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Drug treatment

BMC Ophthalmol. 2016 Mar 24;16(1):31.

The role of sub-retinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration - a phase IV randomised clinical trial with ranibizumab: the FLUID study.

Arnold JJ, Markey CM, Kurstjens NP, Guymer RH.

BACKGROUND: With increasing experience using anti-VEGF therapy for the treatment of neovascular age -related macular degeneration (nAMD), ophthalmologists have shifted away from a "one size fits all" to an "individualised" approach based on disease activity with the aim of achieving a fluid-free retina. The FLUID study investigates the non-inferiority of a Treat and Extend (T&E) protocol of 0.5 mg ranibizumab, which allows treatment extension in the presence of incomplete resolution of sub-retinal fluid (SRF) ≤200 μm at the foveal centre relative to a T&E protocol that requires complete resolution of all retinal fluid (i.e., both SRF and intra-retinal fluid [IRF]) in patients with nAMD.

METHODS/DESIGN: This 24 month, randomised, phase IV trial has completed recruitment of treatment-naïve patients randomised 1:1 to ranibizumab "intensive" treatment (complete resolution of IRF and SRF) or ranibizumab "relaxed" treatment (resolution of IRF or >200 μm SRF only at foveal centre). Patients in both arms follow a T&E regimen where extension decisions are based upon assessment of lesion activity: loss of ≥5 letters of visual acuity, new haemorrhage, presence of IRF and SRF on an optical coherence tomography (OCT) scan. The determination of SRF is conducted at a reading centre while the assessment of IRF is physician-determined. The primary endpoint is the mean change in best-corrected visual acuity (BCVA) from baseline to 24 months. Secondary endpoints include the mean change in central retinal thickness (CRT) from baseline to 12 and 24 months, the number of ranibizumab injections administered at 12 and 24 months, and the pharmacogenomic assessment of AMD Gene Consortium-identified single-nucleotide polymorphisms (SNPs) and their association with treatment response. Three hundred and forty seven (347) patients have been recruited by 16 Australian sites within approximately 16 months. A protocol to adjudicate on SRF has been established by the central reading centre and is demonstrating good concordance with investigator assessment.

DISCUSSION: This study will provide important insights into retreatment criteria for managing nAMD using a T&E regimen. The current paper describes the clinical rationale for using a less intensive treatment approach using ranibizumab and details of the treatment protocol.

TRIAL REGISTRATION NUMBER: NCT01972789 . Date of registration: 24th October 2013.

PMID: 27009515 [PubMed - in process] PMCID: PMC4806513

Acta Ophthalmol. 2016 Mar 24. [Epub ahead of print]

Treat and Extend versus Pro Re Nata regimens of ranibizumab in neovascular age-related macular degeneration: a comparative 12 Month study.

Hatz K, Prünte C.

PURPOSE: To compare outcomes in patients with treatment-naïve neovascular age-related macular degeneration (nAMD) receiving ranibizumab treat and extend (TE) with those receiving ranibizumab pro re nata (PRN) in a clinical setting.

METHODS: During this 12-month retrospective, consecutive, comparative case series, patients received ranibizumab 0.5 mg according to a TE or PRN regimen. Monthly optical coherence tomography (OCT) evaluation was performed during the PRN regimen; retreatment criteria included recurrence of intra-/subretinal fluid, or haemorrhages. During the TE regimen, initial treatment with 4-week intervals was sequentially lengthened by 2 weeks until signs of choroidal neovascularization (CNV) activity recurred. Study end-points included mean change in best corrected visual acuity (BCVA) and central retinal thickness (CRT), mean injection frequency and number of follow-up visits attended.

RESULTS: Baseline characteristics were similar between the TE (n = 70) and PRN (n = 70) groups. Mean change in BCVA from baseline to Month 12 was significantly greater in the TE group than the PRN group (+0.18 ± 0.17 versus +0.07 ± 0.20, p < 0.001). Mean change in CRT from baseline to Month 12 was greater in the TE group than the PRN group (-116 ± 132 versus -58 ± 157 μm, p = 0.019). The number of follow-up visits attended was significantly higher in the PRN group than the TE group (11.9 ± 1.1 versus 8.6 ± 1.9, p < 0.001), while patients in the TE group received more injections during the study than those in the PRN group (8.6 ± 1.9 versus 6.0 ± 1.9, p < 0.001).

CONCLUSION: Ranibizumab administered using a TE regimen in treatment-naïve patients with nAMD provided better visual outcomes with fewer clinic visits, compared with a PRN regimen.

