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MD Research News

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Br J Ophthalmol. 2016 Mar 7. pii: bjophthalmol-2016-308400. doi: 10.1136/bjophthalmol-2016-308400. [Epub ahead of print]

Outcomes of intravitreal anti-VEGF therapy in eyes with both neovascular age-related macular degeneration and diabetic retinopathy.

Bandello F, Corvi F, La Spina C, Benatti L, Querques L, Capuano V, Naysan J, Chen X, Sarraf D, Parodi MB, Souied E, Freund KB, Querques G.

PURPOSE: To investigate the outcomes of intravitreal antivascular endothelial growth factor (VEGF) therapy in eyes with both neovascular age-related macular degeneration (AMD) and diabetic retinopathy (DR).

METHODS: Patients from four high-volume referral centres who presented with neovascular AMD and DR, and received intravitreal anti-VEGF therapy, were included. Data retrieved from medical records and multimodal imaging were analysed.

RESULTS: Forty-one eyes of 38 patients (21 male, 17 female; mean age 78±8 years) were enrolled. Median follow-up was 28±19 (12-72) months with a mean of 9.2±7.4 intravitreal anti-VEGF injections per eye were administrated. Best-corrected visual acuity (BCVA) was 0.5±0.3 logMAR; it improved significantly at 1 year (0.3±0.3 logMAR; p=0.02) and returned to baseline values at last follow-up visit (0.6±0.4 logMAR; p=0.26). Mean central macular thickness (CMT) significantly decreased from 408±150 µm to 328±104 µm at 1 year (p=0.021) and to 335±127 µm at last follow-up visit (p=0.032). The baseline severity of DR was graded as mild non-proliferative DR (NPDR) in 21 (51%) eyes, moderate NPDR in 14 (34%), severe NPDR in 4 (10%) and inactive proliferative DR in 2 (5%). At last follow-up visit, one eye graded as moderate NPDR improved to mild, one eye graded as severe NPDR improved to mild and one eye graded as severe NPDR was inactivated due to panretinal photocoagulation.

CONCLUSIONS: Outcomes analysis of intravitreal anti-VEGF therapy for eyes with both neovascular AMD and DR showed stabilisation of BCVA and reduction of CMT, along with stable or improved DR stage throughout follow-up.

PMID: 26951773 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 Mar 7. [Epub ahead of print]

Short-term choroidal thickness changes in patients treated with either ranibizumab or aflibercept: a comparative study.

Kim JH, Lee TG, Chang YS, Kim CG, Cho SW.

PURPOSE: To compare, in neovascular age-related macular degeneration (AMD) patients, short-term

choroidal thickness changes in eyes treated using ranibizumab with those in eyes treated using aflibercept.

METHODS: This retrospective, observational study included 240 eyes from 240 patients who had been diagnosed with treatment-naive neovascular AMD and treated using three monthly injections of either ranibizumab (ranibizumab group) or aflibercept (aflibercept group). The choroidal thickness change between the time of diagnosis and 3 months later was compared between the two groups. Eyes were then classified into three disease groups: typical neovascular AMD, polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP). Within each disease group, choroidal thickness change was again compared between the two treatment groups.

RESULTS: In the ranibizumab group (n=155), the mean choroidal thicknesses at diagnosis and at 3 months were 255.3±103.9 μm and 242.9±104.8 μm, respectively. In the aflibercept group (n=85), the values were 277.5±119.1 μm and 254.7±114.5 μm, respectively. The decrease was significantly greater in the aflibercept group ($p<0.001$). In the PCV group, the decrease was greater in the aflibercept group ($p=0.001$), whereas the difference was not significant in either the typical neovascular AMD group or the RAP group.

CONCLUSIONS: A greater decrease in choroidal thickness was noted in eyes treated with aflibercept than in eyes treated with ranibizumab. This difference was more marked in PCV than in other subtypes of neovascular AMD.

PMID: 26951770 [PubMed - as supplied by publisher]

Adv Ther. 2016 Mar 7. [Epub ahead of print]

Using Patient-Level Data to Develop Meaningful Cross-Trial Comparisons of Visual Impairment in Individuals with Diabetic Macular Edema.

Sivaprasad S, Regnier SA, Fajnkuchen F, Wright J, Berger AR, Mitchell P, Larsen M.

INTRODUCTION: The aim of this study was to assess the impact of baseline characteristics on visual outcome of patients with diabetic macular edema and compare the results of clinical trials with different patient populations.

METHODS: A model was created with patient-level data from the RESPOND/RESTORE trials to estimate the impact of baseline characteristics on increases in best-corrected visual acuity (BCVA) with anti-vascular endothelial growth factor therapies, measured by letters gained on the Early Treatment Diabetic Retinopathy Study scale from baseline to month 12. Mean BCVA gains with ranibizumab 0.5 mg pro re nata or laser photocoagulation monotherapy were predicted, assuming baseline characteristics equivalent to those in the VIVID-DME/VISTA-DME trials. These results were compared with the gain with aflibercept 2.0 mg every 8 weeks in VIVID-DME/VISTA-DME. Sensitivity analyses assessed outcome robustness.

RESULTS: Baseline BCVA and central retinal thickness differed significantly between trials. In unadjusted data, patients in RESPOND/RESTORE receiving ranibizumab gained an additional 6.6 letters [95% confidence interval (CI): 4.5-8.7] compared with patients receiving laser monotherapy. After adjusting data to assume baseline characteristics equivalent to VIVID-DME/VISTA-DME, patients receiving ranibizumab were predicted to gain an additional 9.9 letters (95% CI: 7.3-12.4) compared with those receiving laser monotherapy. These results were similar (0.1-letter difference in favor of aflibercept; 95% CI: -2.9 to 3.2; $P = 0.94$) to the gain in BCVA in patients receiving aflibercept in VIVID-DME/VISTA-DME compared with those receiving laser monotherapy (10.0 letters, 95% CI: 8.3-11.7).

