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Drug treatment

Case Report Med. 2012;2012:897097. doi: 10.1155/2012/897097. Epub 2012 Oct 30.

Verteporfin photodynamic therapy combined with intravitreal ranibizumab for polypoidal choroidal vasculopathy controversy concerning long-term followup.

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Purpose: To show the long-term results of intravitreal ranibizumab combined with photodynamic therapy (PDT) for the treatment of polypoidal choroidal vasculopathy (PCV).

Methods: We analyzed the progress of two patients for 36 and 58 months, respectively. We only used PDT for the treatment in the area of the active PCV or "hot spot" evident on the indocyanine green angiography (ICGA). The spot size was chosen so as to cover only the active neovascular lesion. We combined intravitreal ranibizumab with PDT when PCV remained active without visible polyps in ICGA or without a response to PDT.

Conclusion: Administration, as required, of verteporfin photodynamic therapy combined with intravitreal ranibizumab is an effective treatment for symptomatic polypoidal choroidal vasculopathy. These data need to be confirmed in large, prospective, and controlled clinical trials which are randomized and carried out over a long period.

PMID: 23197987[PubMed - in process] PMCID: PMC3502857

Case Report Ophthalmol. 2012 Sep;3(3):384-8. doi: 10.1159/000338969. Epub 2012 Nov 7.

Choroidal neovascularization regression on fluorescein angiography after VEGF blockade.

Do DV, Greenwald L, Ibrahim M, Sepah Y, Nguyen QD.

Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, Md., USA.

BACKGROUND: Intravitreal vascular endothelial growth factor (VEGF) inhibitors stabilize vision in a majority of patients with neovascular age-related macular degeneration (AMD) and can improve vision in almost 40% of patients. However, some individuals who respond to anti-VEGF treatment still lose vision due to the

formation of geographic atrophy (GA). While optical coherence tomography is often the primary imaging modality used, fluorescein angiography (FA) can provide useful information on GA development after choroidal neovascularization (CNV) regression.

METHODS: A retrospective chart review was conducted to evaluate the changes seen on FA over a 47-month period for 3 patients with neovascular AMD treated with anti-VEGF inhibitors.

RESULTS: All 3 patients were initially noted to have subfoveal CNV due to AMD at baseline; they were followed up monthly and treated on an as needed basis for at least 47 months with intravitreal VEGF inhibitors. All subjects had regression of their CNV lesions after VEGF blockade. Two subjects developed foveal atrophy.

CONCLUSIONS: This case series depicts the changes on FA seen over a 4-year period and shows that GA can occur with regression of CNV after treatment with VEGF inhibitors.

PMID: 23185181 [PubMed - in process] PMCID: PMC3506058

Drugs Aging. 2012 Dec;29(12):949-56. doi: 10.1007/s40266-012-0031-2.

Ocular Hypertension Following Intravitreal Anti-vascular Endothelial Growth Factor Agents.

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Department of Ophthalmology, The Eye Institute, Medical College of Wisconsin, 925 N. 87th Street, Milwaukee, WI, 53226, USA.

Abstract: Age-related macular degeneration (AMD) is the leading cause of severe vision loss in adults over the age of 65 years. The advent of anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections has revolutionized the management of exudative AMD. However, multiple case series of sustained elevated intraocular pressure (IOP) after intravitreal injections of anti-VEGF agents have been reported. Sustained elevated IOP has been reported with all anti-VEGF agents being used in ophthalmology and even in patients without any prior history of glaucoma. No clear correlations to injection frequency or patient characteristics have emerged from the multiple reports so far, but it appears that patients with pre-existing glaucoma or ocular hypertension and those receiving a greater number of injections with shorter injection intervals may be at a higher risk for developing ocular hypertension related to anti-VEGF agents. Until future studies elucidate the pathophysiology of sustained IOP following anti-VEGF injections, it is prudent to recognize the possibility of elevations in IOP in association with anti-VEGF therapy. Treating physicians should look for subtle optic nerve head changes and IOP measurements suspicious for glaucoma and have a low threshold for treating elevated IOP if the patient is likely to require multiple intravitreal anti-VEGF injections. Ocular hypertension following anti-VEGF injections appears to be amenable to anti-glaucoma treatment and every effort should be made to preserve the peripheral vision in these patients where central vision is already threatened by exudative AMD.

