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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2013 Nov 26. [Epub ahead of print]

Response to anti-VEGF therapy in patients with subretinal fluid and pigment epithelial detachment on spectral-domain optical coherence tomography.

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PURPOSE: To analyse the long-term functional and morphological response of a specific choroidal neovascular membrane (CNV) phenotype to anti-vascular endothelial growth factor (VEGF) therapy.

METHODS: Data from 30 eyes of 30 consecutive patients with subretinal fluid (SRF) and fibrovascular pigment epithelial detachment (PED) due to CNV on spectral-domain optical coherence tomography (SDOCT) with a follow-up of at least 20 months were retrospectively collected. Main outcome measures included change in visual acuity, quantitative and qualitative parameters on SDOCT [photoreceptor layer, outer nuclear layer (ONL), choroid, PED, SRF] and on fluorescein angiography (CNV activity). Subjects were divided into responders and non-responders based on morphological and functional aspects.

RESULTS: An average number of 20.23 ± 9.9 anti-VEGF injections were administered during a mean follow-up of 40.25 ± 13.5 months. Fourteen eyes were categorized as morphological non-responders, 12 as functional non-responders and eight as complete non-responders. Complete non-responders were significantly younger than complete responders (68.5 ± 4.5 vs 74.3 ± 6.8 years; $p < 0.05$) and presented thinner baseline ONL values (68.43 ± 15.2 vs103.5 ± 32.8 μm; $p < 0.05$). Intermediate or large drusen as typical features for age-related macular degeneration (AMD) were less frequently present in complete non-responders; however, this was not statistically significant (62.5 % vs 91.7 %; $p = 0.25$).

CONCLUSIONS: Our preliminary findings indicate that eyes with the specific SDOCT phenotype with isolated fibrovascular PED and SRF frequently demonstrate non-response to anti-VEGF therapy, and the underlying disease mechanism may be different from AMD. Larger prospective trials are required to validate those results, and to develop strategies to improve the morphological as well as functional outcome.

PMID: 24271025 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Nov 22. [Epub ahead of print]

Degree of Decrease in Central Retinal Thickness Predicts Visual Acuity Response to Intravitreal Ranibizumab in Diabetic Macular Edema.

Santos AR, Gomes SC, Figueira J, Nunes S, Lobo CL, Cunha-Vaz JG.

Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal.

Purpose: To characterize factors that may be associated with optimal or suboptimal response to ranibizumab intravitreal injections in diabetic macular edema (DME).

Methods: Fifty-nine eyes with DME treated with ranibizumab were included. All underwent best-corrected visual acuity (BCVA) assessment and optical coherence tomography (OCT) at baseline, 3 and 6 months. Central retinal thickness (CRT) was assessed at each visit, and OCT images were classified according to their morphological patterns.

Results: A mean BCVA increase of 4.78 and 5.52 letters, and a CRT decrease of 80.25 and 106.12 μm were found after 3 and 6 months of treatment ($p < 0.001$). BCVA improvement was found to be dependent on baseline BCVA and the degree of CRT decrease. Twenty-six eyes (44%) showing a CRT decrease ≥20% improved BCVA by 10.3 ± 13.0 letters, whereas 33 eyes (56%) with a CRT decrease <20% had BCVA improvement of 1.8 ± 7.2 letters (odds ratio = 3.31).

Conclusions: The degree of CRT decrease obtained by spectral-domain OCT identifies well the optimal responders to intravitreal ranibizumab and predicts BCVA improvement after treatment.

PMID: 24280908 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Nov 19. pii: S0002-9394(13)00735-6. doi: 10.1016/j.ajo.2013.11.012. [Epub ahead of print]

Management Paradigms for Diabetic Macular Edema.

Mitchell P, Wong TY; Diabetic Macular Edema Treatment Guideline Working Group.

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PURPOSE: To provide evidence-based recommendations for diabetic macular edema (DME) management based on updated information from publications on DME treatment modalities.

DESIGN: Perspective.

METHODS: A literature search for "diabetic macular edema" or "diabetic maculopathy" was performed using the PubMed, Cochrane Library, and ClinicalTrials.gov databases to identify studies from January 1985 to July 2013. Meta-analyses, systematic reviews, and randomized controlled trials with at least 1 year of follow-up published in the past 5 years were preferred sources.

RESULTS: Although laser photocoagulation has been the standard treatment for DME for nearly 3 decades, there is increasing evidence that superior outcomes can be achieved with anti-vascular endothelial growth factor (anti-VEGF) therapy. Data providing the most robust evidence from large phase II and phase III clinical trials for ranibizumab demonstrated visual improvement and favorable safety profile for up to 3 years. Average best-corrected visual acuity change from baseline ranged from 6.1 to 10.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters for ranibizumab, compared to 1.4-5.9 ETDRS letters with laser. The proportion of patients gaining ≥ 10 or ≥ 15 letters with ranibizumab was at least 2-times higher than that of patients treated with laser. Patients were also more likely to experience visual loss with laser than with ranibizumab treatment. Ranibizumab was generally well tolerated in all studies. Studies for bevacizumab, aflibercept and pegaptanib in DME were limited but also in favor of anti-VEGF therapy over laser.