CONCLUSION: After adjusting for baseline characteristics, the difference in letters gained between patients receiving ranibizumab versus aflibercept was non-significant across trials, highlighting the importance of adjusting for baseline characteristics in future comparisons.

PMID: 26951552 [PubMed - as supplied by publisher]

Expert Rev Pharmacoecon Outcomes Res. 2016 Mar 11. [Epub ahead of print]

Review and comparison of methodologies for indirect comparison of clinical trial results: an illustration with ranibizumab and aflibercept.

Regnier S, Alsop J, Wright J, Nixon R, Staines H, Fajnkuchen F.

AIM: To review and compare methods for indirect comparison of aflibercept and ranibizumab in patients with diabetic macular edema.

METHODS: Post-stratification, inverse probability weighting based on simulated data, weight optimization, and regression model techniques were used to compare pooled individual patient-level data from the RESTORE and RESPOND (ranibizumab 0.5 mg as needed after 3 initial monthly doses) studies with summary-level data from the VIVID and VISTA (aflibercept 2.0 mg every 8 weeks after 5 initial monthly doses, 2q8) studies. The impact of adjusting for up to two baseline characteristics was assessed.

RESULTS: All methods provided similar results. After adjustment for baseline best-corrected visual acuity and central retinal thickness, no statistically significant difference in average gain in baseline best-corrected visual acuity from baseline at month 12 was found between ranibizumab 0.5 mg and aflibercept 2q8.

CONCLUSIONS: Weight optimization and regression methods are useful options to adjust for more than one baseline characteristics.

PMID: 26967930 [PubMed - as supplied by publisher]

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):44-8.

Central Retinal Vein Occlusion: A Review of Current Evidence-based Treatment Options.

Patel A, Nguyen C, Lu S.

Abstract: A central retinal vein occlusion (CRVO) can induce an ischemic and hypoxic state with resulting sequelae of macular edema and neovascularization. Many treatment options have been studied. Our review aims to investigate the safety and efficacy of the multiple treatment options of CRVO. A PubMed and Cochrane literature search was performed. Well-controlled randomized clinical trials that demonstrated strong level 1 evidence-based on the rating scale developed by the British Centre for Evidence-Based Medicine were included. Seven clinical trials met inclusion criteria to be included in this review. These included studies that investigated the safety and efficacy of retinal photocoagulation (1 study), intravitreal steroid treatment (2 studies), and antivascular endothelial growth factor treatment (4 studies) for the treatment of CRVO. In addition, studies evaluating surgical treatment options for CRVO were also included. Many treatment modalities have been demonstrated to be safe and efficacious in the treatment of CRVO. These treatment options offer therapeutic benefits for patients and clinically superior visual acuity and perhaps the quality of life after suffering from a CRVO.

PMID: 26957838 [PubMed - in process] PMCID: PMC4759903

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):38-43.

Clinical Trials in Branch Retinal Vein Occlusion.

Panakanti TK, Chhablani J.

Abstract: Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disorder. The management of macular edema has changed considerably over time. The laser is considered the gold standard treatment for over two decades. However, visual recovery with laser is usually slow and incomplete. The advent of intravitreal agents, specifically anti-vascular endothelial growth factors (VEGF) have heralded a new era which promises rapid recovery of vision and quality of vision. Randomized clinical

trials have reported optimal results with anti-VEGF agents (ranibizumab, bevacizumab, and aflibercept) compared to laser therapy or steroids. However, nearly 50% of the patients require repeat intravitreal anti-VEGF therapy up to 4 years after initiating therapy to sustain the visual gains. The adverse events (systemic and ocular) of these agents are minimal. Monotherapy with anti-VEGF agents have been found to provide better results than any combination with laser. This review article summarizes evidence from randomized controlled trials evaluating treatment options for the treatment of macular edema secondary to BRVO with a special focus on anti-VEGF therapy.

PMID: 26957837 [PubMed - in process] PMCID: PMC4759902

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):27-37.

Management of Neovascular Age-related Macular Degeneration: A Review on Landmark Randomized Controlled Trials.

Agarwal A, Aggarwal K, Gupta V.

Abstract: In the last decade, a number of prospective clinical trials with carefully designed study protocols have been conducted for the treatment of neovascular age-related macular degeneration (AMD). These landmark clinical trials such as ANCHOR and MARINA and, more recently, the Comparison of AMD Treatment Trials and VIEW studies have revolutionized the management of neovascular AMD. While AMD continues to remain a leading cause of severe visual loss worldwide, advances in pharmacotherapeutics have led to substantial improvements in the outcome of these patients. The introduction of anti-vascular endothelial growth factor agents has resulted in improvement of visual outcomes and has had a positive impact on the quality of life among elderly population. While the contemporary management of neovascular AMD has been successful in tremendously reducing the visual morbidity, the financial burden of therapy has increased exponentially. To overcome these challenges, newer pharmacologic agents are evaluated for their efficacy and safety in AMD. Ground-breaking advances in bench to bedside research have led to discovery of new pathways that appear to be viable targets for preventing visual loss in AMD. In this review, study designs and results of landmark clinical trials in AMD from the past decade have been summarized.

PMID: 26957836 [PubMed - in process] PMCID: PMC4759900

Aflibercept (Eylea): Treatment of Neovascular (Wet) Age-Related Macular Degeneration (wAMD) [Internet].

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Aug.

CADTH Common Drug Reviews.

