proteins that could serve as potential AMD biomarkers. We found that the plasma levels of phospholipid transfer protein (PLTP) and mannan-binding lectin serine protease (MASP)-1 were increased in AMD patients relative to controls. The receiver operating characteristic curve based on data from an independent set of AMD patients and healthy controls had an area under the curve of 0.936 for PLTP and 0.716 for MASP-1, revealing excellent discrimination between the two groups. A proteogenomic combination model that incorporated PLTP and MASP-1 along with two known risk genotypes of age-related maculopathy susceptibility 2 and complement factor H genes further enhanced discriminatory power. Additionally, PLTP and MASP-1 mRNA and protein expression levels were upregulated in retinal pigment epithelial cells upon exposure to oxidative stress in vitro. These results indicate that PLTP and MASP-1 can serve as plasma biomarkers for the early diagnosis and treatment of AMD, which is critical for preventing AMD-related blindness.

PMID: 27605007

BMC Ophthalmol. 2016 Sep 5;16(1):159. doi: 10.1186/s12886-016-0335-9.

Pathogenesis

Cell Death Dis. 2016 Sep 8;7(9):e2367.

Clearance of autophagy-associated dying retinal pigment epithelial cells - a possible source for inflammation in age-related macular degeneration.

Szatmári-Tóth M, Kristóf E, Veréb Z, Akhtar S, Facskó A, Fésüs L, Kauppinen A, Kaarniranta K, Petrovski G.

ABSTRACT: Retinal pigment epithelial (RPE) cells can undergo different forms of cell death, including autophagy-associated cell death during age-related macular degeneration (AMD). Failure of macrophages or dendritic cells (DCs) to engulf the different dying cells in the retina may result in the accumulation of debris and progression of AMD. ARPE-19 and primary human RPE cells undergo autophagy-associated cell death upon serum depletion and oxidative stress induced by hydrogen peroxide (H₂O₂). Autophagy was revealed by elevated light-chain-3 II (LC3-II) expression and electron microscopy, while autophagic flux was confirmed by blocking the autophago-lysosomal fusion using chloroquine (CQ) in these cells. The autophagy-associated dying RPE cells were engulfed by human macrophages, DCs and living RPE cells in an increasing and time-dependent manner. Inhibition of autophagy by 3-methyladenine (3-MA) decreased the engulfment of the autophagy-associated dying cells by macrophages, whereas sorting out the GFP-LC3 -positive/autophagic cell population or treatment by the glucocorticoid triamcinolone (TC) enhanced it. Increased amounts of IL-6 and IL-8 were released when autophagy-associated dying RPEs were engulfed by macrophages. Our data suggest that cells undergoing autophagy-associated cell death engage in clearance mechanisms guided by professional and non-professional phagocytes, which is accompanied by inflammation as part of an in vitro modeling of AMD pathogenesis.

PMID: 27607582

Vestn Oftalmol. 2016 Jul-Aug;132(4):48-53. [Article in Russian]

[Macular choroidal blood flow in concurrent age-related macular degeneration and primary open-angle glaucoma].

Panova IE, Ermak EM, Shaimova TA, Shaimova VA.

ABSTRACT: Ocular circulation disorders are an important factor in the development of primary open-angle glaucoma (POAG) and age-related macular degeneration (AMD). To date, however, there have been no studies on choroidal blood flow peculiarities in case of concurrent AMD and POAG.

AIM: to determine distinctive features of choroidal blood flow characteristic of concurrent AMD and POAG and to assess their role in disease pathogenesis.

MATERIAL AND METHODS: Macular choroidal blood flow, including blood supply, was assessed in 54 patients (102 eyes) by means of Doppler ultrasound. Three groups were formed: group 1 - 38 eyes with both AMD and POAG; group 2 - 41 eyes with AMD and no signs of optic nerve pathology; and group 3 - 23 eyes with POAG and no signs of AMD. Groups 1 and 2 were subdivided into two subgroups each: A - atrophic AMD and B - macular drusen. The mean patient age was 78.7±8.4 years. The following parameters of choroidal blood flow were of interest: peak systolic velocity (Vps), end diastolic velocity (Ved), time-averaged maximum velocity (Vtamax), and resistance index (RI).

