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MD Research News

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Drug treatment

Clin Ophthalmol. 2011;5:1499-502. Epub 2011 Oct 14.

Evaluation of patients' experiences at different stages of the intravitreal injection procedure - what can be improved?

Tailor R, Beasley R, Yang Y, Narendran N.

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INTRODUCTION: Intravitreal injection of ranibizumab has become one of the most commonly performed ophthalmic procedures. It is timely to conduct an evaluation of the injection procedure from the patient's perspective so as to determine ways to improve patient experience. The purpose of this study was to quantitatively describe patients' experiences of the different stages of the intravitreal injection procedure and provide suggestions for improvement.

METHOD: Following intravitreal injection, patients were administered a questionnaire to score the distress felt for each of ten parts of the whole injection process from the initial waiting to the final instillation of topical antibiotic at the end. A score of higher than 4 was regarded as significantly unpleasant. The proportion of scores above 4 for each step was used to evaluate the relative distress experienced by patients for the different parts of the procedure.

RESULTS: A total of 42 patients were surveyed. The step with the highest percentage of patients scoring more than 4 was the injection step (19%). However, cumulatively, the steps relating to the application of the drape, the speculum, and the removal of drape accounted for 53% of scores greater than 4.

CONCLUSION: There is considerable variation in how patients tolerate different stages of the injection procedure. The needle entry was the most unpleasant step followed by the draping steps cumulatively. Use of subconjunctival anesthesia, a perforated drape, and alternative lid exclusion devices may help to improve the patient's tolerability of the procedure and experience.

PMID: 22069352 [PubMed]

J Ocul Pharmacol Ther. 2011 Nov 8. [Epub ahead of print]

The 12-Month Outcome of Three Consecutive Monthly Intravitreal Injections of Ranibizumab for Myopic Choroidal Neovascularization.

Wu TT, Kung YH.

Department of Ophthalmology, Kaohsiung Veterans General Hospital , Kaohsiung, Taiwan, Republic of China .

Purpose: The aim of this study was to evaluate the 12-month outcomes, efficacy, and safety of three consecutive monthly intravitreal ranibizumab injections for myopic choroidal neovascularization (CNV).

Methods: We retrospectively reviewed the medical records of 25 consecutive eyes that received a loading dose of three consecutive monthly intravitreal injections of ranibizumab for myopic CNV between February, 2008, and March, 2010, with a follow-up of 12 months. Eyes with persistent or recurrent CNV after 3 months received additional ranibizumab injections as needed. Patients' demographic data, best corrected visual acuity (BCVA), CNV findings on fluorescent angiography (FAG), central macular thickness (CMT) on optical coherence tomography (OCT), total number of treatments, and complications were recorded.

Results: Mean baseline BCVA was 0.73 logarithm of the minimum angle of resolution (logMAR) (standard deviation [SD] 0.63), and improved significantly to 0.42 logMAR (SD 0.43) at 1 month, 0.38 logMAR (SD 0.47) at 2 months, 0.34 logMAR (SD 0.43) at 3 months, and 0.34 logMAR (SD 0.40) at 12 months (all P<0.001, Wilcoxon signed-rank test). The average number of injections was 3.44 (SD 0.92). At 12 months, mean improvement was 2.88 lines (SD 2.35), and 20 eyes (80%) showed a gain of at least one line after treatment. At 3 months, OCT showed significant reduction in CMT (P=0.012, two-tailed t-test), and FAG showed significant reduction of mean CNV size from 0.3 (SD 0.16) to 0.19 (SD 0.12) disc area (P=0.007, two-tailed t-test). No angiographic leakage was evident at 3 months in 21 eyes (84%); four eyes (16%) required additional injections for persistent leakage. Two eyes (8%) had recurrent CNV during follow-up and required retreatment. No complications were noted after treatment.

Conclusions: An initial loading dose of three ranibizumab injections is safe and effective in treating myopic CNV, with visual improvement maintained over 12 months.

PMID: 22066662 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Nov 4. [Epub ahead of print]

Effect on Intraocular Pressure in Patients Receiving Unilateral Intravitreal Anti-Vascular Endothelial Growth Factor Injections.

Hoang QV, Mendonca LS, Torre KE, Jung JJ, Tsuang AJ, Freund KB.

Vitreous Retina Macula Consultants of New York, New York, New York; LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Institute, New York, New York; Edward S. Harkness Eye Institute, Columbia University College of Physicians and Surgeons, New York, New York; Department of Ophthalmology, New York University Medical Center, New York, New York.

PURPOSE: We assessed the frequency and predictive factors related to intraocular pressure (IOP) elevation in neovascular age-related macular degeneration (AMD) patients undergoing unilateral intravitreal ranibizumab and/or bevacizumab injections.

DESIGN: Retrospective cohort study.