PMID: 27009503 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Mar 24. [Epub ahead of print]

Patterns of Early and Delayed Visual Response to Ranibizumab Treatment for Neovascular Age-Related Macular Degeneration.

Stoller GL, Kokame GT, Dreyer RF, Shapiro H, Tuomi LL.

IMPORTANCE: Understanding the range of temporal responses to ranibizumab is critical for the assessment of individualized treatment regimens for neovascular age-related macular degeneration.

OBJECTIVE: To examine patterns of visual and anatomical response to ranibizumab treatment.

DESIGN, SETTING, AND PARTICIPANTS: This study is a retrospective subanalysis of HARBOR (a phase 3, double-masked, multicenter, randomized, active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg ranibizumab administered monthly or on an as-needed basis (PRN) in patients with subfoveal neovascular age-related macular degeneration). A total of 1097 patients with neovascular age-related macular degeneration were randomized to intravitreal ranibizumab, 0.5 or 2.0 mg, administered monthly or as needed (PRN) with monthly monitoring. Of the 1097 patients, 1057 were included in the analysis for early responders (best-corrected visual acuity [BCVA] obtained at baseline and month 3), and 988 patients were included in the analysis for delayed responders (BCVA obtained at baseline, month 3, and month 12). The HARBOR study began July 7, 2009, with the primary 12-month end point completed on August 5, 2011, ongoing to 24 months. Data analysis for the subgroup was performed from January 4, 2013, through December 17, 2015.

INTERVENTIONS: Patients were categorized based on BCVA outcomes as early 15-letter responders (gained ≥15 letters from baseline at month 3) or delayed 15-letter responders (did not gain ≥15 letters from

baseline at month 3 but did so at month 12).

MAIN OUTCOMES AND MEASURES: Changes from baseline in BCVA and central foveal thickness (CFT).

RESULTS: In total, 266 early and 135 delayed 15-letter responders were identified. In the 0.5-mg monthly, 0.5-mg PRN, 2.0-mg monthly, and 2.0-mg PRN treatment groups, 63 (24.0%) of 263, 65 (24.6%) of 264, 68 (25.7%) of 265, and 70 (26.4%) of 265 patients were early responders, respectively, and 40 (16.3%) of 246, 31 (12.6%) of 247, 35 (14.1%) of 248, and 29 (11.7%) of 247 patients were delayed responders, respectively. By month 12, early vs delayed responders in the PRN treatment groups received 7.5 vs 7.4 ranibizumab injections, respectively (P = .84). More than 80% of early responders receiving PRN treatment maintained 15-letter or greater gains at month 24. At baseline, early vs delayed responders had worse BCVA (49.8 vs 55.4 letters; P < .001) and greater CFT (374.9 vs 339.0 µm; P = .02), although anatomical results were comparable by month 3 (CFT, 187.7 vs 188.9 µm).

CONCLUSIONS AND RELEVANCE: Improvement of 15 letters or more from baseline occurred in 266 (25.2%) of 1057 patients within 3 months of beginning ranibizumab treatment, whereas an additional 135 (13.7%) of 988 patients achieved this gain by 12 months. The 2 cohorts had similar anatomical temporal response patterns. PRN treatment with monthly monitoring was effective in maintaining early vision gains and allowing delayed vision gains. These results suggest that vision improvement can continue in some patients after macular edema resolves and CFT decreases stabilize.

PMID: 27010625 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2016 Mar;232(3):266-70. Epub 2016 Mar 24.

[About the Effects of VEGF-A Antagonists on Molecular and Cellular Level]. [Article in German]

Strauß O.

Abstract: Anti-VEGF-A therapy is successfully established as a routine therapy to treat wet age-related macular degeneration. Indications have been extended to other retinal diseases. Three different substances have been demonstrated to be active. However, the efficacy of these substances is highly variable in heterogeneous groups of patients and may include non-responders and relapses, so that there may be very individual treatment effects. It is speculated that differences in the molecular properties or structures of the three substances might explain these observations. This article therefore summarises the recent publications on this topic and discusses their relevance. Apart from common features such as VEGF -A affinity, the substances exhibit differences, including the stability of the VEGF-A/molecule complexes and the ability to neutralise angiogenic molecules other than only VEGF-A. At the cellular level, a variety of different methods have been used and the results are often inconsistent. It is therefore not yet possible to predict the clinical properties of VEGF-A neutralising substances on the basis of their known molecular properties or cellular effects.