PMID: 23179897 [PubMed - in process]

BMJ Case Rep. 2012 Nov 28;2012. pii: bcr2012007446. doi: 10.1136/bcr-2012-007446.

Paediatric choroidal osteoma treated with ranibizumab.

Vayalambrone D, Misra A.

Department of Ophthalmology, Ipswich Hospital NHS Trust, Ipswich, UK.

Abstract: An 11-year-old patient presented with blurred vision in both eyes resulting from bilateral choroidal osteoma. The patient was treated with a course of monthly intravitreal injections of ranibizumab for

3 months and this led to improvement of visual acuity. This effect was sustained without the need for further injections over a 2-year period of follow-up.

PMID: 23192581 [PubMed - in process]

Retina. 2012 Nov 27. [Epub ahead of print]

Progressive Optic Nerve Collateralization After Serial Intravitreal Ranibizumab Injections for Central Retinal Vein Occlusion.

Goldberg N, Freund KB.

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PMID: 23190926 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2012 Nov 22. pii: S0161-6420(12)00755-5. doi: 10.1016/j.ophtha.2012.07.091. [Epub ahead of print]

Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration (MERITAGE Study): 12 Month Optical Coherence Tomography and Fluorescein Angiography.

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PURPOSE: To report the optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) results of the Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration study.

DESIGN: Prospective, multicenter, interventional, noncontrolled clinical trial.

PARTICIPANTS: Fifty-three eyes of 53 participants with chronic, active neovascular age-related macular degeneration (AMD) requiring frequent anti-vascular endothelial growth factor retreatment.

METHODS: Participants underwent pars plana vitrectomy with a single 24-gray dose of epimacular brachytherapy (EMB), delivered with an intraocular, handheld, cannula containing a strontium 90/yttrium 90 source positioned over the active lesion. Participants were retreated with ranibizumab administered monthly as needed, using predefined retreatment criteria. Patients underwent FFA at baseline, month 1, and month 12. Patients underwent optical coherence tomography (OCT) at baseline and then monthly for 12 months. The FFA and OCT images were evaluated by independent, central reading facilities.

MAIN OUTCOME MEASURES: Change in OCT centerpoint thickness and angiographic lesion size 12 months after EMB.

RESULTS: Mean centerpoint thickness increased by 50 μ m, from 186 to 236 μ m ($P = 0.292$), but 70% of participants had an increase of less than the mean, with a median increase of only 1.8 μ m. The FFA total lesion size increased slightly by 0.79 mm(2), from 14.69 to 15.48 mm(2) ($P = 0.710$). Total choroidal neovascularization (CNV) area increased by 1.17 mm(2), from 12.94 to 14.12 mm(2) ($P = 0.556$). The classic CNV area decreased substantially by 3.70 mm(2), from 3.90 to 0.20 mm(2) ($P < 0.01$). Predominantly classic lesions showed the greatest response, with mean Early Treatment Diabetic Retinopathy Study visual acuity improving by 1.5 letters (versus -4.0 for all participants combined); mean centerpoint thickness decreased by 43 μ m ($P = 0.875$). The angiographic and OCT response did not correlate with lesion size at baseline.

CONCLUSIONS: In chronic, active, neovascular AMD, EMB is associated with nonsignificant changes in centerpoint thickness and FFA total lesion size over 12 months.

PMID: 23178157 [PubMed - as supplied by publisher]

World J Stem Cells. 2012 Aug 26;4(8):80-6. doi: 10.4252/wjsc.v4.i8.80.

Shaping the eye from embryonic stem cells: Biological and medical implications.

