Issue 7

Monday December 13, 2010

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

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Drug treatment

J Ocul Biol Dis Infor. 2010 Jul 9;3(1):30-4.

The need for validation of large administrative databases: Veterans Health Administration ICD-9CM coding of exudative age-related macular degeneration and ranibizumab usage.

Latkany P, Duggal M, Goulet J, Paek H, Rambo M, Palmisano P, Levin W, Erdos J, Justice A, Brandt C.

Abstract

We performed a validation study by chart review of data for exudative age-related macular degeneration (eAMD) and, because of the Veterans Administration (VA) therapy policy, ranibizumab usage in the largest electronic medical record system in the USA. We reviewed 5,854 distinct patients who visited an ophthalmology clinic within VA Connecticut from January 2006-December 2008. We randomly selected 98 of 138 distinct eAMD patients and 265 of 5,588 non-eAMD patients who did not receive ranibizumab. International Classification of Diseases, Ninth Revision, Clinical Modification coding of eAMD had an excellent positive predictive value of 97.8% (95% confidence interval (CI), 93.5-99.4%). The national Decision Support System (DSS) had an excellent positive predictive value of 100% (95% CI, 79.9-100%) for ranibizumab. However, the negative predictive value of the DSS dispensed ranibizumab decreased to 67.5 (95% CI, 62.1-72.4) because of a change in the way local values were stored that led to errors. Therefore, validation of clinical information over time in large databases is necessary.

PMID: 21139706 [PubMed - in process]

Eur J Ophthalmol. 2010 Nov 18. pii: 27797B04-3E89-4931-A42A-C1ACB3879EDE. [Epub ahead of print]

Does intravitreal injection of ranibizumab increase the risk for macular hole formation and Author's reply.

Walter HS, Gatzioufas Z, El-Husseiny M, Stavridis E, Seitz B.

Department of Ophthalmology, University of Saarland, Homburg/Saar - Germany.

PMID: 21140364 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2010 Nov 10;4:1279-85.

A protocol for the retina surgeon's safe initial intravitreal injections.

Frenkel RE, Haji SA, La M, Frenkel MP, Reyes A.

Eye Research Foundation, Stuart, FL, USA.

Abstract

PURPOSE: To determine the safety of a surgeon's initial consecutive intravitreal injections using a specific protocol and to review the complications that may be attributed to the injection procedure.

DESIGN: A retrospective chart review.

PARTICIPANTS: Fifty-nine patients (30 females, 29 males) received intravitreal injections of pegaptanib, bevacizumab, or ranibizumab as part of their treatment for neovascular age-related macular degeneration. The average patient age was 80 years. Twenty-two patients were diagnosed with or suspected of having glaucoma. Each patient received an average of 5.8 injections.

METHODS: The charts of 59 patients who received a total of 345 intravitreal injections (104 pegaptanib, 74 bevacizumab, 167 ranibizumab) were reviewed. All injections were performed in an office-based setting. Povidone-iodine, topical antibiotics, and eye speculum were used as part of the pre injection procedure. Vision and intraocular pressure were evaluated immediately following each injection.

MAIN OUTCOME MEASURES: Incidence of post injection complications, including but not limited to endophthalmitis, retinal detachment, traumatic cataract, and vitreous hemorrhage.

RESULTS: There were no cases of endophthalmitis, toxic reactions, traumatic cataracts, retinal detachment, or vitreous hemorrhage. There was one case each of lid swelling, transient floaters, retinal pigment epithelial tear, corneal edema, and corneal abrasion. There were five cases of transient no light perception following pegaptanib injections.

CONCLUSION: The incidence of serious complications was very low for the intravitreal injections given. A surgeon's initial intravitreal injections may be performed with a very high degree of safety using this protocol.

PMID: 21139676 [PubMed - in process]

Can J Ophthalmol. 2010 Dec;45(6):590-5.

Effectiveness of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration in a Canadian retina practice: a retrospective review.

Bandukwala T, Muni RH, Schwartz C, Eng KT, Kertes PJ.

Abstract

Objective: To assess the effectiveness of intravitreal ranibizumab for neovascular age-related macular degeneration (AMD) in a tertiary care retina practice and compare these results with published efficacy data from randomized clinical trials.

Design: Nonrandomized, consecutive, single-centre, retrospective chart review analysis.Participants: Ninety -four patients (95 eyes) with neovascular AMD.