PARTICIPANTS: Charts of 207 patients with neovascular AMD who presented to a single physician at a retinal referral practice over a 6-month period were retrospectively reviewed.

METHODS: Data recorded included demographic information, clinical findings, total number of bevacizumab and ranibizumab injections received and IOP at each visit. Increases above baseline IOP of >5, >10, or >15 mmHg on ≥2 consecutive visits while under treatment were noted.

MAIN OUTCOME MEASURES: The frequency of IOP elevation was compared between treated and untreated eyes. In addition, among treated eyes, frequency and odds ratio of experiencing IOP elevation >5

mmHg above baseline on ≥2 consecutive visits was stratified by number of injections. For the main regression analysis, the outcome variable was IOP elevation >5 mmHg on ≥2 consecutive visits and the main independent variable was total number of injections.

RESULTS: On ≥2 consecutive visits, 11.6% of treated versus 5.3% of untreated/control eyes experienced IOP elevation of >5 mmHg. The mean number of injections was higher in those with (24.4; 95% confidence interval [CI], 20.9-28.0; range, 9-39) than without IOP elevation of >5 mmHg (20.4; 95% CI, 18.9-21.8; range, 3-48) on ≥2 consecutive visits. There was an increased odds ratio (5.75; 95% CI, 1.19-27.8; P = 0.03) of experiencing IOP elevation >5 mmHg on ≥2 consecutive visits in patients receiving ≥29 injections compared with ≤12 injections. Of the factors considered, only the total number of injections showed a statistically significant association with IOP elevation >5 mmHg above baseline on ≥2 consecutive visits in treated eyes (P = 0.05).

CONCLUSIONS: A greater number of intravitreal anti-vasular endothelial growth factor injections is associated with an increased risk for IOP elevation >5 mmHg on ≥2 consecutive visits in eyes with neovascular AMD receiving intravitreal ranbizumab and/or bevacizumab.

PMID: 22054994 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Nov 4. [Epub ahead of print]

Expression and Role of VEGF in the Adult Retinal Pigment Epithelium.

Ford KM, Saint-Geniez M, Walshe T, Zahr A, D'Amore PA.

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Purpose: Despite a lack of active angiogenesis, VEGF is expressed in nearly every adult tissue, and recent evidence suggests that VEGF may serve as a survival factor for both vascular and non-vascular tissues. VEGF blockade is a widely used treatment for neovascular diseases such as wet age-related macular degeneration (AMD). Therefore, we sought to evaluate the expression and role of endogenous VEGF in RPE.

Methods: VEGF and VEGFR2 expression in the murine retina were assessed during development. Bevacizumab was used to neutralize VEGF in ARPE-19 cells, and the effects on cell survival and apical microvill were assessed by TUNEL and SEM, respectively. VEGF was systemically neutralized in vivo by adenoviral-mediated overexpression of soluble VEGFR1 (sFlt). RPE and choriocapillaris were analyzed by TEM. Changes in gene expression were evaluated by quantitative real-time PCR.

Results: VEGF expression was detected in the developing RPE as early as E9.5, whereas VEGFR2 expression by RPE began non-uniformly between P6.5 and P8.5. VEGF neutralization in vitro led to increased apoptosis and reduced microvilli density and length. Systemic VEGF neutralization led to transient degenerative changes; RPE were vacuolated and separated from photoreceptor outer segments, and choriocapillaris fenestrations were decreased. VEGF levels were elevated in RPE of Ad-sFlt1 mice at day four, and there was increased expression of the neurotrophic factor NPD1 at day 14.

Conclusion: Our results indicate that VEGF plays a critical role in survival and maintenance of RPE integrity. Potential undesired off-target effects should be considered with chronic use of anti-VEGF agents.

PMID: 22058334 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2011 Aug;74(4):289-91.

Intravitreal injection of ranibizumab for foveal-macular pattern dystrophy: case report.

Ventura AA, Grant LW, Dadgostar H, Lewis H.

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Abstract

In the recent years, anti-angiogenic medications have successfully treated other diseases associated with choroidal neovascularization. The anti-angiogenic therapy alone or combined with LASER and/or steroids has been effective in controlling ocular neovascularization, not only restricted to the treatment of typical membranes due to macular degeneration in the wet form. The discovery and subsequent use of these drugs has revolutionized medicine and ophthalmology. This report illustrates an example of successful treatment in a challenging pathology where it was found important visual and anatomical response after the use of ranibizumab.

PMID: 22068859 [PubMed - in process]

Nihon Ganka Gakkai Zasshi. 2011 Sep;115(9):825-31.

[Cost-effectiveness of ranibizumab, photodynamic therapy and pegaptanib sodium in the treatment of neovascular age-related macular degeneration in Japanese].

[Article in Japanese]

Yanagi Y, Aihara Y, Fukuda T, Hashimoto H.

