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MD Research News

Issue 47

Monday September 19 , 2011

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## Drug treatment

**Am J Ophthalmol. 2011 Sep 9. [Epub ahead of print]**

**Treatment of Polypoidal Choroidal Vasculopathy with Photodynamic Therapy Combined with Intravitreal Injections of Ranibizumab.**

Tomita K, Tsujikawa A, Yamashiro K, Ooto S, Tamura H, Otani A, Nakayama Y, Yoshimura N.

Nakano Eye Clinic, Kyoto, Japan.

PURPOSE: To evaluate the 1-year efficacy and safety of photodynamic therapy (PDT) combined with intravitreal injections of ranibizumab for polypoidal choroidal vasculopathy (PCV).

DESIGN: Retrospective chart review.

METHODS: We retrospectively reviewed the medical records of 63 consecutive patients (66 eyes) with subfoveal PCV who were treated with PDT combined with intravitreal injections of ranibizumab. Of the 66 eyes, 29 had no history of treatment for PCV, 10 had been treated previously with only intravitreal injections of anti-vascular endothelial growth factor agents, and 27 had been treated previously with PDT. All eyes had a minimal follow-up of 12 months.

RESULTS: The combined therapy reduced substantially the exudative change immediately after initiation of treatment. In treatment-naïve eyes, mean VA before treatment (0.47 ± 0.37 logarithm of the minimal angle of resolution [logMAR]) improved to 0.32 ± 0.30 ($P < .01$) at 3 months and to 0.29 ± 0.29 ($P < .01$) at 12 months. Polypoidal lesions were reduced in all eyes and disappeared completely in 79.1% of cases. In eyes treated previously with only anti-vascular endothelial growth factor therapy, some visual improvement was achieved, but in eyes treated previously with PDT, mean visual acuity (0.61 ± 0.45) deteriorated to 0.68 ± 0.52 at 12 months. Of all 66 eyes, 5 showed extensive postoperative subretinal hemorrhage, in 2 of which a vitreous hemorrhage developed, necessitating pars plana vitrectomy.

CONCLUSIONS: PDT combined with ranibizumab led to significant visual recovery in treatment-naïve eyes with PCV, but not in eyes with PCV that had demonstrated recurrence after previous PDT. PDT in combination with ranibizumab still has a risk of the postoperative hemorrhagic complications.

PMID: 21907965 [PubMed - as supplied by publisher]

**Eye (Lond). 2011 Sep 16. doi: 10.1038/eye.2011.223. [Epub ahead of print]**

**Quality of fixation in eyes with neovascular age-related macular degeneration treated with ranibizumab.**

Sivaprasad S, Pearce E, Chong V.

Laser and Retinal Research Unit, Department of Ophthalmology, King's College Hospital, London, UK.

Aims: To define factors that determine the location and stability of fixation in patients with neovascular age-related macular degeneration (NV-AMD) treated with intravitreal ranibizumab injections.

Methods: The location and stability of fixation using microperimetry were determined in 77 eyes treated with ranibizumab for NV-AMD for at least 12 months. All patients were treated with three injections of ranibizumab 0.5 mg, 1 month apart and retreated according to predefined criteria. The fixation parameters were correlated to the visual acuity, and quantitative measures on OCT.

Results: The location of fixation was predominantly central in 52.6%, poor central fixation in 9.2%, and predominantly eccentric fixation in 38.2%. The fixation was stable in 65%, relatively unstable in 25%, and unstable in 10%. Visual acuity was the only factor that determined the stability and location of fixation. The characteristics of fixation were not related to the macular thickness or volume as measured by OCT.

Conclusions: Better visual outcome ensures central and stable fixation. Quantitative measures of OCT parameters do not determine fixation. Further studies on morphological features of the macula may provide some insight into the determinants of fixation.

Eye advance online publication, 16 September 2011; doi:10.1038/eye.2011.223.

PMID:21921956 [PubMed - as supplied by publisher]

**Eye (Lond). 2011 Sep 16. doi: 10.1038/eye.2011.225. [Epub ahead of print]**

**Potential penetration of topical ranibizumab (Lucentis) in the rabbit eye.**

Chen JJ, Ebmeier SE, Sutherland WM, Ghazi NG.

Department of Ophthalmology, University of Virginia, Charlottesville, VA, USA.

Purpose: To assess ranibizumab (Lucentis) penetration into the retina after topical administration in a rabbit model.

Methods: Ranibizumab was topically applied to the right eye of rabbits according to three regimens: every 2 h (q2hr), four times daily (qid), and twice daily (bid). Intraocular penetration of ranibizumab was assessed at 3, 7, 14, 21, and 28 days following initiation of drops. At each time point, the anterior chambers, vitreous cavities, and blood of one of the rabbits from each subgroup were sampled for ranibizumab detection using enzyme-linked immunosorbent assay (ELISA), and both eyes were then enucleated for ranibizumab detection in the retina by confocal immunohistochemistry (CI). Another group of rabbits received intravitreal ranibizumab and was similarly sampled for comparison.

Results: CI showed ranibizumab staining in the right retina after 7 and 14 days of q2hr topical administration in two out of four experiments. No ranibizumab was detected in the left retina at any of the sampling time points. ELISA was positive in the vitreous of the right eye at 14 and 21 days in the q2hr treated rabbits in one out of four experiments. No ranibizumab was detected in the qid and bid subgroups. CI and ELISA of the aqueous and vitreous were consistently positive in the intravitreal group. Mild ranibizumab levels were detected in the blood in both the topical and intravitreal groups.

Conclusions: Topically applied ranibizumab can be detected in the retina following high-frequency

administration in a rabbit model. A trans-scleral route of penetration is suggested.

Eye advance online publication, 16 September 2011; doi:10.1038/eye.2011.225.

PMID:21921952 [PubMed - as supplied by publisher]

**Eye (Lond). 2011 Sep 16. doi: 10.1038/eye.2011.224. [Epub ahead of print]**

**Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12.**

Williams TA, Blyth CP.