Methods: All treatment-naïve patients with neovascular AMD who received ranibizumab and for whom 1 year of follow-up was available were included in the analysis. The following information was gathered from each patient's chart: age, sex, ocular history, treated eye, duration of symptoms at presentation, subtype of choroidal neovascular membrane, Snellen visual acuity at each visit, number of injections, visits, and optical coherence tomography measurements.

Results: Subjects had a mean age of 81 (SD 7.11) years. The mean number of injections was 5.1 (SD 2.85) with a mean of 9.4 (SD 2.27) visits in the 12-month period. Overall, there was a gain of 2.88 (SD 24.6) letters in all eyes, and a loss of 2.5 (SD 23.1) letters in patients who met the visual acuity inclusion criteria for the clinical trials. Of the patients who met the inclusion criteria, 75% lost fewer than 15 letters and 11% gained more than 15 letters.

Conclusions: Visual outcomes in our study patients compared poorly with the clinical trials. Possibilities for the disparity include gaps in the number and frequency of follow-up visits, patient or doctor assessment fatigue, or gaps in optical coherence tomography utilization and the number of injections administered.

PMID: 21135894 [PubMed - in process]

Other treatment

Optom Vis Sci. 2010 Dec 2. [Epub ahead of print]

Traffic Gap Detection for Pedestrians with Low Vision.

Geruschat DR, Fujiwara K, Emerson RS.

*PhD Salus University, Philadelphia, Pennsylvania (DRG), Johns Hopkins University, Baltimore, Maryland (KF), and Western Michigan University, Kalamazoo, Michigan (RSWE).

Abstract

PURPOSE.: Pedestrians with low vision have identified crossing the street as a difficult task. With the increasing complexity of the crossing environment (actuated signals and roundabouts), the challenges are increasing. The purpose of this study was to evaluate the effect of two types of vision loss (central or peripheral) on the ability to detect gaps in traffic.

METHODS.: Forty-one subjects participated with 14 being fully sighted (FS), 10 having central vision loss from age-related macular degeneration (AMD), and 17 having peripheral vision loss from either retinitis pigmentosa or glaucoma. Standing at entry and exit lanes of a roundabout, subjects depressed a handheld trigger to indicate when there was a sufficient gap in traffic to cross the street. A total of twelve 2-min intervals were completed including four of those intervals with occluded hearing.

RESULTS.: No difference was found in the ability of the three subject groups to identify crossable or short gaps. There were significant differences in latency and safety margin. The AMD subjects did not perform as well as the FS or the subjects with retinitis pigmentosa/glaucoma. When hearing was occluded, the two vision loss groups did not show a change in sensitivity but the FS group did, being more sensitive when hearing was occluded.

CONCLUSIONS.: The purpose of this study was to evaluate the effect of low vision on the ability to detect crossable gaps in traffic. The findings suggest that subjects with AMD have an increased risk because they show significant latency in their identification of gaps and this in turn results in a reduction of safety margin.

PMID: 21131877 [PubMed - as supplied by publisher]

Genetics

Mol Vis. 2010 Nov 17;16:2412-24.

Associations of smoking, body mass index, dietary lutein, and the LIPC gene variant rs10468017 with advanced age-related macular degeneration.

Seddon JM, Reynolds R, Rosner B.

Abstract

OBJECTIVE: A novel locus in the hepatic lipase (LIPC) gene was found to be significantly related to advanced age-related macular degeneration (AMD) in our genome-wide association study. We evaluated its association and interaction with previously identified genetic variants and modifiable factors.

METHODS: Participants in the Age-Related Eye Disease Study with advanced AMD (n=545 cases) or no AMD (n=275 controls) were evaluated. AMD status was determined using fundus photography. Covariates included cigarette smoking, body mass index (BMI), and dietary lutein. Individuals were genotyped for the rs10468017 polymorphism in LIPC as well as seven previously identified AMD genetic loci. Unconditional logistic regression analyses were then performed.

RESULTS: The TT genotype of the LIPC variant was associated with a reduced risk of AMD, with odds ratios (OR) of 0.50 (95% confidence interval (CI) 0.20-0.90) and p=0.014 for the TT genotype versus the CC genotype, controlling for age, gender, smoking, body mass index (BMI), and nutritional factors. Controlling for seven other AMD genetic variants, the OR was 0.50, 95% (CI 0.20-1.1, p=0.077). The magnitude of the effect was similar for both atrophic and neovascular forms of AMD. Cigarette smoking and higher BMI increased the risk, while higher dietary lutein reduced the risk of advanced AMD, adjusting for genetic variants. There were no significant interactions between LIPC and smoking, BMI, or lutein. There was a possible association between LIPC and complement factor H (CFH) rs1410996, and a possible interaction effect between LIPC and both CFH rs10033900 and the complement factor I (CFI) variants in terms of risk of AMD.

