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Drug treatment

J Ophthalmol. 2011;2011:602729. Epub 2011 Dec 22.

Effect of intravitreal ranibizumab in the treatment of peripapillary choroidal neovascularisation.

Hamoudi H, Sørensen TL.

Department of Ophthalmology, Copenhagen University Hospital Roskilde and University of Copenhagen, 4000 Roskilde, Denmark.

Abstract

Intravitreal ranibizumab therapy is widely used in treatment of subfoveal choroidal neovascularisation (CNV) in age-related macular degeneration. We wanted to study the effect of intravitreal ranibizumab therapy in peripapillary CNV. A prospective recording of treatment outcomes in twelve eyes (12 patients) with peripapillary CNV with intravitreal injections of ranibizumab was performed. The patients received a series of 3 injections 4-6 weeks apart, and then a new ophthalmic examination was made including OCT and further therapy was given if the peripapillary CNV was still active. Nine patients had idiopathic peripapillary CNV, and in 3 patients it was associated to age-related macular degeneration. Followup had to be at least 6 months. The mean follow-up time was 15.9 (range 9-27) months and the mean number of injections 6.2 (3-10). In 10 patients treatment had resulted in an inactivation of the peripapillary CNV, but 3 of them had reactivation, while 2 patients had no inactivation. Currently, 5 patients are continuous to receive treatment. VA improved in 10 patients. Intravitreal ranibizumab therapy appears to be effective in patients with peripapillary CNV, but in some cases there is repeated reactivation or continuous activity of the peripapillary CNV.

PMID: 22235362 [PubMed - in process] PMCID: PMC3253451

Eye (Lond). 2012 Jan 13. doi: 10.1038/eye.2011.337. [Epub ahead of print]

New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel.

Bandello F, Cunha-Vaz J, Chong NV, Lang GE, Massin P, Mitchell P, Porta M, Prünte C, Schlingemann R, Schmidt-Erfurth U.

Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy.

Abstract

The current standard therapy for patients with diabetic macular oedema (DME)-focal/grid laser photocoagulation-usually does not improve impaired vision, and many patients lose vision despite laser therapy. Recent approval of ranibizumab by the European Medicines Agency to treat visual impairment due to DME fulfils the previously unmet medical need for a treatment that can improve visual acuity (VA) in these patients. We reviewed 1- and 2-year clinical trial findings for ranibizumab used as treatment for DME to formulate evidence-based treatment recommendations in the context of this new therapy. DME with or without visual impairment should be considered for treatment when it fulfils the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria for clinically significant oedema. For DME with centre involvement and associated vision loss due to DME, monthly ranibizumab monotherapy with treatment interruption and re-initiation based on VA stability is recommended. Laser therapy based on ETDRS guidelines is recommended for other forms of clinically significant DME without centre involvement or when no vision loss has occurred, despite centre involvement. Because these recommendations are based on randomised controlled trials of 1-2 years duration, guidance may need updating as long-term ranibizumab data become available and as additional therapeutic agents are assessed in clinical trials.

Eye advance online publication, 13 January 2012; doi:10.1038/eye.2011.337.

PMID: 22241014 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Jan 12. [Epub ahead of print]

Combination therapy with low-dose transpupillary thermotherapy and intravitreal ranibizumab for neovascular age-related macular degeneration: a 24-month prospective randomised clinical study.

Söderberg AC, Algvere PV, Hengstler JC, Söderberg P, Seregard S, Kvanta A.

Karolinska Institutet, St Eriks Eye Hospital, Stockholm, Sweden.

Aim: To compare the effect of combined low-dose transpupillary thermotherapy (TTT) and intravitreal ranibizumab with sham TTT and intravitreal ranibizumab in patients with neovascular age-related macular degeneration (AMD).

Methods: A 24-month, double-masked, randomised, active-controlled clinical trial. 100 patients with primary neovascular AMD were randomly assigned (1:1) to receive intravitreal ranibizumab and sham TTT or intravitreal ranibizumab and low-dose TTT. After an initial loading phase of ranibizumab patients were assigned to receive quarterly low-dose TTT (136 mW/mm) or sham TTT for 24 months. Retreatment with ranibizumab was allowed in both treatment groups using a variable dosing regimen. The primary endpoint was the number of intravitreal injections with ranibizumab. Secondary endpoints included change in best corrected visual acuity (BCVA), central retinal thickness (CRT) and lesion area.

