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MD Research News

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Drug treatment

Eye (Lond). 2014 Oct 3. [Epub ahead of print]

Earlier therapeutic effects associated with high dose (2.0 mg) ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration.

Chan CK, Abraham P, Sarraf D, Nuthi AS, Lin SG, McCannel CA.

Summary statement: Intravitreal high dose (2 mg) ranibizumab may lead to quicker resolution of choroidal neovascularization (CNV) and associated retinal pigment epithelial detachment in eyes with exudative age-related macular degeneration, although it may possibly correlate with RPE tears in certain cases.

Purpose: This prospective study compared the outcomes of 0.5 vs 2.0 mg intravitreal ranibizumab injections (RI) for treating vascularized pigment epithelial detachment (vPED) due to age-related macular degeneration.

Methods: Patients with vPED were randomized to receive 2.0 vs 0.5 mg RI monthly for 12 months or for 4 months and then repeated on a pro-re nata basis. Optical coherence tomography, fundus photography, and fluorescein and indocyanine-green angiography were obtained at baseline and subsequent specific intervals. Outcome measures were best-corrected standardized visual acuities, central 1-mm thickness, surface area (SA), greatest linear diameter (GLD), heights (PED and CNV), and amount of subretinal fluid (SRF) and cystoid macular edema (CME).

Results: Both groups yielded reductions of the central 1-mm thickness, PED and CNV SA and PED height and GLD, SRF, and CME. Vision improvement and reduction in SRF and PED height occurred earlier for eyes receiving the 2.0 mg dose. Cataract progression was similar but RPE tears developed more often with the 2.0 mg dose.

Conclusions: There were similar visual and anatomical outcomes at the end of the study; however, the higher dose yielded more rapid reductions and more complete resolution of the PED, although there was possible increased tendency for an RPE tear with the higher dose.

PMID: 25277305 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2014 Oct;28(5):386-92. doi: 10.3341/kjo.2014.28.5.386. Epub 2014 Sep 18.

Predictive Findings of Visual Outcome in Spectral Domain Optical Coherence Tomography after Ranibizumab Treatment in Age-related Macular Degeneration.

Kwon YH, Lee DK, Kim HE, Kwon OW.

PURPOSE: To investigate which spectral domain optical coherence tomography (SD-OCT) findings predict visual outcome after anti-vascular endothelial growth factor (VEGF) treatment in neovascular age-related macular degeneration (NV-AMD).

METHODS: We reviewed the medical records of patients with treatment-naïve NV-AMD who underwent three or more consecutive anti-VEGF injections. The patients were divided into three groups according to their changes of visual acuity (VA); improved (group I), static (group S), or worsened (group W). We assessed the incidences and values of all available SD-OCT findings of these groups, compared these findings between the three groups and compared the initial values with the post-treatment values.

RESULTS: Better initial VA and longer external limiting membrane (ELM) length were associated with less change in VA after anti-VEGF treatment. The initial VA was mildly correlated with initial photoreceptor inner and outer segment junction (IS/OS) length and initial ELM length. The final VA was also mildly correlated with the final IS/OS length and the final ELM length. VA was significantly changed after anti-VEGF treatment in groups W and I. With regard to incidence, disruption of the IS/OS (IS/OS-D), disruption of the ELM (ELM-D) and ELM length differed significantly between the three groups, particularly ELM-D. The incidences of IS/OS-D and ELM-D in group I were significantly lower than those in groups S and W, and those in group S were also lower than those in group W. The ELM length in group I was significantly longer than it was in groups S and W, and the ELM length in group S was longer than that for group W. However, these three findings did not change after the anti-VEGF treatment.

CONCLUSIONS: Initial IS/OS-D, ELM length and particularly ELM-D can be useful predictors of the visual outcome after anti-VEGF treatment in NV-AMD patients.

PMID: 25276080 [PubMed - in process] PMCID: PMC4179115

Cold Spring Harb Perspect Med. 2014 Oct 3. [Epub ahead of print]

Clinical Characteristics and Current Treatment of Age-Related Macular Degeneration.

Yonekawa Y, Kim IK.

Abstract: Age-related macular degeneration (AMD) is a multifactorial degeneration of photoreceptors and retinal pigment epithelium. The societal impact is significant, with more than 2 million individuals in the United States alone affected by advanced stages of AMD. Recent progress in our understanding of this complex disease and parallel developments in therapeutics and imaging have translated into new management paradigms in recent years. However, there are many unanswered questions, and diagnostic and prognostic precision and treatment outcomes can still be improved. In this article, we discuss the clinical features of AMD, provide correlations with modern imaging and histopathology, and present an overview of treatment strategies.

PMID: 25280900 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Sep 30. [Epub ahead of print]

Refractory subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome.

Jang L, Gianniou C, Ambresin A, Mantel I.

PURPOSE: To investigate the functional outcome of eyes with neovascular AMD (nAMD) and subretinal fluid (SRF) refractory to treatment with ranibizumab.