CONCLUSIONS: Anti-VEGF therapy is superior to laser photocoagulation for treatment of moderate-to-severe visual impairment caused by DME.

PMID: 24269850 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:10-7. doi: 10.1016/S0365-6691(12)70047-3.

[New treatment protocols and follow-up in patients with exudative age-related macular degeneration].[Article in Spanish]

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Abstract: Intravitreal ranibizumab (Lucentis®) injections are the treatment of choice in patients with exudative macular degeneration. In the last few years, several treatment and follow-up strategies have been evaluated with the aim of optimizing the safety and efficacy of this drug. In routine clinical practice, the Pro Re Nata (PRN) and treat-and-extend protocols or variants of the FUSION regimen have been used. PRN protocols are based on regular patient follow-up and on retreatment when there is evidence of reactivation of the lesion, basically determined by loss of visual acuity and persistent or recurrent macular fluid on optical coherence tomography. Treat-and-extend or FUSION protocols are based on early retreatment of the lesion before reactivation occurs with the aim of avoiding the irreversible visual loss that can occur in disease recurrences. There is no ideal treatment and follow-up protocol that could be used as an alternative to the monthly regimen and be applied and reproduced in all patients. Consequently, intravitreal ranibizumab therapy should be individualized in each patient.

PMID: 23380436 [PubMed - in process]

Arch Soc Esp Oftalmol. 2013 Aug 7. pii: S0365-6691(13)00193-7. doi: 10.1016/j.oftal.2013.05.002. [Epub ahead of print]

Initial experience with aflibercept in the management of patients with wet age-related macular degeneration refractory to ranibizumab and/or bevacizumab.

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PMID: 24269436 [PubMed - as supplied by publisher]

A Systematic Review of Intravitreal Bevacizumab for the Treatment of Diabetic Macular Edema [Internet].

Fortin P, Mintzes B, Innes M.

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2012 May.

CADTH Rapid Response Reports.

Excerpt: Diabetic retinopathy (DR) and diabetic macular edema (DME) are microvascular complications of diabetes that are a leading cause of blindness in the diabetic population. DME — which is swelling of the retina due to leakage of fluid from blood vessels within the macula, the central portion of the retina — may

occur at any time during the progression of DR. The goal of treatment is to preserve current visual acuity and reduce the chances of progression to visual loss. Successful laser treatment reduces moderate visual loss but has limited effects on improving visual acuity. Intravitreal injection of corticosteroids, such as triamcinolone acetate, may also moderately improve visual acuity, but these generally offer only short-term improvements in acuity in cases of DME refractory to laser treatment. Moreover, triamcinolone is not licensed by Health Canada for this indication. Ranibizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). It is the only pharmacological therapy licensed in Canada for the treatment of DME. Bevacizumab (Avastin), also derived from a recombinant humanized monoclonal IgG1 antibody that inhibits VEGF, is used clinically in the treatment of DME, although it does not have a Notice of Compliance (NoC) from Health Canada for this indication. It is approved as an antineoplastic, not for the condition under consideration. This systematic review was undertaken to evaluate the effects of intravitreal bevacizumab for the treatment of diabetic macular edema.

Sections

PMID: 24279000 [PubMed]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:54-62.

[From scientific evidence to clinical practice: treatment regimens for macular edema secondary to retinal vein occlusion].[Article in Spanish]

Abraldes MJ, Zapata MA, Gómez-Ulla F, García-Arumí J.

Abstract: Retinal vein occlusion (RVO) is the second most common cause of retinal vascular disease after diabetic retinopathy. Despite the existence of several possible treatment options, none was entirely satisfactory and many patients suffered irreversible visual loss. As a result of the BRAVO, CRUISE and GENEVA trials, ranibizumab and the intravitreal biodegradable implants of dexamethasone has recently been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of RVO secondary edema. In this paper we begin by describing the current treatment options for RVO associated macular edema and continue with the description of the treatment regimen with ranibizumab.

PMID: 24278990 [PubMed - in process]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:46-53.

[BRAVO and CRUISE: ranibizumab for the treatment of macular edema secondary to retinal vein occlusion].[Article in Spanish]

Figueroa MS, Ruiz Moreno JM.

Abstract: This article summarizes the results of the BRAVO and CRUISE trials, two randomized multicenter studies in patients with macular edema secondary to branch and central retinal vein occlusion, respectively. Randomization was 1:1:1 to 0.3 mg of ranibizumab, 0.5 mg of ranibizumab or placebo. Monthly injections were administered for 6 months followed by a 6-month observation period in which treatment on an on-demand (PRN) basis was applied with 0.5 mg ranibizumab. Patients in the control group were also eligible for 0.5 mg ranibizumab treatment in the observation period. The results showed a significant anatomical and visual improvement in both treatment groups 7 days after the intravitreal injection. PRN treatment with monthly follow-up maintained the visual improvements achieved after the first 6 months of treatment. Patients in the control group who received PRN treatment after the first 6 months showed an anatomical improvement similar to that in the treatment groups but less visual improvement.