1] Department of Ophthalmology, University Hospital of Wales, Cardiff, UK [2] Department of Ophthalmology, Royal Gwent Hospital, Newport, UK.

Background:  The beneficial effect of intravitreal ranibizumab in the treatment of neovascular age-related macula degeneration (nAMD) is well known. Outcome data for eyes presenting with visual acuity better than 6/12 is limited.

Aims: To assess the effect of baseline vision on outcome in ranibizumab-treated nAMD eyes, including a subgroup with baseline vision ≥6/12 (<0.30 logmar).DesignProspective, consecutive and interventional case series.

Methods: A consecutive cohort of patients treated with intravitreal ranibizumab for nAMD with 52-week follow-up were studied. Patients who had received previous treatment for nAMD were excluded. Eyes were stratified according to baseline logmar visual acuity into four groups: <0.30 (>6/12), 0.30-0.59 (6/12-6/24), 0.60-0.99 (6/24-6/60) and 1.00-1.20 (6/60-6/96). Intravitreal ranibizumab (0.5 mg in 0.05 ml) was administered in three loading monthly doses followed by PRN dosing according to optical coherence tomography (OCT) findings.

Results: A total of 615 eyes were studied including 88 eyes with baseline vision <0.30. The mean change in logmar letters at 52 weeks was +5.5 (entire study group), -0.5 (<0.30 subgroup), +2.2 (0.30-0.59 subgroup), +6.5 (0.60-0.99 subgroup) and +15.3 (1.00-1.20 subgroup). In the <0.30 subgroup, 60 of 88 eyes (68%) had best-corrected visual acuity (BCVA) equal to or better than baseline and 82 of 88 eyes (93%) lost <15 letters at 52 weeks. Within this subgroup 56 of 67 eyes (84%) maintained UK driving standard BCVA visual acuity over the study period.

Conclusions: This study provides evidence that intravitreal ranibizumab treatment stabilises good vision in nAMD presenting with vision better than 6/12 over 52 weeks follow-up.

Eye advance online publication, 16 September 2011; doi:10.1038/eye.2011.224.

PMID: 21921947[PubMed - as supplied by publisher]

**Klin Oczna. 2011;113(4-6):127-31.**

**[Complications of intravitreal injections--own experience].**

**[Article in Polish]**

Jamrozy-Witkowska A, Kowalska K, Jankowska-Lech I, Terelak-Borys B, Nowosielska A, Grabska-Liberek I.

Z Oddziału Klinicznego Okulistyki Centrum Medycznego Kształcenia Podyplomowego w Warszawie. ajamrozy@poczta.fm

PURPOSE: Authors present complications associated with intravitreal injection performed in Ophthalmic Clinic

CMKP MATERIAL AND METHODS: retrospective study, between January 2006 and July 2009 we performed intravitreal injections with triamcinolone acetonide (Kenalog, 4 mg), ranibizumab (Lucentis, 0.5 mg), bevacizumab (Avastin, 1.25 mg) and pegaptanib (Macugen, 0.3 mg). We treated eyes with age-related macular degeneration, diabetic macular edema, after retinal venous occlusion, with uveitis, Irvine-Gass syndrome, idiopathic juxtafoveolar teleangiectasia and central serous retinopathy.

RESULTS: 943 eyes received intravitreal injections. The most common ocular complication was subconjunctival hemorrhage which was seen in 36% cases. Temporary elevated intraocular pressure above 21 mmHg was noticed in 18 eyes (5%) after anti-VEGF agents injections and in 30 eyes (23.4%) after Kenalog injection. Anterior uveitis developed in sixteen cases (1.7%) from the Avastin (5 eyes) and Lucentis (3 eyes) group. Anterior-posterior inflammation occurred in 8 eyes (0.8%), including four eyes (0.4%) with sterile endophthalmitis (3 following bevacizumab and 1 following ranibizumab injection), one eye (0.1%) with pseudoendophthalmitis (after triamcinolone). There were three cases of suspected endophthalmitis (2 following bevacizumab and 1 following triamcinolone injection). The infectious endophthalmitis after triamcinolone injection was culture-proven and revealed Staphylococcus epidermidis. Cataract formation or progression was noted in 34 eyes totally. In Kenalog group progression of cataract was seen in 23.4% of eyes (30 cases) during 2-years of follow-up and in anti-VEGF agents group--in two cases (0.6%) and 2 cases of iatrogenic cataract. Three diabetic patients suffered systemic adverse events: one patient developed renal insufficiency, one patient developed cerebrovascular accidents and one suffered a myocardial infarction resulting in death.

Conclusions: Intravitreal injections are associated with a low incidence of serious adverse events. The most common ocular complication was subconjunctival hemorrhage. There was one case of serious complication --the culture-proven infectious endophthalmitis after Kenalog injection. Cataract formation and increase of intraocular pressure were more often observed following intravitreal triamcinolone injection.

PMID: 21913440 [PubMed - in process]

**J Coll Physicians Surg Pak. 2011 Sep;21(9):535-8.**

**Visual results following intravitreal bevacizumab in neovascular age-related macular degeneration.**

Iqbal K, Baig J, Jamil AZ, Jamil H, Mirza K, Khan T.

Department of Ophthalmology, Layton Rahmatulla Benevolent Trust Eye Hospital (LRBT), Lahore.

Objective: To determine the visual and anatomic outcome of intravitreal Bevacizumab injection in the treatment of neovascular age-related macular degeneration (AMD).

Study Design: Quasi-experimental study.

Place and Duration of Study: Layton Rahmatulla Benevolent Trust Eye Hospital (LRBT), Lahore, from January to July 2010.

Methodology: Patients who received, one or more intravitreal Bevacizumab injections (1.25 mg per 0.05 ml) for exudative AMD were included in the study.

Outcome measures included standardized visual acuity, optical coherence tomography (OCT), macular thickness, intraocular pressure, and blood pressure at 24 or more weeks follow-up. Descriptive statistics were obtained.