Excerpt: Age-related macular degeneration (AMD) is a degenerative disease of the macula. In Canada, about one million people currently have early AMD and approximately 250,000 have the advanced form of AMD. AMD is the leading cause of registered visual impairment in Canada. The prevalence of blindness due to AMD in Canada has been estimated at more than 100,000. There are two types of AMD: dry AMD and neovascular (wet) AMD (wAMD). While wAMD develops in only 10% to 20% of people with dry AMD, it accounts for more than 90% of those who have advanced vision loss. The hallmark of wAMD is choroidal neovascularization, which is an abnormal angiogenic process modulated by growth factors including vascular endothelial growth factor (VEGF). Currently, there is no cure for wAMD. The goal of treatment is to minimize vision loss and disability in order to maintain independence. The first line of pharmacological therapy for wAMD in Canada is 0.5 mg ranibizumab, a monoclonal antibody that inhibits VEGF and that is administered monthly by intravitreal (IVT) injection. Pegaptanib and photodynamic therapy (PDT) using verteporfin are also indicated for the treatment of wAMD in Canada, but as these treatments are limited to stabilization of the disease and produce little to no improvement in vision, they are generally used as a second-line therapy in clinical practice. For instance, PDT is usually reserved for patients with wAMD for whom IVT injection is not suitable. Bevacizumab is a much larger antibody fragment derived from the same

parent antibody as ranibizumab. It is not approved for treatment of wAMD in Canada, although it is used off -label for treating wAMD in patients who are ineligible for ranibizumab treatment coverage. Aflibercept (Eylea) is a novel VEGF inhibitor that is indicated in Canada for the treatment of patients with wAMD. Aflibercept is supplied as a solution for IVT injection (40 mg/mL) at a dose of 2 mg every eight weeks after three initial monthly injections. The objective of this report was to review the beneficial and harmful effects of aflibercept at the dosing regimen recommended by Health Canada for the treatment of wAMD.

PMID: 26962608 [PubMed] Free Books & Documents

Ranibizumab (Lucentis): Visual Impairment due to Choroidal Neovascularization Secondary to Pathologic Myopia [Internet].

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Aug.

CADTH Common Drug Reviews.

Excerpt: Pathologic myopia (PM) is caused by the progressive and excessive elongation of the axial length of the eyeball. Myopic choroidal neovascularization (CNV) is a complication of PM and is a serious threat to vision. CNV is observed as an abnormal growth of blood vessels located between the neurosensory retina and the retinal pigment epithelium. Symptoms include a decrease in vision, central scotoma, and/or metamorphopsia. PM has a prevalence of 0.084% among adult Canadians, and myopic CNV is a leading cause of visual disability among young adults.> Verteporfin (Visudyne) photodynamic therapy (vPDT) is the standard of care for myopic CNV in Canada. vPDT retards vision loss in patients with subfoveal CNV and stabilizes, rather than improves, visual acuity (VA). The anti-vascular endothelial growth factor (VEGF) therapies, ranibizumab (Lucentis) and bevacizumab (Avastin), have been used off-label as monotherapies for myopic CNV in Canada. Ranibizumab is approved in Canada for the treatment of neovascular (wet) age -related macular degeneration, the treatment of visual impairment due to macular edema secondary to retinal vein occlusion, and the treatment of visual impairment due to diabetic macular edema. Ranibizumab was recently approved by Health Canada for treating visual impairment due to CNV secondary to PM. Ranibizumab is supplied as a 10 mg/mL solution in single-use vials for intravitreal injection. The recommended dose is a single initial 0.5 mg injection followed by monthly injections, administered as needed based on signs of disease activity. The objective of this review was to perform a systematic review of the beneficial and harmful effects of ranibizumab intravitreal injection for the treatment of visual impairment due to CNV secondary to PM in adults.

PMID: 26962598 [PubMed] Free Books & DocumentsFree full text

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):3-12.

Updates on the Clinical Trials in Diabetic Macular Edema.

Demirel S, Argo C, Agarwal A, Parriott J, Sepah YJ, Do DV, Nguyen QD.

Abstract: In this era of evidence-based medicine, significant progress has been made in the field of pharmacotherapeutics for the management of diabetic macular edema (DME). A. number of landmark clinical trials have provided strong evidence of the safety and efficacy of agents such as anti-vascular endothelial growth factors for the treatment of DME. Decades of clinical research, ranging from the early treatment of diabetic retinopathy study to the present-day randomized clinical trials (RCTs) testing novel agents, have shifted the goal of therapy from preventing vision loss to ensuring a maximum visual gain. Systematic study designs have provided robust data with an attempt to optimize the treatment regimens including the choice of the agent and timing of therapy. However, due to a number of challenges in the management of DME with approved agents, further studies are needed. For the purpose of this review, an extensive database search in English language was performed to identify prospective, RCTs testing pharmacological agents for DME. In order to acquaint the reader with the most relevant data from these clinical trials, this review focuses on pharmacological agents that are currently approved or have

widespread applications in the management of DME. An update on clinical trials presently underway for DME has also been provided.

PMID: 26957834 [PubMed - in process] PMCID: PMC4759901

Case Rep Ophthalmol. 2015 Dec 19;6(3):458-61.

Bilateral Refractive Changes in Vascularized Pigment Epithelial Detachment Treated by Anti-VEGF Therapy.

Hanhart J, Chowers I.

Abstract: We report the case of a patient bilaterally treated with anti-VEGF compounds for bilateral massive vascularized retinal pigment epithelial detachment (PED). During the years prior to treatment, PED growth was accompanied by gradual hypermetropization. After right intraocular injection of bevacizumab followed by three bilateral aflibercept injections, the PED flattened resulting in a rapid relative myopization. This case illustrates ocular refractive properties associated with PED and its response to treatment. This case also highlights the importance of assessing refraction in age-related macular degeneration patients experiencing substantial PED amplitude changes.

PMID: 26955349 [PubMed] PMCID: PMC4777956

Retin Cases Brief Rep. 2016 Mar 7. [Epub ahead of print]

COAGULASE-NEGATIVE STAPHYLOCOCCUS-INDUCED FROSTED BRANCH ANGIITIS AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION.