PMID: 24278989 [PubMed - in process]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:38-45.

[From scientific evidence to clinical practice: treatment protocols for diabetic macular edema]. [Article in Spanish]

López-Gálvez MI, García-Campos JM.

Abstract: Diabetic macular edema (DME) is now considered the leading cause of moderate vision loss in type 2 diabetic patients and has a high socioeconomic burden. In recent years, the therapeutic approach to this entity has changed. The role of laser treatment, considered the gold standard in clinical practice worldwide for more than 25 years, has been redefined. To understand current treatment algorithms, the pathophysiology of diabetic macular edema and the role played by vascular endothelial growth factor must be elucidated. Many clinical trials have emerged showing that intravitreal ranibizumab provides effective therapy with an acceptable safety profile. Based in these data, the European Medicines Agency has approved ranibizumab for the treatment of diabetic macular edema. This article aims to discuss new treatment options and the recently developed evidence-based algorithms.

PMID: 24278988 [PubMed - in process]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:27-37.

[Randomized clinical trials in diabetic macular edema].[Article in Spanish]

Cabrera F, Armadá F.

Abstract: Diabetic macular edema (DME) is the main cause of visual acuity impairment in diabetic patients. The current standard therapy for patients with DME (focal/grid laser photocoagulation) usually does not improve impaired vision, and many patients continue to lose vision despite laser therapy. Vascular endothelial growth factor (VEGF) plays a key role in the pathogenesis of DME and is a major candidate as a therapeutic target for the treatment of DME. The advent of intravitreal anti-VEGF drugs, such a ranibizumab, has opened up a new era for the management of DME. The aim of this review is to summarize the evidence supporting the use of ranibizumab in clinical practice. The studies analyzed in this review are prospective, controlled, randomized clinical trials (RCT) that have focused on documenting the therapeutic effect of ranibizumab and its safety, providing encouraging results.

PMID: 24278987 [PubMed - in process]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2013 Nov 26. [Epub ahead of print]

Characterisation of reticular pseudodrusen and their central target aspect in multi-spectral, confocal scanning laser ophthalmoscopy.

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BACKGROUND: To analyse reticular pseudodrusen (RPD) in patients with age-related macular degeneration (AMD) using multi-spectral (MS), confocal scanning laser ophthalmoscopy (cSLO).

METHODS: cSLO images (blue fundus autofluorescence [FAF; exc., λ = 488; em., λ = 500-700 nm], near-infrared reflectance [IR; λ = 820 nm], MS [blue reflectance (BR) λ = 488 nm, green reflectance (GR) λ = 515 nm, IR λ = 820 nm], as well as colour fundus photographs (CFP) were taken of 200 eyes from 100 AMD patients suspected to show RPD on the basis of funduscopy or previous fundus imaging. FAF and IR images were graded by two independent readers. If both readers concordantly confirmed the presence of RPD in both modalities, eyes were subsequently also graded for RPD in MS, BR, GR, green-blue enhanced mode (GBE), and CFP. Besides, FAF, IR, and MS images were evaluated for the presence of a target aspect, which represents a common feature of RPD lesions.

RESULTS: The presence of RPD was confirmed using FAF and IR images by both readers in 130 eyes of 76 patients. In those eyes, both readers concordantly diagnosed RPD in MS images in 124 (95.4 %) eyes (BR: 52 [40.0 %], GR: 63 [48.5 %], GBE: 101 [77.7 %], CF: 27 [20.8 %]). Cohen kappa statistics revealed excellent inter-observer agreement for MS (0.95) and GBE (0.85), substantial agreement for BR (0.75), GR (0.78), and moderate agreement for CFP (0.59). A target aspect within RPD lesions was detected in 45 of 130 (35.0 %) included eyes using FAF and IR. The presence of a target aspect improved the recognition of RPD lesions in all modalities. If a target aspect was present, RPD were diagnosed in 45 eyes (100 %) using MS (GBE: 42 eyes [93.3 %], BR: 30 eyes [66.7 %], GR: 37 eyes [82.2 %], CFP: 17 eyes [37.8 %]). Using MS cSLO, a target aspect could be identified in 75 of 130 (57.7 %) included eyes.

CONCLUSIONS: MS cSLO imaging is equivalent to FAF and IR in identifying RPD in AMD patients. Higher identification rates in BR and GR of those RPD lesions featuring a target aspect confirm the current hypothesis of RPD localisation and its progression further into the photoreceptor layers. MS seems to be more sensitive in identifying a central target aspect in RPD lesions compared to blue FAF and IR.

PMID: 24276561 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Nov 26. pii: iovs.13-12931v1. doi: 10.1167/iovs.13-12931. [Epub ahead of print]

Comparison of Macular Choroidal Thickness in Adult Onset Foveomacular Vitelliform Dystrophy and Age-Related Macular Degeneration.