Results: Fifty eyes with exudative AMD were observed for six months. The mean VA improved from 0.21 ± 0.11 before injections to 0.43 ± 0.11 after injections at six months. Overall, mean OCT macular thickness

decreased by 99 micron at last follow-up. At last follow-up, all eyes received an average of 3.28 ± 0.85 injections. There was no incidence of severe vision loss or adverse effects like endophthalmitis or retinal detachment.

Conclusion: Intravitreal Bevacizumab has the potential for improvement of vision in exudative AMD for at least 6 months.

PMID: 21914409 [PubMed - in process]

**Klin Monbl Augenheilkd. 2011 Sep;228(9):793-800. Epub 2011 Sep 12.**

**[New Developments in the Pharmacological Treatment of Macular Oedema due to Retinal Vein Occlusion].**

**[Article in German]**

Lang GE.

Augenklinik, Universitätsklinikum Ulm.

Abstract

The therapeutic options for retinal vascular diseases have changed due to new study results and the approval of dexamethasone (Ozurdex®) and ranibizumab (Lucentis®) by the EU commission for visual loss caused by macular oedema in retinal vein occlusion. In addition to laser treatment, we have now two approved drugs for the treatment of macular oedema. Therefore it is important to make decisions about the best treatment in retinal vein occlusion. This necessitates knowledge of the posology of the drug and assessment of the advantages and risks of the different treatment modalities. Therefore it is important to know the efficacy and safety data of the different therapies. The approval of dexamethasone and ranibicumab for the treatment of macular oedema in branch and central retinal vein occlusions improves the chances for the outcome, especially concerning visual acuity. The new results from the dexamethasone and ranibizumab studies in matters of efficacy and safety and treatment recommendations are described.

PMID: 21913147 [PubMed - in process]

## Other treatment & diagnosis

**Invest Ophthalmol Vis Sci. 2011 Sep 14. [Epub ahead of print]**

**Subfoveal Choroidal Thickness in Relation to Gender and Axial Length in 93 Danish University Students.**

Li XQ, Larsen M, Munch IC.

Department of Ophthalmology, Glostrup Hospital, Denmark.

Purpose: To investigate the association between subfoveal choroidal thickness and ocular axial length, refractive error and blood pressure in healthy young women and men.

Methods: Cross-sectional observational study of 93 eyes in 93 healthy Danish university students. (mean age 24.9 (± 2.6) years). The submacular choroid was imaged using enhanced-depth imaging spectral domain optical coherence tomography. Subfoveal choroidal thickness was measured by visual inspection and manual fitting of the choroidal borderlines. Study parameters included history, best corrected visual acuity, objective refraction, interferometric ocular axial length, fundus photography and blood pressure manometry.

Results: The mean subfoveal choroidal thickness was 342 (± SD 118) µm, the mean age was 24.9 (± 2.6) years and the mean refractive error of participants was -1.43 (± 2.9) D. In a multiple regression model, subfoveal choroidal thickness decreased by 58.2 µm (CI(95) 42.2 - 74.2 µm, P < 0.001) per mm increase in axial length adjusted for age and gender and subfoveal choroidal thickness was 62 µm (CI(95) 21 … 104 µm, P = 0.0039) thicker in men than in women, adjusted for age and axial length. Arterial blood pressure had no statistical effect on subfoveal choroidal thickness.

Conclusion: In this study of healthy young participants choroidal thickness was 18% higher in men than in women when adjusting for age and axial length. This observation may help explain the effect of gender in conditions related to choroidal thickness such as myopia, central serous chorioretinopathy and age-related macular degeneration.

PMID: 21917938 [PubMed - as supplied by publisher]

**Int J Biochem Cell Biol. 2011 Sep 6. [Epub ahead of print]**

**Small peptides derived from somatotropin domain-containing proteins inhibit blood and lymphatic endothelial cell proliferation, migration, adhesion and tube formation.**

Lee E, Rosca EV, Pandey NB, Popel AS.

Department of Chemical and Biomolecular Engineering, School of Engineering, Johns Hopkins University, Baltimore, MD 21218, United States.

Abstract

Angiogenesis is thoroughly balanced and regulated in health; however, it is dysregulated in many diseases including cancer, age-related macular degeneration, cardiovascular diseases such as coronary and peripheral artery diseases and stroke, abnormal embryonic development, and abnormal wound healing. In addition to angiogenesis, lymphangiogenesis is pivotal for maintaining the immune system, homeostasis of body fluids and lymphoid organs; dysregulated lymphangiogenesis may cause inflammatory diseases and lymph node mediated tumor metastasis. Anti-angiogenic or anti-lymphangiogenic small peptides may play an important role as therapeutic agents normalizing angiogenesis or lymphangiogenesis in disease conditions. Several novel endogenous peptides derived from proteins containing a conserved somatotropin domain have been previously identified with the help of our bioinformatics-based methodology. These somatotropin peptides were screened for inhibition of angiogenesis and lymphangiogenesis using in vitro proliferation, migration, adhesion and tube formation assays with blood and lymphatic endothelial cells. We found that the peptides have the potential for inhibiting both angiogenesis and lymphangiogenesis. Focusing the study on the inhibition of lymphangiogenesis, we found that a peptide derived from the somatotropin conserved domain of transmembrane protein 45A human was the most potent lymphangiogenesis inhibitor, blocking lymphatic endothelial cell migration, adhesion, and tube formation.

PMID: 21920451 [PubMed - as supplied by publisher]

**J Fr Ophtalmol. 2011 Sep 8. [Epub ahead of print]**

**[Current uses and indications for indocyanine green angiography.]**

**[Article in French]**

Desmettre T, Cohen SY, Devoisselle JM, Gaudric A.

Centre d'imagerie et de laser, 221, avenue de l'Hippodrome, 59130 Lambersart, France; Service d'ophtalmologie, hôpital Lariboisière, 2, rue Ambroise-Paré, 75010 Paris, France.