PMID: 27011031 [PubMed - in process]

Open Ophthalmol J. 2016 Feb 4;10:1-4. eCollection 2016.

Morphologic Changes in Patient with Drusen and Drusenoid Pigment Epithelial Detachment after Intravitreal Ranibizumab for Choroidal Neovascular Membrane : A Case Report.

Kim S, Oh J, Kim K.

Abstract: The authors present a case of morphologic changes of drusen and drusenoid pigment epithelial detachment (DPED) after treating choroidal neovascularization (CNV) using ranibizumab in age-related macular degeneration (AMD). A 71-year-old woman has noticed mild visual acuity deterioration in the right eye for several months. She was presented with some drusen and DPED associated with CNV. This patient was given intravitreal injection of 0.5 mg of ranibizumab five times at monthly intervals for treating CNV.

DPED in the temporal and drusen in the superior to macula were diminished, which continued up to 2 months. Intravitreal ranibizumab injection may have influenced with diminishment of drusen and DPED. After 2 months, CNV was recurred.

PMID: 27014379 [PubMed] PMCID: PMC4780511

Oman J Ophthalmol. 2016 Jan-Apr;9(1):44-8.

The effect of intravitreal bevacizumab and ranibizumab on macular edema of the contralateral eye: A comparative study of two anti-VEGFs.

Bakbak B, Ozturk BT, Gonul S, Gedik S.

PURPOSE: To compare the effects of bevacizumab and ranibizumab on the visual function and macular thickness in the contralateral (untreated) eye of patients with bilateral diabetic macular edema (DME).

MATERIALS AND METHODS: Thirty-nine patients with bilateral DME, who had been treated with both bevacizumab and ranibizumab in the same eye, were considered retrospectively for this study. Recorded outcome measurements included the best-corrected visual acuity (BCVA) assessment with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and the central subfield macular thickness (CSMT) measurement of the contralateral, uninjected eye before and at 4 weeks after the injections.

RESULTS: The median BCVA of the uninjected eye was 50 ETDRS letters and the median CSMT was 459 μm preceding the bevacizumab injection whereas at the control appointment, 4 weeks after the injection, the median BCVA had increased to 52 letters (P = 0.098), and the median CSMT had decreased to 390 μm (P = 0.036). The mean interval between the bevacizumab and ranibizumab treatments was 4.79 □ 1.52 months. The measurements of the untreated eye after the ranibizumab treatment showed that the median BCVA decreased from 55 to 52 letters, and the median CSMT increased from 361 μm to 418 μm (P = 0.148 and P = 0.109, respectively).

CONCLUSIONS: In contrast to ranibizumab, the intravitreal administration of bevacizumab resulted in a statistically significant decrease in macular thickness in the untreated eye in patients with bilateral DME.

PMID: 27013828 [PubMed] PMCID: PMC4785708

JAMA Ophthalmol. 2016 Mar 24. [Epub ahead of print]

Managing Neovascular Age-Related Macular Degeneration: Is More Research Needed to Improve Real-world Practice?

Virgili G, Parravano M, Schmucker C.

PMID: 27010383 [PubMed - as supplied by publisher]

Ophthalmologica. 2016 Mar 23. [Epub ahead of print]

Intravitreal Ranibizumab and Aqueous Humor Factors/Cytokines in Major and Macular Branch Retinal Vein Occlusion.

Noma H, Mimura T, Yasuda K, Nakagawa H, Motohashi R, Kotake O, Shimura M.

Abstract: Aqueous humor levels of cytokines and growth/inflammatory factors were measured in 38 patients with macular edema who had major branch retinal vein occlusion (BRVO) or macular BRVO and were treated with intravitreal ranibizumab injection (IRI). Patients with recurrence of macular edema received further IRI as needed. Aqueous humor levels of vascular endothelial growth factor (VEGF), soluble VEGF

receptor-1 (sVEGFR-1), and other cytokines/factors were measured. Compared with major BRVO, macular BRVO was associated with lower aqueous humor levels of sVEGFR-1, its ligands (VEGF and placental growth factor), and other growth/inflammatory factors (platelet-derived growth factor-AA, monocyte chemotactic protein-1, soluble intercellular adhesion molecule-1, interleukin-6, and interleukin-8). The mean number of IRI over 6 months was significantly lower in the macular BRVO group than in the major BRVO group. These findings suggest that macular BRVO requires fewer IRI than major BRVO and is associated with lower aqueous humor levels of various growth/inflammatory factors and cytokines.

