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MD Research News

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Drug treatment

JAMA Ophthalmol. 2015 Oct 29:1-6. [Epub ahead of print]

Comparison of Aflibercept, Bevacizumab, and Ranibizumab for Treatment of Diabetic Macular Edema: Extrapolation of Data to Clinical Practice.

Heier JS, Bressler NM, Avery RL, Bakri SJ, Boyer DS, Brown DM, Dugel PU, Freund KB, Glassman AR, Kim JE, Martin DF, Pollack JS, Regillo CD, Rosenfeld PJ, Schachat AP, Wells JA 3rd; American Society of Retina Specialists Anti-VEGF for Diabetic Macular Edema Comparative Effectiveness Panel.

IMPORTANCE: The Diabetic Retinopathy Clinical Research Network (DRCR Network), sponsored by the National Eye Institute, reported the results of a comparative effectiveness randomized clinical trial (RCT) evaluating the 3 anti-vascular endothelial growth factor (anti-VEGF) agents aflibercept (2.0 mg), bevacizumab (1.25 mg), and ranibizumab (0.3 mg) for treatment of diabetic macular edema (DME) involving the center of the retina and associated with visual acuity loss. The many important findings of the RCT prompted the American Society of Retina Specialists to convene a group of experts to provide their perspective regarding clinically relevant findings of the study.

OBJECTIVES: To describe specific outcomes of the RCT judged worthy of highlighting, to discuss how these and other clinically relevant results should be considered by specialists treating DME, and to identify unanswered questions that merit consideration before treatment.

EVIDENCE REVIEW: The DRCR Network-authored publication on primary outcomes of the comparative effectiveness RCT at 89 sites in the United States. The study period of the RCT was August 22, 2012, to August 28, 2013.

FINDINGS: On average, all 3 anti-VEGF agents led to improved visual acuity in eyes with DME involving the center of the retina and with visual acuity impairment, including mean (SD) improvements by +13.3 (11.1) letters with aflibercept vs +9.7 (10.1) letters with bevacizumab ($P < .001$) and +11.2 (9.4) letters with ranibizumab ($P = .03$). Worse visual acuity when initiating therapy was associated with greater visual acuity benefit of aflibercept (+18.9 [11.5]) over bevacizumab (+11.8 [12.0]) or ranibizumab (14.2 [10.6]) 1 year later ($P < .001$ for interaction with visual acuity as a continuous variable, and $P = .002$ for interaction with visual acuity as a categorical variable). It is unknown whether different visual acuity outcomes associated with the use of the 3 anti-VEGF agents would be noted with other treatment regimens or with adequately repackaged bevacizumab, as well as in patients with criteria that excluded them from the RCT, such as persistent DME despite recent anti-VEGF treatment.

CONCLUSIONS AND RELEVANCE: On average, all 3 anti-VEGF agents led to improved visual acuity in eyes with DME involving the center of the retina and visual acuity impairment. Worse visual acuity when initiating therapy was associated with greater visual acuity benefit of aflibercept over bevacizumab or ranibizumab 1 year later. Care needs to be taken when attempting to extrapolate outcomes of this RCT to differing treatment regimens. With access to adequately repackaged bevacizumab, many specialists might

initiate therapy with bevacizumab when visual acuity is good (ie, 20/32 to 20/40 as measured in the DRCR Network), recognizing that the cost-effectiveness of bevacizumab outweighs that of aflibercept or ranibizumab.

PMID: 26512939 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Oct 29. [Epub ahead of print]

A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration.

Chin-Yee D, Eck T, Fowler S, Hardi A, Apte RS.

PURPOSE: To evaluate the relative efficacy of as needed versus treat and extend regimen for the treatment of neovascular age-related macular degeneration (AMD).

METHODS: We conducted a systematic review of studies that evaluated the efficacy of as needed or treat and extend regimen for neovascular AMD by searching multiple databases up to December 2013. Included studies were selected based on study duration of no less than 12 months, availability of outcome data, treatment protocol for as needed groups or pro re nata (PRN) receiving bevacizumab or ranibizumab, and all studies with treat extend protocols following the 'inject and extend' regimen. The outcome data were pooled and analysed.

RESULTS: 1046 peer reviewed articles meeting our initial search criteria were returned. After further review by two independent reviewers, 8 studies meeting treat and extend protocol and 62 studies meeting PRN protocol were included. The mean improvement in visual acuity in the PRN group was 5.4 ETDRS letters compared with 10.4 ETDRS letters in the treat and extend group. The PRN group received an average of 5.60 injections at 1 year compared with 8.09 in the treat and extend group. Central retinal thickness improved on average by 100.32 µ in the PRN group compared with 87.7 µ in the treat and extend group.

CONCLUSIONS: Though our study suggests superiority of the treat and extend regimen to PRN treatment in a 12-month period, this review demonstrates the need for randomised clinical trials to confirm our findings and to evaluate long-term efficacy outcomes with these regimens compared with monthly therapy.

PMID: 26516125 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2015 Oct 26. [Epub ahead of print]

Aflibercept in exudative age related macular degeneration refractory to ranibizumab. [Article in English, Spanish]

Ruiz Ramos J, Pascual-Camps I, Cuéllar-Monreal MJ, Dolz-Marco R, Fenoll MA, Font-Noguera I, Poveda-Andrés JL, Gallego-Pinazo R.

PURPOSE: The aim of this study is to determine the effectiveness, safety and cost of aflibercept in the treatment of wet age-related macular degeneration (ARMD) refractory to ranibizumab.

METHODS: Retrospective observational study was conducted on patients diagnosed with wet ARMD, and previously treated with ranibizumab. Efficacy variables assessed were changes in visual acuity (BCVA) and anatomical improvements in the most affected eye. Factors associated with improvement of BCVA with aflibercept were also studied. Adverse events related to the aflibercept administration were recorded. Cost analysis data were collected from the hospital perspective, and only taking the direct medical costs into account. Cost-effectiveness analysis was calculated using the aflibercept treatment cost, and effectiveness calculated as BCVA gained.

RESULTS: A total of 50 eyes corresponding to 46 patients were included. The median follow-up period was

4.6 months (range: 1.0-6.0). Improvement in visual acuity after the first 2 doses and at the end of the follow-up period was observed in 32.0 and 28.0% of treated eyes, respectively. None of the variables studied was associated with an improvement in the BCVA after treatment. No significant differences were found in the average monthly cost between treatments.

CONCLUSIONS: Aflibercept is shown to be an effective treatment in a significant number of patients resistant to treatment with ranibizumab, presenting a cost similar to that generated during the final stages of treatment with ranibizumab.

PMID: 26515015 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Oct 30. [Epub ahead of print]

Aflibercept as primary treatment for myopic choroidal neovascularisation: a retrospective study.

Bruè C, Pazzaglia A, Mariotti C, Reibaldi M, Giovannini A.

Aim: The aim of this study is to evaluate long-term efficacy of intravitreal injections of aflibercept as primary treatment for subfoveal/juxtafoveal myopic choroidal neovascularisation (CNV).

Methods: Thirty-eight treatment-naive eyes of thirty-eight patients with subfoveal/juxtafoveal myopic CNV received initial intravitreal aflibercept injections and were followed for at least 18 months. Aflibercept was applied again for persistent or recurrent CNV, as required. Statistical analysis was carried out using SPSS.

Results: Mean patient age was 45.8 years, and mean eye refractive error was -7.79 D. For the total patient group (n=38 eyes), mean logMAR best-corrected visual acuity (BCVA) significantly improved from 0.69 at baseline to 0.15 at 18 months (P<0.01). Over half of the treated eyes obtained resolution with one aflibercept injection. Patients were also grouped according to age, as <50 years (n=20 eyes) and ≥50 years (n=18 eyes). Mean BCVA improvement was significantly greater in eyes of the younger myopic CNV group, compared with those of ≥50 years (0.21 vs 0.35; P<0.05). The mean number of aflibercept injections was 1.8 for the <50 years myopic CNV group, and 3.6 for the ≥50 years myopic CNV group (P<0.001). Correlation between spherical equivalent refraction and final visual acuity reached statistical significance only for the <50 years myopic CNV group (P<0.001; Levene's correlation).