Results: In the per protocol (PP) population (78 patients) the mean number of ranibizumab injections was 8.0 in the sham TTT group versus 6.3 in the TTT group ($p<0.05$). The mean number of injections between 0 -12 months and 13-24 months was 4.8 versus 4.6 ($p>0.05$) and 3.2 versus 1.7 ($p<0.01$) in the sham TTT and TTT groups, respectively. There was no statistically significant difference in BCVA (+4.0 vs +0.9 ETDRS letters), CRT (-49.9% vs -36.4%) or lesion area (-0.3% vs -10.6%) between the treatment groups at the final examination. The results of the intent-to-treat population (92 patients) were similar to the PP population.

Conclusions: Treatment with low-dose TTT significantly reduced the number or intravitreal injections of ranibizumab over 24 months. The results suggest that low-dose TTT can serve as an adjuvant in combination with intravitreal ranibizumab for neovascular AMD.

Clinical trial registration number: The trial is registered at http://clinicaltrails.gov (no NCT00599222).

PMID: 22241923 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Jan 5. [Epub ahead of print]

[Intravitreal injections: AFSSAPS guide to good practice.]

[Article in French]

Bodaghi B, Korobelnik JF, Cochereau I, Hajjar J, Goebel F, Dumarcet N.

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Abstract

Intravitreal injections are very commonly performed in the daily practice of Ophthalmology and become a leading procedure in the management of age-related macular degeneration, diabetic retinopathy, infectious endophthalmitis or retinitis, uveitis and retinal vein occlusions. Based on the comments of a group of experts, including ophthalmologists, pharmacists and hygienists, the French Agency for the Safety of Health Products (AFSSAPS) edited a guide to good practice of intravitreal injections, revisiting those previously published in 2006. The overall experience accumulated during time is a valuable source of information to determine the most appropriate protocol. Therefore, the simplification of the procedure is reasonably proposed even though safety remains a major issue, in order to avoid complications, especially infections.

PMID: 22226388 [PubMed - as supplied by publisher]

Coll Antropol. 2011 Sep;35 Suppl 2:15-8.

Anti-VEGF in treatment of diabetic macular edema.

Boras I, Lazić R, Gabrić N, Lukić M, Dekaris I.

Universitiy Eye Clinic "Svjetlost", Zagreb, Croatia. ivan.boras@svjetlost.hr

Abstract

Diabetic macular edema is the leading cause of moderate visual deterioration in patients with diabetic retinopathy. Ranibizumab blocks vascular endothelial growth factor (VEGF) induced hyperpermeability of blood vessels. In this prospective case series we investigated the efficacy and safety of anti-VEGF treatment in reduction of central retinal thickness (CRT) and improvement in visual acuity (VA) in patients with diabetic macular edema (DME). 9 patients were followed up for 6 months and treated monthly with intravitreal ranibizumab. VA and CRT were measured at each visit. Treatment was discontinued as the peak improvement of either parameter was reached and reinstituted in case of deterioration/recurrence of edema. Study endpoints included: VA using ETDRS chart, CRT and number of injections at 6 months. Mean VA from all 9 patients increased by 0.3 lines of logMAR ($p < 0.05$ compared to baseline), and CRT decreased from 515 +/- 123 microm to 310 +/- 110 microm. The improvement of VA after ranibizumab injection was in correlation with a decrease in CRT. Mean of 4 injections were needed to control the disease during the follow-up period. Ranibizumab treatment was effective in VA and reducing CRT. Several injections were needed to control the disease. Regular OCT examinations and retreatment are advised in order to maintain initially reached VA.

PMID: 22220397 [PubMed - in process]

Arch Ophthalmol. 2012 Jan;130(1):125-6.

Risks of adverse events with therapies for age-related macular degeneration: a response--reply.

Curtis LH, Hammill BG, Schulman KA, Cousins SW.

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PMID: 22232488 [PubMed - in process]

Arch Ophthalmol. 2012 Jan;130(1):124-5.

Risks of adverse events with therapies for age-related macular degeneration: a response.

Williams T, Reeves BC, Foss AJ, Fell G.