PMID: 27003517 [PubMed - as supplied by publisher]

Doc Ophthalmol. 2016 Apr;132(2):111-22. Epub 2016 Mar 21.

The macular function and structure in patients with diabetic macular edema before and after ranibizumab treatment.

Nowacka B, Kirkiewicz M, Mozolewska-Piotrowska K, Lubiński W.

PURPOSE: To evaluate macular function and structure in patients with diabetic macular edema prior to, as well as 3 and 6 months after intravitreal ranibizumab treatment.

PATIENTS AND METHODS: Seventeen eyes of 17 patients with type 2 diabetes mellitus and diabetic macular edema (DME) were treated with intravitreal injections of 0.5 mg ranibizumab. Prior to the first injection, as well as after 3 and 6 months, the following examinations were performed: assessment of distance best-corrected visual acuity (log MAR), perception of metamorphopsia (M-Chart), slit lamp examination of the anterior and posterior segment of the eye (Volk 90D lens), evaluation of the retinal and choroidal circulation (fluorescein angiography), assessment of the structure and thickness of the macula (OCT), as well as evaluation of the macular function (PERG and mfERG).

RESULTS: We observed that ranibizumab significantly improved visual acuity after 3 and 6 months from the beginning of the treatment, which was a consequence of reduced macular edema and vascular leakage. There was a statistically significant decrease in metamorphopsia frequency at month 3; however, at month 6 it was a statistically insignificant when compared to the baseline. The results of electrophysiological examinations revealed no improvement in ranibizumab-treated patients.

CONCLUSION: Improvement of visual acuity and reduction in macular thickness were maintained up to the 6-month follow-up. The results of electrophysiological examinations revealed that ranibizumab injections tend to stabilize bioelectrical macular function of the outer, middle and inner retinal layers, which was impossible to recognize on the basis of visual acuity and OCT. Therefore, the electrophysiological examinations should be used as an additional objective tool for the evaluation of the anti-VEGF treatment effectiveness in DME.

PMID: 27000269 [PubMed - in process]

Other treatment & diagnosis

Screening for Impaired Visual Acuity in Older Adults: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation [Internet].

Editors - Chou R, Dana T, Bougatsos C, Grusing S, Blazina I.

Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Mar. Report No.: 14-05209-EF-1.

U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.

BACKGROUND: Impaired visual acuity is common in older adults. In 2009, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to assess the balance of benefits and harms of screening

for visual acuity in older adults (I statement).

PURPOSE: This review updates the prior USPSTF review and will be used by the USPSTF to update its 2009 recommendation. It focuses on screening for impaired visual acuity and treatment of the following conditions: uncorrected refractive errors, cataracts, and age-related macular degeneration (AMD).

DATA SOURCES: We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and MEDLINE (2008 to January 2016) and manually reviewed reference lists.

STUDY SELECTION: At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on screening versus no screening, delayed screening, or usual care; the diagnostic accuracy of screening tests in primary care settings; and treatment versus sham therapy, placebo, or no treatment for uncorrected refractive errors, cataracts, and AMD.

DATA EXTRACTION: We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. Two investigators independently applied criteria developed by the USPSTF to rate the quality of each study as good, fair, or poor using a consensus process.

DATA SYNTHESIS (RESULTS): Three cluster-randomized trials (all previously included in the 2009 USPSTF review) found no difference between vision screening versus no vision screening, usual care, or delayed screening on vision and other clinical outcomes. New evidence on the effectiveness of treatments versus placebo, sham, or no treatment was limited and did not change prior conclusions that effective treatments are available for uncorrected refractive error, cataracts, and AMD. New evidence on the diagnostic accuracy of screening tests for impaired visual acuity was also limited and did not change conclusions that screening questions or a questionnaire are inaccurate compared to a visual acuity test (e.g., the Snellen eye chart) or that a visual acuity test has suboptimal accuracy compared to a comprehensive ophthalmological examination; however, the clinical relevance of visual conditions identified on a comprehensive ophthalmological examination but not associated with impaired visual acuity is uncertain.

LIMITATIONS: We included previously published systematic reviews, only included English-language studies, and could not assess for publication bias due to small numbers of studies.

CONCLUSIONS: Impaired visual acuity is common in older adults, effective treatments are available for common causes of impaired visual acuity, and vision impairment can be identified noninvasively using the Snellen or other visual acuity chart. However, direct evidence found that vision screening in older adults in primary care settings is not effective for improving visual acuity or other clinical outcomes.