Conclusions: Intravitreal aflibercept provides long-term visual acuity improvement in myopic CNV. The <50 years old myopic CNV group had significantly fewer injections, with greater visual acuity improvement. Intravitreal aflibercept in myopic CNV does not require the three-injection loading phase used for aflibercept treatment of neovascular age-related macular degeneration.

PMID: 26514244 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2015 Oct 29:1-9. [Epub ahead of print]

Systemic Safety of Prolonged Monthly Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema: A Systematic Review and Meta-analysis.

Avery RL, Gordon GM.

IMPORTANCE: Anti-vascular endothelial growth factor (VEGF) therapy is commonly used to treat numerous retinal conditions and appears safe, yet controversy remains regarding systemic safety.

OBJECTIVE: To evaluate the systemic safety of intravitreous anti-VEGF injections in high-risk patients with diabetic macular edema (DME) and to investigate separately the subgroup of these patients with the highest level of exposure to anti-VEGF monthly treatment for 2 years.

DATA SOURCES: A search of MEDLINE, Cochrane Central Register of Controlled Trials, clincaltrials.gov, and ophthalmology congress abstracts January 1, 1947, to May 19, 2015.

STUDY SELECTION: Randomized clinical trials were selected that evaluated monthly anti-VEGF injections

for DME for 2 years and reported the outcome measures of cerebrovascular accidents, myocardial infarctions, arteriothrombotic events, and mortality.

DATA EXTRACTION AND SYNTHESIS: Two reviewers collected data independently from each study for the meta-analysis. Data were pooled using a fixed-effects model and analyzed from November 6, 2014, to June 28, 2015. Peto odds ratios with 95% CIs were calculated.

MAIN OUTCOMES AND MEASURES: Primary end points included cerebrovascular accidents and all-cause mortality in the highest-dose arms. Secondary outcomes included myocardial infarctions, arteriothrombotic events, and vascular-related death.

RESULTS: Of 1126 articles reviewed, 598 were removed as duplicate studies and 524, for lack of monthly treatment data for 2 years, leaving 4 studies for the meta-analysis that met the search criteria: 2 trials using monthly aflibercept and 2 using monthly ranibizumab, representing 1328 patients. The primary evaluation (1078 patients) combined the monthly aflibercept and the 0.5-mg ranibizumab arms and yielded an increased risk for death compared with sham and laser treatments (odds ratio [OR], 2.98; 95% CI, 1.44-6.14; P = .003). Analysis including monthly aflibercept and 0.5-mg ranibizumab yielded an increased risk for cerebrovascular accidents (OR, 2.33; 95% CI, 1.04-5.22; P = .04) and vascular death (OR, 2.51; 95% CI, 1.08-5.82; P = .03). No definitive increased risk for myocardial infarctions and arteriothrombotic events was seen with all dose combinations.

CONCLUSIONS AND RELEVANCE: In this meta-analysis of anti-VEGF agents for patients with DME, assessment of the highest-level exposure group (those high-risk patients with DME who received 2 years of monthly treatment) revealed a possible increased risk for death and potentially for cerebrovascular accidents. Consideration of total exposure to anti-VEGF agents when treating those at high risk for vascular disease may be important.

PMID: 26513684 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Oct 27. [Epub ahead of print]

SYMPTOMATIC DYNAMIC VITREOMACULAR TRACTION INDUCED BY NEAR-VISION.

Griffin DR, Tadrus MN, Jensen RB, Richmond PP.

PURPOSE: To report a case of dynamic vitreomacular traction secondary to near-response vision demonstrated by optical coherence tomography imaging of macular anatomical changes both pre and post induced near-vision.

METHODS: Case report and literature review.

RESULTS: Dynamic vitreomacular traction led to significant foveal anatomical changes on optical coherence tomography after approximately 15 minutes of induced near-vision, which was associated with bilateral central metamorphopsia that self-resolved after approximately 15-30 minutes. The patient eventually experienced improvement of symptoms in one eye after spontaneous vitreomacular detachment, while the other eye still remained symptomatic.

DISCUSSION: The near-vision complex affects movement of the posterior vitreous humor, which may actively contribute to dynamic vitreomacular traction. Therefore, cases of transient central blurring after a self-induced near-response mechanism should be investigated for potential dynamic vitreomacular traction syndrome.

PMID: 26510004 [PubMed - as supplied by publisher]

Dev Ophthalmol. 2016;55:232-45. Epub 2015 Oct 26.

Therapeutic Monoclonal Antibodies and Fragments: Bevacizumab.

Klein A, Loewenstein A.

Abstract: Bevacizumab (Avastin) is a recombinant humanized monoclonal immunoglobulin antibody that has two antigen-binding domains and blocks all active forms of vascular endothelial growth factor-A. It was originally designed and is still in use as antitumor agent (for colorectal and non-small cell lung cancers). Besides inhibiting vessel growth and neovascularization, the drug promotes the regression of existing microvessels and induces 'normalization' of surviving mature vasculature, stabilizes vessels and prevents leakage. Its molecular weight is 149 kDa and its estimated terminal half-life is approximately 20 days for both men and women. The effectiveness and safety of bevacizumab was proven in retrospective and prospective controlled clinical trials for the treatment of neovascular age-related macular degeneration, neovascularization in proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusion and retinopathy of prematurity, especially for zone I. Uncontrolled trials have shown its effectiveness in various other conditions as myopic and uveitic choroidal neovascularization and neovascular glaucoma. There are no absolute contraindications to intravitreal injection though it is recommended to withhold treatment in patients who have recently suffered from a cardiovascular or cerebrovascular event and during pregnancy. Ocular complications from intravitreal use are usually mild and transient (corneal abrasion, chemosis, subconjunctival hemorrhage and vitreous hemorrhage). Bacterial endophthalmitis is rare (about 0.1%). New or progressive subretinal hemorrhages, tears of the retinal pigment epithelium and an increased incidence of geographic atrophy have also been reported.

PMID: 26502311 [PubMed - in process]

Dev Ophthalmol. 2016;55:147-53.Epub 2015 Oct 26.

Retinal Vein Occlusion.

Sawada O, Ohji M.

Abstract: The primary treatment against macular edema with retinal vein occlusion (RVO) has changed from observation in central RVO (CRVO) and laser photocoagulation in branch RVO (BRVO) to administration of intravitreal agents based on anti-vascular endothelial growth factor (VEGF) or anti-inflammatory strategies. Anti-VEGF treatment such as ranibizumab, bevacizumab, or aflibercept improved vision by 13.9-16.2 letters (best-corrected visual acuity) after 12 months versus baseline in patients with macular edema secondary to CRVO. A long-term study showed that reduced follow-up and fewer retreatments resulted in worsening visual acuity. Intravitreal therapy with anti-inflammatory agents stabilized visual acuity in CRVO. However, increased intraocular pressure and cataract progression were frequently observed. Anti-VEGF agents such as ranibizumab or bevacizumab improved visual acuity by 15.5-18.3 letters in patients with macular edema secondary to BRVO after 12 months. The improved vision remained during the long-term follow-up. There was no significant difference between standard care and intravitreal triamcinolone groups in BRVO, and increased intraocular pressure and cataract progression occurred frequently in the triamcinolone group. Anti-VEGF intravitreal administration resulted in good vision in CRVO and BRVO patients and is employed as a primary therapy. Anti-VEGF therapy requires frequent observations and intravitreal injections to maintain good vision.

PMID: 26501219 [PubMed - in process]

Dev Ophthalmol. 2016;55:1-6. Epub 2015 Oct 26.

Evolving Knowledge in Pharmacologic Treatments of Age-Related Macular Degeneration.

Soubrane Daguet G, Risard-Gasiorowski S, Massamba N.

Abstract: Modern retinal drug therapy is a result of the recent challenges and breakthroughs in chemistry, physics, genetics, cell biology and biotechnologies. Specific pharmaceutical and pharmacokinetic characteristics of a drug are of major importance and contribute to its ability to penetrate targeted ocular tissues in order to result in effective therapeutic concentrations. In addition, the drugs should maintain a prolonged time of activity and be safe with minimal local and systemic toxicity. The transporter vehicle or drug delivery system is crucial in order to enhance ocular tissue penetration and establish controlled drug release. Administration methods should be local, thereby reducing systemic side effects, and, ideally, treatment should be noninvasive. Within the group of so-called classic therapies, the use of pharmacologic treatments has become widespread for most severe retinal diseases. Thereby, ocular therapy of diseases like exudative age-related macular degeneration has improved markedly. Moreover, new metabolic pathways have been identified, new molecules have emerged, new synthesis technologies have been discovered, and new formulae conceived. These developments have opened new avenues for limiting disease progression.