Colozza G, Locker M, Perron M.

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Abstract: Organogenesis is regulated by a complex network of intrinsic cues, diffusible signals and cell/cell or cell/matrix interactions that drive the cells of a prospective organ to differentiate and collectively organize in three dimensions. Generating organs in vitro from embryonic stem (ES) cells may provide a simplified system to decipher how these processes are orchestrated in time and space within particular and between neighboring tissues. Recently, this field of stem cell research has also gained considerable interest for its potential applications in regenerative medicine. Among human pathologies for which stem cell-based therapy is foreseen as a promising therapeutic strategy are many retinal degenerative diseases, like retinitis pigmentosa and age-related macular degeneration. Over the last decade, progress has been made in producing ES-derived retinal cells in vitro, but engineering entire synthetic retinas was considered beyond reach. Recently however, major breakthroughs have been achieved with pioneer works describing the extraordinary self-organization of murine and human ES cells into a three dimensional structure highly resembling a retina. ES-derived retinal cells indeed assemble to form a cohesive neuroepithelial sheet that is endowed with the intrinsic capacity to recapitulate, outside an embryonic environment, the main steps of retinal morphogenesis as observed in vivo. This represents a tremendous advance that should help resolving fundamental questions related to retinogenesis. Here, we will discuss these studies, and the potential applications of such stem cell-based systems for regenerative medicine.

PMID: 23189212 [PubMed - in process] PMCID: PMC3506970

J Neuroinflammation. 2012 Nov 26;9(1):257. [Epub ahead of print]

670-nm light treatment reduces complement propagation following retinal degeneration.

Rutar M, Natoli R, Albarracin R, Valter K, Provis J.

ABSTRACT: Complement activation is associated with the pathogenesis of age-related macular degeneration (AMD). We aimed to investigate whether 670-nm light treatment reduces the propagation of complement in a light-induced model of atrophic AMD.

METHODS: Sprague-Dawley (SD) rats were pretreated with 9 J/cm² 670-nm light for 3 minutes daily over 5 days; other animals were sham treated. Animals were exposed to white light (1,000 lux) for 24 h, after which animals were kept in dim light (5 lux) for 7 days. Expression of complement genes was assessed by quantitative polymerase chain reaction (qPCR), and immunohistochemistry. Counts were made of C3-expressing monocytes/microglia using in situ hybridization. Photoreceptor death was also assessed using outer nuclear layer (ONL) thickness measurements, and oxidative stress using immunohistochemistry for 4-hydroxynonenal (4-HNE).

RESULTS: Following light damage, retinas pretreated with 670-nm light had reduced immunoreactivity for the oxidative damage marker 4-HNE in the ONL and outer segments, compared to controls. In conjunction, there was significant reduction in retinal expression of complement genes C1s, C2, C3, C4b, C3aR1, and

C5r1 following 670 nm treatment. In situ hybridization, coupled with immunoreactivity for the marker ionized calcium binding adaptor molecule 1 (IBA1), revealed that C3 is expressed by infiltrating microglia/monocytes in subretinal space following light damage, which were significantly reduced in number after 670 nm treatment. Additionally, immunohistochemistry for C3 revealed a decrease in C3 deposition in the ONL following 670 nm treatment.

CONCLUSIONS: Our data indicate that 670-nm light pretreatment reduces lipid peroxidation and complement propagation in the degenerating retina. These findings have relevance to the cellular events of complement activation underling the pathogenesis of AMD, and highlight the potential of 670-nm light as a non-invasive anti-inflammatory therapy.

PMID: 23181358 [PubMed - as supplied by publisher]

PLoS One. 2012;7(11):e48631. doi: 10.1371/journal.pone.0048631. Epub 2012 Nov 26.

A pilot study of morphometric analysis of choroidal vasculature in vivo, using en face optical coherence tomography.

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PURPOSE: To study the ability of volumetric spectral domain optical coherence tomography (SD-OCT) to perform quantitative measurement of the choroidal vasculature in vivo.