METHODS: Retrospective chart review of consecutive treatment-refractory SRF in nAMD despite monthly ranibizumab injections during 12 months or more. Data were evaluated for baseline characteristics, location of the refractory SRF, mean visual acuity (VA) change, number of injections, and timepoint of first complete disappearance of SRF.

RESULTS: Forty-five eyes in 44 patients (mean age of 76 years) were included. The mean follow-up was 32.4 months (range 12-73 months). The mean number of injections was 11.6 in the first year and 27.5 over follow-up. The refractory SRF was located subfoveally in 66.7 %. In 12 eyes (26.7 %), complete absorption of SRF was found after a mean of 22.6 months (range, 13-41 months). Mean VA increased by 10.4, 8.2, and 8.6 letters by month 12, 24, and 36, respectively.

CONCLUSIONS: Neovascular AMD with SRF refractory to monthly retreatment with ranibizumab may still allow good and maintained visual improvement, even if the fluid is located subfoveally. SRF may progressively absorb under continuous monthly treatment. The necessity to treat refractory SRF with monthly injections could be questioned and would need future investigations.

PMID: 25267418 [PubMed - as supplied by publisher]

Retina. 2014 Sep 30. [Epub ahead of print]

A RANDOMIZED CONTROLLED TRIAL OF PANRETINAL PHOTOCOAGULATION WITH AND WITHOUT INTRAVITREAL RANIBIZUMAB IN TREATMENT-NAIVE EYES WITH NON-HIGH-RISK PROLIFERATIVE DIABETIC RETINOPATHY.

Ferraz DA, Vasquez LM, Preti RC, Motta A, Sophie R, Bittencourt MG, Sepah YJ, Monteiro ML, Nguyen QD, Takahashi WY.

PURPOSE: To compare the efficacy of panretinal photocoagulation (PRP) and intravitreal ranibizumab injection with PRP alone in patients with treatment-naive bilateral non-high-risk proliferative diabetic retinopathy.

METHODS: Sixty eyes of 30 patients were randomized either to the study group (SG) receiving PRP plus 2 ranibizumab injections or to the control group (CG) receiving PRP alone. Mean change in best-corrected visual acuity and in optical coherence tomography were compared at baseline and 1, 3, and 6 months.

RESULTS: Best-corrected visual acuity was significantly better at 6 months in the SG; however, there was decrease in best-corrected visual acuity in the CG. Central macula thickness decreased significantly at 6 months in SG when compared with baseline (-47.6 μm, $P < 0.001$) and did not reveal significant difference in the CG. In eyes with diabetic macular edema, best-corrected visual acuity increased by 3.6 letters ($P = 0.06$) in the SG and decreased by 4.4 letters in the CG ($P = 0.003$). Central macula thickness decreased by 69.3 μm ($P = 0.001$) in the SG and decreased by 45.5 μm ($P = 0.11$) in the CG.

CONCLUSION: Intravitreal ranibizumab in combination with PRP can be an effective treatment in eyes with non-high-risk proliferative diabetic retinopathy and diabetic macular edema.

PMID: 25272318 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Jun 11. [Epub ahead of print]

Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis.

Schmid MK, Bachmann LM, Fäs L, Kessels AG, Job OM, Thiel MA.

TOPIC: To quantify the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and

aflibercept in age-related macular degeneration (AMD).

CLINICAL RELEVANCE: There is an ongoing debate about the optimal treatment of AMD with these three antivascular endothelial growth factor (anti-VEGF) treatments.

METHODS: Network meta-analyses. (Pre)Medline, EMBASE, SCOPUS, Cochrane Library (until April 2013), Science Citation Index and reference lists were searched for placebo-controlled randomised trials or head-to-head comparisons. Outcomes were 1-year follow-up data of visual acuity (letters gained) and serious (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events. Two investigators independently assessed eligibility and quality of included studies and extracted data.

RESULTS: 11 trials (enrolling 8341 patients) assessing five active treatments were included. Compared with placebo, all anti-VEGF treatments had a significantly higher percentage of letters gained: ranibizumab 0.3 mg 2.39% (95% CI 1.59 to 3.19; p<0.001), ranibizumab 0.5 mg 3.56% (95% CI 2.58 to 4.13; p<0.001), bevacizumab 1.25 mg 2.14% (95% CI 0.47 to 3.82; p=0.012), aflibercept 0.5 mg 2.91% (95% CI 0.99 to 4.82; p=0.003) and aflibercept 2 mg 3.44% (95% CI 1.73 to 5.14; p<0.001). Compared with placebo, serious side effects were higher in all other treatments: ranibizumab 0.3 mg 4.41% (95% CI 3.42 to 5.40; p<0.001), ranibizumab 0.5 mg 5.33% (95% CI 4.37 to 6.30; p<0.001), bevacizumab 1.25 mg 5.58% (95% CI 3.567 to 7.60; p<0.001), aflibercept 0.5 mg 5.65% (95% CI (3.28 to 8.02; p<0.001) and aflibercept 2 mg 5.29% (95% CI 3.18 to 7.39; p<0.001). Compared with placebo, systemic thrombotic events also occurred more often in all other treatments.