PMID: 26501927 [PubMed - in process]

Dev Ophthalmol. 2016;55:246-51. Epub 2015 Oct 26.

Therapeutic Monoclonal Antibodies and Fragments: Ranibizumab.

Smith AG, Kaiser PK.

Abstract: Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody Fab fragment against all isoforms of vascular endothelial growth factor-A, which was developed specifically for intraocular use. Ranibizumab has been extensively investigated in clinical trials on choroidal neovascularization from wet age-related macular degeneration and pathologic myopia, as well as macular edema due to diabetic retinopathy and retinal vein occlusion. Numerous randomized, controlled clinical trials have shown this medication to be effective in improving both vision as well as anatomical outcomes, and the medication has repeatedly shown to have an acceptable safety profile.

PMID: 26501149 [PubMed - in process]

Dev Ophthalmol. 2016;55:282-94. Epub 2015 Oct 26.

Fusion Proteins: Aflibercept (VEGF Trap-Eye).

Sarwar S, Bakbak B, Sadiq MA, Sepah YJ, Shah SM, Ibrahim M, Do DV, Nguyen QD.

Abstract: Vascular endothelial growth factor (VEGF) inhibitors currently used to treat eye diseases have included monoclonal antibodies, antibody fragments, and an aptamer. A different method of achieving VEGF blockade in retinal diseases includes the concept of a cytokine trap. Cytokine traps are being evaluated for the treatment of various diseases that are driven by excessive cytokine levels. Traps, such as VEGF Trap, consist of two extracellular cytokine receptor domains fused together to form a human IgG. Aflibercept (VEGF Trap-Eye) is a soluble fusion protein which combines ligand-binding elements taken from the extracellular components of VEGF receptor (VEGFR)-1 and VEGFR-2 fused to the Fc portion of IgG. This protein contains all human amino-acid sequences, which minimizes the potential for immunogenicity in human patients. The chapter will summarize the chemical properties of aflibercept and the various studies that have demonstrated a role of aflibercept in the management of retinal vascular diseases such as neovascular age-related macular degeneration, diabetic retinopathy, macular edema, and retinal vein occlusion.

PMID: 26501481 [PubMed - in process]

Dev Ophthalmol. 2016;55:391-8. Epub 2015 Oct 26.

Future Perspectives: Agents on the Horizon.

Maya JR, Sadiq MA, Agarwal A, Kaiser PK, Stoller GL, Sepah YJ, Nguyen QD.

Abstract: As demonstrated in the previous chapters of this textbook, retinal pharmacotherapeutics is a rapidly developing area. The enormous burden of disease in an aging population will hopefully be met by significant improvements in our understanding and treatment of disease processes such as age-related macular degeneration (AMD) and diabetic retinopathy. This chapter will provide perspectives on select anti-angiogenic drugs currently in development, as well as therapies directed against the complement cascade for the treatment of AMD, and an anti-inflammatory monoclonal antibody for the treatment of diabetic macular edema, among others, that have not been discussed elsewhere in this book. The mechanism of action of a number of drugs under discussion differs enough to have the potential to control neovascularization in several different ways, potentially allowing for more effective management of this process with fewer treatments.

PMID: 26501694 [PubMed - in process]

Dev Ophthalmol. 2016;55:302-9. Epub 2015 Oct 26.

Emixustat and Lampalizumab: Potential Therapeutic Options for Geographic Atrophy.

Jack LS, Sadiq MA, Do DV, Nguyen QD.

Abstract: Two novel classes of medications are currently under extensive investigation for the treatment of dry age-related macular degeneration (AMD). Emixustat, an orally administered visual cycle inhibitor, and lampalizumab, an intravitreally administered monoclonal body directed against complement factor D, have shown promise in phase 2 clinical trials in the treatment of nonneovascular (dry) AMD. Lampalizumab is currently being evaluated in a large, multicenter, phase 3 clinical trial for dry AMD - geographic atrophy.

PMID: 26501510 [PubMed - in process]

Dev Ophthalmol. 2016;55:276-81. Epub 2015 Oct 26.

Sirolimus for Retinal and Uveitic Diseases.

Agarwal A, Rajagopalan N, Hassan M, Sadiq MA, Soliman MK, Afridi R, Sepah YJ, Nguyen QD.

Abstract: Chronic inflammation plays an important role in the pathogenesis of ocular diseases such as diabetic retinopathy, uveitis and age-related macular degeneration. Activation and proliferation of naïve T cells may result in pathological changes responsible for significant visual morbidity. Sirolimus (earlier termed rapamycin) is a novel drug that inhibits cellular kinases and, thereby, inhibits T-cell proliferation. Preclinical studies in experimental models have shown promising results with the use of this pharmacological agent in various ocular conditions. Subsequently, early phase I/II studies have provided encouraging safety and efficacy data. This chapter focuses on the mechanisms of action, preclinical study results and data from human clinical trials of sirolimus in human eye diseases. Key highlights from ongoing phase III clinical trials are also provided. Sirolimus, thus, appears to be an important addition to the armamentarium of steroid-sparing therapeutic agents that act on various steps in the inflammatory pathway.

PMID: 26501229 [PubMed - in process]

Curr Pharm Des. 2015 Oct 27. [Epub ahead of print]

Modern drug delivery systems for targeting the posterior segment of the eye.

Peptu CA, Popa M, Savin C, Popa RF, Ochiuz L.

Abstract: Some of the most dangerous diseases of the eye are related to the posterior segment. Diseases such as age-related macular degeneration,cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis and retinitis pigmentosa are difficult to treat using classical methods because of the many internal barriers of the eye which affect the drug efficiency. In this review, we will summarize the main research directions in the field of medicamentous treatment of posterior eye disorders belonging to the controlled drug delivery concept. The review is starting with the most important knowledge regarding anatomy and pathology of the posterior segment of the eye and is continuing with the current treatment methods of the eye posterior segment illnesses and drawbacks of these methods, the drugs administration pathways to the posterior segment of the eye. The last three sections present the state of the art regarding the latest discoveries including the commercial products in the modern drug delivery systems; the main classes of materials treated in the present review are implants, hydrogels and nano- microparticulate systems.

PMID: 26503152 [PubMed - as supplied by publisher]

Dev Ophthalmol. 2016;55:125-36. Epub 2015 Oct 26.

Neovascular Age-Related Macular Degeneration.

Shao J, Choudhary MM, Schachat AP.

Abstract: Age-related macular degeneration (AMD) is the leading cause of severe vision loss in individuals over the age of 50 years. Choroidal neovascularization (CNV) is the hallmark of 'wet' or 'exudative' AMD, and is responsible for approximately 90% of cases of severe vision loss due to AMD. Vascular endothelial growth factor (VEGF) is a key component in the development and progression of wet AMD. Since the approval of ranibizumab in 2006, VEGF inhibitors have rapidly altered the treatment and standard of care for wet AMD. Ranibizumab, bevacizumab, and aflibercept are now the most widely used anti-VEGF agents for the treatment of wet AMD. This chapter discusses the pharmacologic properties, pharmacokinetics, safety, and efficacy of these medications, as well as revisits landmark clinical trials that establish these drugs as gold standards in care. While these medications have greatly and positively altered the way we treat AMD, there are still many economic and therapeutic limitations with our current therapy regimens. There continue to be advancements and innovations in exploring alternative and new treatment modalities, as well as combining existing treatment options to improve efficacy, and reduce cost and patient burden.

PMID: 26501146 [PubMed - in process]

Ophthalmology. 2015 Oct 20. [Epub ahead of print]

A Phase 1 Study of Intravitreous E10030 in Combination with Ranibizumab in Neovascular Age-Related Macular Degeneration.

Jaffe GJ, Eliott D, Wells JA, Prenner JL, Papp A, Patel S.