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PMID: 22232487 [PubMed - in process]

Other treatment and diagnosis

Retina. 2012 Jan 4. [Epub ahead of print]

SEGREGATION OF OPHTHALMOSCOPIC CHARACTERISTICS ACCORDING TO CHOROIDAL THICKNESS IN PATIENTS WITH EARLY AGE-RELATED MACULAR DEGENERATION.

Switzer DW Jr, Mendonça LS, Saito M, Zweifel SA, Spaide RF.

Vitreous, Retina, Macula Consultants of New York and the LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear and Throat Hospital, New York, New York.

PURPOSE: To investigate the association of fundus features with choroidal thickness in eyes with early age-related macular degeneration.

METHODS: Consecutive patients with age-related macular degeneration were evaluated. Major exclusionary criteria included late age-related macular degeneration (central geographic atrophy or choroidal neovascularization), macular laser therapy, myopia greater than -6 diopters, past vitreoretinal surgery, or central serous chorioretinopathy. Charts and multimodal imaging were reviewed for refraction, cataract, hypertension, diabetes, open-angle glaucoma, β-zone peripapillary atrophy, fundus tessellation, pigmentary changes, drusen, subretinal drusenoid deposits (also known as reticular pseudodrusen). Data measured from enhanced-depth imaging spectral-domain optical coherence tomography included subfoveal choroidal thickness, central foveal thickness, outer nuclear layer thickness, inner segment to retinal pigment epithelium aggregate thickness, presence of subretinal drusenoid deposit, and outer retinal hyperreflective layers (including the band corresponding to overlap between retinal pigment epithelium apical processes and outer segments). Correlations were calculated among the measured variables, fundus features, open-angle glaucoma, and visual acuity.

RESULTS: In 90 eyes of 70 early age-related macular degeneration patients with mean visual acuity 20/31 (logarithm of the minimum angle of resolution 0.193), subfoveal choroidal thickness showed a significant inverse correlation with age ($P = 0.004$) and increasing myopic spherical equivalent refractive error ($P = 0.023$). Subfoveal choroidal thickness was thinner in eyes with fundus tessellation ($P < 0.001$), subretinal drusenoid deposit ($P = 0.023$), an absence of conventional drusen ($P < 0.001$), the presence of β-zone peripapillary atrophy ($P < 0.001$), and in eyes with a diagnosis of open-angle glaucoma ($P = 0.003$) or an absent band on optical coherence tomography corresponding to overlap between outer segment and retinal pigment epithelium apical processes ($P = 0.022$).

CONCLUSION: Major ocular manifestations in early age-related macular degeneration and open-angle

glaucoma are associated with the choroid-the main blood supply in the eye. Theories concerning the pathogenesis of these two diseases should incorporate interactions involving the choroid.

PMID: 22222760 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Jan 5. [Epub ahead of print]

Choroidal changes associated with reticular pseudodrusen.

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Department of Ophthalmology, Centre Hospitalier Intercommunal de Creteil University Paris Est Creteil, Creteil, France.

Purpose: To analyze choroidal changes associated with reticular pseudodrusen by indocyanine green angiography (ICGA) and enhanced-depth-imaging spectral-domain optical coherence tomography (EDI SD-OCT).

Methods: Twenty-two consecutive patients (22 eyes) with reticular pseudodrusen, and without medium/large drusen, underwent ICGA and EDI OCT. Twenty-one age and sex matched subjects (21 eyes) with early age-related macular degeneration (AMD), and without pseudodrusen, also underwent EDI OCT.

Results: Mean age of patients with reticular pseudodrusen and with early AMD was 82.5±0.9 and 79.3±4.4 year-old, respectively (p=0.9), and 59.0% and 76.2% were women, respectively (p=0.7). On ICGA, reticular patterns appeared as hypofluorescent, not overlying the large choroidal vessels. Areas of iso/hyperfluorescence on ICGA, occurring adjacently to reticular patterns, appeared on OCT as subretinal deposits. The mean subfoveal choroidal thickness was significantly reduced in the group with reticular pseudodrusen compared with the control group (174.6±10.1 and +241.4±16.5, respectively; p<0.001). At all measurement points but the 3000-μm superior to the fovea, the choroidal thickness of eyes with reticular pseudodrusen appeared thinner than that of the control group. Interestingly, the choroid of eyes with reticular pseudodrusen appeared thicker at 3000-μm superior to the fovea compared with all other measurement points.