RESULTS: Groups 1, 3, and 2A had an evident choroidal hypoperfusion in the macular area (decreased Vtamax) with uncompensated perfusion deficit, despite autoregulation efforts (decreased Vps, Ved, decreased or normal RI). Group 2B demonstrated a significantly higher rate of choroidal hyperperfusion (increased Vps, Ved, Vtamax, and RI).

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CONCLUSION: Concurrent AMD and POAG are notable for choroidal hypoperfusion in the macular area that leads to inadequate trophism of the neurosensory retina and can aggravate the course of AMD contributing to progression of its atrophic form.

PMID: 27600895

Arch Pharm Res. 2016 Sep 7. [Epub ahead of print]

Mitochondria and the NLRP3 inflammasome: physiological and pathological relevance.

Yu JW, Lee MS.

ABSTRACT: The NLRP3 inflammasome is assembled and activated in certain types of myeloid cells upon sensing microbe-derived toxins or host-derived danger signals. Activation of the NLRP3 inflammasome by endogenous ligands has been discovered in various disorders, including metabolic syndrome, type 2 diabetes, atherosclerosis, gout, reperfusion injury of the heart, neurodegeneration, such as Alzheimer's disease, chronic kidney diseases, and macular degeneration of the eyes. Despite the potential significance of the NLRP3 inflammasome in the pathogenesis of several diseases, details on the activation mechanism of the NLRP3 inflammasome by a variety of stimulators have yet to be reported. Emerging evidence suggests that mitochondrial events are associated with NLRP3 activation in disease conditions. Mitochondrial dysfunction acts upstream of NLRP3 activation by providing reactive oxygen species (ROS) to trigger NLRP3 oligomerization or by inducing α -tubulin acetylation to relocate mitochondria to the proximity of NLRP3. In addition, mitochondria work as a platform for inflammasome assembly. Mitochondrial events may also lie downstream of NLRP3 activation. While the molecular mechanisms of mitochondrial dysfunction associated with NLRP3 activation are still unclear, they may involve the perturbation of mitochondria by K^+ efflux and subsequent intracellular disequilibrium. Thus, mitochondria and NLRP3 machinery appear to be closely interwoven at multiple levels.

PMID: 27600432

Neurobiol Aging. 2016 Aug 12;47:168-179. [Epub ahead of print]

Mitochondrial ferritin affects mitochondria by stabilizing HIF-1 α in retinal pigment epithelium: implications for the pathophysiology of age-related macular degeneration.

Wang X, Yang H, Yanagisawa D, Bellier JP, Morino K, Zhao S, Liu P, Vigers P, Tooyama I.

ABSTRACT: Mitochondrial ferritin (FtMt) is believed to play an antioxidant role via iron regulation, and FtMt gene mutation has been reported in age-related macular degeneration (AMD). However, little is known about FtMt's functions in the retina and any links to AMD. In this study, we observed age-related increase in FtMt and hypoxia-inducible factor-1 α (HIF-1 α) in murine retinal pigment epithelium (RPE). FtMt overexpression in ARPE-19 cells stabilized HIF-1 α , and increased the secretion of vascular endothelial growth factor. Conversely, HIF-1 α stabilization reduced the protein level of the mature, functional form of FtMt. FtMt-overexpressing ARPE-19 cells exhibited less oxidative phosphorylation but unchanged production of adenosine triphosphate, enhanced mitochondrial fission, and triggered mitophagy in a HIF-1 α -dependent manner. These findings suggest that increased FtMt in RPE may be protective via triggering mitophagy but cause wet AMD by inducing neovascularization due to increased vascular endothelial growth factor secretion. However, reduced level of functional FtMt in RPE under hypoxia may allow dry AMD through susceptibility to age-related stress.

PMID: 27599360

Stem Cells

Stem Cells Transl Med. 2016 Sep 9. [Epub ahead of print]

Multimodal Delivery of Isogenic Mesenchymal Stem Cells Yields Synergistic Protection From Retinal Degeneration and Vision Loss.

Bakondi B, Girman S, Lu B, Wang S.