Abstract

A full interpretation of indocyanine green angiography images involves not only optical issues but also pharmacokinetic and biochemical aspects. These issues may involve biochemical changes in the fluorescence yield and the affinity of the molecule for lipoproteins and phospholipids. For age related macular degeneration (AMD), the advent of photodynamic therapy and especially anti-VEGF drugs has increased the use of OCT in assessing treatment response and guiding retreatment. The ease and advantages of OCT have become increasingly associated with a decreasing interest in ICG angiography, which is becoming less well suited for the current management of AMD. An aging population, the efficacy of anti-VEGF drugs and the relative rarity of polypoidal choroidal vasculopathy (PCV) in Europe are factors contributing to our proportional increase in AMD patients. However, aside from AMD, the indications for ICG angiography remain little changed over the last decade: it remains important in diagnosing PCV and choroidal hemangiomas, since their prognosis and treatment are specific. Similarly, for certain inflammatory conditions such as Multiple Evanescent White Dot Syndrome (MEWDS) or Birdshot chorioretinitis, the value of ICG angiography remains significant. In addition, for the treatment of chronic Central Serous Chorioretinopathy, ICG angiography helps to find sites of leakage which otherwise might have been missed. The ICG angiographic appearance in this setting may also have prognostic value. Although the indications for ICG angiography are currently decreasing for AMD, these other conditions represent a large enough number of patients to justify the continued use of this original test, which remains complementary to other chorioretinal imaging techniques.

PMID: 21907446 [PubMed - as supplied by publisher]

**Klin Oczna. 2011;113(4-6):161-4.**

**[Guality of life in patients with age-related macular degeneration - medical and social problem].**

**[Article in Polish]**

Muzyka-Woźniak M, Misiuk-Hojło M, Wesolowska A.

Z Katedry i Kliniki Okulistyki Akademii Medycznej we Wrocławiu. maria-muzyka@tlen.pl

Abstract

Age-related macular degeneration (AMD) is a leading cause of blindness over the age of 50 in western countries. People with AMD are suffering from serious vision-related disability and their social life is compromised.

PURPOSE: The aim of our study was to assess quality of life (QoL) in patients with exudative AMD.

MATERIAL AND METHODS: The study group was 100 patients treated for AMD, the control group were 30 age and sex matched subjects without ophthalmic disorders. Patients were treated with anti-VEGF therapy, by means of National Eye Institute Visual Function Questionnaire (NEI VFQ-25). As well as visual function, the NEI-VFQ investigates social functioning, mental health and dependency.

RESULTS: There was statistically significant difference in QoL overall score between study group and control group. Patients with AMD obtained 51.1 (+/- 20.5 ) overall score, control group reached 83.7 (+/- 11.7) overall score, p = 0.001. Detailed analysis of study group revealed low acceptance of the disease and strong dependency.

CONCLUSIONS: QoL in patients with AMD assessed with NEI VFQ-25, is significantly impaired. Low quality of life and difficulties in performing daily activities point at the need of formal psychological and social care.

PMID: 21913448 [PubMed - in process]

**Retina. 2011 Sep 8. [Epub ahead of print]**

**NON-FULL-THICKNESS MACULAR HOLES REASSESSED WITH SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.**

Michalewska Z, Michalewski J, Odrobina D, Nawrocki J.

From the Ophthalmic Clinic, "Jasne Blonia"ul. Lodz, Poland.

PURPOSE: The aim of this study was to describe spectral domain optical coherence tomography characteristics and evolution of non-full-thickness macular holes, with a bed of retinal tissue present in the outer retinal layers, which the author will henceforth refer to as non-full-thickness macular holes (NFMHs).

METHODS: Retrospective observational study of 10,239 consecutive spectral domain optical coherence tomographic examinations was conducted, to select patients with idiopathic NFMH. We measured the following parameters: visual acuity, type of NFMH, coexistence of epiretinal membranes, photoreceptor layer defects, central and maximum retinal thickness, and diameters of the fovea defect. Patients with a history of diabetes; previous vein occlusions, with age-related macular degeneration; high and medium myopia; a previous history of retinal detachment; or macular edema were excluded.

RESULTS: Four subtypes of NFMH were distinguished among 125 eyes (116 patients): macular pseudohole (21 eyes), paralamellar macular holes (34 eyes), pseudoholes with lamellar defects (25 eyes), and lamellar macular holes (45 eyes). We observed different fovea appearances on consecutive B-scans in 54% of eyes. Epiretinal membranes coexisted in 100% of cases. Photoreceptor layer defects, seen in 29% of cases, were the most important factor correlating with visual acuity. Other factors correlating with visual acuity were maximum retinal thickness and outer diameter of the fovea defect. We noted epiretinal membranes in the second eye in 32 cases. Sixty-six patients were followed up for a mean time of 14 months. Non-full-thickness macular hole formation was documented in five cases.

CONCLUSION: Spectral domain optical coherence tomography images presented of four different morphologic types NFMH, which may change during the natural course of the disease. High resolution of spectral domain optical coherence tomography enabled the visualization of photoreceptor defects, a feature not previously described. Moreover, epiretinal membranes and fovea contour localized beneath the outer plexiform layer were noted in all cases.

PMID: 21909051 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2011 Sep 9. [Epub ahead of print]**

**VISUAL FUNCTIONING AND QUALITY OF LIFE UNDER LOW LUMINANCE - EVALUATION OF THE GERMAN LOW LUMINANCE QUESTIONNAIRE.**

Finger RP, Fenwick E, Owsley C, Holz FG, Lamoureux EL.

Department of Ophthalmology, University of Bonn, Germany.

Purpose: To validate the German-translated Low Luminance Questionnaire (LLQ), a vision-related quality of life (VRQoL) scale assessing mainly mesopic and scotopic functioning, and determine the relationship between the severity of vision impairment, ocular conditions and low luminance-related visual functioning.

Methods: 274 participants, 184 patients with visual acuity <6/12 or a long standing symptomatic eye condition and 90 controls, were recruited from an outpatient clinic at a German eye hospital. Participants underwent a clinical examination and completed the German LLQ and VF-14 scales. The validity and psychometric properties of the scales were assessed using Rasch analysis exploring key indices such as instrument unidimensionality, discriminant ability and targeting of item difficulty to patient ability. Multivariate analyses of low luminance functioning were adjusted for conventional visual functioning (VF-14 scores).