Conclusions: We showed that the reticular patterns appeared as hypofluorescent lesions on ICGA, closely abutting, but not overlying the large choroidal vessels. In eyes with reticular pseudodrusen, EDI OCT revealed an overall thinned choroid.

PMID: 22222508 [PubMed - as supplied by publisher]

J Rehabil Res Dev. 2011;48(9):1101-8.

Effect of depression on actual and perceived effects of reading rehabilitation for people with central vision loss.

Grant P, Seiple W, Szlyk JP.

The Chicago Lighthouse for People Who Are Blind or Visually Impaired, Low Vision Research Laboratory, 1850 W. Roosevelt Rd, Chicago, IL 60616. patricia.grant@chicagolighthouse.org.

Abstract

To investigate the relationship between depression and quantitative measures of visual function, we recruited 18 subjects with central scotomas from macular degeneration who were enrolled in a reading rehabilitation program. Psychological batteries and reading assessments were administered prior to rehabilitation; reading assessments and a measure of adaptation to vision loss were administered following

rehabilitation. We investigated relationships between reported levels of depressive symptoms and reading and adaptation outcome measures by using Pearson product moment correlation analysis. Results revealed a significant relationship between depression levels and reading acuity difference scores ($r(16) = 0.54$, $p = 0.02$) and changes in adaptation to vision loss levels ($r(16) = 0.62$, $p = 0.01$), suggesting that those who reported greater depressive symptoms did not respond as well functionally to reading rehabilitation but reported greater improvement in levels of adaptation to vision loss following rehabilitation. Future research should focus on defining standard methods to assess and remediate depression as part of the rehabilitation process.

PMID: 22234714 [PubMed - in process]

Coll Antropol. 2011 Sep;35 Suppl 2:157-60.

The role of the spectral domain ocular coherence tomography in detection of age-related macular degeneration.

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Abstract

Age-related macular degeneration (ARMD) is one of the most common causes of the vision loss and blindness in developed countries. Among other harmful effects, exposure to the UV radiation is the most prominent factor for the development of the disorder. Using the method of SD OCT (Spectral Domain Ocular Coherence Tomography) we performed measurement of the neurosensory retinal thickness of 19 eyes of low vision patients from the population of Primorsko-Goranska County of Republic of Croatia, with dry form of the terminal macular degeneration. These results we compared with control measurements performed on 28 eyes of healthy, normal vision subjects from same County. We determined following parameters: central foveal thickness (CFT), macular volume (MV) and mean foveal thickness (MFT) in the both groups. Results showed statistically significant reduction of CFT in the group of normal vision female patients when compared to males, while any significant difference of CFT between total groups of normal vision individuals and low vision patients was not detected. Furthermore, we noticed statistically significant ($p < 0.000001$) decrease of the MV in the group of the low vision patients in comparison to healthy subjects and statistically significant ($p < 0.000001$) reduction of the MFT of the low vision patients when compared to normal vision individuals. In our study we detected the absence of any significant difference of the CFT between healthy and low vision population, what looks like controversial finding, because neurosensory retina in the ARMD is thin and atrophic, but on the other side it is known that fixation point in low vision patients is translocated from the damaged fovea to extrafoveal region, usually above the fovea, where neurosensory retina is of the normal thickness, but with the less sensitivity. Furthermore, our results suggest possible connection of higher incidence of ARMD with lower CFT in females. Owing to the thicker neurosensory retina in males and better protection, damaging effect of the UV irradiation, which is the proven factor of ARMD development, is smaller. From the evolutionary point of view it is possible that males in all vertebrates have more resistant macula because during the evolutionary process they have spent much more time outside in the sunlight than females.

PMID: 22220425 [PubMed - in process]

Clin Hemorheol Microcirc. 2012 Jan 3. [Epub ahead of print]

The importance of rheological parameters in the therapy of the dry form of age-related macular degeneration with rheohaemapheresis.

Bláha M, Rencová E, Langrová H, Lánská M, Bláha V, Studnička J, Rozsíval P, Malý R, Fátorová I, Filip S, Držata J, Hejsek L, Malý J.