PMID: 27010054 [PubMed] Free Books & Documents

Sci Rep. 2016 Mar 24;6:23268.

Cortical thickness in human V1 associated with central vision loss.

Burge WK, Griffis JC, Nenert R, Elkhetali A, DeCarlo DK, Ver Hoef LW, Ross LA, Visscher KM.

Abstract: Better understanding of the extent and scope of visual cortex plasticity following central vision loss is essential both for clarifying the mechanisms of brain plasticity and for future development of interventions to retain or restore visual function. This study investigated structural differences in primary visual cortex between normally-sighted controls and participants with central vision loss due to macular degeneration (MD). Ten participants with MD and ten age-, gender-, and education-matched controls with normal vision were included. The thickness of primary visual cortex was assessed using T1-weighted anatomical scans, and central and peripheral cortical regions were carefully compared between well-characterized participants with MD and controls. Results suggest that, compared to controls, participants with MD had significantly thinner cortex in typically centrally-responsive primary visual cortex - the region of cortex that normally

receives visual input from the damaged area of the retina. Conversely, peripherally-responsive primary visual cortex demonstrated significantly increased cortical thickness relative to controls. These results suggest that central vision loss may give rise to cortical thinning, while in the same group of people, compensatory recruitment of spared peripheral vision may give rise to cortical thickening. This work furthers our understanding of neural plasticity in the context of adult vision loss.

PMID: 27009536 [PubMed - in process] PMCID: PMC4806312

Acta Ophthalmol. 2016 Mar 24. [Epub ahead of print]

Drusen maculopathy: a risk factor for visual deterioration.

Algvere PV, Kvanta A, Seregard S.

Abstract: Age-related macular degeneration (AMD), the most common cause of visual loss after the age of 65, displays a degeneration of the retinal pigment epithelial (RPE) cells and photoreceptors in the retinal centre (macula). The central macula (fovea) that contains mostly cone photoreceptors mediates the high visual acuity. Drusen maculopathy may lead to visual deterioration. Drusen are extracellular deposits of debris that accumulate on Bruch's membrane. Drusen attract inflammatory, immunological and vasoactive stimuli. RPE and photoreceptor cells overlying drusen exhibit biochemical and morphological signs of degeneration. Strong and intermittent light exposure (photons) induces the formation of free radicals in the very high oxygen tension milieu of the retina. The negative effects of irradiation stimulate accumulation of lipofuscin in RPE and photoreceptor cells leading to mitochondrial dysfunction and apoptotic cell death. A hydrophobic barrier is built up in Bruch's membrane reducing diffusion to the choroid. Hereditary and inflammatory factors modify the risk for AMD. There is a genetic dysregulation of the complement system leading to inappropriate complement activation. The genetic polymorphism of complement factor H (CFH) and age-related maculopathy susceptibilty 2 (ARMS2) increase the risk of progression to advanced AMD. The photoelectric effect creates free radicals, resulting in a continuous increase of lipofuscin formation and impairing mitochondrial activity. In addition, inflammation and complement dysregulation contribute to the formation of drusen and vasoproliferative reactions with neovascularization. Antioxidants neutralize reactive oxygen species and reduce lipofuscin accumulation in RPE and photoreceptor cells. For prophylactic treatment of drusen maculopathy, high doses of antioxidants such as vitamins C and E, lutein, zeaxanthine and zinc are used according to the Age-Related Eye Disease Study 2 (AREDS 2). The risk of developing advanced AMD was reduced by 27% at 10 years follow-up. No adverse events were noted.

PMID: 27009526 [PubMed - as supplied by publisher]

N Am J Med Sci. 2016 Jan;8(1):56-60.

Ocular Adnexal Lymphoma Presenting with Visual Loss.

Gulati S, Corrêa ZM, Karim N, Medlin S.

CONTEXT: Elderly patients with visual loss often have age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract as common causes of visual loss. Other less common etiologies should be considered, especially in those presenting with systemic associations.

CASE REPORT: The patient discussed in our review is an 80-year-old female, with a history of diabetic retinopathy and macular degeneration who presented with a sudden deterioration of vision. While this was initially attributed to diabetic retinopathy, she was eventually noted to have a salmon patch lesion in her conjunctiva, diagnosed on biopsy to be a diffuse large B-cell lymphoma.

CONCLUSION: Because of the significant rate of disseminated disease among patients with lymphomas in the orbit that carries a worse prognosis, early diagnosis is essential to promote better overall survival of these patients. We describe here a patient diagnosed with conjunctival lymphoma associated with pronounced visual loss and review the literature on this subject.