METHODS: Choroidal vascular density and vessel size were quantified using en face choroidal scans from various depths below the retinal pigment epithelium (RPE) in 58 eyes of 58 patients with either epiretinal membranes (ERM), early age-related macular degeneration (AMD), or reticular pseudo-drusen (RPD). For each patient, we used the macular volume scan (6×6 mm cube) for vessel quantification, while high-definition (HD) cross-section raster scans were used to qualitatively assess vascularity of the choroidal sub-layers, and measure choroidal thickness.

RESULTS: Of the 58 patients, more were female (66% versus 34% male), of whom 14 (24%) had ERM, 11 (19%) early AMD, and 33 (57%) RPD. Compared to intact choriocapillaris in all ERM (100%), none of the RPD and only 5/11 (45%) early AMD eyes had visible choriocapillaris on either cross section or C-scans (p-value<0.001). When comparing select regions from the most superficial C-scans, early AMD group had lowest vascular density and RPD had highest (p-value 0.04). Qualitative evaluation of C-scans from all three groups revealed a more granular appearance of the choriocapillaris in ERM versus increased stroma and larger vessels in the RPD eyes.

CONCLUSIONS: SD-OCT can be used to qualitatively and quantitatively assess choroidal vascularity in vivo. Our findings correlate to previously reported histopathologic studies. Lack of choriocapillaris on HD cross-sections or C-scans in all RPD and about half of early AMD eyes suggests earlier choroidal involvement in AMD and specifically, RPD.

PMID: 23189132 [PubMed - in process] PMCID: PMC3506620

Invest Ophthalmol Vis Sci. 2012 Nov 27. pii: iovs.12-10508v1. doi: 10.1167/iov.12-10508. [Epub ahead of print]

Trial frame refraction versus autorefraction among new patients in a low vision clinic.

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PURPOSE: To determine the relationship between refractive error as measured by autorefraction and that measured by trial frame refraction among a sample of adults with vision impairment seen in a university-based low vision clinic and to determine if autorefraction might be a suitable replacement for trial frame refraction.

METHODS: A retrospective chart review of all new patients ≥ 19 years old seen over an 18-month period was conducted and the following data collected: age, gender, primary ocular diagnosis, entering distance visual acuity, habitual correction, trial frame refraction, autorefraction and distance visual acuity measured after trial frame refraction. Trial frame refraction and autorefraction were compared using paired t-tests, Intra-class correlations and Bland-Altman plots.

RESULTS: Final analyses included 440 patients for whom both trial frame refraction and autorefraction data were available for the better eye. Participants were mostly female (59%) with a mean age of 68 years (SD=20). Age-related macular degeneration was the most common etiology for vision impairment (44%). Values for autorefraction and trial frame refraction were statistically different, but highly correlated for the spherical equivalent power ($r=0.92$), the cylinder power ($r=0.80$) and overall blurring strength (0.89). Although the values of the cross-cylinders J0 and J45 were similar, they were poorly correlated (0.08 and 0.15, respectively). The range of differences in spherical equivalent power was large (-8.6 to 4.9).

CONCLUSIONS: Autorefraction is highly correlated with trial frame refraction. Differences are sometimes substantial, making autorefraction an unsuitable substitute for trial frame refraction.

PMID: 23188726 [PubMed - as supplied by publisher]

J Biomed Biotechnol. 2012;2012:354979. doi: 10.1155/2012/354979. Epub 2012 Oct 14.

Ocriplasmin for vitreoretinal diseases.

Tsui I, Pan CK, Rahimy E, Schwartz SD.

Retina Division, Jules Stein Eye Institute, University of California, Los Angeles, CA 90095, USA.