IInd Department of Internal Medicine, Haematology, Medical Faculty and Faculty Hospital, Charles University, Hradec Králové, Czech Republic.

Abstract

To date, rheological treatment is the only chance to control the advanced dry form of age-related macular degeneration and arrest its progression to legal blindness. Rheohaemapheresis can change the main rheological parameters, blood and plasma viscosity, as well as change erythrocyte aggregability, improve erythrocyte flexibility and lead to substantial improvement when other methods of therapy fail. In this study, we describe changes in the levels of rheological efficacy indicators after rheohaemapheresis and their clinical significance in the dry form of age-related macular degeneration (AMD). Seventy-two patients with AMD were randomised; 34 controls, and 38 patients were treated with rheohaemapheresis (separator Cobe Spectra + Evaflux filter). After the procedures, α2-macroglobulin levels decreased by approximately 58%, fibrinogen by approximately 65%, IgM by approximately 67%, LDL cholesterol by approximately 71%, apolipoprotein B by approximately 65%, and lipoprotein (a) by approximately 42%. These decreases correspond with a decrease in blood and plasma viscosity (14/12%), clinical improvement (arrest of disease progression, even visual improvement in some cases), and heretofore-unreported improvement (even reattachment) of drusen retinal pigment epithelium detachment. Our modification of rheohaemapheresis is safe (5.4% of patients experienced clinically insignificant side effects).

PMID: 22240359 [PubMed - as supplied by publisher]

Brain Nerve. 2012 Jan;64(1):47-57.

[Perspectives regarding the potential use of human induced pluripotent stem cells for the development of and research on medicinal products].

[Article in Japanese]

Hayakawa T, Mizuguchi H.

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Abstract

Human induced pluripotent stem cells (hiPSCs) are expected to be used in various life science areas, ranging from basic research to medical applications. This article describes perspectives regarding the potential use of hiPSCs, especially in Japan, for manufacturing products related to regenerative medicine as well as for establishing cell-based assay/screening systems that can be used for effective and efficient assessment of candidates for new drugs. The applications of hiPSCs include the following: hiPSC-derived retinal pigment epithelial cells for treating age-related macular degeneration; potential corneal reconstruction by using a combination of various relevant hiPSC-derived differentiated cells; potential treatment of Parkinson's disease by using dopaminergic neurons generated from hiPSCs; potential treatment of spinal cord injury by using neural stem/progenitor cells generated from hiPSCs; potential treatment of chronic heart failure by using hiPSC-derived functional cardiomyocytes; and development of cell-based drug toxicity screening and drug effect assay systems involving cells such as cardiomyocytes, hepatocytes, and neural cells that are differentiated from hiPSCs and can be used in the early phase of new drug development. The current situation regarding the development of guidelines for ensuring the quality and safety of hiPSC-derived medicinal products has also been described.

PMID: 22223501 [PubMed - in process]

Eye (Lond). 2012 Jan 6. doi: 10.1038/eye.2011.218. [Epub ahead of print]

Validity of EuroQOL-5D, time trade-off, and standard gamble for age-related macular degeneration in the Singapore population.

Au Eong KG, Chan EW, Luo N, Wong SH, Tan NW, Lim TH, Wagle AM.

1] Department of Ophthalmology and Visual Sciences, Khoo Teck Puat Hospital, Singapore [2] Department of Ophthalmology and Visual Sciences, Alexandra Hospital, Singapore [3] Singapore International Eye Cataract Retina Centre, Mount Elizabeth Medical Centre, Singapore.

Background/aims: Utility values of age-related macular degeneration (AMD) in Asian patients are unknown. This study aims to assess utility values and construct validity of the EuroQOL-5D (EQ-5D), time trade-off (TTO), and standard gamble (SG) instruments in the Singapore multi-ethnic AMD population.

Methods: Cross-sectional, two-centre, institution-based study. Visual acuity (VA), clinical AMD severity, and utility scores on the EQ-5D, TTO, and SG were obtained from 338 AMD patients. VA was analysed in terms of the better-seeing eye (BEVA), worse-seeing eye (WEVA), and weighted average of both eyes (WVA). We evaluated SG on the perfect health-death (SG(death)) and binocular perfect vision-binocular blindness (SG(blindness)) scales. Construct validity was determined by testing a priorihypotheses relating the EQ-5D, TTO, and SG utility scores to VA and clinical AMD severity.