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Purpose: To compare Macular Choroidal Thickness (MCT) in eyes with adult onset foveo-macular vitelliform dystrophy (AOFVD) and eyes with age-related macular degeneration (AMD).

Methods: Five groups of 38 patients each were included in a prospective, observational, comparative study: 1) AOFVD eyes with fluid accumulation 2) AOFVD fellow eyes without fluid (early stage) 3) advanced exudative (wet) AMD 4) advanced dry AMD and 5) healthy normal eyes. All study eyes underwent a comprehensive ophthalmologic examination. MCT was measured using Spectralis (Heidelberg Engineering, Heidelberg, Germany) enhanced depth imaging optical coherence tomography (EDI-OCT).

Results: Subfoveal Choroidal thickness (SFCT) in AOFVD with subretinal fluid (325.66+/-85.98 µm) was significantly (p<0.001) thicker compared with that in exudative AMD (158.55 µm +/- 57.87) and in dry AMD (157.53 µm +/- 67.08). Also, in AOFVD, choroid was significantly (p=0.001) thicker than that in the normal group (255.87+/- 87.46). However, in AOFVD, there was no significant difference (p = 0.69) between the SFCT in the study eye and in the fellow eye (317.66 µm +/- 90.04). The choroidal thickness at each of the other 12 measured points showed similar results.

Conclusions: This study demonstrates choroidal thickening in AOFVD in contrast with the choroidal thinning observed in advanced AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in exudative AMD. Choroidal thickness measurement could help differentiate the challenging diagnosis between exudative AMD and the advanced stage of AOFVD (with fluid accumulation but without choroidal neovascularization).

PMID: 24282233 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Nov 27. [Epub ahead of print]

The incidental findings of age-related macular degeneration during diabetic retinopathy screening.

Gangwani R, Lai WW, Sum R, McGhee SM, Chan CW, Hedley AJ, Wong D.

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BACKGROUND: The purpose of this study was to determine the reliability of detecting age-related macular degeneration (AMD) during screening for diabetic retinopathy (DR).

METHODS: This prospective study included 2,003 subjects with diabetes mellitus who underwent photographic screening for DR. The reliability of detecting AMD lesions was tested by interobserver and intraobserver agreement, and the sensitivity and specificity of diagnosing AMD at different grades of severity were tested using the consensus grading of a group as the reference standard.

RESULTS: DR affected 24.7 % of the subjects. The age-standardized prevalence of early AMD was 17.9 %, and late AMD was 0.1 %. The interobserver and intraobserver agreement for grading AMD was substantial (k = 0.72 and 0.71 respectively, p < 0.001). It was equally good in those with different severities of DR. There was also no difference in sensitivity and specificity of detecting AMD in those with different levels of DR (sensitivity 62-68 % and specificity 97-98 %).

CONCLUSION: Intermediate- and high-risk AMD that warrant treatment with zinc and anti-oxidant supplements could be reliably detected during screening for diabetic retinopathy.

PMID: 24281784 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2012 Dec;87 Suppl 1:18-26. doi: 10.1016/S0365-6691(12)70048-5.

[Contributions to the treatment of atypical forms of age-related macular degeneration].[Article in Spanish]

Esteban González E, Cervera Taulet E.

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Abstract: We performed a study of the two clinical entities with a differential diagnosis with wet age-related macular degeneration, namely, idiopathic polypoidal choroidal vasculopathy (IPCV) and retinal angiomatous proliferation. We analyze the clinical and funduscopic characteristics of these entities as well as their differences with wet age-related macular degeneration. We present two cases that are representative of these two entities. The therapeutic possibilities, results and the latest publications are analyzed and compared. A statistical analysis of the latest publications is also presented.

PMID: 23380437 [PubMed - in process]

Ophthalmologica. 2013 Nov 21. [Epub ahead of print]

Polypoidal Choroidal Vasculopathy: Clinical Features and Genetic Predisposition.

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Abstract: Polypoidal choroidal vasculopathy (PCV) is currently recognized as a phenotype of age-related macular degeneration (AMD). PCV is believed to be a type of choroidal neovascularization, although some cases of PCV show a distinct vascular abnormality of the choroidal vessels. PCV often shows several unique clinical manifestations which are apparently different from typical neovascular AMD (tAMD). In addition, the natural course and response to treatment are often different between tAMD and PCV. Moreover, recent genetic studies suggested a possible difference in the genetic susceptibility to disease between tAMD and PCV, as well as the existence of heterogeneity among PCV cases. In viewing the accumulation of knowledge about PCV, we have summarized the recent literature regarding PCV in this review article to improve the understanding of this clinical entity including possible susceptibility genes. We will also discuss the optimal treatment strategies for PCV in accordance with the results of recent clinical and genetic studies. © 2013 S. Karger AG, Basel.

PMID: 24280967 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2013 Nov 22. [Epub ahead of print]

The yellow intraocular lens and the natural ageing lens.