Results: The 30 item German LLQ initially displayed poor fit to the Rasch model. Following Rasch-guided iterative adjustments to the scale, a 23-item LLQ emerged as a valid and unidimensional scale. Visual functioning under low luminance consistently declined with worsening vision loss. Compared to patients with no vision impairment, those with mild, or moderate/severe vision impairment recorded significantly poorer low luminance functioning scores (mean change -6.33 and -16.62; p=0.032 and p<0.001, respectively). Age-related macular degeneration and cataract were independently associated with low luminance visual functioning, as was worse self-reported health.

Conclusions: Low luminance functioning is considerably compromised in visually-impaired patients even at the mild spectrum of visual acuity loss. Additionally, the impact of age-related macular degeneration and cataract on patients' low luminance functioning is substantial independent of vision impairment.

PMID: 21908584 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2011 Sep 9. [Epub ahead of print]**

**A Free Retinal Pigment Epithelium-Choroid Graft in Patients With Exudative Age-Related Macular Degeneration: Results up to 7 Years.**

Zeeburg EJ, Maaijwee KJ, Missotten TO, Heimann H, van Meurs JC.

Rotterdam Ophthalmic Institute, Rotterdam, The Netherlands; Rotterdam Eye Hospital, Rotterdam, The Netherlands.

PURPOSE: To report and analyze long-term best-corrected visual acuity (BCVA) outcomes following a free autologous retinal pigment epithelium (RPE)-choroid graft translocation in patients with exudative age-related macular degeneration (AMD).

DESIGN: Prospective cohort study.

METHODS: setting: Institutional.study population: One hundred and thirty consecutive patients (133 eyes) with AMD underwent RPE-choroid graft translocation between October 2001 and February 2006. All patients had a subfoveal choroidal neovascular membrane with or without hemorrhage and/or an RPE tear. All were either ineligible for or nonresponsive to photodynamic therapy, the standard treatment at the time of surgery.observation procedures: Data collection included preoperative and postoperative visual acuity measurements, fundus photography, fluorescein and indocyanine green angiography, and microperimetry.main outcome measures: Postoperative BCVA.

RESULTS: The mean preoperative BCVA was 20/250. Four years after surgery, 15% of the eyes had a BCVA of >20/200, and 5% had a BCVA of ≥20/40. One patient achieved a BCVA of 20/32, which was maintained at 7 years after surgery. Complications consisted of proliferative vitreoretinopathy (n = 13), recurrent neovascularization (n = 13), and hypotony (n = 2).

CONCLUSIONS: RPE-choroid graft transplantation may maintain macular function for up to 7 years after surgery, with relatively low complication and recurrence rates. Retinal sensitivity, BCVA data, and fixation on the graft suggest that the graft, rather than simply the removal of submacular hemorrhage and/or choroidal neovascular membrane, was responsible for the preservation of macular function. This surgery may be an alternative for patients with AMD who cannot undergo other standard treatment.

PMID: 21907969 [PubMed - as supplied by publisher]

**JRSM Short Rep. 2011 Aug;2(8):64. Epub 2011 Aug 1.**

**Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study.**

Muen WJ, Hewick SA.

Highland NHS Trust , Inverness, Scotland , UK.

OBJECTIVES: To evaluate the quality of referrals to a neovascular age-related macular degeneration clinic from optometrists using the standard Rapid Access Referral Form (RARF) from the Royal College of Ophthalmologists.

DESIGN: A prospective study. Prospective data were gathered from all optometry referrals using the RARF, between the periods of December 2006 to August 2009. These were assessed for accuracy of history, clinical signs and final diagnosis as compared to a macula expert.

SETTING: Highlands NHS Trust.

PARTICIPANTS: All patients referred to the eye department at NHS Highlands Trust using the RARF.

MAIN OUTCOME MEASURES: The symptoms of neovascular age-related macular degeneration correctly identified by optometrists, and the signs of neovascular age-related macular degeneration correctly identified by optometrists.

RESULTS: Fifty-four RARFs were received during this period, there was an overall agreement with symptomatology in 57.4% of cases. Optometrists scored less well in recognizing the clinical signs of neovascular age-related macular degeneration, with the poorest scores for recognizing macular oedema (44.4%) and drusen (51.9%). Twenty (37%) patients referred had neovascular age-related macular degeneration.

CONCLUSIONS: RARFs make up the minority of referrals to the neovascular age-related macular degeneration clinic. Optometrists find it difficult to accurately elicit the signs of macula disease.

PMID: 21912730 [PubMed - in process] PMCID: PMC3166265

**Invest Ophthalmol Vis Sci. 2011 Sep 12. [Epub ahead of print]**

**Computerized Macular Pathology Diagnosis in Spectral Domain Optical Coherence Tomography Scans Based on Multi-Scale Texture and Shape Features.**

Liu YY, Ishikawa H, Chen M, Wollstein G, Duker JS, Fujimoto JG, Schuman JS, Rehg JM.

School of Interactive Computing, Georgia Institute of Technology, Atlanta, GA;

Purpose:To develop an automated method to identify the normal macula and three macular pathologies (macular hole (MH), macular edema (ME), and age-related macular degeneration (AMD)) from the fovea-centered cross sections in three-dimensional (3D) spectral domain optical coherence tomography (SD-OCT) images.

Methods:A sample of SD-OCT macular scans (Macular Cube 200x200 scan protocol; Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) were obtained from healthy subjects and subjects with MH and/or ME and/or AMD (dataset for development (326 scans from 136 subjects (193 eyes)), and dataset for testing (131 scans from 37 subjects (58 eyes))). Fovea-centered cross-sectional slice for each of SD-OCT images was encoded using spatially-distributed multi-scale texture and shape features. Three ophthalmologists labeled each fovea-centered slice- independently and the majority opinion for each pathology was used as the ground truth. Machine learning algorithms were used to identify the discriminative features automatically. Two-class Support Vector Machine classifiers were trained to identify the presence of normal macula and each of the three pathologies separately. The area under the receiver operating characteristic curve (AUC) was calculated to assess the performance.