CONCLUSIONS: The study revealed only a modest superiority of aflibercept 2 mg and ranibizumab 0.5 mg over other formulations and dosages.

PMID: 25271911 [PubMed - as supplied by publisher]

Ophthalmologe. 2014 Oct 4. [Epub ahead of print]

[Treatment of serous macular retinal detachment with antihistamines.] [Article in German]

Kirschfeld K.

Abstract: The etiology of retinal detachment in central serous retinopathy (CSR) is unknown; however, three facts are generally accepted: (1) the serous exudate which raises the layers of the receptors/pigment epithelium is formed due to hyperpermeability in the choriocapillaries, (2) patients frequently suffer from headaches and (3) stress promotes the incidence of CSR. A high blood plasma histamine concentration can cause the abovementioned symptoms which suggests that histamine might provoke CSR. Within 1 week after administration of the antihistamine loratadin a considerable reduction in the retinal exudate and restoration of vision were observed. This supports the hypothesis that histamine could be involved in the process of retinal detachment. Further investigations and large scale clinical trials should clarify if this hypothesis can be proved or disproved and whether antihistamines can be used for age-related macular degeneration (AMD).

PMID: 25278347 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Biomed Res Int. 2014;2014:741538. Epub 2014 Sep 9.

Hyperautofluorescence in outer retinal layers thinning.

Bertolotto M, Borgia L, Iester M.

Purpose: To evaluate if paracentral hyperautofluorescence (HAF) retinal regions, which can be occasionally found and analyzed by optical coherence tomography (OCT), were related to retinal layer changes and to detect which layer was involved.

Methods: This is a cross-sectional and retrospective study. 648 OCT files were revised. OCTs that showed a paracentral HAF area by using the fundus autofluorescence imaging in Heidelberg Spectralis (Heidelberg Engineering, Germany) were selected. Then retinal layer morphology was analyzed observing OCT scans and a retinal thickness was measured.

Results: 31 patients were selected: 20 patients had chronic serous epitheliopathy (CSE), 8 patients had resolved central serous chorioretinopathy (CSC), and 3 patients wet age related macular degeneration (ARMD). The HAF zones corresponded to areas of thickness reduction of the external hyporeflective band. In all these areas the retinal pigment epithelium was not atrophic and the neuroepithelium was more or less dystrophic. In particular the retinal thickness was 264 um, 232 um, and 243 um in wet ARMD, CSE, and CSC, respectively; the reduction was significant ($P < 0.01$) compared to the same area of the other eye.

Discussion: The presence of HAF imaging might be mostly due to a "window effect" rather than an accumulation of lipofuscin.

PMID: 25276816 [PubMed - in process] PMCID: PMC4174970

World J Cardiol. 2014 Sep 26;6(9):968-84. doi: 10.4330/wjc.v6.i9.968.

J Fr Ophtalmol. 2014 Sep 29. [Epub ahead of print]

Choroidal neovascularization associated with extensive macular atrophy with pseudodrusen-like appearance.

Kamami-Levy C, Querques G, Rostaqui O, Blanco-Garavito R, Souied EH.

PURPOSE: Extensive macular atrophy with pseudodrusen-like appearance (EMAP) is a recently described entity. We describe the first observations of choroidal neovascularization (CNV) associated with EMAP in 3 patients.

METHODS: Nineteen consecutive patients with EMAP were retrospectively investigated for the presence of CNV and treatment outcomes. Each patient underwent a complete ophthalmologic examination including color fundus photograpy, fluorescein angiography (FA), indocyanine green angiography (ICG) and spectral-domain optical coherence tomography (SD-OCT).

RESULTS: Retrospective analysis revealed choroidal neovascularization in 3 patients (4 eyes) out of 19 patients with EMAP. In these patients, laser photocoagulation or intravitreal injections of ranibizumab led to resolution of retinal exudation with limited functional improvement.

CONCLUSION: CNV is a possible complication of EMAP, a recently reported form of macular atrophy resembling geographic atrophy. Laser photocoagulation and anti-VEGF treatment appear to be two valuable therapeutic options.

PMID: 25278483 [PubMed - as supplied by publisher]

Stem Cells Transl Med. 2014 Oct 1. [Epub ahead of print]

Engineering Efficient Retinal Pigment Epithelium Differentiation From Human Pluripotent Stem Cells.

Lane A, Philip LR, Ruban L, Fynes K, Smart M, Carr A, Mason C, Coffey P.