PMID: 27011948 [PubMed] PMCID: PMC4784184

Pathogenesis

Mol Vis. 2016 Feb 27;22:189-202. eCollection 2016.

Regulation of signaling events involved in the pathophysiology of neovascular AMD.

Wang H, Hartnett ME.

Abstract: Neovascular age-related macular degeneration (AMD) is a complex disease in which an individual's genetic predisposition is affected by aging and environmental stresses, which trigger signaling pathways involving inflammation, oxidation, and/or angiogenesis in the RPE cells and choroidal endothelial cells (CECs), to lead to vision loss from choroidal neovascularization. Antiangiogenic therapies have greatly improved clinical outcomes in the last decade; however, vision improves in less than half of patients treated for neovascular AMD, and treatments remain inadequate for atrophic AMD. Many studies focus on genetic predisposition or the association of outcomes in trials of human neovascular AMD but are unable to evaluate the effects between different cell types involved in AMD and the signaling events that take place to cause pathologic biologic events. This manuscript complements other reviews in that it describes what is known generally in human AMD studies and clinical trials testing methods to inhibit vascular endothelial growth factor (VEGF inhibitors) and presents pathologic signaling events that develop in two important cell types, the RPE cells and the CECs, when stimulated by stresses or placed into conditions similar to what is currently understood to occur in neovascular AMD. This manuscript complements other reviews by discussing signaling events that are activated by cell-cell or cell-matrix interactions. These considerations are particularly important when considering growth factors, such as VEGF, which are important in physiologic and pathologic processes, or GTPases that are present but active only if GTP bound. In either case, it is essential to understand the role of signaling activation to distinguish what is pathologic from what is physiologic. Particularly important is the essential role of activated Rac1 in CEC transmigration of the RPE monolayer, an important step in blindness associated with neovascular AMD. Other concepts discussed include the importance of feed-forward loops that overwhelm mechanisms that seek to restore homeostasis in cells and the importance of regulating, instead of abolishing, signaling events in a chronic, complex disease, such as neovascular AMD. These concepts are important as we move to the next stages in developing treatments for neovascular AMD. A novel therapeutic strategy that will be discussed is activating an isoform of the GTPase, Rap1, which can regulate downstream signaling and a pathologic feed -forward loop leading to Rac1 activation and migration of CECs.

PMID: 27013848 [PubMed - in process] PMCID: PMC4789180

Oncotarget. 2016 Mar 22. [Epub ahead of print]

MicroRNA signatures in vitreous humour and plasma of patients with exudative AMD.

Ménard C, Rezende FA, Miloudi K, Wilson A, Tétreault N, Hardy P, SanGiovanni JP, De Guire V, Sapieha P.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness worldwide affecting individuals over the age of 50. The neovascular form (NV AMD) is characterized by choroidal neovascularization (CNV) and responsible for the majority of central vision impairment. Using non-biased microRNA arrays and individual TaqMan qPCRs, we profiled miRNAs in the vitreous humour and plasma of patients with NV AMD. We identified a disease-associated increase in miR-146a and a decrease in miR-106b and miR-152 in the vitreous humour which was reproducible in plasma. Moreover, miR-146a/miR-106b ratios discriminated patients with NV AMD with an area under the Receiver Operating Characteristic curve (ROC AUC) of 0,977 in vitreous humour and 0,915 in plasma suggesting potential for a blood-based diagnostic. Furthermore, using the AMD Gene Consortium (AGC) we mapped a NV AMD-associated SNP (rs1063320) in a binding site for miR-152-3p in the HLA-G gene. The relationship between our detected miRNAs and NV AMD related genes was also investigated using gene sets derived from the Ingenuity Pathway Analysis (IPA). To our knowledge, our study is the first to correlate vitreal and plasma miRNA signatures with NV AMD, highlighting potential future worth as biomarkers and providing insight on NV

AMD pathogenesis.

PMID: 27015561 [PubMed - as supplied by publisher]

PLoS One. 2016 Mar 25;11(3):e0152522.

Anti-Human VEGF Repebody Effectively Suppresses Choroidal Neovascularization and Vascular Leakage.