Results:The cross-validation AUC result on the development dataset was 0.976, 0.931, 0,939, and 0.938,

and the AUC result on the hold-out testing set was 0.978, 0.969, 0.941, and 0.975, for identifying normal macula, MH, ME, and AMD, respectively.

Conclusion:The proposed automated data-driven method successfully identified various macular pathologies (all AUC > 0.94). This method may effectively identify the discriminative features without relying on a potentially error-prone segmentation module.

PMID: 21911579 [PubMed - as supplied by publisher]

## Pathogenesis

**Invest Ophthalmol Vis Sci. 2011 Sep 14. [Epub ahead of print]**

**Upregulation of CCR3 by age-related stresses promotes choroidal endothelial cell migration via VEGF-dependent and independent signaling.**

Wang H, Wittchen ES, Jiang Y, Ambati B, Grossniklaus HE, Hartnett ME.

Department of Ophthalmology, The John Moran Eye Center, University of Utah, Salt Lake City, UT;

Purpose: To explore the molecular mechanisms by which the chemokine receptor CCR3 and a ligand CCL11 regulate choroidal endothelial cell (CEC) migration and the interactions with the VEGF signaling pathway.

Methods: Human retinal sections from young and aged donor normal eyes were immunolabeled. By real-time PCR, CCR3 mRNA was measured in RPE/choroids obtained from young and aged human donor eyes and in cultured CECs exposed to hydrogen peroxide (H(2)O(2)). CCR3 ligand, CCL11-, or VEGF-stimulated CEC migration was also measured in the presence of a CCR3 inhibitor or control using fluorescence microscopy. Activation of Rac1, phosphorylated Akt as a readout for phosphoinositol 3-kinase signaling, and VEGFR2 activation were measured in CECs incubated with CCL11, VEGF, or combined CCL11/VEGF.

Results: CCR3 was expressed to a greater level in older compared to younger human retinas or RPE/choroids. Ligand-activated CCR3 increased CEC migration, which was inhibited by the CCR3 inhibitor. Rac1 activity, p-Akt and p-VEGFR2 were significantly increased in CECs incubated with CCL11. The CCR3 inhibitor prevented VEGF-induced CEC migration and Rac1 activation in CECs. Rac1 activity was additively increased in CECs treated with CCL11 and VEGF compared to that in cells with CCL11 or VEGF treatment alone. Ligand-activated CCR3 caused VEGFR2 phosphorylation and co-immunoprecipitation of VEGFR2 and CCR3.

Conclusions: Activated CCR3 promotes CEC migration and Rac1 activation and causes an association with and activation of VEGFR2. Crosstalk between CCR3 and VEGF signaling exists and may be important in choroidal neovascularization (CNV) in human age-related macular degeneration (AMD).

PMID: 21917937 [PubMed - as supplied by publisher]

**Klin Monbl Augenheilkd. 2011 Sep;228(9):762-70. Epub 2011 Sep 12.**

**[Myopic CNV].**

**[Article in German]**

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Abstract

Choroidal neovascularisation secondary to pathological myopia is the most common cause of severe visual impairment in myopic patients younger than 50 years old. The typical features of myopic CNV in contrast to age-related macular degeneration as well as the anatomic characteristics have an impact on the parameters of the baseline and follow-up examinations. As the usually small fibrovascular lesions show a rapid progression in the spontaneous course of the disease and lead to irreversible damage to the photoreceptors, prompt initiation of treatment is mandatory. The superior functional results of anti-VEGF drugs provide the reason for the first-line status of this treatment modality. Increasing safety data and consistent results of prospective pilot trials have proved photodynamic therapy to be inferior. There are signs that PRN-based treatment algorithms may allow for less frequent dosing than in other retinal diseases.

PMID: 21913145 [PubMed - in process]

**Mol Med Report. 2011 Sep 9. doi: 10.3892/mmr.2011.582. [Epub ahead of print]**

**EGCG protects against UVB-induced apoptosis via oxidative stress and the JNK1/c-Jun pathway in ARPE19 cells.**

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Abstract

Ultraviolet B (UVB) radiation is part of the spectrum of light produced by the sun. This form of radiation has been implicated as one of the potential etiological factors causing age-related macular degeneration (AMD). Oxidative injury to the retinal pigment epithelium (RPE) has also been thought to play a key role in AMD. The aim of the present study was to determine the mechanism by which UVB causes damage to the RPE cells, whether it occurs through oxidative stress and the mitogen-activated protein kinase (MAPK) pathway and whether the green tea extract, (-)-epigallocatechin gallate (EGCG), has a protective role. Cell viability assays were used to determine the viability of the cells under different conditions. Cell death caused by apoptosis was determined using fluorescein isothiocyanate conjugated-annexin V/PI labeling, followed by flow cytometry. Intracellular reactive oxygen species (ROS) levels were measured by flow cytometry. Western blot analysis was used to detect UVB-induced MAPK signaling pathways. The findings showed that UVB induced apoptosis, which increased intracellular ROS in ARPE19 cells. Inhibition of c-Jun NH2-terminal kinase (JNK) with a specific inhibitor augmented this apoptosis, and anisomycin (an activator of JNK) attenuated this apoptosis. In addition, UVB decreased the phosphorylation of JNK1 and c-Jun. Finally, EGCG reduced the ROS generation and apoptosis, and also partially blocked the decreased phosphorylation of JNK1 and c-Jun by UVB irradiation. The findings show that UVB irradiation is able to induce apoptosis in ARPE19 cells through oxidative stress, but EGCG treatment attenuates this damage. In this situation, the JNK pathway plays an anti-apoptotic role. The use of selective activators or antioxidants may be useful in reducing the oxidative damage occurring in AMD.