Gensure RH, Hsu J, Federman J, Park C, Spirn MJ.

PURPOSE: To describe a case of frosted branch angiitis after intravitreal ranibizumab injection.

METHODS: Retrospective chart review.

RESULTS: A patient with a history of neovascular age-related macular degeneration underwent intravitreal ranibizumab injection and subsequently developed coagulase-negative Staphylococcus endophthalmitis with findings of frosted branch angiitis.

CONCLUSION: Endophthalmitis presenting as frosted branch angiitis is a rare complication after intravitreal anti-vascular endothelial growth factor injection. Early recognition is critical to optimize outcomes. To our knowledge, this is the second reported case of frosted branch angiitis as a presentation of endophthalmitis with coagulase-negative Staphylococcus.

PMID: 26954782 [PubMed - as supplied by publisher]

Drug Saf. 2016 Mar 7. [Epub ahead of print]

Intravitreal Bevacizumab and Cardiovascular Risk in Patients with Age-Related Macular Degeneration: Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies.

Mikačić I, Bosnar D.

INTRODUCTION: Intravitreal bevacizumab (IVTB) is used to treat age-related macular degeneration (ARMD), although its use is off-label and its cardiovascular safety has not been unequivocally established.

OBJECTIVES: Our objective was to assess the cardiovascular safety of IVTB in patients with ARMD.

METHODS: We conducted a systematic review and meta-analysis of published randomized controlled trials (RCTs) and observational studies.

RESULTS: Of the 2028 non-duplicate records, five RCTs versus ranibizumab (N = 3038, 12/24 months), four RCTs comparing different regimens (N = 809, 12/23 months), one RCT versus pegaptanib, photodynamic therapy (PDT), or sham (N = 131, 12 months), and three observational studies versus PDT, ranibizumab, or pegaptanib (~150,000 or 1666 patients/12 months and 317 patients/1-2 years, respectively) had a low risk of bias/high quality and ≥20 patients per arm with ≥6 months and ≥3 injections of treatment. RCT-based comparisons with PDT or pegaptanib are negligible. Observational data have not demonstrated differences [all-cause mortality, myocardial infarction (MI), stroke], but the level of evidence is "very low" (imprecise, indirect). RCT-based comparisons with ranibizumab did not demonstrate differences regarding some outcomes, although certain point estimates were at the level of a relevant harm/benefit [all-cause mortality odds ratio (OR) 1.103, 95 % confidence interval (CI) 0.641-1.898; vascular mortality OR 1.380, 95 % CI 0.476-3.997; MI OR 0.551, 95 % CI 0.265-1.146; stroke OR 0.657, 95 % CI 0.260-1.660; transitory ischemic attack OR 1.536, 95 % CI 0.444-5.313; atherothrombotic events (ATEs) OR 1.007, 95 % CI 0.641-1.593; venous thromboembolism OR 2.325, 95 % CI 0.963-5.612] or suggested a higher risk with bevacizumab (hypertension OR 7.512, 95 % CI 1.056-52.3), but estimates were based on sparse data, were extremely imprecise, and commonly exhibited considerable heterogeneity/inconsistency. The level of evidence per outcome was "low" or "very low". Observational data did not demonstrate difference (all-cause mortality, MI, stroke), or suggested a higher risk with bevacizumab (ATE), but were imprecise and indirect (level of evidence "very low"). RCT-based comparisons of different IVTB regimens suffered from the same limitations.

CONCLUSION: Published data on IVTB in AMRD provide only a low level of evidence on its cardiovascular safety and do not support any finite conclusions.

PMID: 26951234 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2016 Mar 8;16(1):25.

Peripapillary choroidal thickness after intravitreal ranibizumab injections in eyes with neovascular age-related macular degeneration.

Yun C, Oh J, Choi KE, Hwang SY, Kim SW, Huh K.

BACKGROUND: The purpose of this study was to investigate peripapillary choroidal thickness (CT) in eyes with neovascular age-related macular degeneration (AMD) and to assess whether peripapillary CT is affected by intravitreal injection of ranibizumab (IVR) in eyes with neovascular AMD.

METHODS: Peripapillary and subfoveal CT were measured in spectral domain optical coherence tomography images from 39 eyes of neovascular AMD patients and 39 eyes of age-matched controls retrospectively. The patients were treated with 0.5 mg IVR monthly for 3 months and retreated as needed. Peripapillary CT at baseline, 3 months and 6 months was measured at four locations (superior, nasal, inferior and temporal areas).

RESULTS: The mean peripapillary and subfoveal baseline CTs of the eyes with neovascular AMD (153.3 ± 45.3 μm and 228.6 ± 78.6 μm) were not different from those of the controls (149.0 ± 42.3 μm and 221.4 ± 54.1 μm; P = 0.665 and P = 0.639, respectively). Subfoveal CT decreased at 3 months (213.8 ± 75.8 μm, P < 0.001) and 6 months (215.1 ± 72.8 μm, P = 0.002) following IVR treatment. Mean peripapillary CT did not show significant changes at 3 months (149.6 ± 43.8 μm, P = 0.156) or 6 months (150.0 ± 43.4 μm, P = 0.187). Subanalysis revealed that only temporal peripapillary CT decreased from baseline (167.1 ± 54.5 μm) to 3 months (159.4 ± 50.8 μm, P = 0.010) and was sustained at 6 months (160.6 ± 49.6, P = 0.026). However, superior, nasal and inferior peripapillary CT did not show significant changes after IVR.

CONCLUSIONS: Changes in peripapillary CT after IVR were limited to the macular area. This result may suggest that IVR does not affect CT outside of the macula in the eyes of patients with neovascular AMD.

PMID: 26951107 [PubMed - in process] PMCID: PMC4782363

Nippon Ganka Gakkai Zasshi. 2016 Jan;120(1):28-34.