Hwang DE, Ryou JH, Oh JR, Han JW, Park TK, Kim HS.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness among people over the age of 60. Vascular endothelial growth factor (VEGF) plays a major role in pathological angiogenesis in AMD. Herein, we present the development of an anti- human VEGF repebody, which is a small-sized protein binder consisting of leucine-rich repeat (LRR) modules. The anti-VEGF repebody selected through a phage-display was shown to have a high affinity and specificity for human VEGF. We demonstrate that this repebody effectively inhibits in vitro angiogenic cellular processes, such as proliferation and migration, by blocking the VEGF-mediated signaling pathway. The repebody was also shown to have a strong suppression effect on choroidal neovascularization (CNV) and vascular leakage in vivo. Our results indicate that the anti-VEGF repebody has a therapeutic potential for treating neovascular AMD as well as other VEGF-involved diseases including diabetic retinopathy and metastatic cancers.

PMID: 27015541 [PubMed - as supplied by publisher]

Curr Eye Res. 2016 Mar 25:1-10. [Epub ahead of print]

Retinal Pigment Epithelial Cell Apoptosis is Influenced by a Combination of Macrophages and Soluble Mediators Present in Age-Related Macular Degeneration.

Devarajan G, Niven J, Forrester JV, Crane IJ.

PURPOSE: Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly population aged ≥60 years. Previous studies have shown that retinal pigment epithelial cell (RPE) degeneration is one of the early and crucial stages in AMD. It has been suggested that microglia and macrophages may be involved in the impairment of RPE, but how they and RPE are influenced by other factors present as AMD develops is unclear. Therefore the purpose of this study was to determine the role of macrophages in RPE degeneration in the presence of cytokines and oxidative stress likely to be present as AMD develops.

METHODS: A co-culture model system was set up using bone marrow-derived macrophages and brain or retinal microglia cultured with RPE. Cytokines (IL-1β, TNF-α, IFN-γ, and IL-6) and oxidized low-density lipoprotein were included in the culture at concentrations estimated to be likely during AMD, and apoptosis of RPE cells determined using flow cytometry to detect annexin V.

RESULTS: Macrophages were shown capable of enhancing the apoptosis of RPE cells in a contact-dependent manner. IL-1β, IFN-γ, IL-6, TNF-α, and oxLDL increased apoptosis; they increased RPE cell apoptosis directly, increased the susceptibility of RPE to subsequent apoptosis in the presence of microglia/macrophages, and increased the ability of microglia/macrophages to cause apoptosis.

CONCLUSIONS: These findings indicate that microglia and macrophages are capable of enhancing the degeneration of RPE, which are crucial in AMD development. However this is dependent on the microenvironment present as AMD develops.

PMID: 27015409 [PubMed - as supplied by publisher]

Curr Mol Med. 2016 Mar 24. [Epub ahead of print]

STAT3 activation in circulating monocytes contributes to neovascular age-related macular degeneration.

Chen M, Lechner J, Zhao J, Toth L, Hogg R, Silvestri G, Kissenpfennig A, Chakravarthy U, Xu H1.

Abstract: Infiltrating macrophages are critically involved in pathogenic angiogenesis such as neovascular age-related macular degeneration (nAMD). Macrophages originate from circulating monocytes and three subtypes of monocyte exist in humans: classical (CD14+CD16-), non-classical (CD14-CD16+) and intermediate (CD14+CD16+) monocytes. The aim of this study was to investigate the role of circulating monocyte in neovascular age-related macular degeneration (nAMD). Flow cytometry analysis showed that the intermediate monocytes from nAMD patients expressed higher levels of CX3CR1 and HLA-DR compared to those from controls. Monocytes from nAMD patients expressed higher levels of phosphorylated Signal Transducer and Activator of Transcription 3 (pSTAT3), and produced higher amount of VEGF. In the mouse model of choroidal neovascularization (CNV), pSTAT3 expression was increased in the retina and RPE/choroid, and 49.24% of infiltrating macrophages express pSTAT3. Genetic deletion of the Suppressor of Cytokine Signalling 3 (SOCS3) in myeloid cells in the LysM-Cre+/-:SOCS3fl/fl mice resulted in spontaneous STAT3 activation and accelerated CNV formation. Inhibition of STAT3 activation using a small peptide LLL12 suppressed laser-induced CNV. Our results suggest that monocytes, in particular the intermediate subset of monocytes are activated in nAMD patients. STAT3 activation in circulating monocytes may contribute to the development of choroidal neovascularisation in AMD.

PMID: 27009107 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2016 Mar 23;11(3):e0152047. eCollection 2016.

Whole Exome Sequencing in Patients with the Cuticular Drusen Subtype of Age-Related Macular Degeneration.