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PURPOSE: To perform cost-utility analysis of ranibizumab, photodynamic therapy (PDT) and pegaptanib sodium treatment of neovascular age-related macular degeneration (AMD) with subfoveal choroidal neovascularization.

MATERIALS AND METHODS: The analyses were performed on a 75-year old man with the starting visual acuity of letter score of 50 on an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, with the affected eye having better sight than the contralateral eye, for the time horizons of 1 and 11 year (s). Visual acuity data from the large controlled studies for ranibizumab, photodynamic therapy and pegaptanib sodium, were applied. The results were compared with best supportive care (BSC) data. Cost indications included direct medical costs and costs related with social blindness. Utility values were estimated from the time trade off method. This analysis was performed from a societal perspective.

RESULTS: In the 1-year model, cost of treatment was dominant in the treatment groups, whereas the cost of blindness was dominant in the BSC. In the 11-year model, influence of cost of blindness resulted in the increasing costs for BSC. Of note, ranibizumab and PDT were less costly and showed an increase in utility compared to the BSC. Pegaptanib sodium was found to be costly. Sensitivity analysis found that the results were robust to changes in various model parameters.

CONCLUSION: In the current model, ranibizumab and PDT confer quality-adjusted life years (QALY) gains and are less costly compared to BSC in the lifetime treatment. In contrast, pegaptanib sodium treatment could be considered to be of minimal cost-effectiveness. Ranibizumab and PDT confer excellent value in the models of the lifetime treatment.

PMID: 22073599 [PubMed - in process]

Ophthalmologica. 2011 Nov 1. [Epub ahead of print]

Long-Term Follow-Up of Myopic Choroidal Neovascularization Treated with Ranibizumab.

Franqueira N, Cachulo ML, Pires I, Fonseca P, Marques I, Figueira J, Silva R.

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Purpose: To evaluate the long-term safety and efficacy of intravitreal ranibizumab in the treatment of myopic choroidal neovascularization (CNV).

Methods: Three-year retrospective, nonrandomized, interventional case series. Forty eyes of 39 patients with myopic CNV were included; 15 with previous photodynamic therapy, and 25 naïve eyes. Best-corrected visual acuity (BCVA) changes, central foveal thickness (CFT), and number of treatments were assessed, from baseline to month 36.

Results: Mean visual acuity improved from 55.4 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at baseline to 59.7 letters at 12 months ($p = 0.07$), 61.8 letters at 24 months ($p = 0.008$) and 63.4 letters at 36 months ($p = 0.039$). Twenty-five percent of the patients gained ≥15 letters (3 lines) at 12 months, 30% at 24 months and 35% at 36 months. There was a mean reduction of 80 μm in CFT ($p < 0.001$). A mean of 4.1 injections were performed in the first year, 2.4 in the second year and 1.1 in the third year. Fifty-three percent of the eyes had no need for treatment during the third year of follow-up.

Conclusions: Intravitreal ranibizumab seems to be an effective and safe therapeutic procedure to treat CNV in highly myopic eyes, with a high proportion of patients gaining or stabilizing BCVA at a 3-year follow-up.

PMID: 22056757 [PubMed - as supplied by publisher]

Eye (Lond). 2011 Nov 4. doi: 10.1038/eye.2011.193. [Epub ahead of print]

Comment on 'Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab'

Vallance JH.

Ninewells Hospital, Dundee, UK.

PMID: 22056862 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Curr Eye Res. 2011 Nov 9. [Epub ahead of print]

Early Age-Related Macular Degeneration in Patients with Myocardial Infarction.

Liutkeviciene R, Lesauskaite V, Zaliuniene D, Zaliaduonyte-Peksiene D, Cimbalas A, Jasinskas V, Gustiene O, Simonyt S, Tamosiunas A.

Department of Ophthalmology, Lithuanian University of Health Sciences , Medicine Academy, Kaunas , Lithuania.

Purpose: To investigate the prevalence of early age-related macular degeneration (AMD) in patients with acute myocardial infarction (MI).

Methods: Enrolled in the study were 262 acute MI patients (MI group), aged 40-64 years, as well as 1,155 non-MI persons, aged 40-64 years, from a random sample (reference group) of the Kaunas population.

Results: The prevalence of early AMD in the random sample was 7.3%, while in MI patients, the prevalence was 54.5% ($P<0.001$). For all age groups, the prevalence of early AMD was significantly ($P<0.005$) higher in MI patients than in reference-group persons. In the reference group, the prevalence of early AMD

increased significantly with age, whereas no such trend was observed in the MI group. At the 45- to 54-year -olds, the prevalence was significantly higher in males than in females (9.9% vs. 3.7%; P<0.05) in the reference group, while overall, the prevalence of early AMD in the males and females of the much larger reference group was 8.6% versus 6.2%, respectively (P>0.05). It increased more with age for females (3.7% and 10.8% at the age 45-54 and 55-64 years, P<0.05, respectively) while in males, frequency of AMD did not differ significantly between latter age groups (9.9% vs. 11.6%; P>0.05).