Abstract: Human embryonic stem cells (hESCs) are a promising source of retinal pigment epithelium (RPE) cells: cells that can be used for the treatment of common and incurable forms of blindness, such as age-related macular degeneration. Although most hESC lines will produce a number of clusters of pigmented RPE cells within 30-50 days when allowed to spontaneously differentiate, the timing and efficiency of differentiation is highly variable. This could prove problematic in the design of robust processes for the large scale production of RPE cells for cell therapy. In this study we sought to identify, quantify, and reduce the sources of variability in hESC-RPE differentiation. By monitoring the emergence of pigmented cells over time, we show how the cell line, passaging method, passage number, and seeding density have a significant and reproducible effect on the RPE yield. To counter this variability, we describe the production of RPE cells from two cell lines in feeder-free, density controlled conditions using single cell dissociation and seeding that is more amenable to scaled up production. The efficacy of small molecules in directing differentiation toward the RPE lineage was tested in two hESC lines with divergent RPE differentiation capacities. Neural induction by treatment with a bone morphogenetic protein inhibitor, dorsomorphin, significantly enhanced the RPE yield in one cell line but significantly reduce it in another, generating instead a Chx10 positive neural progenitor phenotype. This result underlines the necessity to tailor differentiation protocols to suit the innate properties of different cell lines.

PMID: 25273541 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2014 Sep 30;14(1):114.

Intraoperative and fluorescein angiographic findings of a secondary macular hole associated with age-related macular degeneration treated by pars plana vitrectomy.

Okamoto T, Shinoda H, Kurihara T, Nagai N, Tsubota K, Ozawa Y1.

BACKGROUND: Macular hole results from a tractional force at the vitreo-retinal interface which is developed by modification and subsequent degeneration of the posterior precortical vitreous and the internal limiting membrane (ILM). Meanwhile, the wet type of age-related macular degeneration (AMD) is caused by the submacular formation of choroidal neovascularization (CNV). Although exudative changes derived from CNV may cause epiretinal membrane (ERM) formation, which can also cause tractional force at the vitreo-retinal interface, there have been few reports of AMD-associated macular hole development in which the full thickness of the retinal tissue is completely torn by the tractional force. Moreover, intraoperative finding of macular hole associated with AMD with a possible involvement of subretinal lesion has not been described.

CASE PRESENTATION: A 78-year-old man diagnosed with wet AMD with subretinal fluid and mild cataract received 8 treatments with intravitreal pegaptanib. After AMD remission, he developed a secondary macular hole in the same eye. He underwent a pars plana vitrectomy that successfully closed the macular hole. Intraoperatively, it was found that the patient's vitreous was formed and that the ERM and ILM were adherent, suggesting the involvement of a tractional force at the vitreo-retinal interface due to an inflammatory reaction related to AMD and/or intravitreally injected chemical compounds, resulting in macular hole development. Changes in the condition of his AMD and the RPE were observed on a fluorescein angiogram (FA) and an indocyanine green angiogram (IA) that preceded macular hole development, suggesting that subretinal changes may also have been involved in the pathogenesis.

CONCLUSION: These clinical data, including the intraoperative findings and the temporal changes in the angiograms, suggest that an inflammatory reaction at the vitreo-retinal interface and subretinal lesion related to AMD contribute to the macular hole development in AMD patients treated with intravitreal injection.

PMID: 25270019 [PubMed - in process]

J Glaucoma. 2014 Oct-Nov:S30-3.

Extracellular, stem cells and regenerative ophthalmology.

Wang Y, Xie T.

Abstract: Retinal degenerative diseases, including retinitis pigmentosa, age-related macular degeneration, and glaucoma, still lack effective medical treatments. The stem cell-based regenerative approach has been proposed to treat these degenerative diseases. The major challenge for regenerative ophthalmology is to produce enough desirable retinal neurons in vitro from various stem cell types. Extracellular matrix proteins are important for stem cell self-renewal and differentiation in various systems. They have also been used in combination with various growth factors to expand retinal stem cells and produce desirable retinal neuronal types. This review summarizes our current understanding of how extracellular matrix proteins regulate stem cell function and discusses their application in regenerative ophthalmology.

PMID: 25275901 [PubMed - in process]

Pathogenesis

Exp Eye Res. 2014 Sep 30. [Epub ahead of print]

Iron upregulates melanogenesis in cultured retinal pigment epithelial cells.

Wolkow N, Li Y, Maminishkis A, Song Y, Alekseev O, Iacovelli J, Song D, Lee JC, Dunaief JL.

Abstract: The purpose of our studies was to examine the relationship between iron and melanogenesis in retinal pigment epithelial cells, as prior observations had suggested that iron may promote melanogenesis. This relationship has potential clinical importance, as both iron overload and hyperpigmentation are associated with age-related macular degeneration (AMD). Human fetal retinal pigment epithelial cells and ARPE-19 cells were treated with iron in the form of ferric ammonium citrate, after which quantitative RT-PCR and electron microscopy were performed. Melanogenesis genes tyrosinase, tyrosinase-related protein 1, Hermansky-Pudlak Syndrome 3, premelanosome protein and dopachrome tautomerase were upregulated, as was the melanogenesis-controlling transcription factor, microphthalmia-associated transcription factor (MITF). Iron-treated cells had increased pigmentation and melanosome number. Multiple transcription factors upstream of MITF were upregulated by iron.