PMID: 21909619 [PubMed - as supplied by publisher]

**World J Biol Chem. 2011 Aug 26;2(8):184-92.**

**Methionine sulfoxide reductase A: Structure, function and role in ocular pathology.**

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Abstract

Methionine is a highly susceptible amino acid that can be oxidized to S and R diastereomeric forms of methionine sulfoxide by many of the reactive oxygen species generated in biological systems. Methionine sulfoxide reductases (Msrs) are thioredoxin-linked enzymes involved in the enzymatic conversion of methionine sulfoxide to methionine. Although MsrA and MsrB have the same function of methionine reduction, they differ in substrate specificity, active site composition, subcellular localization, and evolution. MsrA has been localized in different ocular regions and is abundantly expressed in the retina and in retinal pigment epithelial (RPE) cells. MsrA protects cells from oxidative stress. Overexpression of MsrA increases resistance to cell death, while silencing or knocking down MsrA decreases cell survival; events that are mediated by mitochondria. MsrA participates in protein-protein interaction with several other cellular proteins. The interaction of MsrA with α-crystallins is of utmost importance given the known functions of the latter in protein folding, neuroprotection, and cell survival. Oxidation of methionine residues in α-crystallins results in loss of chaperone function and possibly its antiapoptotic properties. Recent work from our laboratory has shown that MsrA is co-localized with αA and αB crystallins in the retinal samples of patients with age-related macular degeneration. We have also found that chemically induced hypoxia regulates the expression of MsrA and MsrB2 in human RPE cells. Thus, MsrA is a critical enzyme that participates in cell and tissue protection, and its interaction with other proteins/growth factors may provide a target for therapeutic strategies to prevent degenerative diseases.

PMID: 21909460 [PubMed - in process] PMCID: PMC3163237

**PLoS One. 2011;6(8):e23789. Epub 2011 Aug 31.**

**Amyloid triggers extensive cerebral angiogenesis causing blood brain barrier permeability and hypervascularity in Alzheimer's disease.**

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Abstract

Evidence of reduced blood-brain barrier (BBB) integrity preceding other Alzheimer's disease (AD) pathology provides a strong link between cerebrovascular angiopathy and AD. However, the "Vascular hypothesis", holds that BBB leakiness in AD is likely due to hypoxia and neuroinflammation leading to vascular deterioration and apoptosis. We propose an alternative hypothesis: amyloidogenesis promotes extensive neoangiogenesis leading to increased vascular permeability and subsequent hypervascularization in AD. Cerebrovascular integrity was characterized in Tg2576 AD model mice that overexpress the human amyloid precursor protein (APP) containing the double missense mutations, APPsw, found in a Swedish family, that causes early-onset AD. The expression of tight junction (TJ) proteins, occludin and ZO-1, were examined in conjunction with markers of apoptosis and angiogenesis. In aged Tg2576 AD mice, a significant increase in the incidence of disrupted TJs, compared to age matched wild-type littermates and young mice of both genotypes, was directly linked to an increased microvascular density but not apoptosis, which strongly supports amyloidogenic triggered hypervascularity as the basis for BBB disruption. Hypervascularity in human patients was corroborated in a comparison of postmortem brain tissues from AD and controls. Our results demonstrate that amylodogenesis mediates BBB disruption and leakiness through promoting neoangiogenesis and hypervascularity, resulting in the redistribution of TJs that maintain the barrier and thus, provides a new paradigm for integrating vascular remodeling with the pathophysiology observed in AD. Thus the extensive angiogenesis identified in AD brain, exhibits parallels to the neovascularity evident in the pathophysiology of other diseases such as age-related macular degeneration.

PMID: 21909359 [PubMed - in process] PMCID: PMC3166122

# Genetics

**Am J Ophthalmol. 2011 Sep 8. [Epub ahead of print]**

**Evaluation of New and Established Age-Related Macular Degeneration Susceptibility Genes in the Women's Health Initiative Sight Exam (WHI-SE) Study.**

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PURPOSE: To assess whether established and newly reported genetic variants, independent of known lifestyle factors, are associated with the risk of age-related macular degeneration (AMD) among women participating in the Women's Health Initiative Sight Exam (WHI-SE) Genetic Ancillary Study.

DESIGN: Multicenter case-control study.

METHODS: One hundred and forty-six women with intermediate and late stages of AMD and 1269 subjects without AMD underwent ocular examinations and fundus photography to determine stage of AMD. Fourteen polymorphisms at or near 11 genes, including previously confirmed genes CFH, ARMS2/HTRA1, C2, C3, and CFI; recently reported AMD genes in the high-density lipoprotein cholesterol (HDL) pathway LIPC, ABCA1, CETP, and LPL; TIMP3/SYN3, a known ocular gene recently linked with AMD; and APOE, were assessed using logistic regression analysis.

RESULTS: After adjustment for demographic, behavioral, and other genetic factors, a protective effect was detected among TT carriers compared with non-carriers for the HDL pathway gene, LIPC rs493258, for intermediate and late AMD (OR [95% confidence interval]: 0.3 [0.2-0.7], P = .003). Variants in CFH rs1410996, ARMS2/HTRA1 A69S, and C3 R102G were significantly associated with an increased risk of AMD. Individuals with the homozygous CFI rs10033900 TT genotype had a 2.9 [1.2-7.2]-fold increased risk, and those with the CFH Y402H GG genotype had a 2.2 [1.0-4.8]-fold higher risk of developing AMD compared with non-carriers. APOE4 carriers may have a reduced risk of intermediate/late AMD (OR = 0.5 [0.3-0.9], P = .015. Suggestive associations were seen between AMD and the HDL pathway genes CETP and LPL.

CONCLUSION: In this unique national cohort of women, we found associations with established AMD-related genetic factors and the recently reported LIPC gene in the HDL pathway. These findings may help develop novel therapeutic targets to treat or delay the onset of the disease.

PMID: 21906714 [PubMed - as supplied by publisher]

**Mol Diagn Ther. 2011 Aug 1;15(4):195-210. doi: 10.2165/11592270-000000000-00000.**

**Genetic Predictors of Response to PhotodynamicTherapy.**

Parmeggiani F, Gemmati D, Costagliola C, Semeraro F, Perri P, D'Angelo S, Romano MR, De Nadai K, Sebastiani A, Incorvaia C.