PURPOSE: To assess the safety and tolerability of E10030 (Fovista; Ophthotech, New York, NY), a platelet -derived growth factor (PDGF) antagonist, when administered in combination with an anti-vascular endothelial growth factor (VEGF) agent, ranibizumab (Lucentis; Genentech, South San Francisco, CA) 0.5 mg, by intravitreal injection in participants with neovascular age-related macular degeneration (NVAMD).

DESIGN: Prospective phase 1 clinical trial.

PARTICIPANTS: A total of 23 participants diagnosed with NVAMD and aged 50 years or older were

enrolled.

METHODS: Part 1 included 15 participants. Three participants received a single intravitreal E10030 (0.03 mg) injection and were subsequently given intravitreal ranibizumab (0.5 mg) injections at weeks 2, 6, and 10. Twelve participants (3 per group) received E10030 (0.03, 0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) at day 0, month 1, and month 2 in an ascending manner. In Part 2 (8 participants), E10030 (0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) was injected at day 0, month 1, and month 2.

MAIN OUTCOME MEASURES: Safety at week 12 was the primary outcome and included assessment of vital signs, laboratory tests, and serial eye examinations. Other safety metrics included assessment through week 24 of Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA) and biomarker changes evaluated by optical coherence tomography (OCT) and fluorescein angiography (FA).

RESULTS: All doses of intravitreal E10030 administered in combination with ranibizumab were well tolerated. No dose-limiting toxicities or relevant safety events were noted at any dose level during the study. Investigators did not report adverse events related to E10030 or ranibizumab. Mean VA change was a gain of 14 letters, and 59% of participants gained ≥15 letters from baseline at week 12. On FA at week 12, there was an 85.5% mean reduction from baseline in choroidal neovascularization (CNV) size. On OCT at the week 12 visit, there was a mean decrease in center point thickness and central subfield thickness of 38.9% and 33.7%, respectively.

CONCLUSIONS: Intravitreal E10030 administered at doses up to 3 mg in combination with ranibizumab was well tolerated without evidence of systemic or ocular toxicity in participants with NVAMD. The changes in both mean VA and imaging biomarkers suggest a favorable short-term safety profile for the combination therapy of E10030 and ranibizumab.

PMID: 26499921 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2015 Nov;43(8):707-10.

To dry or not too dry: should we be more tolerant of stable subretinal fluid in patients receiving anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration?

Razavi H, Arnold J, Guymer R.

PMID: 26498270 [PubMed - in process]

Dev Ophthalmol. 2016;55:376-80. Epub 2015 Oct 26.

Regulatory and Economic Considerations of Retinal Drugs.

Shah AR, Williams GA.

Abstract: The advent of anti-VEGF therapy for neovascular age-related macular degeneration and macular edema secondary to retinal vein occlusion and diabetes mellitus has prevented blindness in tens of thousands of people. However, the costs of these drugs are without precedent in ophthalmic drug therapeutics. An analysis of the financial implications of retinal drugs and the impact of the Food and Drug Administration on treatment of retinal disease must include not only an evaluation of the direct costs of the drugs and the costs associated with their administration, but also the cost savings which accrue from their clinical benefit. This chapter will discuss the financial and regulatory issues associated with retinal drugs.

PMID: 26502165 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2015 Nov;122(11):2155-6.

Should We Add Screening of Age-Related Macular Degeneration to Current Screening Programs for Diabetic Retinopathy?

Chew EY, Schachat AP.

Author information

PMID: 26498078 [PubMed - in process]

J Ophthalmol. 2015;2015:429251. Epub 2015 Oct 4.

Acute-Onset Vitreous Hemorrhage of Unknown Origin before Vitrectomy: Causes and Prognosis.

Kim DY, Joe SG, Baek S, Kim JG, Yoon YH, Lee JY.

Purpose: To analyze causes and prognosis of acute-onset preoperatively unknown origin vitreous hemorrhage (VH).

Methods: This study included patients who underwent vitrectomy for acute-onset preoperatively unknown origin VH. The underlying causes of VH, which were identified after vitrectomy, were analyzed. And overall visual prognosis of unknown origin VH was analyzed. Risk scoring system was developed to predict visual prognosis after vitrectomy.

Results: 169 eyes were included. Among these, retinal vein occlusion (RVO), retinal break, and age-related macular degeneration (AMD) were identified in 74 (43.8%), 50 (29.6%), and 21 (12.4%) patients, respectively. After vitrectomy, logMAR BCVA significantly improved from 1.93 ± 0.59 to 0.47 ± 0.71. However, postoperative BCVA in AMD eyes were significantly poorer than others. Poor visual prognosis after vitrectomy was associated with old age, poor preoperative vision in both eyes, and drusen in the fellow eye.

Conclusions: RVO, retinal break, and AMD are the most common causes of acute-onset preoperatively unknown origin VH and the most common causes of VH change with age. The visual prognosis of unknown origin VH is relatively good, except among AMD patients. Older patients with poor preoperative BCVA in both eyes and patients with AMD in the fellow eye are at a higher risk of poor visual prognosis following vitrectomy.

PMID: 26504593 [PubMed] PMCID: PMC4609453

Br J Ophthalmol. 2015 Oct 26.[Epub ahead of print]

Prevalence and clinical correlates of focal choroidal excavation in eyes with age-related macular degeneration, polypoidal choroidal vasculopathy and central serous chorioretinopathy.

Lim FP, Wong CW, Loh BK, Chan CM, Yeo I, Lee SY, Mathur R, Wong D, Wong TY, Cheung CM.

PURPOSE: To describe the prevalence and clinical characteristics of focal choroidal excavation (FCE) in patients with exudative maculopathy due to age-related macular degeneration with choroidal neovascularisation (AMD-CNV), polypoidal choroidal vasculopathy (PCV) and central serous chorioretinopathy (CSC).

METHODS: Three hundred and forty-three patients (343 presenting eyes and 255 fellow unaffected eyes) from consecutive patients presenting with untreated AMD-CNV, PCV or CSC are prospectively recruited.

Two independent retinal specialists masked to the clinical diagnosis graded the presence of FCE by examining the findings from spectral-domain optical coherence tomography (SD-OCT). The frequency and clinical characteristics of FCE in each of the three clinical diagnosis groups were compared.

RESULTS: The diagnosis in the presenting eye was AMD-CNV in 92 patients, PCV in 149 patients, retinal angiomatous proliferation (RAP) in 3 patients and CSC in 99 patients; 255 fellow eyes free of clinical diseases were also graded. The prevalence of FCE was 2.3% (total 14 eyes; 10 presenting eyes, 4 fellow eyes) out of 598 eyes examined. In presenting eyes, FCE was most prevalent in PCV (6.0%), followed by AMD-CNV (1.0%) and CSC (0%), p=0.02. In fellow eyes, the prevalence of FCE was 2.9%, 0% and 1.2% in patients with PCV, AMD-CNV and CSC, respectively. Eyes with FCE had a significantly longer axial length (24.93±1.65 mm vs 23.49±1.10 mm, p<0.001), but otherwise, all other characteristics were similar.

CONCLUSIONS: FCE is more common in PCV than AMD-CNV and CSC. Disturbance in the choroid/retinal pigment epithelium/Bruch membrane interface affected by FCE may be linked to the pathogenesis of PCV and AMD-CNV.

PMID: 26504178 [PubMed - as supplied by publisher]

Retina. 2015 Nov;35(11):2229-35.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF TYPE 3 NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Kuehlewein L, Dansingani KK, de Carlo TE, Bonini Filho MA, Iafe NA, Lenis TL, Freund KB, Waheed NK, Duker JS, Sadda SR, Sarraf D.

PURPOSE: To characterize the vascular structure of Type 3 neovascularization secondary to age-related macular degeneration using optical coherence tomography angiography.

METHODS: Optical coherence tomography angiography cube scans (3 mm × 3 mm) were acquired in 29 eyes of 24 patients with Type 3 lesions secondary to age-related macular degeneration using the RTVue XR Avanti with AngioVue, Split-spectrum amplitude-decorrelation, and motion correction technology. Automated layer segmentation boundaries were adjusted to best visualize the neovascular complex on en face projection images.