PMID: 25277027 [PubMed - as supplied by publisher]

J Immunol Res. 2014;2014:483960. Epub 2014 Sep 4.

Complement System in Pathogenesis of AMD: Dual Player in Degeneration and Protection of Retinal Tissue.

Kawa MP, Machalinska A, Roginska D, Machalinski B.

Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness among the elderly, especially in Western countries. Although the prevalence, risk factors, and clinical course of the disease are well described, its pathogenesis is not entirely elucidated. AMD is associated with a variety of biochemical abnormalities, including complement components deposition in the retinal pigment epithelium-Bruch's membrane-choriocapillaris complex. Although the complement system (CS) is increasingly recognized as mediating important roles in retinal biology, its particular role in AMD pathogenesis has not been precisely defined. Unrestricted activation of the CS following injury may directly damage retinal tissue and recruit immune cells to the vicinity of active complement cascades, therefore detrimentally causing bystander damage to surrounding cells and tissues. On the other hand, recent evidence supports the notion

that an active complement pathway is a necessity for the normal maintenance of the neurosensory retina. In this scenario, complement activation appears to have beneficial effect as it promotes cell survival and tissue remodeling by facilitating the rapid removal of dying cells and resulting cellular debris, thus demonstrating anti-inflammatory and neuroprotective activities. In this review, we discuss both the beneficial and detrimental roles of CS in degenerative retina, focusing on the diverse aspects of CS functions that may promote or inhibit macular disease.

PMID: 25276841 [PubMed - as supplied by publisher] PMCID: PMC4168147

Biochim Biophys Acta. 2014 Sep 28;1843(12):3038-3046. [Epub ahead of print]

Decline in cellular clearance systems induces inflammasome signaling in human ARPE-19 cells.

Piippo N, Korkmaz A, Hytti M, Kinnunen K, Salminen A, Atalay M, Kaarniranta K, Kauppinen A.

Abstract: Retinal pigment epithelium (RPE) plays a major role in the maintenance of photoreceptors, and degeneration of RPE results in the development of age-related macular degeneration (AMD). Accumulation of intracellular protein aggregates, increased oxidative stress, and chronic inflammation are all factors damaging the functionality of aged RPE cells. Here, we report that inhibition of proteasomal degradation with MG-132 and autophagy with bafilomycin A1 resulted in the release of IL-1β but not that of IL-18 in human ARPE-19 cells. NLRP3 receptor became upregulated, and caspase-1, the functional component of an inflammasome complex, was activated. In addition to accumulating intracellular protein aggregates, inhibition of degradation systems induced oxidative stress which was demonstrated by elevated amounts of intracellular 4-hydroxynonenal (HNE)-protein adducts. Along with IL-1β, exposure to MG-132 and bafilomycin A1 resulted in the secretion of IL-8. A low concentration (1pg/ml) of IL-1β was capable of triggering significant IL-8 production which also became attenuated by treatment with a specific caspase-1 inhibitor. These results suggest that decline in intracellular degradation systems results not only in increased amounts of intracellular protein aggregates and oxidative stress but also in the activation of NLRP3 inflammasomes, arisen as a result of elevated production of biologically active IL-1β.

PMID: 25268952 [PubMed - as supplied by publisher]

Angiogenesis. 2014 Oct 2. [Epub ahead of print]

The carboxyl terminus of VEGF-A is a potential target for anti-angiogenic therapy.

Carter JG, Gammons MV, Damodaran G, Churchill AJ, Harper SJ, Bates DO.

Abstract: Anti-VEGF-A therapy has become a mainstay of treatment for ocular neovascularisation and in cancer; however, their effectiveness is not universal, in some cases only benefiting a minority of patients. Anti-VEGF-A therapies bind and block both pro-angiogenic VEGF-Axxx and the partial agonist VEGF-Axxxb isoforms, but their anti-angiogenic benefit only comes about from targeting the pro-angiogenic isoforms. Therefore, antibodies that exclusively target the pro-angiogenic isoforms may be more effective. To determine whether C-terminal-targeted antibodies could inhibit angiogenesis, we generated a polyclonal antibody to the last nine amino acids of VEGF-A165 and tested it in vitro and in vivo. The exon8a polyclonal antibody (Exon8apab) did not bind VEGF-A165b even at greater than 100-fold excess concentration, and dose dependently inhibited VEGF-A165 induced endothelial migration in vitro at concentrations similar to the VEGF-A antibody fragment ranibizumab. Exon8apab can inhibit tumour growth of LS174t cells implanted in vivo and blood vessel growth in the eye in models of age-related macular degeneration, with equal efficacy to non-selective anti-VEGF-A antibodies. It also showed that it was the VEGF-Axxx levels specifically that were upregulated in plasma from patients with proliferative diabetic retinopathy. These results suggest that VEGF-A165-specific antibodies can be therapeutically useful.