[Six Months Outcome in Patients with Macular Edema Due to Retinal Vein Occlusion Treated with Ranibizumab]. [Article in Japanese]

Sakanishi Y, Ouchi A, Ito R, Ebihara N.

PURPOSE: To assess the efficacy of intravitreal ranibizumab in the treatment of macular edema due to branch and central retinal vein occlusion for 6 month.

SUBJECTS AND METHODS: This study was retrospective, 32 eyes with branch retinal vein occlusion (BRVO) and 15 eyes with central retinal vein occlusion (CRVO) treated with intravitreal ranibizumab injections were investigated. We estimated the changes in visual acuity, central retinal thickness and average number of injections over 6 month. We also investigated which pre-injection factors were important in patients who improved following a single-dose injection.

RESULTS: The average number of injections was 1.9 in BRVO and 2.5 in CRVO. The visual acuity and central retinal thickness were improved in both BRVO and CRVO at 6 months, compared with those before injection. In patients with BRVO, it was indicated that the thinner the central fovea thickness prior to injection, the higher the rate of sustained effect following a single-dose administration.

CONCLUSION: Intravitreal ranibizumab injection is effective for macular edema with retinal vein occlusion.

PMID: 26950966 [PubMed - in process]

Ophthalmology. 2016 Mar 1. [Epub ahead of print]

Intravitreal Tissue Plasminogen Activator, Ranibizumab, and Gas Injection for Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy.

Kitagawa Y, Shimada H, Mori R, Tanaka K, Yuzawa M.

PURPOSE: To investigate the efficacy of intravitreal injection of recombinant tissue plasminogen activator (rt-PA), ranibizumab, and gas without vitrectomy for submacular hemorrhage.

DESIGN: Prospective, interventional, consecutive case series.

PARTICIPANTS: Twenty consecutive patients (20 eyes) with submacular hemorrhage secondary to exudative age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV).

METHODS: Ranibizumab, rt-PA (25 μg/0.05 ml), and 100% perfluoropropane (0.3 ml) were injected intravitreally, followed by 2-day prone positioning.

MAIN OUTCOME MEASURES: The primary outcome measure was best-corrected visual acuity (BCVA) 6 months after treatment. Secondary outcome measures included central retinal thickness (CRT), central pigment epithelial detachment (PED) thickness, central ellipsoid zone, recurrence rate, and complications.

RESULTS: Underlying disease was exudative AMD in 1 eye and PCV in 19 eyes. Submacular hemorrhage ranged in size from 2 to 31 disc diameters. Complete displacement of submacular hemorrhage was achieved in 17 eyes (85%), and partial displacement was achieved in 3 eyes (15%). Snellen BCVA improved from 20/139 before treatment to 20/65 at 6 months ($P = 0.0061$). Mean change in Early Treatment Diabetic Retinopathy Study score from baseline was +13 letters ($P = 0.0040$). Mean CRT decreased from 599 μm before treatment to 208 μm at 6 months ($P < 0.0001$), and central PED thickness decreased from 188 to 88 μm ($P = 0.0140$). Three eyes developed vitreous hemorrhage, and 1 eye developed retinal detachment; all were treated surgically, and Snellen BCVA improved at 6 months ($P = 0.0012$). Recurrence was observed in 10 eyes (50%) within 6 months, but visual acuity was preserved with intravitreal injection of anti-vascular endothelial growth factor (VEGF) pro re nata (PRN). The factors that affect BCVA at 6 months after treatment were pre- and posttreatment central ellipsoid zone ($P = 0.0366$ and $P = 0.0424$),

pretreatment BCVA (P = 0.0015), and pre- and posttreatment central PED thickness (P = 0.0046, P = 0.0021).

CONCLUSIONS: Subretinal hemorrhage treatment by intravitreal injection of rt-PA, ranibizumab, and gas is useful to achieve hemorrhage displacement and lesion improvement. To preserve visual acuity, early detection of posttreatment recurrence and intravitreal anti-VEGF injection PRN are necessary.

PMID: 26949121 [PubMed - as supplied by publisher]

Eur J Pharmacol. 2016 Mar 3. [Epub ahead of print]

Treatment for neovascular age related macular degeneration: The state of the art.

Eandi CM, Alovisi C, De Sanctis U, Grignolo FM.

Abstract: With the introduction in the clinical practice of drugs inhibiting vascular endothelial growth factor (VEGF) the visual outcomes of patients with neovascular age related macular degeneration (AMD) dramatically improved. Since 2006 repeated intravitreal injections of anti-VEGF became the standard of care for the treatment of neovascular AMD. This review provides an overview of available data form clinical trials supporting the use of anti-VEGF molecules for the treatment of this condition. Several questions remain open, in particular the regimen of treatment, the frequency of injection, the safety of the different drugs, and the poor response to the treatment in some cases. Therefore, new agents and alternative delivery are currently under evaluation.

PMID: 26948315 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2016 Mar 8. [Epub ahead of print]

Efficacy of vitrectomy and inner limiting membrane peeling in age-related macular degeneration resistant to anti-vascular endothelial growth factor therapy, with vitreomacular traction or epiretinal membrane.

Kimura S, Morizane Y, Toshima S, Hosogi M, Kumase F, Hosokawa M, Shiode Y, Fujiwara A, Shiraga F.

PURPOSE: We assessed the efficacy of vitrectomy and inner limiting membrane (ILM) peeling, followed by anti-vascular endothelial growth factor (VEGF) therapy, anti-VEGF-resistant age-related macular degeneration (AMD) due to vitreomacular traction (VMT) or epiretinal membrane (ERM).