CONCLUSIONS: LIPC is associated with reduced risk of advanced AMD, independent of demographic and environmental variables. Both genetic susceptibility and behavioral and lifestyle factors modify the risk of developing AMD.

PMID: 21139980 [PubMed - in process]

Mol Vis. 2010 Nov 3;16:2273-8.

Lack of association of CFD polymorphisms with advanced age-related macular degeneration.

Zeng J, Chen Y, Tong Z, Zhou X, Zhao C, Wang K, Hughes G, Kasuga D, Bedell M, Lee C, Ferreyra H, Kozak I, Haw W, Guan J, Shaw R, Stevenson W, Weishaar PD, Nelson MH, Tang L, Zhang K.

Abstract

PURPOSE: Age-related macular degeneration (AMD) is the most common cause of irreversible central vision loss worldwide. Research has linked AMD susceptibility with dysregulation of the complement cascade. Typically, complement factor H (CFH), complement factor B (CFB), complement component 2 (C2), and complement component 3 (C3) are associated with AMD. In this paper, we investigated the association between complement factor D (CFD), another factor of the complement system, and advanced AMD in a Caucasian population.

METHODS: Six single nucleotide polymorphisms (SNPs), rs1683564, rs35186399, rs1683563, rs3826945, rs34337649, and rs1651896, across the region covering CFD, were chosen for this study. One hundred and seventy-eight patients with advanced AMD and 161 age-matched normal controls were genotyped. Potential positive signals were further tested in another independent 445 advanced AMD patients and 190 controls. $\chi(2)$ tests were performed to compare the allele frequencies between case and control groups.

RESULTS: None of the six SNPs of CFD was found to be significantly associated with advanced AMD in our study.

CONCLUSIONS: Our findings suggest that CFD may not play a major role in the genetic susceptibility to AMD because no association was found between the six SNPs analyzed in the CFD region and advanced AMD.

PMID: 21139680 [PubMed - in process]

Pathogenesis & epidemiology

Proteomics Clin Appl. 2008 May;2(5):762-75. doi: 10.1002/prca.200780094.

Proteomics as a research tool in clinical and experimental ophthalmology.

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Abstract

It is estimated that 37 million people worldwide suffer from blindness and 124 million people have impaired vision. While the relatively recently developed therapies, antivascular endothelial growth factor inhibitors for the treatment of age-related macular degeneration, and prostaglandin analogues for the treatment of glaucoma are beneficial for some patients, there are many individuals with sight-threatening diseases for whom no effective pharmacological therapy is available. For many of these diseases, the molecular mechanisms remain to be comprehensively elucidated, thus precluding the design of successful therapies against specific pathological targets. The current review summarises recent attempts to elucidate molecular mechanisms of ocular diseases, including diabetic retinal disease, age-related macular degeneration and inherited blindness using proteomic methodologies. A novel hypothesis can be generated from global protein expression analysis of disease tissue, which can then be addressed with cellular and in vivo functional studies. For example, the identification of extracellular carbonic anhydrase from the vitreous of diabetic retinopathy patients using MS based proteomics led to the elucidation of a new pathway involved in intraretinal edema, which could be inhibited by a number of agents targeting different proteins in this pathway in relevant animal models. The potential of protein biomarkers for diagnosis and the identification of novel disease mechanisms are also discussed.

PMID: 21136873 [PubMed - in process]

Proteomics Clin Appl. 2007 Aug;1(8):876-88. doi: 10.1002/prca.200700105. Epub 2007 Jul 18.

Proteomics in ocular fluids.

Grus FH, Joachim SC, Pfeiffer N.

Experimental Ophthalmology, Department of Ophthalmology, Johannes Gutenberg University, Mainz, Germany. grus@eye-research.org.

Abstract

The focus of this article is to review recent techniques in proteomic analysis of ocular fluids. These fluids include tears, aqueous humor, and vitreous, they will also be compared to serum analysis. Furthermore, we attempt to summarize some disease correlated biomarkers in ocular fluids that were discovered through different proteomic techniques in eye diseases like dry eye, glaucoma, age-related macular degeneration, uveitis, or diabetic retinopathy. This review is trying to point out the importance of these biomarkers for clinical applications.