PMID: 25274272 [PubMed - as supplied by publisher]

World J Cardiol. 2014 Sep 26;6(9):968-84.

Angiotensin II-related hypertension and eye diseases.

Marin Garcia PJ, Marin-Castaño ME.

Abstract: Systemic vascular disease, especially hypertension, has been suspected as a risk factor for some eye diseases including, diabetic retinopathy and age-related macular degeneration. Hypertension can contribute to chronic diseases by hemodynamic injury and/or cellular actions induced by hypertension-related hormones or growth factors. Among the most important is Angiotensin II (Ang II), which controls blood pressure and induces different cellular functions that may be dependent or independent of its effect on blood pressure. Importantly, as is true for heart, kidney and other organs, the renin-angiotensin system (RAS) is present in the eye. So, even in the absence of hypertension, local production of Ang II could be involved in eye diseases. The goal of this manuscript is to review the most relevant scientific evidence supporting the role of the RAS activation, in the development of age-related macular degeneration and diabetic retinopathy, and highlight the importance of Ang II in the etiology of these diseases.

PMID: 25276298 [PubMed] PMCID: PMC4176806

Molecules. 2014 Sep 26;19(10):15391-407.

Design and Synthesis of C-Terminal Modified Cyclic Peptides as VEGFR1 Antagonists.

Wang L, Gagey-Eilstein N, Broussy S, Reille-Seroussi M, Huguenot F, Vidal M, Liu WQ.

Abstract: Previously designed cyclic peptide antagonist c[YYDEGLEE]-NH2 disrupts the interaction between vascular endothelial growth factor (VEGF) and its receptors (VEGFRs). It represents a promising tool in the fight against cancer and age-related macular degeneration. We described in this paper the optimization of the lead peptide by C-terminal modification. A new strategy for the synthesis of cyclic peptides is developed, improving the cyclisation efficiency. At 100 µM, several new peptides with an aromatic group flexibly linked at C-terminal end showed significantly increased receptor binding affinities in competition ELISA test. The most active peptide carrying a coumarin group may be a useful tool in anti-angiogenic biological studies.

PMID: 25264829 [PubMed - in process]

Mol Cell Neurosci. 2014 Sep 28. [Epub ahead of print]

A novel protective role for the innate immunity Toll-Like Receptor 3 (TLR3) in the retina via Stat3.

Patel AK, Hackam AS.

Abstract: The innate immune system and inflammatory pathways play key roles in numerous diseases of the central nervous system (CNS). Recent evidence indicates that innate immunity induces both pathogenesis and protection during neuronal injury. To test the possibility that the conflicting roles of innate immunity in the CNS depends on the cellular environment in which innate immunity is stimulated, we analyzed the effect of Toll-Like Receptor 3 (TLR3) activation on neuronal survival in the presence and absence of oxidative injury in a mouse model system. We demonstrated that activation of TLR3 by the double stranded RNA activator, Poly (I:C), during paraquat induced oxidative stress, significantly protected mouse photoreceptors, as measured by increased retinal structure, function, and improved visual acuity. In contrast, TLR3 activation without concurrent oxidative injury was neurotoxic. The neurotoxic and protective effects of Poly (I:C) stimulation were absent in TLR3 knockout animals, which indicates that protection by Poly (I:C) is dependent on the TLR3 signaling pathway. Furthermore, we identified the pro-survival transcription factor Stat3 as a necessary mechanism for protection. Knockdown of Stat3 using lentivirally

delivered shRNA abolished the protective effects of TLR3 signaling in the retina during oxidative stress. Therefore, TLR3 activation in the context of oxidative stress triggers protective instead of pathogenic signaling, suggesting that TLR3 is a potential therapeutic target for neurodegeneration where oxidative stress is a significant contributor.

PMID: 25264029 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2014 Sep 25. [Epub ahead of print]

Age-Related Macular Degeneration and Mortality in Community-Dwelling Elders: The Age, Gene/ Environment Susceptibility Reykjavik Study.

Fisher DE, Jonasson F, Eiriksdottir G, Sigurdsson S, Klein R, Launer LJ, Gudnason V, Cotch MF.

OBJECTIVE: To investigate the association between age-related macular degeneration (AMD) and mortality in older persons.

DESIGN: Population-based prospective cohort study.

PARTICIPANTS: Participants 67 to 96 years of age (43.1% male) enrolled between 2002 and 2006 in the Age, Gene/Environment Susceptibility-Reykjavik Study.

METHODS: Retinal photographs of the macula were acquired digitally and evaluated for the presence of AMD lesions using the Wisconsin Age-Related Maculopathy grading scheme. Mortality was assessed prospectively through 2013 with cause of death available through 2009. The association between AMD and death, resulting from any cause and specifically cardiovascular disease (CVD), was examined using Cox proportional hazards regression with age as the time scale, adjusted for significant risk factors and comorbid conditions. To address a violation in the proportional hazards assumption, analyses were stratified into 2 groups based on the mean age at death (83 years).