RESULTS: A distinct neovascular complex could be identified in 10 (34%) eyes, all of which were active on optical coherence tomography imaging. In all 10 eyes, the neovascular complex appeared as a small tuft of bright, high-flow tiny vessels with curvilinear morphology located in the outer retinal layers with a feeder vessel communicating with the inner retinal circulation (i.e., deep retinal capillary plexus). The mean (SD) size of the neovascular complex measured 0.07 (± 0.07) mm.

CONCLUSION: With optical coherence tomography angiography, it is possible to identify small intraretinal neovascular complexes communicating with the deep retinal capillary plexus in eyes with Type 3 neovascularization secondary to age-related macular degeneration. Qualitative and quantitative analyses of Type 3 neovascular complexes can be performed using optical coherence tomography angiography.

PMID: 26502007 [PubMed - in process]

Dev Ophthalmol. 2016;55:167-75. Epub 2015 Oct 26.

Choroidal Neovascularization Secondary to Myopia, Infection and Inflammation.

Weber ML, Heier JS.

Abstract: Choroidal neovascularization (CNV) is a significant cause of vision loss in all age groups. The most common cause of CNV is age-related macular degeneration (AMD). However, CNV can also occur as

a secondary manifestation of various inherited and acquired conditions, including pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, and various hereditary, traumatic or inflammatory disorders. Fluorescein angiography and optical coherence tomography are useful tools in the diagnosis and evaluation of CNV. Treatment options are similar to those for CNV secondary to AMD, specifically anti-angiogenic therapy, but including laser photocoagulation, photodynamic therapy and surgery. Anti-angiogenic therapy has been associated with better visual outcomes than other treatment modalities and is now advocated as the first-line therapy for CNV secondary to myopia, infection and inflammation.

PMID: 26501802 [PubMed - in process]

Dev Ophthalmol. 2016;55:7-17. Epub 2015 Oct 26.

Retinal Anatomy and Pathology.

Gupta MP, Herzlich AA, Sauer T, Chan CC.

Abstract: Normal retina contains neuroretina and retinal pigment epithelium. The neuroretina consists of outer and inner segments of photoreceptors (rods and cones), external limiting membrane, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, nerve fiber layer and internal limiting membrane. There is a broad spectrum of retinal pathology including congenital abnormalities, dystrophies, degenerations (notably age-related macular degeneration), retinal vascular diseases, toxicities, inflammatory diseases, neoplasms, retinal detachment, trauma and retinal involvement of systemic diseases. This chapter presents a few major pathological processes in retinal diseases, especially processes that are amenable to pharmacotherapeutics.

PMID: 26502225 [PubMed - in process]

Dev Ophthalmol. 2016;55:330-6. Epub 2015 Oct 26.

Photosensitizers and Photodynamic Therapy: Verteporfin.

Battaglia Parodi M, La Spina C, Berchicci L, Petruzzi G, Bandello F.

Abstract: Photodynamic therapy (PDT) is a phototherapy in which a photosensitive dye is injected into a peripheral vein and activated by light in order to occlude choroidal vessels or change their permeability. PDT has been largely applied in the treatment of choroidal neovascularization (CNV), especially CNV related to age-related macular degeneration, but was also of benefit in other diseases, including central serous chorioretinopathy and choroidal hemangioma.

PMID: 26501167 [PubMed - in process]

Dev Ophthalmol. 2016;55:112-24. Epub 2015 Oct 26.

Nonneovascular Age-Related Macular Degeneration.

Michels S, Garhöfer G.

Abstract: The discovery of several genetic variants associated with an increased risk for age-related macular degeneration (AMD) has led to a completely new understanding of AMD. In addition to the known modifiable risk factors, genetic risk factors may also help to assess the risk to progress to nonneovascular AMD. Recently published primary studies have indicated that genetic risk analysis may be valuable in the selection of the currently available antioxidant therapy. So far, the best evidence for preventing progression to nonneovascular AMD comes from the Age-Related Eye Disease Studies (AREDS) I and II. These studies indicate that high doses of antioxidants can reduce the risk of progression to the advanced form of

the disease. However, the recent evaluation of the addition of either lutein and zeaxanthin, or x03C9;-3 long -chain polyunsaturated fatty acids, or both, to the established AREDS I formulation did not significantly reduce the risk of developing advanced AMD. There is clearly a large unmet medical need for new therapeutic options for nonneovascular AMD. The modulation of the complement cascade is - despite initially disappointing outcomes obtained with blocking complement factor 5 - currently the most promising approach to the treatment of nonneovascular AMD.

PMID: 26502209 [PubMed - in process]

Dev Ophthalmol. 2016;55:317-21. Epub 2015 Oct 26.

Ocular Gene Therapy.

Campbell JP, McFarland TJ, Stout JT.

Abstract: Ocular gene therapy involves the introduction of an exogenous gene product to a host's cellular and genetic machinery for endogenous production of a desired gene product. The eye represents an ideal target organ due to its easy visibility and accessibility, and several trials have demonstrated proof-of-principle safety and efficacy in a subtype of Leber's congenital amaurosis. There are numerous ongoing clinical trials exploring gene therapy in other retinal diseases. In autosomal recessively inherited retinal degenerations, the introduced gene product replaces a known genetically deficient gene product and provides restoration of function. In other disease states, such as neovascular age-related macular degeneration, the delivered gene product modulates existing proteins within a cell, such as vascular endothelial growth factor, for a desired therapeutic effect. This latter approach may have broader applications in other diseases such as diabetes and other retinal vascular diseases that are as yet unrealized. This review summarizes the current state of clinical research in ocular gene therapy focusing on those diseases in which the technology has reached clinical trials.

PMID: 26502313 [PubMed - in process]

Pathogenesis

Dev Ophthalmol. 2016;55:28-37. Epub 2015 Oct 26.

Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors.

Rubio RG, Adamis AP.

Abstract: Systematic study of the mechanisms underlying pathological ocular neovascularization has yielded a wealth of knowledge about pro- and anti-angiogenic factors that modulate diseases such as neovascular age-related macular degeneration. The evidence implicating vascular endothelial growth factor (VEGF) in particular has led to the development of a number of approved anti-VEGF therapies. Additional proangiogenic targets that have emerged as potential mediators of ocular neovascularization include hypoxia-inducible factor-1, angiopoietin-2, platelet-derived growth factor-B and components of the alternative complement pathway. As for VEGF, knowledge of these factors has led to a product pipeline of many more novel agents that are in various stages of clinical development in the setting of ocular neovascularization. These agents are represented by a range of drug classes and, in addition to novel small- and large-molecule VEGF inhibitors, include gene therapies, small interfering RNA agents and tyrosine kinase inhibitors. In addition, combination therapy is beginning to emerge as a strategy to improve the efficacy of individual therapies. Thus, a variety of agents, whether administered alone or as adjunctive therapy with agents targeting VEGF, offer the promise of expanding the range of treatments for ocular neovascular diseases.

PMID: 26502333 [PubMed - in process]

Curr Pharm Des. 2015 Oct 29. [Epub ahead of print]

Redox mechanisms in pathological angiogenesis in the retina: roles for NADPH oxidase.

Chan EC, Liu GS, Dusting GJ.

Abstract: Pathological angiogenesis in the retina is a leading cause of serious vision loss in potentially blinding eye diseases, including proliferative diabetic retinopathy, retinopathy of prematurity and the wet form of age-related macular degeneration. Hypoxia is thought to be the driver of pathological angiogenesis, and transcription factors such as hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF) are key mediators in these processes. Current treatments employ either laser photocoagulation or intravitreal injection of therapeutic antibodies for VEGF, in order to arrest the growth of leaky blood vessels in the avascular vitreous cavity and to restore visual acuity. However, all such therapeutic approaches are limited by low or variable efficacy, and the inconvenience, risk and financial burden of such treatments, which need to be given frequently. The lack of non-invasive and efficacious therapy has therefore driven the search for alternative strategies. We have been interested in the roles of reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, which when produced intracellularly at low concentration can act as second messengers to regulate physiological and pathological angiogenesis. Accumulating evidence suggests NADPH oxidase-dependent ROS are involved in regulation of the angiogenic signalling pathways of HIF and VEGF. Suppressing pathological neovascularisation in the retina by manipulating such redox mechanisms appears to be an attractive and clinically translatable therapeutic strategy to treat proliferative neovascular eye diseases. Here we provide a brief overview of the roles of NADPH oxidase in the sensing and regulation processes involving HIF and VEGF that contribute to the development of pathological angiogenesis in the retina.