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California San Diego, Shiley Eye Center, La Jolla, CA, USA.

PURPOSE OF REVIEW: The purpose of this study is to review and evaluate the advantages and disadvantages of blue light (400-480nm) filtering intraocular lenses (IOLs) when compared with the ultraviolet (UV)-blocking IOLs.

RECENT FINDINGS: Theories that blue light could be related to the pathogenesis of age-related macular degeneration (AMD) have led to the use of yellow tinted IOLs in cataract surgery to filter short wavelength light. In spite of the potential benefits, some concerns have been raised. The potential advantages of the blue light filtering IOLs are that they could better mimic the conditions of phakia and therefore be more protective for the retina in decreasing the incidence of AMD. However, the potential disadvantages are that blue light filtering could negatively affect scotopic vision and circadian rhythms in older patients.

SUMMARY: These advantages and disadvantages of blue light filtering IOLs have not been proven clinically and thus many questions remain. Studies have shown that each type of IOL may have its own benefits and the type of IOL should be picked on the basis of patients' specific situations. In cataract surgery, considerations such as preexisting AMD, night vision problems or sleep problems may be considered with the choice of IOL.

PMID: 24270599 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2013 Aug 1. pii: S0365-6691(13)00162-7. doi: 10.1016/j.oftal.2013.04.005. [Epub ahead of print]

Current trends in the rehabilitation of age related macular degeneration: IOL-VIP a promising future.

[Article in English, Spanish]

Pérez-Tejeda AA, Lázaro Izquierdo Y, Linares-Guerra M, Acuña-Pardo A, González Díaz RE.

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PMID: 24269444 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2012 Dec 25. pii: S0365-6691(12)00535-7. doi: 10.1016/j.oftal.2012.11.004. [Epub ahead of print]

Multiple retinal pigment epithelial detachments: a case report.

[Article in English, Spanish]

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CASE REPORT: A 47 year-old female who presented with a bilateral idiopathic multiple pigment epithelial detachment (PED) in a routine visit. This pathology is shown as a rare clinical manifestation, where the outcome is resolution of localized atrophy of the pigment epithelium, with a good functional prognosis.

DISCUSSION: PED is a common clinical manifestation in several chorioretinal diseases, particularly in macular degeneration associated with age. Idiopathic PED can be considered as a kind of central type II serous chorioretinopathy. Fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) are complementary tests to study the number, extension, and nature of these PED.

PMID: 24269392 [PubMed - as supplied by publisher]

Pathogenesis

Pharmacol Ther. 2013 Nov 25. pii: S0163-7258(13)00220-9. doi: 10.1016/j.pharmthera.2013.11.002. [Epub ahead of print]

The Ocular Renin-Angiotensin System: A Therapeutic Target for the Treatment of Ocular Disease.

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Abstract: The renin-angiotensin system (RAS) is most well-known for its role in regulation and dysregulation of blood pressure as well as fluid and electrolyte homeostasis. Due to its ability to cause cardiovascular disease, the RAS is the target of a multitude of drugs that antagonize its pathophysiological effects. While the "classical" RAS is a systemic hormonal system, there is an increasing awareness of the existence and functional significance of local RASs in a number of organs, e.g., liver, kidney, heart, lungs, reproductive organs, adipose tissue, adrenal. The eye is one of these organs where a compelling body of evidence has demonstrated the presence of a local RAS. Individual components of the RAS have been shown to be present in many structures of the eye and their potential functional significance in ocular disease states is described. Because the eye is one of the most important and complex organs in the body, this review also discusses the implications of dysregulation of the systemic RAS on the pathogenesis of ocular diseases and how pharmacological manipulation of the RAS might lead to novel or adjunctive therapies for ocular disease states.

PMID: 24287313 [PubMed - as supplied by publisher]

BMB Rep. 2013 Dec 1. pii: 2491. [Epub ahead of print]

Increased 26S proteasome non-ATPase regulatory subunit 1 in the aqueous humor of patients with age-related macular degeneration.

Lee H, Choi AJ, Kang GY, Park HS, Kim HC, Lim HJ, Chung H.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the world. Evidence indicates that the suppression of the ubiquitin-proteasome system (UPS) contributes to the accumulation of toxic proteins and inflammation in retinal pigment epithelium (RPE), the functional abnormalities and/or the degeneration of which are believed to be the initiators and major pathologies of AMD. To identify new protein associations with the altered UPS in AMD, we used LC-ESI-MS/MS to perform a proteomic analysis of the aqueous humor (AH) of AMD patients and matched control subjects. Six UPS-related proteins were present in the AH of the patients and control subjects. Four of the proteins, including 26S proteasome non-ATPase regulatory subunit 1 (Rpn2), were increased in patients, according to semi-quantitative proteomic profiling. An LC-MRM assay revealed a significant increase of Rpn2 in 15 AMD patients compared to the control subjects, suggesting that this protein could be a biomarker for AMD.