Conclusion: We conclude that the prevalence of early AMD is significantly higher in patients with MI than in a random sample of the population.

PMID: 22070427 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Nov 7. [Epub ahead of print]

Determinants of Fixation in Eyes with Neovascular Age-Related Macular Degeneration Treated with Intravitreal Ranibizumab.

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PURPOSE: To correlate the anatomic features of the macula with functional parameters like location and stability of fixation in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab injections.

DESIGN: Retrospective analysis.

METHODS: The location and stability of fixation were determined in 41 eyes of 41 patients treated with ranibizumab for neovascular age-related macular degeneration for at least 12 months. All patients underwent 3 injections of ranibizumab 1 month apart and were retreated according to predefined criteria. The fixation parameters measured with microperimetry were correlated to visual acuity, qualitative measures on optical coherence tomography, and patterns of autofluorescence.

RESULTS: The location of fixation was predominantly central in 68.29%, poor central in 2.4%, and predominantly eccentric in 29.27%. The fixation was stable in 80.5%, relatively unstable in 7.3%, and unstable in 12.2%. The factors that determined central and stable location of fixation were better visual acuity (P = .004), absence of subretinal thickening (P = .003), intact subfoveal third hyperreflective band (P = .006), and intact external limiting membrane (P = .036). Autofluorescence pattern within the 4-degree circle of fovea did not correlate with fixation characteristics. However, complete absence of autofluorescence in this area was a poor prognostic indicator for central fixation.

CONCLUSIONS: Anatomic characteristics of the macula determine fixation patterns in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab injections. Further studies focused on eyes with complete absence of autofluorescence in the central 4-degree circle of fovea may help to define the disease characteristics in this group.

PMID: 22071230 [PubMed - as supplied by publisher]

Ann Clin Psychiatry. 2011 Nov;23(4):277-84.

Treatment of depression associated with age-related macular degeneration: A double-blind, randomized, controlled study.

Brody BL, Field LC, Roch-Levecq AC, Moutier CY, Edland SD, Brown SI.

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BACKGROUND: Depression is frequently found in patients with age-related macular degeneration (AMD). The purpose of this study was to assess the effectiveness of escitalopram in treating major and minor depression in AMD patients.

METHODS: We conducted a crossover, randomized, double-blind, placebo-controlled, 16-week study comparing escitalopram with placebo. Inclusion criteria included reduced vision from AMD and major or minor depression, with a 17-item Hamilton Rating Scale for Depression (HAMD-17) score of ≥10. Participants were randomly assigned to receive either escitalopram or placebo for 8 weeks and then crossed over to the other treatment. The primary outcome was change on the total HAMD-17 score with escitalopram treatment compared with placebo.

RESULTS: We enrolled 16 AMD patients (mean age 79.1), 12 with major depression and 4 with minor depression. Mean HAMD-17 score at enrollment was 16.1 ± 4.2, and mean visual acuity in the better eye was 20/70. During escitalopram treatment, participants showed a significant reduction in HAMD-17 scores compared with placebo treatment (P = .01).

CONCLUSIONS: These findings suggest escitalopram may be an effective treatment for depression associated with age-related macular degeneration.

PMID: 22073385 [PubMed - in process]

Epidemiology

Ophthalmic Epidemiol. 2011 Dec;18(6):253-8.

Is Bilateral Age-related Macular Degeneration Less Common in Asians than Caucasians?

Kawasaki R, Wang JJ, Amirul FM, Rochtchina E, Aung T, Saw SM, Mitchell P, Wong TY.

Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne , Victoria , Australia.

Purpose: To compare the frequency and pattern of bilateral involvement of early and late age-related macular degeneration (AMD) between Asian Malays and Caucasians.

Methods: We used cross-sectional data from the baseline examination for subjects aged 50-79 years in the Singapore Malay Eye Study (SiMES) (N = 2,453) and the Blue Mountains Eye Study (BMES) (N = 3,265). We assessed AMD signs using a common protocol modified from the Wisconsin Age-related Maculopathy Grading System at the University of Sydney. We compared frequencies or proportions of AMD cases with bilateral involvement between the two populations.

Results: There were 173 cases and 169 cases with any AMD (either early or late AMD in at least one eye), and 78 cases (45.1%) and 52 cases (30.8%) with bilateral AMD in the BMES and the SiMES, respectively. Age-standardized frequency of bilateral involvement was comparable between the BMES (29.5%, 95% confidence interval(CI) 18.5-40.5%) and the SiMES (25.6%, 95%CI 17.0-34.0%). Older age was associated with higher risk of bilateral AMD (gender-adjusted odds ratio per 1 year for the BMES and the SiMES: 1.08 [95% CI 1.05-1.11] and 1.06 [95% CI 1.02-1.10], respectively).