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Abstract

In Western countries, therapeutic management of patients affected by choroidal neovascularization (CNV) secondary to different typologies of macular degeneration represents a major health care problem. Age-related macular degeneration is the disease most frequently associated with CNV development. Schematically, CNVs can be distinguished into classic and occult subtypes, which are characterized by variable natural history and different responsiveness to some therapeutic procedures. At present, the dramatic vision loss due to CNV can be mainly treated by two interventional strategies, which are utilizable

in either single or combined modalities: photodynamic therapy with verteporfin (PDT-V), and intravitreal administration of drugs acting against vascular endothelial growth factor. The combined use of PDT-V and anti-angiogenic drugs represents one of the most promising strategies against neovascular macular degeneration, but it unavoidably results in an expensive increase in health resource utilization. However, the positive data from several studies serve as a basis for reconsidering the role of PDT-V, which has undergone a renaissance prompted by the need for a more rational therapeutic approach toward CNV. New pharmacogenetic knowledge of PDT-V points to exploratory prospects to optimize the clinical application of this intriguing photothrombotic procedure. In fact, a Medline search provides data regarding the role of several single nucleotide polymorphisms (SNPs) as genetic predictors of CNV responsiveness to PDT-V. Specifically, correlations between SNPs and different levels of PDT-V efficacy have been detected by examining the gene variants influencing (i) thrombo-coagulative pathways, i.e. methylenetetrahydrofolate reductase (MTHFR) 677C>T (rs1801133), factor V (F5) 1691G>A (rs6025), prothrombin (F2) 20210G>A (rs1799963), and factor XIII-A (F13A1) 185G>T (rs5985); (ii) complement activation and/or inflammatory processes, i.e. complement factor H (CFH) 1277T>C (rs1061170), high-temperature requirement factor A1 (HTRA1) promoter -512G>A (rs11200638), and two variants of the C-reactive protein (CRP) gene (rs2808635 and rs876538); and (iii) production and bioavailability of vascular endothelial growth factor (VEGFA -2578C>A [rs699947] and rs2146323). This article critically evaluates both the clinical plausibility and the opportunity to utilize the most important SNP-response interactions of PDT-V for an effective upgrade of the current anti-CNV therapeutic scenario. In addition, the pharmacogenetics of a very severe post-PDT-V adverse event, i.e. a decrease in acute vision, is briefly discussed. A comprehensive appraisal of the findings reviewed in this article should be carefully considered to design future trials aimed at verifying (after proper genotypic stratification of the enrolled patients) whether these innovative pharmacogenetic approaches will be able to improve the multifaceted interventional management of neovascular macular degeneration.

PMID: 21913742 [PubMed - in process]

**Mol Immunol. 2011 Sep 13. [Epub ahead of print]**

**c-Jun and c-Fos regulate the complement factor H promoter in murine astrocytes.**

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Abstract

The complement system is a critical component of innate immunity that requires regulation to avoid inappropriate activation. This regulation is provided by many proteins, including complement factor H (CFH), a critical regulator of the alternative pathway of complement activation. Given its regulatory function, mutations in CFH have been implicated in diseases such as age-related macular degeneration and membranoproliferative glomerulonephritis, and central nervous system diseases such as Alzheimer's disease, Parkinson's disease, and a demyelinating murine model, experimental autoimmune encephalomyelitis (EAE). There have been few investigations on the transcriptional regulation of CFH in the brain and CNS. Our studies show that CFH mRNA is present in several CNS cell types. The murine CFH (mCFH) promoter was cloned and examined through truncation constructs and we show that specific regions throughout the promoter contain enhancers and repressors that are positively regulated by inflammatory cytokines in astrocytes. Database mining of these regions indicated transcription factor binding sites conserved between different species, which led to the investigation of specific transcription factor binding interactions in a 241base pair (bp) region at -416bp to -175bp that showed the strongest activity. Through supershift analysis, it was determined that c-Jun and c-Fos interact with the CFH promoter in astrocytes in this region. These results suggest a relationship between cell cycle and complement

regulation, and how these transcription factors and CFH affect disease will be a valuable area of investigation.

PMID: 21920606[PubMed - as supplied by publisher]

**Nat Genet. 2011 Sep 11. doi: 10.1038/ng.938. [Epub ahead of print]**

**Genome-wide association study identifies two susceptibility loci for exudative age-related macular degeneration in the Japanese population.**

Arakawa S, Takahashi A, Ashikawa K, Hosono N, Aoi T, Yasuda M, Oshima Y, Yoshida S, Enaida H, Tsuchihashi T, Mori K, Honda S, Negi A, Arakawa A, Kadonosono K, Kiyohara Y, Kamatani N, Nakamura Y, Ishibashi T, Kubo M.

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Abstract

Age-related macular degeneration (AMD), the leading cause of irreversible blindness in the world, is a complex disease caused by multiple environmental and genetic risk factors. To identify genetic factors that modify the risk of exudative AMD in the Japanese population, we conducted a genome-wide association study and a replication study using a total of 1,536 individuals with exudative AMD and 18,894 controls. In addition to CFH (rs800292, P = 4.23 × 10(-15)) and ARMS2 (rs3750847, P = 8.67 × 10(-29)) loci, we identified two new susceptibility loci for exudative AMD: TNFRSF10A-LOC389641 on chromosome 8p21 (rs13278062, combined P = 1.03 × 10(-12), odds ratio = 0.73) and REST-C4orf14-POLR2B-IGFBP7 on chromosome 4q12 (rs1713985, combined P = 2.34 × 10(-8), odds ratio = 1.30). Fine mapping revealed that rs13278062, which is known to alter TNFRSF10A transcriptional activity, had the most significant association in 8p21 region. Our results provide new insights into the pathophysiology of exudative AMD.

PMID: 21909106 [PubMed - as supplied by publisher]