Abstract: Fibronectin and laminin are clinically relevant plasmin receptors in the eye. Located at the vitreo-retinal interface, they are cleaved by ocriplasmin (Microplasmin, ThromboGenics, Iselin, NJ), a novel ophthalmic medication. A series of clinical trials to study ocriplasmin for the treatment of vitreoretinal diseases such as vitreomacular traction, macular hole, and exudative age-related macular degeneration are underway. The results are promising and may impact patient care.

PMID: 23193358 [PubMed - in process] PMCID: PMC3496214

Future Med Chem. 2012 Nov;4(17):2139-40. doi: 10.4155/fmc.12.171.

Interview with Chi-Chao Chan.

Chan CC.

National Eye Institute at National Institutes of Health, 10 Center Drive, 10/10N103, Bethesda, MD 20892-1857, USA. chanc@nei.nih.gov.

Abstract: Chi-Chao Chan, an American board certified ophthalmologist, is the Chief of Immunopathology Section, Laboratory of Immunology and the Head of Histology Core at the National Eye Institute at National Institutes of Health (USA). In 1967, Dr Chan graduated from Chungzhan Medical College in Guangzhou,

China and then earned her AB (1972), as well as MD (1975) at Johns Hopkins University (USA). Currently, her research is focusing on primary intraocular (vitreoretinal) lymphoma; uveitis (intraocular inflammatory diseases); and the molecular pathology, animal models, and genetic epidemiology of age-related macular degeneration. Dr Chan spoke to Future Medicinal Chemistry, about the challenges ophthalmic research faces and how the aging population could lead to better drugs. Interview conducted by Isaac Bruce, Commissioning Editor.

PMID: 23190100 [PubMed - in process]

J Cataract Refract Surg. 2012 Dec;38(12):2198-9. doi: 10.1016/j.jcrs.2012.10.016.

Predictability of postoperative visual acuity in patients with dry age-related macular degeneration using the retinal acuity meter.

Milia M, Giannopoulos T, Asteriades S, Vakalis T, Stavrakas P, Tranos P.

PMID: 23195260 [PubMed - in process]

Pathogenesis

Future Med Chem. 2012 Nov;4(17):2153-61. doi: 10.4155/fmc.12.169.

Autophagy regulating kinases as potential therapeutic targets for age-related macular degeneration.

Kaarniranta K, Kauppinen A, Blasiak J, Salminen A.

Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland.

Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss in the elderly in the developed countries. The number of AMD patients will double during the next decades due to increasing number of aged people. Chronic oxidative stress, inflammation and accumulation of protein-rich deposits both in the retinal pigment epithelium lysosomes and under the retinal pigment epithelium herald the onset of AMD. The disease can be divided into dry and wet AMD forms. The dry form of the disease is more prevalent accounting for up to 90% of all cases. Continued intraocular injections are the current treatment strategy to prevent progression of wet AMD. It is a major challenge to develop new drugs that could prevent or at least ease the symptoms of the increasing population of AMD patients. Since AMD pathology is clearly associated with accumulated protein deposits, the autophagy clearance system might represent a potential future therapeutic target for AMD as is thoroughly discussed here.

PMID: 23190104 [PubMed - in process]

Bioconjug Chem. 2012 Nov 26. [Epub ahead of print]

High Affinity VEGF Antagonists by Oligomerization of a Minimal Sequence VEGF-Binding Domain.

Stefano J, Bird J, Kyazike J, Cheng AW, Boudanova E, Dwyer M, Hou L, Qiu H, Matthews G, O'Callaghan M, Pan CQ.