PMID: 26510439 [PubMed - as supplied by publisher]

PLoS One. 2015 Oct 30;10(10):e0141597. eCollection 2015.

Comparison of Mouse and Human Retinal Pigment Epithelium Gene Expression Profiles: Potential Implications for Age-Related Macular Degeneration.

Bennis A, Gorgels TG, Ten Brink JB, van der Spek PJ, Bossers K, Heine VM, Bergen AA.

BACKGROUND: The human retinal pigment epithelium (RPE) plays an important role in the pathogenesis of age related macular degeneration (AMD). AMD is the leading cause of blindness worldwide. There is currently no effective treatment available. Preclinical studies in AMD mouse models are essential to develop new therapeutics. This requires further in-depth knowledge of the similarities and differences between mouse and human RPE.

METHODS: We performed a microarray study to identify and functionally annotate RPE specific gene expression in mouse and human RPE. We used a meticulous method to determine C57BL/6J mouse RPE signature genes, correcting for possible RNA contamination from its adjacent layers: the choroid and the photoreceptors. We compared the signature genes, gene expression profiles and functional annotations of the mouse and human RPE.

RESULTS: We defined sets of mouse (64), human (171) and mouse-human interspecies (22) RPE signature genes. Not unexpectedly, our gene expression analysis and comparative functional annotation suggested that, in general, the mouse and human RPE are very similar. For example, we found similarities for general features, like "organ development" and "disorders related to neurological tissue". However, detailed analysis of the molecular pathways and networks associated with RPE functions, suggested also multiple species-specific differences, some of which may be relevant for the development of AMD. For example, CFHR1, most likely the main complement regulator in AMD pathogenesis was highly expressed in human RPE, but almost absent in mouse RPE. Furthermore, functions assigned to mouse and human RPE expression profiles indicate (patho-) biological differences related to AMD, such as oxidative stress, Bruch's membrane, immune-regulation and outer blood retina barrier.

CONCLUSION: These differences may be important for the development of new therapeutic strategies and translational studies in age-related macular degeneration.

PMID: 26517551 [PubMed - in process]

Sci Rep. 2015 Oct 28;5:15702.

Choroidal neovascularization is inhibited via an intraocular decrease of inflammatory cells in mice lacking complement component C3.

Tan X, Fujiu K, Manabe I, Nishida J, Yamagishi R, Nagai R, Yanagi Y.

Abstract: In early age-related macular degeneration (AMD), complement component C3 can be observed in drusen, which is the accumulation of material beneath the retinal pigment epithelium. The complement pathways, via the activation of C3, can upregulate the expression of cytokines and their receptors and the recruitment of inflammatory leukocytes, both of which play an important role in the development of choroidal neovascularization (CNV) in exudative AMD. Laser-induced CNV lesions were found to be significantly smaller in C3(-/-) mice than in wild-type mice. By using flow cytometry, we demonstrated that the proportions of intraocular granulocytes, CD11b(+)F4/80(+)Ly6C(hi) and CD11b(+)F4/80(+)Ly6C(lo) cells, were lower in C3(-/-) mice than in wild-type mice as early as day 1 after laser injury, and the proportions of granulocytes and three macrophage/monocyte subsets were significantly lower on day 3. In contrast, C3(-/-) mice had more granulocytes and CD11b(+)F4/80(+)Ly6C(hi) cells in peripheral blood than wild-type mice after injury. Further, the expression levels of Vegfa164 were upregulated in intraocular Ly6C (hi) macrophages/monocytes of C3(-/-) mice, but not as much as in wild-type mice. Collectively, our data demonstrate that despite a more pronounced induction of systemic inflammation, inhibition of complement factor C3 suppresses CNV by decreasing the recruitment of inflammatory cells to the lesion.

PMID: 26507897 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Oct 1;56(11):6906-13.

Melanopsin-Mediated Post-Illumination Pupil Response in Early Age-Related Macular Degeneration.

Maynard ML, Zele AJ, Feigl B.

PURPOSE: To determine whether melanopsin-expressing intrinsically photosensitive retinal ganglion cell (ipRGC) inputs to the pupil light reflex (PLR) are affected in early age-related macular degeneration (AMD).

METHODS: The PLR was measured in 40 participants (20 early AMD and 20 age-matched controls) using a custom-built Maxwellian view pupillometer. Sinusoidal stimuli (0.5 Hz, 11.9 seconds duration, 35.6° diameter) were presented to the study eye and the consensual pupil response was measured to lights with high melanopsin excitation (464 nm [blue]) and with low melanopsin excitation (638 nm [red]) that biased activation to the outer retina. Two melanopsin PLR metrics were quantified: the phase amplitude percentage (PAP) during the sinusoidal stimulus presentation and the post-illumination pupil response (PIPR). The PLR during stimulus presentation was analyzed using latency to constriction, the transient pupil response and maximum pupil constriction metrics. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curves.

RESULTS: The blue PIPR was significantly less sustained in the early AMD group ($P < 0.001$). The red PIPR was not significantly different between groups ($P > 0.05$). The PAP and blue stimulus constriction amplitude were significantly lower in the early AMD group ($P < 0.05$). There was no significant difference between groups in the latency or transient amplitude for both stimuli ($P > 0.05$). ROC analysis showed excellent diagnostic accuracy for the blue PIPR metrics (area under the curve > 0.9).

CONCLUSIONS: This is the initial report that the melanopsin-controlled PIPR is dysfunctional in early AMD. The noninvasive, objective measurement of the ipRGC controlled PIPR has excellent diagnostic accuracy

for early AMD.

PMID: 26505464 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Oct 1;56(11):6873-8.

Rare Variants in the Functional Domains of Complement Factor H Are Associated With Age-Related Macular Degeneration.

Triebwasser MP, Roberson ED, Yu Y, Schramm EC, Wagner EK, Raychaudhuri S, Seddon JM, Atkinson JP.

PURPOSE: Age-related macular degeneration (AMD) has a substantial genetic risk component, as evidenced by the risk from common genetic variants uncovered in the first genome-wide association studies. More recently, it has become apparent that rare genetic variants also play an independent role in AMD risk. We sought to determine if rare variants in complement factor H (CFH) played a role in AMD risk.

METHODS: We had previously collected DNA from a large population of patients with advanced age-related macular degeneration (A-AMD) and controls for targeted deep sequencing of candidate AMD risk genes. In this analysis, we tested for an increased burden of rare variants in CFH in 1665 cases and 752 controls from this cohort.

RESULTS: We identified 65 missense, nonsense, or splice-site mutations with a minor allele frequency ≤ 1%. Rare variants with minor allele frequency ≤ 1% (odds ratio [OR] = 1.5, P = 4.4 × 10-2), 0.5% (OR = 1.6, P = 2.6 × 10-2), and all singletons (OR = 2.3, P = 3.3 × 10-2) were enriched in A-AMD cases. Moreover, we observed loss-of-function rare variants (nonsense, splice-site, and loss of a conserved cysteine) in 10 cases and serum levels of FH were decreased in all 5 with an available sample (haploinsufficiency). Further, rare variants in the major functional domains of CFH were increased in cases (OR = 3.2; P = 1.4 × 10-3) and the magnitude of the effect correlated with the disruptive nature of the variant, location in an active site, and inversely with minor allele frequency.

CONCLUSIONS: In this large A-AMD cohort, rare variants in the CFH gene were enriched and tended to be located in functional sites or led to low serum levels. These data, combined with those indicating a similar, but even more striking, increase in rare variants found in CFI, strongly implicate complement activation in A-AMD etiopathogenesis as CFH and CFI interact to inhibit the alternative pathway.

PMID: 26501415 [PubMed - in process]

Dev Ophthalmol. 2016;55:310-6. Epub 2015 Oct 26.

Platelet-Derived Growth Factor Inhibitors: A Potential Therapeutic Approach for Ocular Neovascularization.

Sadiq MA, Hanout M, Sarwar S, Hassan M, Agarwal A, Sepah YJ, Do DV, Nguyen QD.