Results: The mean utilities on the EQ-5D, TTO, SG(death), and SG(blindness) were 0.89, 0.81, 0.86, and 0.90, respectively. EQ-5D scores correlated weakly with BEVA, WEVA, and WVA (Pearson's correlation coefficients -0.291, -0.247, and -0.305 respectively, P<0.001 for all). SG(death) and SG(blindness) demonstrated no correlation with BEVA, WEVA, or WVA (Pearson's correlation coefficients, range -0.06 to -0.125). TTO showed weak association only with WEVA and WVA (correlation coefficients -0.237, -0.228, P<0.0001), but not with BEVA (correlation coefficient -0.161). Clinical AMD severity correlated with EQ-5D and SG(death), but not with TTO and SG(blindness) (P=0.004, 0.002, 0.235, and 0.069, respectively).

Conclusions: AMD has a negative impact on utilities, although utility scores were high compared with Western cohorts. EQ-5D, TTO, and SG showed suboptimal construct validity, suggesting that health status utilities may not be sufficiently robust for cost-utility analyses in this population.

Eye advance online publication, 6 January 2012; doi:10.1038/eye.2011.218.

PMID: 22222257 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Jan 3. [Epub ahead of print]

[Perception of objects and scenes in age-related macular degeneration.]

[Article in French]

Tran TH, Boucart M.

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Abstract

Vision related quality of life questionnaires suggest that patients with AMD exhibit difficulties in finding objects and in mobility. In the natural environment, objects seldom appear in isolation. They appear in a spatial context which may obscure them in part or place obstacles in the patient's path. Furthermore, the luminance of a natural scene varies as a function of the hour of the day and the light source, which can

alter perception. This study aims to evaluate recognition of objects and natural scenes by patients with AMD, by using photographs of such scenes. Studies demonstrate that AMD patients are able to categorize scenes as nature scenes or urban scenes and to discriminate indoor from outdoor scenes with a high degree of precision. They detect objects better in isolation, in color, or against a white background than in their natural contexts. These patients encounter more difficulties than normally sighted individuals in detecting objects in a low-contrast, black-and-white scene. These results may have implications for rehabilitation, for layout of texts and magazines for the reading-impaired and for the rearrangement of the spatial environment of older AMD patients in order to facilitate mobility, finding objects and reducing the risk of falls.

PMID: 22221712 [PubMed - as supplied by publisher]

Pathogenesis

J Neurochem. 2012 Jan 5. doi: 10.1111/j.1471-4159.2012.07647.x. [Epub ahead of print]

Retinal cone and rod photoreceptor cells exhibit differential susceptibility to light-induced damage.

Okano K, Maeda A, Chen Y, Chauhan V, Tang J, Palczewska G, Sakai T, Tsuneoka H, Palczewski K, Maeda T.

Department of Pharmacology Department of Ophthalmology & Visual Sciences, Case Western Reserve University, Cleveland, 44106, U.S. A. Polgenix, Inc., Cleveland, 44106, U.S. A. Department of Ophthalmology, Jikei University School of Medicine, Tokyo, 105, Japan.

Abstract

All-trans-retinal and its condensation-products can cause retinal degeneration in a light-dependent manner and contribute to the pathogenesis of human macular diseases such as Stargardt's disease and age-related macular degeneration (AMD). Although these toxic retinoid by-products originate from rod and cone photoreceptor cells, the contribution of each cell type to light-induced retinal degeneration is unknown. Here the primary objective was to learn whether rods or cones are more susceptible to light-induced, all-trans-retinal-mediated damage. Previously, we reported that mice lacking enzymes that clear all-trans-retinal from the retina, ATP-binding cassette transporter 4 (ABCA4) and retinol dehydrogenase 8 (RDH8), manifested light-induced retinal dystrophy. We first examined early-stage-AMD patients and found retinal degenerative changes in rod-rich rather than cone-rich regions of the macula. We then evaluated transgenic mice with rod-only and cone-like-only retinas in addition to progenies of such mice inbred with Rdh8(-/-) Abca4(-/-) mice. Of all these strains, Rdh8(-/-) Abca4(-/-) mice with a mixed rod-cone population showed the most severe retinal degeneration under regular cyclic light conditions. Intense light exposure induced acute retinal damage in Rdh8(-/-) Abca4(-/-) and rod-only mice but not cone-like-only mice. These findings suggest that progression of retinal degeneration in Rdh8(-/-) Abca4(-/-) mice is affected by differential vulnerability of rods and cones to light.