Abstract: Vascular endothelial growth factor (VEGF) neutralizing antagonists including antibodies or receptor extracellular domain Fc fusions have been applied clinically to control angiogenesis in cancer, wet age-related macular degeneration, and edema. We report here the generation of high-affinity VEGF-binding domains by chemical linkage of the second domain of the VEGF receptor Flt-1 (D2) in several configurations. Recombinant D2 was expressed with a 13 a.a. C-terminal tag, including a C-terminal cysteine to enable its

dimerization by disulfide bond formation or by attachment to divalent PEGs and oligomerization by coupling to multivalent PEGs. Disulfide-linked dimers produced by Cu⁺⁺ oxidation of the free-thiol form of the protein demonstrated pM affinity for VEGF in solution, comparable to that of a D2-Fc fusion (sFLT01) and ~50-fold higher than monomeric D2, suggesting the 26 a.a. tag length between the two D2 domains permits simultaneous interaction of both faces of the VEGF homodimer. Extending the separation between the D2 domains by short PEG spacers from 0.35kD to 5kD produced a modest ~2-fold increase in affinity over the disulfide, thus defining the optimal distance between the two D2 domains for maximum affinity. By surface plasmon resonance (SPR), a larger (~5-fold) increase in affinity was observed by conjugation of the D2 monomer to the termini of 4-arm PEG, and yielding a product with a larger hydrodynamic radius than sFLT01. The higher affinity displayed by these D2 PEG tetramers than either D2 dimer or sFLT01 was largely a consequence of a slower rate of dissociation, suggesting the simultaneous binding by these tetramers to neighboring surface-bound VEGF. Finally, disulfide-linked D2 dimers showed a greater resistance to autocatalytic fragmentation than sFLT01 under elevated temperature stress, indicating such minimum-sequence constructs may be better suited for sustained-release formulations. Therefore, these constructs represent novel Fc-independent VEGF antagonists with ultra-high affinity, high stability, and a range of hydrodynamic radii for application to multiple therapeutic targets.

PMID: 23176598 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2012 Dec;154(6 Suppl):S53-S62.e1. doi: 10.1016/j.ajo.2011.08.045.

Vision health disparities in the United States by race/ethnicity, education, and economic status: findings from two nationally representative surveys.

Zhang X, Cotch MF, Ryskulova A, Primo SA, Nair P, Chou CF, Geiss LS, Barker LE, Elliott AF, Crews JE, Saaddine JB.

Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia. Electronic address: XZhang4@cdc.gov.

PURPOSE: To assess vision health disparities in the United States by race/ethnicity, education, and economic status.

DESIGN: Cross-sectional, nationally representative samples.

METHODS: We used national survey data from the National Health and Nutrition Examination Survey (NHANES) and the National Health Interview Survey (NHIS). Main outcome measures included, from NHANES, age-related eye diseases (ie, age-related macular degeneration [AMD], cataract, diabetic retinopathy [DR], glaucoma) and from NHIS, eye care use (ie, eye doctor visits and cannot afford eyeglasses when needed) among those with self-reported visual impairment. The estimates were age- and sex-standardized to the 2000 US Census population. Linear trends in the estimates were assessed by weighted least squares regression.

RESULTS: Non-Hispanic whites had a higher prevalence of AMD and cataract surgery than non-Hispanic blacks, but a lower prevalence of DR and glaucoma (all $P < .001$ in NHANES 2005-2008). From 1999 to 2008, individuals with less education (ie, <high school vs >high school) and lower income (poverty income ratio [PIR] <1.00 vs ≥ 4.00) were consistently less likely to have had an eye care visit in the past 12 months compared with their counterparts (all $P < .05$). During this period, inability to afford needed eyeglasses increased among non-Hispanic whites and Hispanics (trend $P = .004$ and $P = .007$; respectively), those with high school education (trend $P = .036$), and those with PIR 1.00-1.99 (trend $P < .001$).

CONCLUSIONS: Observed vision health disparities suggest a need for educational and innovative interventions among socioeconomically disadvantaged groups.

PMID: 23158224 [PubMed - in process]

Genetics

PLoS One. 2012;7(11):e49905. doi: 10.1371/journal.pone.0049905. Epub 2012 Nov 21.

Single Nucleotide Polymorphisms in MCP-1 and Its Receptor Are Associated with the Risk of Age Related Macular Degeneration.