METHODS: We identified six patients with anti-VEGF-resistant AMD due to VMT or ERM amongst a total of 588 patients with AMD (821 eyes) referred to Okayama University Hospital between February 2012 and May 2014. These patients underwent vitrectomy to release the VMT (4 cases) or remove the ERM (2 cases), along with ILM peeling. The regimen used for intravitreal injections of anti-VEGF reagents after surgery was based on the severity of exudative changes in each patient. Preoperative and postoperative best-corrected visual acuity (BCVA) and central retinal thickness (CRT) measurements were compared.

RESULTS: After vitrectomy and ILM peeling, all six patients responded to anti-VEGF therapy, which was then able to maintain dry retinas. Mean BCVA did not improve significantly (0.49 ± 0.28 before vs. 0.43 ± 0.38 after surgery, P = 0.538). However, mean CR was significantly decreased after surgery, from 423 ± 83.5 μm to 257 ± 75.8 μm (P = 0.0078).

CONCLUSIONS: Vitrectomy and ILM peeling followed by anti-VEGF therapy may be a useful therapeutic option for anti-VEGF-resistant AMD with VMT or ERM.

PMID: 26951250 [PubMed - as supplied by publisher]

J Ophthalmic Inflamm Infect. 2016 Dec;6(1):9. Epub 2016 Mar 10.

Adjunctive use of systematic retinal thickness map analysis to monitor disease activity in punctate inner choroidopathy.

Madhusudhan S, Keane PA, Denniston AK.

Abstract: A challenge in the management of 'white dot syndromes' is the lack of sensitive objective measures of disease activity. Retinal thickness maps from spectral domain optical coherence tomography (SD-OCT) inform treatment decisions in other retinal conditions such as age-related macular degeneration and diabetic maculopathy. In this report, we demonstrate their value in providing quantitative monitoring of a patient with punctate inner choroidopathy (PIC). Retinal thickness maps referenced against a baseline scan reliably detected focal areas of increased macular volume in active PIC lesions during symptomatic episodes, highlighting these as 'hot spots' that could be quantified, providing an objective basis for treatment decisions.

PMID: 26965893 [PubMed]

Ophthalmology. 2016 Mar 4. [Epub ahead of print]

Anatomic Clinical Trial Endpoints for Nonexudative Age-Related Macular Degeneration.

Schaal KB, Rosenfeld PJ, Gregori G, Yehoshua Z, Feuer WJ.

TOPIC: To review the role of anatomic endpoints in clinical trials for the study of nonexudative age-related macular degeneration (AMD) with an emphasis on a novel composite endpoint for the study of emerging therapies for intermediate AMD (iAMD).

CLINICAL RELEVANCE: Unlike clinical trials for exudative AMD, it is impractical to use the change in visual acuity (VA) as a primary endpoint for the study of nonexudative AMD. By the time VA has been lost in nonexudative AMD, proof-of-concept early-stage clinical trials would take years to run, and drug development would be a near impossible task. Surrogate endpoints are needed that reliably predict future vision loss and can be easily measured. Anatomic changes that correlate with disease progression in nonexudative AMD offer the greatest promise as primary endpoints.

METHODS: In preparation for this review, the electronic PubMed database was searched for relevant research pertaining to anatomic endpoints for the study of nonexudative AMD. Paper selection was based on our knowledge of the field with the goal to be as inclusive as possible. Whenever possible, recent review articles and results from large clinical trials, preferably with outcomes from many years of follow-up were favored over trials of short duration.

RESULTS: The most commonly used anatomic endpoint for the study of late, nonexudative AMD is the growth of geographic atrophy (GA). The advantages of studying GA include the appreciation that its enlargement through the foveal center leads to significant vision loss through the availability of natural history studies, the understanding that prevention of this growth would preserve vision in the future, the ability to reliably measure GA using different imaging strategies, and the development appropriate statistical tools that reliably predict the growth of GA over time. The major disadvantage of using GA is that significant, irreversible disease progression has already occurred. The use of drusen volume as a predictor of disease progression and the use of a composite endpoint that incorporates drusen growth, formation of GA, and formation of neovascularization offers an opportunity to study therapies at an earlier stage of AMD with a greater likelihood of preserving better vision over a lifetime.

CONCLUSIONS: Anatomic endpoints for the study of nonexudative AMD are needed to accelerate drug development, and the availability of optical coherence tomography algorithms capable of reliably measuring drusen morphology offer the best opportunity to study therapies for iAMD.

PMID: 26952592 [PubMed - as supplied by publisher]

Medicine (Baltimore). 2016 Mar;95(10):e2967.

Assessment of Choroidal Microstructure and Subfoveal Thickness Change in Eyes With Different Stages of Age-Related Macular Degeneration.

Lu L, Xu S, He F, Liu Y, Zhang Y, Wang J, Wang Z, Fan X.

Abstract: Age-related macular degeneration (AMD) is a major cause of irreversible blindness. Choroidal structural changes seem to be inevitable in AMD pathogenesis. Our study revealed associated choroidal microstructural changes in AMD eyes.The aim of the study was to compare choroidal microstructural changes in eyes with AMD of different stages.The study was a retrospective, cross-sectional case series.The participants comprised of 32 age-matched normal eyes as controls, and 26 fellow uninvolved eyes of intermediate/late AMD, 29 of early AMD, 28 of intermediate AMD, and 39 of late AMD.All subjects underwent comprehensive ophthalmologic examination. The choroid images, including subfoveal choroidal thickness, percentage of Sattler layer area, and en face images of the choroid, were obtained using spectral-domain optical coherence tomography.The main outcome measures were subfoveal choroidal thickness changes, percentage of Sattler layer area changes, and en face images of the choroid in AMD eyes.One hundred fifty-four eyes of 96 individuals with mean age of 67.1±9.2 years were included. The mean subfoveal choroidal thickness was 295.4±56.8 μm in age-matched normal eyes, 306.7±68.4 μm in fellow uninvolved eyes with AMD, 293.8±80.4 μm in early AMD, 215.6±80.4 μm in intermediate AMD, and 200.4±66.6 μm in late AMD ($F=14.2$, all $P<0.001$). Choroidal thickness was greater in early AMD eyes than in intermediate/late AMD eyes ($P<0.001$). Mean percentage of Sattler layer area in each group showed a similar tendency. Microstructure of the choroid showed reduced vascular density of Sattler layer areas in late AMD eyes compared with normal eyes.Decreasing subfoveal choroidal thickness and percentage of Sattler layer area were demonstrated in the progression of AMD. The choroidal change was related to atrophy of the microstructural changes of underlying capillaries and medium-sized vessels.