Conclusions: The frequency of bilateral AMD was comparable between Asian Malays in the SiMES and the Caucasian population of the BMES. Other than older age, we did not find any characteristics associated with the bilateral involvement of AMD.

PMID: 22053833 [PubMed - in process]

Pathogenesis

FASEB J. 2011 Nov 8. [Epub ahead of print]

Heat treatment of retinal pigment epithelium induces production of elastic lamina components and antiangiogenic activity.

Sekiyama E, Saint-Geniez M, Yoneda K, Hisatomi T, Nakao S, Walshe TE, Maruyama K, Hafezi-Moghadam A, Miller JW, Kinoshita S, D'Amore PA.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in the Western world. In advanced AMD, new vessels from choriocapillaris (CC) invade through the Bruch's membrane (BrM) into the retina, forming choroidal neovascularization (CNV). BrM, an elastic lamina that is located between the retinal pigment epithelium (RPE) and CC, is thought to act as a physical and functional barrier against CNV. The BrM of patients with early AMD are characterized by decreased levels of antiangiogenic factors, including endostatin, thrombospondin-1 (TSP-1), and pigment epithelium-derived factor (PEDF), as well as by degeneration of the elastic layer. Motivated by a previous report that heat increases elastin expression in human skin, we examined the effect of heat on human ARPE-19 cell production of BrM components. Heat treatment stimulated the production of BrM components, including TSP-1, PEDF, and tropoelastin in vitro and increased the antiangiogenic activity of RPE measured in a mouse corneal pocket assay. The effect of heat on experimental CNV was investigated by pretreating the retina with heat via infrared diode laser prior to the induction of CNV. Heat treatment blocked the development of experimental CNV in vivo. These findings suggest that heat treatment may restore BrM integrity and barrier function against new vessel growth.-Sekiyama, E., Saint-Geniez, M., Yoneda, K., Hisatomi, T., Nakao, S., Walshe, T. E., Maruyama, K., Hafezi-Moghadam, A., Miller, J. W., Kinoshita, S., D'Amore, P. A. Heat treatment of retinal pigment epithelium induces production of elastic lamina components and anti-angiogenic activity.

PMID: 22067481 [PubMed - as supplied by publisher]

Aging Clin Exp Res. 2011 Aug;23(4):264-7.

Serum superoxide dismutase and malondialdehyde levels in a group of Chinese patients with age-related macular degeneration.

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BACKGROUND AND AIMS: The aim of this study was to investigate superoxide dismutase (SOD) activity together with malondialdehyde (MDA) levels in a group of Chinese patients with age-related macular degeneration (AMD).

METHODS: Serum SOD activity and MDA levels were analysed in 56 AMD patients with subtypes (early dry, geographic atrophy, and wet) and 34 healthy controls matched with age and sex.

RESULTS: Serum MDA levels were significantly higher in AMD (3.68±1.06 nmol/mL) than in controls (2.83±0.43 nmol/mL; p=0.000), and was significantly higher in wet AMD (3.79±0.79 nmol/mL) than in early dry AMD (3.26±0.99 nmol/mL; p=0.038). Serum SOD activity was significantly higher in AMD (87.12±13.22 U/mL) than in controls (79.91±11.80 U/mL; p=0.012), and slightly higher in wet AMD (89.52±16.25 U/mL) than in GA (83.62±9.75 U/mL; p=0.275) and early dry AMD (81.64±18.90 U/mL; p=0.093). There was a positive correlation between serum MDA levels and SOD activities in AMD patients and controls (r=0.320, p=0.002).

CONCLUSIONS: The observed increase in SOD activity in our study may be related to increased MDA levels, as a compensatory regulation in response to oxidative stress in AMD patients. The present data also demonstrate that oxido-reduction disturbance may be hypothesized in the pathogenesis of AMD.

PMID: 22067370 [PubMed - in process]

Acta Ophthalmol. 2011 Nov 8. doi: 10.1111/j.1755-3768.2011.02295.x. [Epub ahead of print]

Complement system activation and endothelial dysfunction in patients with age-related macular degeneration (AMD): possible relationship between AMD and atherosclerosis.