PMID: 24286321 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Nov 23. pii: S0014-4835(13)00333-3. doi: 10.1016/j.exer.2013.11.006. [Epub ahead of print]

Anti-angiogenic effect of the basement membrane protein nidogen-1 in a mouse model of choroidal

neovascularization.

Semkova I, Kociok N, Karagiannis D, Nischt R, Smyth N, Paulsson M, Strauß O, Joussen AM.

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Abstract: In patients with age-related macular degeneration disruption of the integrity of the retinal pigment epithelium (RPE) and Bruch's membrane (BrM), precedes choroidal neovascularization (CNV). We investigated the role of the basement membrane (BM) proteins nidogen-1 and nidogen-2 for the development of experimental CNV. Laser-induced CNV was studied in Nid1-/- and Nid2-/- mice and wild type (WT) controls by fluorescein angiography, by immune histochemistry of flat mounts or paraffin sections to analyse expression pattern of nidogen-1 and -2 and nidogen binding BM proteins, and by western blotting. The influence of VEGF and bFGF on the mRNA expression of nidogen-1 was studied in vitro. Nidogen-1 protein is present in the BM of the inner limiting membrane (ILM), the retinal capillaries, and the choroid/sclera and CNV. Nidogen-2 protein is also found in these BMs but with a weaker expression in the ILM. In the retina the absence of nidogen-1 does not influence the expression of nidogen-2 and vice versa and does not influence the expression of the BM components collagen IV, laminin γ1, and perlecan. In Nid1 -/- mice, CNV lesions showed increased vessel leakage during angiography and the CNV area was larger than in WT or nidogen-2 deficient mice. Laser treatment led to up-regulation of nidogen-1 protein expression in the sclera/choroid of nidogen-2 deficient or WT mice. The treatment of HUVECs with VEGF leads to a reduced expression of nidogen-1 mRNA whereas its expression remained unchanged in RPE cells. In conclusion, nidogen-1 produced by the endothelial cells acts as a factor to help stabilizing the BM, thus preventing the sprouting of new vessels or the infiltration of endothelial cells. In this sense nidogen-1 is essential to provide an anti-angiogenic environment of differentiated vessels.

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Biochim Biophys Acta. 2013 Nov 22. pii: S0167-4889(13)00401-1. doi: 10.1016/j.bbamcr.2013.11.010. [Epub ahead of print]

Alpha-crystallin-mediated protection of lens cells against heat and oxidative stress-induced cell death.

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Abstract: In addition to their key role as structural lens proteins, α-crystallins also appear to confer protection against many eye diseases, including cataract, retinitis pigmentosa, and macular degeneration. Exogenous recombinant α-crystallin proteins were examined for their ability to prevent cell death induced by heat or oxidative stress in a human lens epithelial cell line (HLE-B3). Wild type αA- or αB-crystallin (WT-αA and WT-αB) and αA- or αB-crystallins, modified by the addition of a cell penetration peptide (CPP) designed to enhance the uptake of proteins into cells (gC-αB, TAT-αB, gC-αA), were produced by recombinant methods. In vitro chaperone-like assays were used to assay the ability of α-crystallins to protect client proteins from chemical or heat induced aggregation. In vivo viability assays were performed in HLE-B3 to determine whether pre-treatment with α-crystallins reduced death after exposure to oxidative or heat stress. Most of the five recombinant α-crystallin proteins tested conferred some in vitro protection from protein aggregation, with the greatest effect seen with WT-αB and gC-αB. All α-crystallins displayed significant protection to oxidative stress induced cell death, while only the αB-crystallins reduced cell death induced by thermal stress. Our findings indicate that the addition of the gC tag enhanced the protective effect of αB-crystallin against oxidative but not thermally-induced cell death. In conclusion, modifications that increase the uptake of α-crystallin proteins into cells, without destroying their chaperone-like activity and anti-apoptotic functions, create the potential to use these proteins therapeutically.

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Mo Med. 2013 Sep-Oct;110(5):429-36.

A case for neuroprotection in ophthalmology: developments in translational research.

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Abstract: Cellular aging occurs by the lifelong accumulation of oxidative damage leading to neuronal apoptosis, termed 'neurodegeneration', and the functional deficits of aging. Loss of visual function is one of the most important quality of life measures for older adults. We discuss recent clinical and laboratory advances in the neuroprotective treatment of the aging eye with particular emphasis on the three major ocular neurodegenerative conditions: glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR).

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Pharmacokinetics of macrolactin A and 7-O-succinyl macrolactin A in mice.