MAIN OUTCOME MEASURES: Mortality resulting from all causes and CVD.

RESULTS: Among 4910 participants, after a median follow-up of 8.6 years, 1742 died (35.5%), of whom 614 (35.2%) had signs of AMD at baseline. Cardiovascular disease was the cause of death for 357 people who died before the end of 2009, of whom 144 (40%) had AMD (101 with early disease and 43 with late disease). After considering covariates, including comorbid conditions, having early AMD at any age or having late AMD in individuals younger than 83 years (n = 4179) were not associated with all-cause or CVD mortality. In individuals 83 years of age and older (n = 731), late AMD was associated significantly with increased risk of all-cause mortality (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.20-2.57) and CVD-related mortality (HR, 2.37; 95% CI, 1.41-3.98). In addition to having AMD, older individuals who died were more likely to be male and to have low body mass index, impaired cognition, and microalbuminuria.

CONCLUSIONS: Competing risk factors and concomitant conditions are important in determining mortality risk resulting from AMD. Individuals with early AMD are not more likely to die than peers of comparable age. Late AMD becomes a predictor of mortality by the mid-octogenarian years.

PMID: 25264026 [PubMed - as supplied by publisher]

Genetics

Mamm Genome. 2014 Oct 2. [Epub ahead of print]

Genetic basis of age-dependent synaptic abnormalities in the retina.

Higuchi H, Macke EL, Lee WH, Miller SA, Xu JC, Ikeda S, Ikeda A.

Abstract: Understanding the normal aging process will help us determine the mechanisms of how age-related diseases are caused and progress. A/J inbred mice have been shown to exhibit accelerated aging phenotypes in the retina including increased inflammation and photoreceptor cell degeneration, which resemble human aging symptoms. C57BL/6J (B6) inbred mice are less susceptible for these abnormalities, indicating the existence of genetic factor(s) that affect their severity. In this study, we determined that another age-dependent phenotype, ectopic synapse formation, is also accelerated in the A/J retina compared to the B6 retina. Through genetic mapping utilizing recombinant inbred strains, we identified quantitative trait loci (QTLs) on chromosome 7 and 19, which contribute to abnormal retinal synapses as well as other age-dependent phenotypes. Using consomic single chromosome substitution lines where a single chromosome is from A/J and the rest of the genome is B6, we investigated the individual effect of each QTL on retinal aging phenotypes. We observed that both QTLs independently contribute to abnormal retinal synapses, reduction in the number of cone cells, and an up-regulation of retinal stress marker, glial fibrillary acidic protein (GFAP). Mice with a single chromosome substitution on chromosome 19 also exhibited an increase in inflammatory cells, which is characteristic of aging and age-related macular degeneration. Thus, we identified QTLs that are independently capable of affecting the severity and progression of age-dependent retinal abnormalities in mice.

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FPR1 interacts with CFH, HTRA1 and smoking in exudative age-related macular degeneration and polypoidal choroidal vasculopathy.

Liang XY, Chen LJ, Ng TK, Tuo J, Gao JL, Tam PO, Lai TY, Chan CC, Pang CP.

Purpose: To determine the genetic association of an inflammation-related gene, formyl peptide receptor 1 (FPR1), in exudative age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Methods: The coding region of FPR1 gene was sequenced in 554 unrelated Chinese individuals: 155 exudative AMD patients, 179 PCV patients, and 220 controls. Interactions and combined effects of FPR1 with complement factor H (CFH), high temperature requirement factor A1 (HTRA1), and smoking were also investigated.

Results: A total of 28 polymorphisms in FPR1 were identified. Single nucleotide polymorphisms (SNP) rs78488639 increased the risk to exudative AMD (P=0.043) and PCV (P=0.016), whereas SNP rs867229 decreased the risk to exudative AMD (P=0.0026), but not PCV. Homozygous G allele of rs1042229 was associated with exudative AMD (P=0.0394, odds ratio (OR)=2.27, 95% confident interval: 1.08-4.74), but not with PCV. Exudative AMD, but not PCV, was associated with the heterozygous genotypes of rs2070746 (P=0.019, OR=0.57) and rs867229 (P=0.0082, OR=0.54). Significantly, interactions were identified among FPR1 rs78488639, CFH rs800292, and HTRA1 rs11200638 in both exudative AMD and PCV. Combined heterozygous risk alleles of CFH rs800292 GA and FPR1 rs78488639 CA were posed to PCV ($P=2.22 \times 10^{-4}$, OR=10.47), but not exudative AMD. Furthermore, FPR1 rs78488639 CA combining with HTRA1 rs11200638 and smoking was also predisposed risks to exudative AMD and PCV.

Conclusion: FPR1 is associated with exudative AMD and PCV in a Hong Kong Chinese cohort. FPR1 rs78488639 interacted with CFH rs800292, HTRA1 rs11200638, and smoking, enhancing risk to exudative AMD and PCV.