PMID: 26962799 [PubMed - in process]

Int J Ophthalmol. 2016 Jan 18;9(1):145-52. eCollection 2016.

Photobiomodulation for the treatment of retinal diseases: a review.

Geneva II.

Abstract: Photobiomodulation (PBM), also known as low level laser therapy, has recently risen to the attention of the ophthalmology community as a promising new approach to treat a variety of retinal conditions including age-related macular degeneration, retinopathy of prematurity, diabetic retinopathy, Leber's hereditary optic neuropathy, amblyopia, methanol-induced retinal damage, and possibly others. This review evaluates the existing research pertaining to PBM applications in the retina, with a focus on the mechanisms of action and clinical outcomes. All available literature until April 2015 was reviewed using PubMed and the following keywords: "photobiomodulation AND retina", "low level light therapy AND retina", "low level laser therapy AND retina", and "FR/NIR therapy AND retina". In addition, the relevant references listed within the papers identified through PubMed were incorporated. The literature supports the conclusion that the low-cost and non-invasive nature of PBM, coupled with the first promising clinical reports and the numerous preclinical-studies in animal models, make PBM well-poised to become an important player in the treatment of a wide range of retinal disorders. Nevertheless, large-scale clinical trials will be necessary to establish the PBM therapeutic ranges for the various retinal diseases, as well as to gain a deeper understanding of its mechanisms of action.

PMID: 26949625 [PubMed] PMCID: PMC4768515

Transl Vis Sci Technol. 2016 Mar 4;5(2):3. eCollection 2016.

Automated Retinal Image Analysis for Evaluation of Focal Hyperpigmentary Changes in

Intermediate Age-Related Macular Degeneration.

Schmitz-Valckenberg S, Göbel AP, Saur SC, Steinberg JS, Thiele S, Wojek C, Russmann C, Holz FG, For The Modiamd-Study Group.

PURPOSE: To develop and evaluate a software tool for automated detection of focal hyperpigmentary changes (FHC) in eyes with intermediate age-related macular degeneration (AMD).

METHODS: Color fundus (CFP) and autofluorescence (AF) photographs of 33 eyes with FHC of 28 AMD patients (mean age 71 years) from the prospective longitudinal natural history MODIAMD-study were included. Fully automated to semiautomated registration of baseline to corresponding follow-up images was evaluated. Following the manual circumscription of individual FHC (four different readings by two readers), a machine-learning algorithm was evaluated for automatic FHC detection.

RESULTS: The overall pixel distance error for the semiautomated (CFP follow-up to CFP baseline: median 5.7; CFP to AF images from the same visit: median 6.5) was larger as compared for the automated image registration (4.5 and 5.7; $P < 0.001$ and $P < 0.001$). The total number of manually circumscribed objects and the corresponding total size varied between 637 to 1163 and 520,848 pixels to 924,860 pixels, respectively. Performance of the learning algorithms showed a sensitivity of 96% at a specificity level of 98% using information from both CFP and AF images and defining small areas of FHC ("speckle appearance") as "neutral."

CONCLUSIONS: FHC as a high-risk feature for progression of AMD to late stages can be automatically assessed at different time points with similar sensitivity and specificity as compared to manual outlining. Upon further development of the research prototype, this approach may be useful both in natural history and interventional large-scale studies for a more refined classification and risk assessment of eyes with intermediate AMD.

TRANSLATIONAL RELEVANCE:

Automated FHC detection opens the door for a more refined and detailed classification and risk assessment of eyes with intermediate AMD in both natural history and future interventional studies.

PMID: 26966639 [PubMed]

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):13-26.

Update on Clinical Trials in Dry Age-related Macular Degeneration.

Taskintuna I, Elsayed ME, Schatz P.

Abstract: This review article summarizes the most recent clinical trials for dry age-related macular degeneration (AMD), the most common cause of vision loss in the elderly in developed countries. A literature search through websites https://www.pubmed.org and https://www.clinicaltrials.gov/, both accessed no later than November 04, 2015, was performed. We identified three Phase III clinical trials that were completed over the recent 5 years Age-Related Eye Disease Study 2 (AREDS2), implantable miniature telescope and tandospirone, and several other trials targeting a variety of mechanisms including, oxidative stress, complement inhibition, visual cycle inhibition, retinal and choroidal blood flow, stem cells, gene therapy, and visual rehabilitation. To date, none of the biologically oriented therapies have resulted in improved vision. Vision improvement was reported with an implantable mini telescope. Stem cells therapy holds a potential for vision improvement. The AREDS2 formulas did not add any further reduced risk of progression to advanced AMD, compared to the original AREDS formula. Several recently discovered pathogenetic mechanisms in dry AMD have enabled development of new treatment strategies, and several of these have been tested in recent clinical trials and are currently being tested in ongoing trials. The rapid development and understanding of pathogenesis holds promise for the future.

PMID: 26957835 [PubMed - in process] PMCID: PMC4759891

Sci Rep. 2016 Mar 11;6:22867.

Establishment of a cone photoreceptor transplantation platform based on a novel cone-GFP reporter mouse line.

Smiley S, Nickerson PE, Wallace VA, et al.