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Abstract 1. As promising anti-macular degeneration and/or anti-tumour agents, a better understanding of the pharmacokinetics of macrolactin A (MA) and 7-O-succinyl macrolactin A (SMA) is essential. Thus, we evaluated the pharmacokinetics of MA and SMA after intravenous, oral, or intraperitoneal administration of each drug to mice. 2. Both hepatic and extra-hepatic extractions of MA were expected based on the rapid total body clearance (CL) of MA. MA also showed a large steady-state volume of distribution (Vss) in mice. A relatively slower CL (by 54.1%) and smaller Vss (by 85.8%) were observed for SMA than for MA. In accordance with the larger Vss values of MA than of SMA, the mouse tissues studied had good affinity to MA but less affinity to SMA. 3. Both MA and SMA had an extremely low oral extent of absolute bioavailability (F). This could have been a result of the instability of MA and SMA in the gastrointestinal tract, supported by their unstable property in acidic buffer. Gastrointestinal and/or hepatic first-pass extraction of MA and SMA may be other reasons. 4. The pharmacokinetic profiles of both MA and SMA were much improved (greater AUC and F values) following intraperitoneal administration than following oral administration due to avoidance of acidic degradation and/or gastrointestinal first-pass extraction.

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Epidemiology

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CURRENT KNOWLEDGE AND TRENDS IN AGE-RELATED MACULAR DEGENERATION: Genetics, Epidemiology, and Prevention.

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PURPOSE: To address the most dynamic and current issues concerning human genetics, risk factors, pharmacoeconomics, and prevention regarding age-related macular degeneration.

METHODS: An online review of the database Pubmed and Ovid was performed, searching for the key words: age-related macular degeneration, AMD, pharmacoeconomics, risk factors, VEGF, prevention, genetics and their compound phrases. The search was limited to articles published since 1985 to date. All returned articles were carefully screened and their references were manually reviewed for additional relevant data. The webpage www.clinicaltrials.gov was also accessed in search of relevant research trials.

RESULTS: A total of 366 articles were reviewed, including 64 additional articles extracted from the references and 25 webpages and online databases from different institutions. At the end, only 244 references were included in this review.

CONCLUSION: Age-related macular degeneration is a complex multifactorial disease that has an uneven manifestation around the world but with one common denominator, it is increasing and spreading. The economic burden that this disease poses in developed nations will increase in the coming years. Effective preventive therapies need to be developed in the near future.

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Genetics

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Affinity purification of human factor h on polypeptides derived from streptococcal m protein: enrichment of the y402 variant.

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Abstract: Recent studies indicate that defective activity of complement factor H (FH) is associated with several human diseases, suggesting that pure FH may be used for therapy. Here, we describe a simple method to isolate human FH, based on the specific interaction between FH and the hypervariable region (HVR) of certain Streptococcus pyogenes M proteins. Special interest was focused on the FH polymorphism Y402H, which is associated with the common eye disease age-related macular degeneration (AMD) and has also been implicated in the binding to M protein. Using a fusion protein containing two copies of the M5-HVR, we found that the Y402 and H402 variants of FH could be efficiently purified by single-step affinity chromatography from human serum containing the corresponding protein. Different M proteins vary in their binding properties, and the M6 and M5 proteins, but not the M18 protein, showed selective binding of the FH Y402 variant. Accordingly, chromatography on a fusion protein derived from the M6-HVR allowed enrichment of the Y402 protein from serum containing both variants. Thus, the exquisite binding specificity of a bacterial protein can be exploited to develop a simple and robust procedure to purify FH and to enrich for the FH variant that protects against AMD.

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Prospective Study of Common Variants in CX3CR1 and Risk of Macular Degeneration: Pooled Analysis From 5 Long-term Studies.

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IMPORTANCE: The CX3CR1 gene is implicated as a candidate gene for age-related macular degeneration (AMD) through several lines of evidence. There is uncertainty, however, as to whether common genetic variants in CX3CR1 alter risk of AMD, since prior studies have been inconsistent and mostly limited to evaluation of 2 nonsynonymous variants, T280M (rs3732378) and V249I (rs3732379).

OBJECTIVE: To determine if common variants in CX3CR1 predict future risk of AMD.

DESIGN, SETTING, AND PARTICIPANTS: Prospective nested case-control study within 5 large study populations with long-term follow-up. We measured genotypes for T280M, V249I, and 13 other common single-nucleotide polymorphisms (SNPs) of the CX3CR1 gene among people who developed AMD (n = 1110, including 369 with neovascular AMD) and 2532 age- and sex-matched controls.

MAIN OUTCOMES AND MEASURES: We determined the incidence rate ratios (RR) and 95% CIs for incidence of AMD for each variant and examined interactions with other AMD-associated variants and modifiable risk factors.

RESULTS: In additive genetic models, we identified nonsignificant associations with AMD for T280M (RR, 0.87; P = .07) and 3 other SNPs, rs2853707 (RR, 0.88; P = .07), rs12636547 (RR, 0.85; P = .10), and rs1877563 (RR, 0.84; P = .06), 1 of which, rs2853707, is positioned in the CX3CR1 promoter region and was associated with neovascular AMD (RR, 0.75; P = .03). We observed that a recessive model was a better fit to the data for some SNPs, with associations between rs11715522 and AMD (RR, 1.27; P = .03) and between rs2669845 (RR, 3.10; P = .04), rs2853707 (RR, 0.48; P = .050), and rs9868689 (RR, 0.31; P = .02) and neovascular AMD. Moreover, in exploratory analyses, we identified a number of possible interactions including between V249I and rs2669845 and dietary intake of ω-3 fatty acids (P = .004 and P = .009, respectively) for AMD; between rs2669845 and obesity (P = .03) for neovascular AMD; between T280M and complement component 3 (C3) R102G for AMD (P = .03); between rs2669845 and Y402H in complement factor H for AMD (P = .04); and between rs2669845, rs2853707, and V249I and C3 R102G for neovascular AMD (P = .008; .04; and .002, respectively).