PMID: 22220722 [PubMed - as supplied by publisher]

Exp Mol Med. 2012 Jan 9. [Epub ahead of print]

The discovery of placenta growth factor and its biological activity.

Falco SD.

Abstract

Angiogenesis is a complex biological phenomenon crucial for a correct embryonic development and for

post-natal growth. In adult life, it is a tightly regulated process confined to the uterus and ovary during the different phases of the menstrual cycle and to the heart and skeletal muscles after prolonged and sustained physical exercise. Conversly, angiogenesis is one of the major pathological changes associated with several complex diseases like cancer, atherosclerosis, arthritis, diabetic retinopathy and age-related macular degeneration (Carmeliet and Jain, 2011). Among the several molecular players involved in angiogenesis, some members of VEGF family, VEGF-A, VEGF-B and placental growth factor (PlGF), and the related receptors VEGF receptor 1 (VEGFR-1, also known as Flt-1) and VEGF receptor 2 (VEGFR-2, also known as Flk-1 in mice and KDR in human) have a decisive role (De Falco et al., 2002). In this review, we describe the discovery and molecular characteristics of PlGF, and discuss the biological role of this growth factor in physiological and pathological conditions.

PMID: 22228176 [PubMed - as supplied by publisher]

Chem Biol Drug Des. 2012 Jan 10. doi: 10.1111/j.1747-0285.2012.01324.x. [Epub ahead of print]

Molecular Dynamics in Drug Design: New Generations of Compstatin Analogs.

Tamamis P, López de Victoria A, Gorham RD Jr, Bellows-Peterson ML, Pierou P, Floudas CA, Morikis D, Archontis G.

Department of Bioengineering, University of California, Riverside, California 92521, USA. Department of Physics, University of Cyprus, PO20537, CY1678, Nicosia, Cyprus. Department of Chemical and Biological Engineering, Princeton University, Princeton, New Jersey 08544, USA.

Abstract

We report the computational and rational design of new generations of several tryptophan-rich peptides from the compstatin family. The binding efficacy of the peptides has been tested using extensive molecular dynamics-based structural and physicochemical analysis, using 32 atomic-detail trajectories in explicit water for 22 peptides bound to human, rat, or mouse target protein C3, to a total of 257 nanoseconds. The criteria for the new designs are: (i) optimization for high binding affinity and for the balance between hydrophobicity and polarity to improve solubility compared to known compstatin analogs; and (ii) development of dual specificity anti-human-rat/mouse C3 analogs, which is important for use in animal models for disease, given the species specificity of known compstatin analogs. Three of the new analogs have been analyzed in more detail as they possess strong and novel binding characteristics and are promising candidates for further optimization. This work paves the way for the development of an improved therapeutic for age-related macular degeneration, and other complement system-mediated diseases, compared to known compstatin variants. © 2012 John Wiley & Sons A/S.

PMID: 22233517 [PubMed - as supplied by publisher]

Histol Histopathol. 2012 Mar;27(3):357-64.

Immunohistochemical localization of complement regulatory proteins in the human retina.

Fett AL, Hermann MM, Muether PS, Kirchhof B, Fauser S.

Center of Ophthalmology, University of Cologne, Cologne, Germany.

Abstract

Age-related macular degeneration (AMD) is a complex disease. Genetic studies have found strong associations between AMD and variants of several complement pathway-associated genes. The regulation of the complement cascade seems to be critical in the pathogenesis of AMD. In 45 human donor eyes immunohistochemistry was performed using antibodies directed against major regulators of the