Abstract: Retinochoroidal vascular diseases are the leading causes of blindness in the developed world. They include diabetic retinopathy, retinal vein occlusion, retinopathy of prematurity, age-related macular degeneration (AMD), and pathological myopia, among many others. Several different therapies are currently under consideration for the aforementioned disorders. In the following section, agents targeting platelet-derived growth factors (PDGF) are discussed as a potential therapeutic option for retinochoroidal vascular diseases. PDGF play an important role in the angiogenesis cascade that is activated in retinochoroidal vascular diseases. The mechanism of action, side effects, efficacy, and the potential synergistic role of these agents in combination with other treatment options is discussed. The future of treatment of retinochoroidal vascular diseases, particularly neovascular AMD, has become more exciting due to agents like PDGF antagonists.

PMID: 26501397 [PubMed - in process]

Dev Ophthalmol. 2016;55:46-56. Epub 2015 Oct 26.

Complement Activation and Inhibition in Retinal Diseases.

Kleinman ME, Ambati J.

Abstract: Within the past several decades, a brigade of dedicated researchers from around the world has provided essential insights into the critical niche of immune-mediated inflammation in the pathogenesis of age-related macular degeneration (AMD). Yet, the question has lingered as to whether disease-initiating events are more or less dependent on isolated immune-related responses, unimpeded inflammation, endogenous pathways of age-related cell senescence and oxidative stress, or any of the other numerous molecular derangements that have been identified in the natural history of AMD. There is now an abundant cache of data signifying immune system activation as an impetus in the pathogenesis of this devastating condition. Furthermore, recent rigorous investigations have revealed multiple inciting factors, including several important complement-activating components, thus creating a new array of disease-modulating targets for the research and development of molecular therapeutic interventions. While the precise in vivo effects of complement activation and inhibition in the progression and treatment of AMD remain to be determined, ongoing clinical trials of the first generation of complement-targeted therapeutics are hoped to yield critical data on the contribution of this pathway to the disease process.

PMID: 26501209 [PubMed - in process]

Ophthalmic Res. 2015;54(4):195-203. Epub 2015 Oct 27.

Complement Stimulates Retinal Pigment Epithelial Cells to Undergo Pro-Inflammatory Changes.

Lueck K, Busch M, Moss SE, Greenwood J, Kasper M, Lommatzsch A, Pauleikhoff D, Wasmuth S.

BACKGROUND/AIMS: We examined the effect of human complement sera (HCS) on retinal pigment epithelial (RPE) cells with respect to pro-inflammatory mediators relevant in early age-related macular degeneration (AMD).

METHODS: RPE cells were treated with complement-containing HCS or with heat-inactivated (HI) HCS or C7-deficient HCS as controls. Cells were analysed for C5b-9 using immunocytochemistry and flow cytometry. Interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) were quantified by ELISA and RT-PCR. Tumour necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), were analysed by Western blotting. The intracellular distribution of nuclear factor (NF)-x03BA;B was investigated by immunofluorescence.

RESULTS: A concentration-dependent increased staining for C5b-9 but no influence on cell viability was observed after HCS treatment. ELISA and RT-PCR analysis revealed elevated secretion and expression of IL-6, IL-8, and MCP-1. Western blot analysis showed a concentration-dependent increase in ICAM-1, VCAM-1, and TNF-α in response to HCS, and immunofluorescence staining revealed nuclear translocation of NF-x03BA;B.

CONCLUSION: This study suggests that complement stimulates NF-x03BA;B activation in RPE cells that might further create a pro-inflammatory environment. All these factors together may support early AMD development.

PMID: 26502094 [PubMed - as supplied by publisher]

Dev Ophthalmol. 2016;55:38-45. Epub 2015 Oct 26.

Ocular Immunity and Inflammation.

Albini TA, Davis JL.

Abstract: Complex immunologic mechanisms are involved in multiple intraocular diseases. The field of immunology has aided greatly in better understanding and treating inflammation in the posterior segment. While traditional therapy has relied on drugs such as corticosteroids and antimetabolites that exert there effects by multiple mechanisms, the more recently developed biologic immune modulators involve specific mechanisms of action with the potential to significantly reduce side effects relative to more traditional agents. Better understanding of diseases such as age-related macular degeneration or diabetic retinopathy has led to the appreciation of immune mechanisms involved in these diseases and has suggested potential targets for therapy.

PMID: 26501148 [PubMed - in process]

Epidemiology

Maturitas. 2015 Oct 21. [Epub ahead of print]

Age-related eye disease and gender.

Zetterberg M.

Abstract: Worldwide, the prevalence of moderate to severe visual impairment and blindness is 285 millions, with 65% of visually impaired and 82% of all blind people being 50 years and older. Meta-analyses have shown that two out of three blind people are women, a gender discrepancy that holds true for both developed and developing countries. Cataract accounts for more than half of all blindness globally and gender inequity in access to cataract surgery is the major cause of the higher prevalence of blindness in women. In addition to gender differences in cataract surgical coverage, population-based studies on the prevalence of lens opacities indicate that women have a higher risk of developing cataract. Laboratory as well as epidemiologic studies suggest that estrogen may confer antioxidative protection against cataractogenesis, but the withdrawal effect of estrogen in menopause leads to increased risk of cataract in women. For the other major age-related eye diseases; glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy, data are inconclusive. Due to anatomic factors, angle closure glaucoma is more common in women, whereas the dominating glaucoma type; primary open-angle glaucoma (POAG), is more prevalent in men. Diabetic retinopathy also has a male predominance and vascular/circulatory factors have been implied both in diabetic retinopathy and in POAG. For AMD, data on gender differences are conflicting although some studies indicate increased prevalence of drusen and neovascular AMD in women. To conclude, both biologic and socioeconomic factors must be considered when investigating causes of gender differences in the prevalence of age-related eye disease.

PMID: 26508081 [PubMed - as supplied by publisher]

Surv Ophthalmol. 2015 Oct 27. [Epub ahead of print]

Association of Age-Related Macular Degeneration and Reticular Macular Disease with Cardiovascular Disease.

Rastogi N, Smith RT.

Abstract: Age-related macular degeneration is the leading cause of adult blindness in the developed world. Thus, major endeavors to understand the risk factors and pathogenesis of this disease have been undertaken. Reticular macular disease is a proposed subtype of age-related macular degeneration correlating histologically with subretinal drusenoid deposits located between the retinal pigment epithelium and the inner segment ellipsoid zone. Reticular lesions are more prevalent in females and in older age groups and are associated with a higher mortality rate. Risk factors for developing age-related macular degeneration include hypertension, smoking, and angina. Several genes related to increased risk for age-related macular degeneration and reticular macular disease are also associated with cardiovascular disease. Better understanding of the clinical and genetic risk factors for age-related macular degeneration

and reticular macular disease has led to the hypothesis that these eye diseases are systemic. A systemic origin may help to explain why reticular disease is diagnosed more frequently in females as males suffer cardiovascular mortality at an earlier age, prior to the age of diagnosis of reticular macular disease and age -related macular degeneration.

PMID: 26518628 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2015 Oct 28. doi: 10.1111/aos.12885. [Epub ahead of print]

The prevalence of exfoliation syndrome in Turkey.

Kılıç R, Karagöz N, Çetin AB, Çakmak Y, Sezer H, Özay Y, Çomçalı SÜ, Dursun A.

PURPOSE: To investigate the prevalence of the exfoliation syndrome and its relationship with ocular and cardiovascular diseases in the Central Anatolia region of Turkey.

METHODS: This cross-sectional and population-based study was conducted at the Sivas Province among the population aged 40 years and over. The diagnosis of XFS was made when exfoliative material was found on the anterior lens capsule or iris on slit-lamp examination. The subjects were divided into an XFS group and a non-XFS group according to the presence of exfoliative material, and the groups were compared for the presence of glaucoma, cataract, age-related macular degeneration, phacodonesis, hypertension, diabetes mellitus, coronary artery disease, smoking and alcohol-use frequency.

RESULTS: XFS was present in 63 subjects consisting of 42 males (8.0%) and 21 females (3.6%) for an overall rate of 5.7% (95% CI: 0.054-0.060). Once we adjusted the values for age, we found a statistically significant relationship of increased age and male gender with the presence of XFS ($p = 0.001$, $p = 0.027$, respectively). The relationship between XFS and glaucoma, cataract and phacodonesis was found to be statistically significant ($p = 0.001$). No relationship was found between exfoliation syndrome and hypertension, diabetes mellitus and coronary artery disease.