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Complement Factor H Y402H and LOC387715 A69S Polymorphisms in Association with Age-Related Macular Degeneration in Iran.

Nazari Khanamiri H, Ghasemi Falavarjani K, Sanati MH, Aryan H, Irani A, Hashemi M, Modarres M, Parvaresh MM, Nikeghbali A.

PURPOSE: To determine the frequency of complement factor H (Y402H) and age related macular degeneration susceptibility gene 2 (A69S) single nucleotide polymorphisms in patients with age-related macular degeneration (AMD) and in matched non-AMD controls in an Iranian population.

METHODS: Seventy patients with AMD and 86 age- and sex-matched controls were recruited and examined. Peripheral blood sample was obtained from all subjects for DNA extraction and direct sequencing of Y402H and A69S genes. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association of Y402H and A69S polymorphisms with AMD were determined.

RESULTS: The frequencies of both homozygous and heterozygous genotypes were significantly higher in cases than controls for both Y402H and A69S polymorphisms. In comparison to the wild genotypes, OR for AMD associated with Y402H and A69S polymorphisms were 1.9 (95% CI, 1.1-3.2) and 2.2 (95%CI, 1.6-3.1), respectively. Joint risk analysis considering both genes revealed a higher risk of AMD when polymorphisms were present for both genes.

CONCLUSION:

Y402H and A69S polymorphisms were strongly associated with AMD in this Iranian population.

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Diet & lifestyle

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Neuroprotective action of resveratrol.

Bastianetto S, Ménard C2, Quirion R3.

Abstract: Low-to-moderate red wine consumption appeared to reduce age-related neurological disorders including macular degeneration, stroke, and cognitive deficits with or without dementia. Resveratrol has been considered as one of the key ingredients responsible for the preventive action of red wine since the stilbene displays a neuroprotective action in various models of toxicity. Besides its well documented free radical scavenging and anti-inflammatory properties, resveratrol has been shown to increase the clearance of beta-amyloid, a key feature of Alzheimer's disease, and to modulate intracellular effectors associated with oxidative stress (e.g. heme oxygenase), neuronal energy homeostasis (e.g. AMP kinase), program cell death (i.e. AIF) and longevity (i.e. sirtuins). This article summarizes the most recent findings on mechanisms of action involved in the protective effects of this multi target polyphenol, and discusses its possible roles in the prevention of various age-related neurological disorders.

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Potential therapeutic effects of baicalein, baicalin, and wogonin in ocular disorders.

Xiao JR, Do CW, To CH.

Abstract: Ocular diseases such as cataract, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy are the leading causes of blindness. The elderly population is at particular risk of developing one or more of these age-related ocular diseases. By virtue of multiple bioactivities, effort has been made to develop dietary flavonoids as complimentary therapies for ocular disorders. Dietary intake of flavonoids has been reported to reduce the risk of cataract and AMD. This review focuses on the main flavones baicalein, baicalin, and wogonin isolated from the Chinese medicinal herb, Scutellariae radix (SR), which has been widely used in Asian countries for the treatment of many diseases. Interest in SR has grown recently following new findings that suggest multiple routes of therapeutic action. This review will summarize the diverse pharmacological properties, therapeutic roles, and mechanisms of these flavones of SR in cellular and animal models of ocular diseases.

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Factors affecting reading speed in patients with diabetic macular edema treated with laser photocoagulation.

Pearce E, Sivaprasad S, Chong NV.

PURPOSE: To study the factors that may affect reading speed in patients with diabetic macular edema previously treated with laser photocoagulation.

METHODS: Consecutive patients with type II diabetes treated with laser photocoagulation for diabetic macular edema (DME) at least twelve months previously, with best corrected visual acuity of better than 65 letters (approximately 20/40) measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts were included in this study. Patients previously treated with pan-retinal photocoagulation, vitrectomy, intravitreal steroid or anti-VEGF therapy were excluded. Any other ocular co-morbidities that may influence reading ability such as cataract, glaucoma or macular degeneration were also excluded. All patients were refracted by a certified examiner, the following measurements were collected: best corrected visual acuity (BCVA), contrast sensitivity with Pelli-Robson chart, reading speed with MNREAD chart, microperimetry with Nidek MP1, and central subfield thickness with Zeiss spectral domain optical coherent topography.

RESULTS: The slow reading group had poorer contrast sensitivity ($p=0.001$), reduced retinal sensitivity ($p=0.027$) and less stable fixation ($p=0.013$). Most interestingly the reduced retinal sensitivity findings were driven by the microperimetry value on the right subfield ($p=0.033$), (nasal to the fovea in the right eye and temporal to the fovea in the left eye). Multiple linear regression analysis showed that contrast sensitivity is probably the most important factor that affects reading speed ($p=0.001$).

CONCLUSION: Reduced retinal sensitivity after laser treatment is associated with reduced reading speed in patients with diabetic macular edema.

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