PMID: 21136741 [PubMed - in process]

J Cell Physiol. 2010 Dec 6. [Epub ahead of print]

Modulation of oxidative stress responses in the human retinal pigment epithelium following treatment with vitamin C.

Yin J, Thomas F, Lang JC, Chaum E.

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Abstract

Oxidative stress (OS) in the retina plays an important role in the development and progression of age-related macular degeneration (AMD). Our previous work has shown that OS can quantitatively regulate the expression of AP-1 family genes in the retinal pigment epithelium (RPE). In this study we sought to determine whether AP-1 genes can be used as cellular biomarkers of OS to evaluate the efficacy of ascorbate, the major aqueous-phase antioxidant in the blood, in reducing OS in RPE cells in vitro. Human ARPE19 cells were pretreated with increasing levels of ascorbate (0-500μM) for 3 days which was then removed from the medium. Oxidative stress was induced 24 hours later by the addition of hydrogen peroxide for 1- to 4-hours, to bring the final media concentration of H(2)O(2) to 500μM. FosB, c-Fos, and ATF3 gene expression was examined from 0-24-hours after OS. Pretreatment with 200μM ascorbate maximally reduced the transcriptional OS-response of AP-1 genes by up to 87% after 1 and 4 hours, compared to controls. 100μM ascorbate provided a statistically significant, but far more modest effect. Ascorbate supplementation of 100-200μM appears to strongly inhibit OS-induced activation of AP-1 in vitro, but pretreatment with higher levels of ascorbate conferred no additional advantage. These studies suggest that there are optimal levels of antioxidant supplementation to the RPE in vitro. Laboratory assays based upon transcription factor biomarkers may be useful to define beneficial molecular responses to new antioxidants, alternative dosing regimens, and to explore therapeutic efficacy in OS models in vitro. © 2010 Wiley-Liss, Inc.

PMID: 21136491 [PubMed - as supplied by publisher]

Mol Vis. 2010 Nov 18;16:2425-37.

Expression and distribution of the class III ubiquitin-conjugating enzymes in the retina.

Mirza S, Plafker KS, Aston C, Plafker SM.

Abstract

PURPOSE: Mounting evidence implicates chronic oxidative stress as a significant pathogenic factor in the development and progression of retinopathies, including age-related macular degeneration (AMD). The age -dependent toxic accumulation of oxidatively damaged proteins, lipids, and DNA in susceptible cells of the retina arises, at least in part, from a decreased capacity to eliminate these damaged biomolecules. The goal of this study was to determine the expression patterns and function of class III ubiquitin-conjugating enzymes (UbcM3, UBE2E2, and UbcM2) in the retina. These enzymes have been implicated in the ubiquitin-dependent degradation of oxidatively damaged and misfolded proteins.

METHODS: Complementary western blotting and immunohistochemistry was performed with specific antibodies to determine the retinal cell expression pattern of each enzyme. Additional analyses using antibodies raised against UbcM2 were performed to determine the relative levels of the enzyme in lysates derived from various mouse organs as compared to the retina. An established light-damage model of oxidative stress-induced retinal degeneration was used to determine alterations in the susceptibility of mice harboring a single intact allele of UbcM2. Ubiquitin charging and auto-ubiquitylation assays were done to assess the catalytic state of UbcM2 following photo-oxidative stress.

RESULTS: Expression of the class III ubiquitin-conjugating enzymes in the retina, from highest to lowest, is UbcM2>UbcM3>UBE2E2. In addition to being the most robustly expressed, UbcM2 is further distinguished by its expression in photoreceptors and retinal pigment epithelial cells. UbcM2 is expressed in most mouse

tissues analyzed and is most abundant in the retina. Studies using a bright-light-damage model of acute oxidative stress in mice harboring a single disrupted allele of UbcM2 revealed that a 58% reduction in enzyme levels did not increase the susceptibility of photoreceptors to acute photo-oxidative toxicity. This result may be explained by the observation that UbcM2 retained an intact and functional active site following exposure to acute bright light.

CONCLUSIONS: The class III ubiquitin-conjugating enzymes, and in particular UbcM2, are expressed in the retina and may function to counter the accumulation of oxidatively damaged and misfolded proteins. A 58% reduction in UbcM2 does not increase the susceptibility of photoreceptors to an acute photo-oxidative stress, suggesting the existence of compensating enzymes and/or that the remaining UbcM2 activity is sufficient to target oxidatively damaged proteins for destruction.

PMID: 21139979 [PubMed - in process]