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Abstract

Age-related macular degeneration (AMD) shares several pathological and epidemiological similarities with systemic atherosclerosis (AS). First, an association between AS and AMD is apparent from the analyses of the histological and biochemical structure of atherosclerotic plaques in the vascular walls and retinal drusen, the hallmark of AMD. Second, there is considerable evidence implicating endothelial dysfunction in the pathogenesis of both disorders, and cellular oxidative stress appears to be a common denominator underlying this process. Moreover, there are observations that the complement system (CS) triggering inflammatory response contributes to the onset and advancement of both diseases. The CS plays a role in the generation of drusen and neovascularization in AMD as well as in vascular endothelium activation, cell damage and ultimately atherosclerotic plaque formation in the course of systemic arteriosclerosis. It is widely recognized that both AMD and AS are not only related to local stimulation of the CS, but also result in its systemic activation. In addition, a specific Y402H polymorphism of the complement inhibitor factor H has been found to be associated with the incidence of both AMD and AS. Here, we propose a linking hypothesis between CS activation, endothelial dysfunction and the pathogenesis of two common and age-related pathological processes, AS and AMD. We also discuss the potential therapeutic value of pharmacological modulation of CS activation in these disorders.

PMID: 22067048 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2011 Dec;18(6):259-63.

Chronic Kidney Disease, Early Age-related Macular Degeneration, and Peripheral Retinal Drusen.

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Department of Family Medicine, Konkuk University Medical Center, Konkuk University School of Medicine , Seoul , Korea.

Purpose: To evaluate the association between chronic kidney disease (CKD) and early age-related macular degeneration (AMD) and peripheral retinal drusen in Korean adults 50 years and older.

Methods: This study included 3008 participants aged 50-87 years. Early AMD was assessed from retinal photographs based on modified Wisconsin AMD grading system and peripheral retinal drusen were assessed with a standardized examination. We defined CKD as estimated glomerular filtration rate of 60mL/min/1.73m(2) and below according to the Modification of Diet in Renal Disease equation. Logistic regression was used to examine the association between early AMD, peripheral retinal drusen, and CKD.

Results: There were 88 subjects with early AMD and 42 subjects with peripheral retinal drusen. After adjusting for age, gender, body mass index, smoking status, hypertension, and diabetes mellitus, a significant association was found between CKD and peripheral retinal drusen as well as early AMD. Subjects with CKD were more likely to have early AMD (OR, 1.68; 95% CI, 1.04-2.72) and peripheral retinal drusen (OR, 2.01; 95% CI, 1.02-3.99) than those without CKD.

Conclusions: CKD was associated with peripheral retinal drusen as well as early AMD in Korean adults 50 years and older.

PMID: 22053834 [PubMed - in process]

Exp Eye Res. 2011 Nov 2. [Epub ahead of print]

A novel melano-lysosome in the retinal epithelium of rhesus monkeys.

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Abstract

The large phagocytic load that confronts the retinal pigment epithelium (RPE) is thought to play a possible role in the pathogenesis of age related macular degeneration (AMD) that afflicts both humans and monkeys. Our knowledge of how RPE degrades phagosomes and other intra-cellular material by lysosomal action is still rudimentary. In this paper we examine organelles that play a role in this process, melanosome, lysosomes and phagosomes, in the RPE of young and old rhesus monkeys in order to better understand lysosomal autophagy and heterophagy in the RPE and its possible role in AMD. We used electron microscopy to detect and describe the characteristics of melanosomes and lysosome-like organelles in the macular RPE of rhesus monkeys (Macaca mulatta) that were 1, 6, 24, 24, 26 and 35 years of age. The measurements include the number, shape and size of these organelles located in the basal, middle and apical regions of RPE cells. Phaagosomes were also examined but not counted or measured for size or shape because of their rarity. Melanosomes were homogeneously dark with a circular or elliptical shape and decreased in number with age. Smaller melanosomes were more common at the basal side of the RPE. Among the small melanosomes, we found an organelle that was losing melanin in varying degrees; in some cases was nearly devoid of melanin. Because of the melanin loss, we considered this organelle to be a unique type of autophagic melano-lysosome, which we called a Type 1 lysosome. We found another organelle, more canonically lysosomal, which we called a Type 2 lysosome. This organelle was composed of a light matrix containing melanosomes in various stages of degradation. Type 2 lysosomes without melanosomes were rare. Type 2 lysosomes increased while Type 1 decreased in number with age. Phagosomes were rare in both young and old monkeys. They made close contact with Type 2 lysosomes which we considered responsible for their degradation. Melanosomes are being lost from monkey RPE with age. Much of this loss is carried out by two types of lysosomes. One, not defined as unique before, appears to be autophagic in digesting its own melanin; it has been called a Type 1 lysosome. The other, a more canonical lysosome, is both heterophagic in digesting phagosomes and autophagic in digesting local melanosomes; it has been called a Type 2 lysosome. Type 1 lysosomes decrease while type 2 lysosomes increase with age. The loss of melanin is considered to be detrimental to the RPE since it reduces melanin's protective action against light toxicity and oxidative stress. Phagosomes appear to be degraded by membrane contacts with Type 2 lysosomes. The loss of melanin and the buildup of Type 2 lysosomes occur at an earlier age in monkeys than humans implying that a greater vulnerability to senescence accelerates the rate of AMD in monkeys.