ABSTRACT: We previously demonstrated that subretinal injection (SRI) of isogenic mesenchymal stem cells (MSCs) reduced the severity of retinal degeneration in Royal College of Surgeons rats in a focal manner. In contrast, intravenous MSC infusion (MSCIV) produced panoptic retinal rescue. By combining these treatments, we now show that MSCIV supplementation potentiates the MSCSRI-mediated rescue of photoreceptors and visual function. Electrophysiological recording from superior colliculi revealed 3.9-fold lower luminance threshold responses (LTRs) and 22% larger functional rescue area from combined treatment compared with MSCSRI alone. MSCIV supplementation of sham (saline) injection also improved LTRs 3.4-fold and enlarged rescue areas by 27% compared with saline alone. We confirmed the involvement of MSC chemotaxis for vision rescue by modulating C-X-C chemokine receptor 4 activity before MSCIV but without increased retinal homing. Rather, circulating platelets and lymphocytes were reduced 3 and 7 days after MSCIV, respectively. We demonstrated MSCSRI-mediated paracrine support of vision rescue by SRI of concentrated MSC-conditioned medium and assessed function by electroretinography and optokinetic response. MSC-secreted peptides increased retinal pigment epithelium (RPE) metabolic activity and clearance of photoreceptor outer segments *ex vivo*, which was partially abrogated by antibody blockade of trophic factors in concentrated MSC-conditioned medium, or their cognate receptors on RPE. These data support multimodal mechanisms for MSC-mediated retinal protection that differ by administration route and synergize when combined. Thus, using MSCIV as adjuvant therapy might improve cell therapies for retinal dystrophy and warrants further translational evaluation.

SIGNIFICANCE: Despite hundreds of clinical trials, just one stem cell treatment has been approved for the U.S. market. Additional treatments nearing clinical acceptance use bone marrow mesenchymal stem cells for inflammatory and immune-related conditions. This is because safety has been established over decades of testing, and cell transplants prolong life-saving organ and tissue grafts. In the present study, the intravenous delivery of mesenchymal stem cells enhanced the vision rescue from primary cell grafts into diseased retinæ. This combined transplant strategy could improve functional outcomes for cell-based therapies, expand their utility, and expedite their clinical acceptance.

PMID: 27612514

Diet, Lifestyle and Low Vision

Systemic confounders affecting serum measurements of omega-3 and -6 polyunsaturated fatty acids in patients with retinal disease.

Bühler AD, Bucher F, Augustynik M, Wöhr J, Martin G, Schlunck G, Agostini H, Böhringer D, Pütz G, Stahl A.

BACKGROUND: Omega-3 polyunsaturated fatty acids (PUFAs) have a highly anti-angiogenic effect in animal models. However, the clinical relevance of omega-3PUFAs in human retinal pathologies remains unclear. The ARED 2 study found no effect of omega-3 PUFA supplementation on progression of age related macular degeneration (AMD). The aim of this study was to compare serum levels of omega-3- and omega-6 PUFAs between patients with diabetic retinopathy (DR), AMD and retinal vein occlusion (RVO), and to identify potential confounders of serum level measurements.

METHODS: Venous blood samples were collected from 44 patients with DR, 25 with AMD, 12 with RVO and 27 controls. The lipid phase was extracted and analyzed using mass spectrometry. Retinal disease staging was done by indirect funduscopy and FAG where appropriate. Patient demographics and medical history including current medication and fasting state were acquired. Tukey contrasts for multiple comparisons of the mean and linear regression analysis were used for statistical analysis.

RESULTS: Our data revealed no significant differences in omega-6 PUFA serum levels between patients with AMD, DR, RVO and controls ($p > 0.858$). Uncorrected omega-3 PUFA levels were significantly higher in patients with AMD compared to DR but not compared to controls ($p = 0.004$). However, after correcting for possible confounders such as body mass index (BMI), age, sex, fasting and use of statins, no statistically significant difference remained for serum omega-3 PUFA levels. Fasting was identified as an independent confounder of total omega-6 PUFAs, three individual omega-6 PUFAs and one omega-3 PUFA ($p < 0.0427$). Statin use was identified as an independent confounder of α -linolenic acid (an omega-3 PUFA; $p = 0.0210$).

CONCLUSION: In this pilot study with relatively low patient numbers, we report significant differences in serum levels of omega-3 PUFAs among patients with different types of retinal diseases. However, these differences were not robust for disease specificity after correction for possible confounders in our cohort. Our results demonstrate that serum lipid profiles need to be interpreted with caution since they are significantly altered by variables like fasting and medication use independent from the underlying disease. Correcting for respective confounders is thus necessary to compare serum lipid profiles in clinical studies.

PMID: 27596098

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