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Department of Neurology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population. We have shown previously that mice deficient in monocyte chemoattractant protein-1 (MCP1/CCL2) or its receptor (CCR2) develop the features of AMD in senescent mice, however, the human genetic evidence so far is contradictory. We hypothesized that any dysfunction in the CCL2 and its receptor result could be the contributing factor in pathogenesis of AMD.

METHODS AND FINDINGS: 133 AMD patients and 80 healthy controls were enrolled for this study. Single nucleotide Polymorphism for CCL2 and CCR2 was analyzed by real time PCR. CCL2 levels were determined by enzyme-linked immunosorbent assay (ELISA) after normalization to total serum protein and percentage (%) of CCR2 expressing peripheral blood mononuclear cells (PBMCs) was evaluated using Flow Cytometry. The genotype and allele frequency for both CCL2 and CCR2 was found to be significantly different between AMD and normal controls. The CCL2 ELISA levels were significantly higher in AMD patients and flow Cytometry analysis revealed significantly reduced CCR2 expressing PBMCs in AMD patients as compared to normal controls.

CONCLUSIONS: We analyzed the association between single nucleotide polymorphisms (SNPs) of CCL2 (rs4586) and CCR2 (rs1799865) with their respective protein levels. Our results revealed that individuals possessing both SNPs are at a higher risk of development of AMD.

PMID: 23185481 [PubMed - in process] PMCID: PMC3503775

Cell Rep. 2012 Nov 29;2(5):1151-8. doi: 10.1016/j.celrep.2012.10.013. Epub 2012 Nov 21.

Hypomethylation of the IL17RC Promoter Associates with Age-Related Macular Degeneration.

Wei L, Liu B, Tuo J, Shen D, Chen P, Li Z, Liu X, Ni J, Dagur P, Sen HN, Jawad S, Ling D, Park S, Chakrabarty S, Meyerle C, Agron E, Ferris FL 3rd, Chew EY, McCoy JP, Blum E, Francis PJ, Klein ML, Guymer RH, Baird PN, Chan CC, Nussenblatt RB.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population worldwide. Although recent studies have demonstrated strong genetic associations between AMD and SNPs in a number of genes, other modes of regulation are also likely to play a role in the etiology of this disease. We identified a significantly decreased level of methylation on the IL17RC promoter in AMD patients. Furthermore, we showed that hypomethylation of the IL17RC promoter in AMD patients led to an elevated expression of its protein and messenger RNA in peripheral blood as well as in the affected retina and choroid, suggesting that the DNA methylation pattern and expression of IL17RC may potentially serve as a biomarker for the diagnosis of AMD and likely plays a role in disease pathogenesis.

PMID: 23177625 [PubMed - in process]

Neurobiol Aging. 2012 Nov 20. pii: S0197-4580(12)00534-9. doi: 10.1016/j.neurobiolaging.2012.10.023. [Epub ahead of print]

Aurin tricarboxylic acid self-protects by inhibiting aberrant complement activation at the C3 convertase and C9 binding stages.

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Abstract: Aberrant complement activation is known to exacerbate the pathology in a spectrum of degenerative diseases of aging. We previously reported that aurin tricarboxylic acid (ATA) is an orally effective agent which prevents formation of the membrane attack complex of complement. It inhibits C9 attachment to tissue bound C5b678 and thus prevents bystander lysis of host cells. In this study, we investigated the effects of ATA on the alternative complement pathway. We found that ATA prevented cleavage of the tissue bound properdin-C3b-Factor B complex into the active C3 convertase enzyme properdin-C3b-Factor Bb. This inhibition was reversed by adding Factor D to the serum. Using enzyme-linked immunosorbent type assays, we established that ATA binds directly to Factor D and C9 but not to properdin or other complement proteins. We conclude that ATA, by inhibiting at two stages of the alternative pathway, might be a particularly effective therapeutic agent in conditions such as macular degeneration, paroxysmal nocturnal hemoglobinemia, and rheumatoid arthritis, in which activation of the alternative complement pathway initiates self damage.

PMID: 23177218 [PubMed - as supplied by publisher]

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