PMID: 22056912 [PubMed - as supplied by publisher]

Clin Exp Immunol. 2011 Dec;166(3):333-7. doi: 10.1111/j.1365-2249.2011.04482.x.

The major risk alleles of age-related macular degeneration (AMD) in CFH do not play a major role in rheumatoid arthritis (RA).

Trouw LA, Böhringer S, Daha NA, Stahl EA, Raychaudhuri S, Kurreeman FA, Stoeken-Rijsbergen G, Houwing-Duistermaat JJ, Huizinga TW, Toes RE.

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Abstract

Because activation of the alternative pathway (AP) of the complement system is an important aspect of both age-related macular degeneration (AMD) and rheumatoid arthritis (RA), we wished to address the question whether genetic risk factors of the AP inhibitor complement factor H (CFH) for AMD would also be risk factors for RA. For this purpose we genotyped single nucleotide polymorphisms (SNPs) in a Dutch set of RA patients and controls. Similarly, a meta-analysis using a Spanish cohort of RA as well as six large genome-wide association studies (GWAS) studies was performed. For these SNPs we analysed more than 6000 patients and 20 000 controls. The CFH variants, I62V, Y402H, IVS1 and IVS10, known to associate strongly with AMD, did not show a significant association with the risk of developing RA despite a strong statistical power to detect such differences. In conclusion, the major risk alleles of AMD in CFH do not have a similar effect on developing RA.

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Persistent Inflammation Subverts Thrombospondin-1-Induced Regulation of Retinal Angiogenesis and Is Driven by CCR2 Ligation.

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Abstract

Neovascular retinal disease is a leading cause of blindness orchestrated by inflammatory responses. Although noninfectious uveoretinitis is mediated by CD4(+) T cells, in the persistent phase of disease, angiogenic responses are observed, along with degeneration of the retina. Full clinical manifestation relies on myeloid-derived cells, which are phenotypically distinct from, but potentially sharing common effector responses to, age-related macular degeneration. To interrogate inflammation-mediated angiogenesis, we investigated experimental autoimmune uveoretinitis, an animal model for human uveitis. After the initial acute phase of severe inflammation, the retina sustains a persistent low-grade inflammation with tissue-infiltrating leukocytes for over 4 months. During this persistent phase, angiogenesis is observed as retinal neovascular membranes that arise from inflamed venules and postcapillary venules, increase in size as the disease progresses, and are associated with infiltrating arginase-1(+) macrophages. In the absence of thrombospondin-1, retinal neovascular membranes are markedly increased and are associated with arginase-1(-) CD68(+) macrophages, whereas deletion of the chemokine receptor CCR2 resulted in reduced retinal neovascular membranes in association with a predominant neutrophil infiltrate. CCR2 is important for macrophage recruitment to the retina in experimental autoimmune uveoretinitis and promotes chronicity in the form of a persistent angiogenesis response, which in turn is regulated by constitutive expression of angiogenic inhibitors like thrombospondin-1. This model offers a new platform to dissect the molecular and cellular pathology of inflammation-induced ocular angiogenesis.

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Genetics

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Associations between genetic polymorphisms of insulin-like growth factor axis genes and risk for age-related macular degeneration.

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Purpose: Our objective was to investigate if insulin-like growth factor (IGF) axis genes, together with a novel dietary risk factor, dietary glycemic index (dGI), and body mass index (BMI) affect the risk for age-related macular degeneration (AMD).

Methods: We used a case-control design with 962 subjects originally recruited through the Age-Related Eye Disease Study (AREDS) Genetic Repository. After excluding those with missing covariates or invalid calorie intake (n=23), diabetes (n=59), and non-Caucasian race (n=16), 864 participants were used in this study, including 209 AREDS category 1 participants (control group), 354 category 2 or 3 participants (drusen group), and 301 category 4 participants (advanced AMD group). A total of 25 single nucleotide polymorphisms (SNPs) selected from IGF-1 (n=9), IGF-2 (n=1), IGF binding protein 1 (IGFBP1) (n=3), IGFBP3 (n=3), acid-labile subunit of IGFBP (IGFALS) (n=2), IGF1 receptor (IGF1R) (n=4), and IGF2R (n=3) were genotyped. SNP-AMD associations were measured with genotype-, allele X2 tests and Armitage's trend test. Odds ratios (OR), 95% confidence intervals (CIs) and SNP-exposure interactions were evaluated by multivariate logistic regression.

Results: One SNP (rs2872060) in IGF1R revealed a significant association with advanced AMD (P-Allele=0.0009, P-Trend=0.0008; significance level was set at 0.05/25=0.002 for multiple comparisons). The risk allele (G) in the heterozygous and homozygous state (OR=1.67 and 2.93; 95% CI: 1.03-2.71 and 1.60-5.36, respectively) suggests susceptibility and suggests an additive effect on AMD risk. Further stratification analysis remained significant for both neovascularization (OR=1.49 and 2.61; 95% CI: 0.90-2.48 and 1.39-4.90, respectively) and geographic atrophy (OR=2.57 and 4.52; 95% CI: 0.99-6.71 and 1.49-13.74, respectively). The G allele interaction analysis with BMI was significant for neovascularization (P=0.042) but not for geographic atrophy (P=0.47). No significant interaction was found with dGI.