CONCLUSIONS AND RELEVANCE: This study failed to identify significant associations between common CX3CR1 variants and AMD after considering the number of SNPs analyzed and multiple comparisons. However, we observed evidence consistent with recessive modes of association and that an effect of CX3CR1 variants may depend on other factors including dietary intake of ω-3 fatty acids, obesity, and genotypes at CFH Y402H and C3 R102G. If replicated in other populations, these findings would support a role for CX3CR1 in AMD but also suggest that its role may involve mechanisms that are independent of the T280M/V249I variations.

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Human Complement Factor H and Factor H-Like Protein 1 Are Expressed in Human Retinal Pigment Epithelial Cells.

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Background: A common haplotype in the gene for the regulator of the alternative pathway of complement activation factor H has been linked to individual predisposition to age- related macular degeneration (AMD).

Methods: In this study, retinal pigment epithelial (RPE) cells, i.e. immortalized ARPE-19 as well as primary human RPE cells, were investigated for expression of factor H and FHL-1 by immunohistochemistry and in situ hybridization analysis.

Results: Factor H and the alternative spliced product FHL-1 are expressed in RPE cells, i.e. in immortalized ARPE-19 and primary human RPE cells. Factor H and FHL-1 expression was induced in a dose-dependent manner in ARPE-19 cells upon treatment with the inflammatory marker interleukin-6 (IL-6). In situ hybridization experiments confirmed an elevated expression rate of the factor H gene in IL-6-treated ARPE-19 cells. AMD is characterized by complement-associated inflammatory processes in the retina. Thus, local synthesis of complement regulators affects the protection of retinal cells and may be involved in the pathogenesis at the RPE-choroid interface.

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Detecting Rare Haplotype-Environment Interaction With Logistic Bayesian LASSO.

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Abstract: Two important contributors to missing heritability are believed to be rare variants and gene-environment interaction (GXE). Thus, detecting GXE where G is a rare haplotype variant (rHTV) is a pressing problem. Haplotype analysis is usually the natural second step to follow up on a genomic region that is implicated to be associated through single nucleotide variants (SNV) analysis. Further, rHTV can tag associated rare SNV and provide greater power to detect them than popular collapsing methods. Recently we proposed Logistic Bayesian LASSO (LBL) for detecting rHTV association with case-control data. LBL shrinks the unassociated (especially common) haplotypes toward zero so that an associated rHTV can be identified with greater power. Here, we incorporate environmental factors and their interactions with haplotypes in LBL. As LBL is based on retrospective likelihood, this extension is not trivial. We model the joint distribution of haplotypes and covariates given the case-control status. We apply the approach (LBL-GXE) to the Michigan, Mayo, AREDS, Pennsylvania Cohort Study on Age-related Macular Degeneration (AMD). LBL-GXE detects interaction of a specific rHTV in CFH gene with smoking. To the best of our knowledge, this is the first time in the AMD literature that an interaction of smoking with a specific (rather than pooled) rHTV has been implicated. We also carry out simulations and find that LBL-GXE has reasonably good powers for detecting interactions with rHTV while keeping the type I error rates well controlled. Thus, we conclude that LBL-GXE is a useful tool for uncovering missing heritability.

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Diet & lifestyle

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A Multivitamin Supplement and Cataract and Age-Related Macular Degeneration in a Randomized Trial of Male Physicians.

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PURPOSE: To test whether long-term multivitamin supplementation affects the incidence of cataract or age -related macular degeneration (AMD) in a large cohort of men.

DESIGN: Randomized, double-blind, placebo-controlled trial.

PARTICIPANTS: A total of 14 641 US male physicians aged ≥50 years.

INTERVENTION: Daily multivitamin or placebo.

MAIN OUTCOME MEASURES: Incident cataract and visually significant AMD responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-reports confirmed by medical record review.

RESULTS: During an average of 11.2 years of treatment and follow-up, a total of 1817 cases of cataract and 281 cases of visually significant AMD were confirmed. There were 872 cataracts in the multivitamin group and 945 cataracts in the placebo group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.83-0.99; P = 0.04). For visually significant AMD, there were 152 cases in the multivitamin group and 129 cases in the placebo group (HR, 1.19; 95% CI, 0.94-1.50; P = 0.15).

CONCLUSIONS: These randomized trial data from a large cohort of middle-aged and older US male physicians indicate that long-term daily multivitamin use modestly and significantly decreased the risk of cataract but had no significant effect on visually significant AMD.

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