complement system: complement factor H (CFH), decay accelerating factor (DAF/CD55), complement receptor 1 (CR1/CD35), and membrane cofactor protein (MCP/CD46). All eyes were classified in AMD and controls. 11 eyes were graded as early AMD. 34 eyes were controls. In all eyes staining was found in intercapillary pillars of choroid adjacent to Bruch's membrane for CFH, at the basal surface of RPE cells for MCP, and at the apical side of the retinal pigment epithelium for CR1. DAF immunoreactivity was increased along the inner segments of rod and cone photoreceptor cells at the level of the external limiting membrane Labeling of soft drusen was found for CFH and CR1. In addition, DAF and CR1 showed staining of ganglion cells in all eyes. CFH and particularly MCP showed decreased or absent staining in eyes with early AMD adjacent to Bruch's membrane. The overlapping expression of regulators at the level of Bruch's membrane and the retinal pigment epithelium shows the importance of this site for control of the complement system. Decreased and therefore unbalanced expression of regulators, as shown in this study for CFH and MCP, may ultimately lead to AMD.

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Genetics

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Significance of C2/CFB Variants in Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy in a Japanese Population.

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Purpose: To determine whether genetic variants in the complement component 2 and factor B genes (C2/CFB) locus are associated with the risk of developing typical age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV) in a Japanese population.

Methods: We genotyped 4 single nucleotide polymorphisms (SNPs) across the C2/CFB locus of the patients with typical AMD (n = 455) or PCV (n = 581) and of 865 controls. Differences in the observed genotypic distribution between the case and control groups were tested by logistic regression analysis for age and gender adjustments. Significant associations were confirmed using a second control group of 336 cataract patients. A further model adjusting for age-related maculopathy susceptibility 2 (ARMS2) A69S, complement factor H (CFH) I62V, age, gender, and smoking status was performed for confirming their independent association from other covariates.

Results: C2 rs547154 and CFB rs541862 were significantly associated with typical AMD and PCV in a Japanese population ($P < 0.05$). These 2 SNPs were also significantly associated with typical AMD and PCV in evaluation using the second control cohort ($P < 0.05$). Furthermore, we found an independent association of C2/CFB variants for both typical AMD and PCV from age, gender, smoking, and genetic background of ARMS2 A69S and CFH I62V (vs typical AMD, $P = 0.0073$, odds ratio [OR] = 0.47; vs PCV, $P = 0.0083$, OR = 0.53).

Conclusions: C2/CFB variants play a protective role in the risk of developing neovascular AMD and PCV in the Japanese population.

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Population differences in genetic risk for age-related macular degeneration and implications for genetic testing.

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Diet

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The role of omega6 to omega3 ratio in development and progression of age-related macular degeneration.

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Abstract

The aim of this study is to investigate possible connection between omega-6/omega-3 fatty acid ratio and development and progression of Age-Related Macular Degeneration (ARMD). We examined 125 patients diagnosed with ARMD and divided into 5 groups of 25 patients according to CARMS (Clinical Age-Related Maculopathy Staging System). Control group consists of 51 patients with similar ages, without ARMD. All of them underwent stereobiomicroscopy, fundus photography and fluorescein angiography. Dietary fatty acids intake was measured using food frequency questionnaire (FFQ). The FFQ was based on previously validated questionnaire (DIETQ, Tinuviel Software, Warington, Ches, UK) and FFQ2 from Blue MountainEye Study. The data were analysed using food nutritient dana from McCance and Widdowson's Food Composition Tables, supplemented with a food fatty acid content database (Foodbase, London, UK). We noticed statistically significant difference between omega-6/omega-3 ratio in neovascular ARMD (stage 5) and all other groups including control group ($p = 0.000020$). The ratio in Stage 5 was about 11:1 like in Western diet. Stage 4-geographic atrophy (GA) has statistically significant difference in o-mega-6/omega-3 ratio compared with stage 1 ($p = 0.000571$), stage 2 ($p = 0.000112$) and stage3 ($p = 0.000430$). The ratio in first three groups is about 7-7.5:1 (greater then Mediteran-4-5:1, but lower then Western Diet-10-20:1). There is no statistically significant difference between first three stages ($p > 0.05$) and stage 4 and control group ($p = 0.172388$). Omega-6/omega-3 ratio is connected with development of neovascular ARMD. Decreased ratio protects against neovascular ARMD. On the contrary, GA seems to be connected with prolonged sunlight exposure (the ratio is about 6:1). It is good to know that changing nutrition habits someone can prevent development of severe neovascular form of ARMD because intravitreal anti-VEGF therapy limitations.

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