CONCLUSION: The prevalence of exfoliation syndrome was 5.7% in this population-based study. There was a statistically significant relationship between XFS and advancing age and male gender.

PMID: 26508674 [PubMed - as supplied by publisher]

Genetics

Dev Ophthalmol. 2016;55:57-62. Epub 2015 Oct 26.

Genetics in Retinal Diseases.

Riaz M, Baird PN.

Abstract: The phenotypic presentation of retinal diseases is typically underpinned by the presence of genetic variation represented by either polymorphic changes, mutations, copy number variations or epigenetic changes. Retinal dystrophies can broadly be divided into two forms, either monogenic (single-gene) or complex (multifactorial) diseases. Recent advances in molecular techniques such as genome-wide association studies and next-generation sequencing have revolutionized the discovery of genetic variants associated with different retinal disorders, including retinitis pigmentosa and age-related macular degeneration. Understanding the genetic profile of the disease not only helps in diagnostics but also in gene therapy, as recently shown for Leber's congenital amaurosis. Following the elucidation of many genetic features of retinal diseases, the task is now to make sense of this large amount of data to better understand as well as experimentally prove the physiological process of the retinal disease genes and the mechanisms behind the diseases. This in turn will lead to improved gene-based therapies and personalize treatments for patients.

PMID: 26501365 [PubMed - in process]

Dev Ophthalmol. 2016;55:205-11.Epub 2015 Oct 26.

Retinal Hereditary and Degenerative/Dystrophic Diseases (Non-Age-Related Macular Degeneration).

Battaglia Parodi M, La Spina C, Corradetti G, Berchicci L, Petruzzi G, Bandello F.

Abstract: The definition of hereditary retinal diseases includes heterogeneous conditions leading to significant visual impairment. Great strides are being made in the management of many of these dystrophies, with many ongoing trials aiming to ascertain if a pharmacological therapy can reverse or at least stop the natural course of these disorders. In addition, good results have also been achieved in the treatment of typical complications of inherited dystrophies such as cystoid macular edema and choroidal neovascularization.

PMID: 26502105 [PubMed - in process]

Genet Mol Res. 2015 Oct 16;14(4):12567-76.

Association between a functional genetic polymorphism (rs2230199) and age-related macular degeneration risk: a meta-analysis.

Zhang MX, Zhao XF, Ren YC, Geng TT, Yang H, Feng T, Jin TB, Chen C.

Abstract: The association between the rs2230199 C>G single nucleotide polymorphism (SNP) in complement component 3 and age-related macular degeneration (AMD) risk has been examined extensively but the results are not consistent among studies. The aim of this study was to perform a meta-analysis of all available studies on this SNP in relation to AMD. The comprehensive databases of PubMed, Medline, Web of Knowledge, CNKI, and Google Scholar were searched for case-control studies investigating the association between the rs2230199 polymorphism and AMD susceptibility. ORs with 95% CIs were estimated to assess the association. Sensitivity analysis, test of heterogeneity, cumulative meta-analysis, and assessment of bias were also performed. A total of 15 published studies including 5593 cases and 5181 controls were used in this meta-analysis. Overall, the rs2230299 SNP was significantly associated with the risk of AMD in the overall population under the additive model (OR = 1.571, 95%CI = 1.414-1.745, P = 0.000), dominant model (OR = 1.681, 95%CI = 1.521-1.858, P = 0.000), and allelic model (OR = 1.597, 95%CI = 1.470-1.734, P = 0.000). In the subgroup analysis by ethnicity, the same results were found in Caucasian populations, while no significant correlations were found in Asian populations for all comparison models. In conclusion, our meta-analysis provides evidence that the rs2230199 polymorphism contributes to the development of AMD. Further large-scale multicenter epidemiological studies are warranted to confirm this finding.

PMID: 26505407 [PubMed - in process]

Sci Rep. 2015 Oct 27;5:15711.

CETP/LPL/LIPC gene polymorphisms and susceptibility to age-related macular degeneration.

Wang YF, Han Y, Zhang R, Qin L, Wang MX, Ma L.

Abstract: Three high-density lipoprotein (HDL)-related loci have been reported to be associated with age-related macular degeneration (AMD), but the results were inconsistent. In this study, the cholesteryl ester transfer protein (CETP) rs3764261 variant was significantly associated with an increased risk of AMD (odds ratio [OR] = 1.13, 95% confidence interval [CI]: 1.05-1.21, P < 0.001), and the hepatic lipase (LIPC) rs10468017 variant was associated with a significantly decreased risk of AMD (OR = 0.81, CI: 0.76-0.86, P < 0.001). Individuals carrying the lipoprotein lipase (LPL) rs12678919 polymorphism (A → G) had no significant change in the risk of developing AMD (OR = 1.01, CI: 0.92-1.10, P = 0.17). After adjusting for the complement factor H (CFH) gene, both CETP and LPL conferred a significantly increased AMD risk

(ORCETP = 1.17, CI: 1.08-1.26, P < 0.001; ORLPL = 1.11, CI: 1.01-1.22, P = 0.02). Subgroup analysis based on ethnicity revealed a significant association between the CETP variant and AMD in both Americans (OR = 1.12, CI: 1.02-1.23, P = 0.01) and Europeans (OR = 1.10, CI: 1.01-1.19, P = 0.011). This meta-analysis revealed that both CETP rs3764261 and LIPC rs10468017 polymorphisms were significantly associated with AMD risk. After adjustment for the CFH gene, CETP/LPL conferred a significantly increased susceptibility to the disease, indicating potential interactions among genes in the complement system and the lipid metabolism pathway.

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Diet, lifestyle and low vision

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Lutein Leads to a Decrease of Factor D Secretion by Cultured Mature Human Adipocytes.

Tian Y, Kijlstra A, Renes J, Wabitsch M, Webers CA, Berendschot TT.

Purpose: Complement plays an important role in the pathogenesis of age related macular degeneration (AMD) and trials are currently being conducted to investigate the effect of complement inhibition on AMD progression. We previously found that the plasma level of factor D (FD), which is the rate limiting enzyme of the complement alternative pathway, was significantly decreased following lutein supplementation. FD is synthesized by adipose tissue, which is also the main storage site of lutein. In view of these findings we tested the hypothesis whether lutein could affect FD synthesis by adipocytes.

Methods: A cell line of mature human adipocytes was incubated with 50 μg/mL lutein for 24 and 48 h, whereafter FD mRNA and protein expression were measured.

Results: Lutein significantly inhibited adipocyte FD mRNA expression and FD protein release into adipocyte culture supernatants.

Conclusions: Our earlier observations showing that a daily lutein supplement in individuals with early signs of AMD lowered the level of circulating FD might be caused by blocking adipocyte FD production.

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Impact of Wet Macular Degeneration on the Execution of Natural Actions.

Boucart M, Delerue C, Thibaut M, Szaffarczyk S, Hayhoe M, Tran TH.

PURPOSE: To use eye movements to investigate how people with a central scotoma might be impaired in the execution of natural actions and whether task familiarity affects performance.

METHODS: Sixteen participants with AMD and 16 age-matched controls performed two natural actions: (1) a familiar sandwich-making task and (2) a less familiar model-building task. In each action, task-relevant and task-irrelevant objects were placed on a table, covering 90°. The participants were asked to execute the actions without a time constraint. Eye movements were recorded.

RESULTS: The people with AMD were significantly slower than the controls, both in the exploration phase (before the first reaching movement) and in the working phase (execution of action), especially in the unfamiliar task. Gaze duration was longer on relevant than irrelevant objects in both groups and tasks, as might be expected. However, for the participants with AMD, gaze durations were longer on all of the objects, whether relevant or irrelevant, except in the more familiar task. This suggests that participants with AMD take longer to extract the information they need but that this can be counteracted when the task items

are familiar. The number of saccades/min of the task was significantly greater for the people with AMD than for the controls.

CONCLUSIONS: The present results show that people with AMD can accomplish natural actions efficiently, but need longer gaze durations and more eye movements than normally sighted people. This effect can be reduced when executing a familiar task.

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