Conclusion: These data suggest a role of IGF1R on the risk for advanced AMD in this group of subjects.

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Gene transfer for ocular neovascularization and macular edema.

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Abstract

Diseases complicated by abnormal growth of vessels or excessive leakage are the most prevalent cause of moderate or severe vision loss in developed countries. Recent progress unraveling the molecular pathogenesis of several of these disease processes has led to new drug therapies that have provided major benefits to patients. However, those treatments often require frequent intraocular injections, and despite monthly injections, some patients have a suboptimal response. Gene transfer of antiangiogenic proteins is an alternative approach that has the potential to provide long-term suppression of

neovascularization (NV) and/or excessive vascular leakage in the eye. Studies in animal models of ocular NV have demonstrated impressive results with a number of transgenes, and a clinical trial in patients with advanced neovascular age-related macular degeneration has provided proof-of-concept. Two ongoing clinical trials, one using an adeno-associated viral (AAV) vector to express a vascular endothelial growth factor-binding protein and another using a lentiviral vector to express endostatin and angiostatin, will provide valuable information that should help to inform future trials and provide a foundation on which to build.Gene Therapy advance online publication, 10 November 2011; doi:10.1038/gt.2011.164.

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Analysis of candidate genes for age-related macular degeneration subtypes in the Japanese population.

Tanaka K, Nakayama T, Yuzawa M, Wang Z, Kawamura A, Mori R, Nakashizuka H, Sato N, Mizutani Y.

PURPOSE: Age-related macular degeneration (AMD) is thought to be a polygenetic disease. It is divided into three subtypes; neovascular AMD (nAMD), polypoidal choroidal vasculopathy, and retinal angiomatous proliferation (RAP). These subtypes are thought to have different pathophysiological and genetic backgrounds. We aimed to investigate the relationships between single nucleotide polymorphisms (SNPs) in candidate genes and subtypes of AMD in the Japanese population.

METHODS: We genotyped 685 AMD patients and 277 controls for four SNPs of the selected candidate genes: rs800292 in complement factor H, rs10490924 in age-related maculopathy susceptibility 2 (ARMS2), rs2301995 in elastin (ELN), and rs1801133 in methylenetetrahydrofolate reductase (MTHFR). Case-control studies were performed using these AMD subtypes. Logistic regression analysis was performed using a history of hypertension, diabetes mellitus, and smoking as cardiovascular risks.

RESULTS: The genotype-dominant or recessive distribution of all four SNPs differed significantly between the controls and the AMD patients. In the subtype analysis, there were significant differences between the controls and the AMD patients in genotype distributions. This was true for all AMD subtype analyses of both rs800292 (complement factor H) and rs10490924 (ARMS2). Logistic regression analysis indicated the TT genotype of the ARMS2 gene to be significantly more common in RAP patients ($p=1.54\times10(-13)$, odds ratio: 22.18). In contrast, there were significant differences in the genotype distribution between the controls and nAMD patients only for rs2301995 (ELN, $p=0.022$) and rs1801133 (MTHFR, $p=2.50\times10(-3)$).

CONCLUSIONS: Our results indicate that SNPs of the ARMS2 gene may serve as strong genetic markers of RAP, and that SNPs of the ELN and MTHFR genes are potential genetic markers for nAMD.

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Diet

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Beyond AREDS: Is There a Place for Antioxidant Therapy in the Prevention/Treatment of Eye Disease?

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Abstract

Age-related macular degeneration (AMD), the major cause of blindness in adults (65 years of age and older), and diabetic retinopathy, the major cause of blindness in working adults, are chronic, progressive diseases with multifaceted etiologies that are not fully understood. Progression and lack of treatment of both diseases may lead to the advanced stage with neovascularization. Although the detailed cellular mechanisms leading to the development of AMD and diabetic retinopathy remain elusive, oxidative damage to the retina and its pigment epithelium are considered to be involved. Clinical studies have shown that the progression of AMD can be slowed down by nutritional antioxidants, but trials with antioxidants for diabetic retinopathy (very limited in number) have been inconclusive. Long-term administration of the AREDS antioxidants, the same nutritional antioxidants that have been demonstrated to slow the progression of AMD, have yielded exciting results in preventing the pathogenesis of retinopathy in diabetic rodents. These results suggest the merit of testing the AREDS antioxidants in a clinical trial to prevent the development and/or progression of diabetic retinopathy, with the possibility of reducing the impact of this common vision-threatening disease.

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