Duvvari MR, van de Ven JP, Geerlings MJ, Saksens NT, Bakker B, Henkes A, Neveling K, Rosario MD, Westra D, van den Heuvel LP, Schick T, Fauser S, Boon CJ, Hoyng CB, Jong EK, Hollander AI.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in elderly people worldwide. Cuticular drusen (CD) is a clinical subtype of AMD, which typically displays an earlier age at onset, and has a strong genetic component. Genetic studies support a role for rare sequence variants in CD susceptibility, and rare sequence variants in the CFH gene have been identified in 8.8% of CD cases. To further explore the role of rare variants in CD, we performed whole exome sequencing (WES) in 14 affected members of six families and 12 sporadic cases with CD. We detected rare sequence variants in CFH and FBLN5, which previously were shown to harbor rare variants in patients with CD. In addition, we detected heterozygous rare sequence variants in several genes encoding components of the extracellular matrix (ECM), including FBLN1, FBLN3/EFEMP1, FBLN5, FBLN6/HMCN1, FBN2, and COL15A1. Two rare pathogenic variants were identified in the COL15A1 gene: one in a sporadic case and another was found to segregate in a family with six affected individuals with CD. In addition, two rare pathogenic variants were identified in the FGL1 gene in three unrelated CD cases. These findings suggest that alterations in the ECM and in the coagulation pathway may play a role in the pathogenesis of CD. The identified candidate genes require further analyses in larger cohorts to confirm their role in the CD subtype of AMD. No evidence was found of rare sequence variants in a single gene that segregate with CD in the six families, suggesting that the disease is genetically heterogeneous.

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Omics in Ophthalmology: Advances in Genomics and Precision Medicine for Leber Congenital Amaurosis and Age-Related Macular Degeneration.

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Abstract: The genomic revolution has had a huge impact on our understanding of the genetic defects and disease mechanisms underlying ophthalmic diseases. Two examples are discussed here. The first is Leber congenital amaurosis (LCA), a severe inherited retinal dystrophy leading to severe vision loss in children, and the second is age-related macular degeneration (AMD), the most common cause of vision loss in the elderly. Twenty years ago, the genetic causes of these diseases were unknown. Currently, more than 20 LCA genes have been identified, and genetic testing can now successfully identify the genetic defects in at least 75% of all LCA cases. Gene-specific treatments have entered the clinical trial phase for three LCA genes, and for seven LCA genes gene-specific therapies have been tested in model systems. Age-related macular degeneration is a multifactorial disease caused by a combination of genetic and environmental factors. Currently, more than 40 loci have been identified for AMD, accounting for 15%-65% of the total genetic contribution to AMD. Despite the progress that has been made so far, genetic testing is not yet recommended for AMD, but this may change if we move to clinical trials or treatments that are dependent on an individual's genotype. The identification of serum or plasma biomarkers using other "-omics" technologies may further improve predictive tests and our understanding of the disease mechanisms of AMD. Ultimately, it is anticipated that predictive tests will help to stratify patients for the most suitable therapy, which will enable the development of precision medicine, tailored to individual needs.

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Diet, lifestyle and low Vision

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Impairment of visual memory for objects in natural scenes by simulated central scotomata.

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Abstract: Because of the close link between foveal vision and the spatial deployment of attention, typically only objects that have been foveated during scene exploration may form detailed and persistent memory representations. In a recent study on patients suffering from age-related macular degeneration, however, we found surprisingly accurate visual long-term memory for objects in scenes. Normal exploration patterns that the patients had learned to rereference saccade targets to an extrafoveal retinal location. This rereferencing may allow use of an extrafoveal location as a focus of attention for efficient object encoding into long-term memory. Here, we tested this hypothesis in normal-sighted observers with gaze-contingent central scotoma simulations. As these observers were inexperienced in scene exploration with central vision loss and had not developed saccadic rereferencing, we expected deficits in long-term memory for objects. We used the same change detection task as in our patient study, probing sensitivity to object changes after a period of free scene exploration. Change detection performance was significantly reduced for two types of scotoma simulation diminishing foveal and parafoveal vision-a visible gray disc and a more subtle image warping-compared with unimpaired controls, confirming our hypothesis. The impact of a smaller scotoma covering specifically foveal vision was less distinct, leading to a marginally significant decrease of long-term memory performance compared with controls. We conclude that attentive encoding of objects is deficient when central vision is lost as long as successful saccadic rereferencing has not yet developed.

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