Abstract: We report successful retinal cone enrichment and transplantation using a novel cone-GFP reporter mouse line. Using the putative cone photoreceptor-enriched transcript Coiled-Coil Domain Containing 136 (Ccdc136) GFP-trapped allele, we monitored developmental reporter expression, facilitated the enrichment of cones, and evaluated transplanted GFP-labeled cones in wildtype and retinal degeneration mutant retinas. GFP reporter and endogenous Ccdc136 transcripts exhibit overlapping temporal and spatial expression patterns, both initiated in cone precursors of the embryonic retina and persisting to the adult stage in S and S/M opsin(+) cones as well as rod bipolar cells. The trapped allele does not affect cone function or survival in the adult mutant retina. When comparing the integration of GFP (+) embryonic cones and postnatal Nrl(-/-) 'cods' into retinas of adult wildtype and blind mice, both cell types integrated and exhibited a degree of morphological maturation that was dependent on donor age. These results demonstrate the amenability of the adult retina to cone transplantation using a novel transgenic resource that can advance therapeutic cone transplantation in models of age-related macular degeneration.

PMID: 26965927 [PubMed - in process]

Eur J Pharmacol. 2016 Mar 3. [Epub ahead of print]

Targeting the complement system for the management of retinal inflammatory and degenerative diseases.

Xu H, Chen M.

Abstract: The retina, an immune privileged tissue, has specialized immune defense mechanisms against noxious insults that may exist in diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR), uveoretinitis and glaucoma. The defense system consists of retinal innate immune cells (including microglia, perivascular macrophages, and a small population of dendritic cells) and the complement system. Under normal aging conditions, retinal innate immune cells and the complement system undergo a low-grade activation (parainflammation) which is important for retinal homeostasis. In disease states such as AMD and DR, the parainflammatory response is dysregulated and develops into detrimental chronic inflammation. Complement activation in the retina is an important part of chronic inflammation and may contribute to retinal pathology in these disease states. Here, we review the evidence that supports the role of uncontrolled or dysregulated complement activation in various retinal degenerative and angiogenic conditions. We also discuss current strategies that are used to develop complement-based therapies for retinal diseases such as AMD. The potential benefits of complement inhibition in DR, uveoretinitis and glaucoma are also discussed, as well as the need for further research to better understand the mechanisms of complement-mediated retinal damage in these disease states.

PMID: 26948311 [PubMed - as supplied by publisher]

Pathogenesis

Biochem Biophys Res Commun. 2016 Mar 7. [Epub ahead of print]

Regulation of aryl hydrocarbon receptor-mediated transcription in ARPE-19 cells.

Jin HL, Jeong KW.

Abstract: The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor with pleiotropic effects in normal physiology or vascular development, xenobiotic metabolism, and cancer. A previous study

has reported that BRG1, a component of the SWI/SNF complex, is a coactivator for AHR and is recruited to the promoter region of the CYP1A1 gene in mouse hepatocytes. Recent data suggest that AHR is also expressed in human retinal pigment epithelial cells (ARPE-19), which play a crucial role in retinal physiology and the visual cycle. Multiple studies have shown that the AHR plays an important role in the pathogenesis of retinal diseases including age-related macular degeneration. However, the mechanism of AHR transcriptional activation in retinal pigment cells has not been reported. Here, we demonstrate that the AHR signaling pathway is active in ARPE-19 cells, as in hepatocytes, but with different target gene specificity. We also found that chromatin remodeling by the BRG1-containing SWI/SNF complex is required for the AHR-mediated expression of target genes in ARPE-19 cells. We identified a novel enhancer region (-12 kb) of the CYP1A1 gene in ARPE-19 cells, to which both AHR and BRG1 are recruited in a ligand-dependent manner. BRG1 is associated with the AHR in ARPE-19 cells, and the C-terminal activation domain of the AHR directly interacts with BRG1. Furthermore, depletion of BRG1 caused a reduction in chromatin accessibility at the CYP1A1 enhancer. These results suggest that ARPE-19 cells possess an AHR-mediated transcription pathway with different target gene specificity, and that BRG1 is required for AHR-mediated transcription in ARPE-19 cells.

PMID: 26966070 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):1017-30.

Potential Therapeutic Agents Against Retinal Diseases Caused by Aberrant Metabolism of Retinoids.

Liu X, Chen J, Liu Z, Li J, Yao K, Wu Y.

Abstract: The retinoid (visual) cycle is a complex enzymatic pathway that operates in the retina for the regeneration of 11-cis-retinal (11-cis-Ral), the inherent visual chromophore indispensable for vision. Deficiencies in the retinoid metabolism are involved in pathologic mechanisms of several forms of retinal diseases including age-related macular degeneration, Stargardt's disease, and Leber's congenital amaurosis, for which no effective cures presently exist. Nevertheless, the interference of abnormal retinoid metabolism with chemicals has been considered to be a promising strategy aimed at alleviating these retinal dysfunctions. Moreover, since gene therapy is gaining increasing importance in clinical practice, the modulation of key enzymes implicated with the retinoid cycle at a genetic level will hold great promise for the treatment of patients with degenerative diseases of the retina.

PMID: 26962698 [PubMed - in process]

Sci Rep. 2016 Mar 10;6:22889.

Complement factor H binding of monomeric C-reactive protein downregulates proinflammatory activity and is impaired with at risk polymorphic CFH variants.

Molins B, Fuentes-Prior P, Adán A, Antón R, Arostegui JI, Yagüe J, Dick AD.

Abstract: Inflammation and immune-mediated processes are pivotal to the pathogenic progression of age-related macular degeneration (AMD). Although plasma levels of C-reactive protein (CRP) have been shown to be associated with an increased risk for AMD, the pathophysiological importance of the prototypical acute-phase reactant in the etiology of the disease is unknown, and data regarding the exact role of CRP in ocular inflammation are limited. In this study, we provide mechanistic insight into how CRP contributes to the development of AMD. In particular, we show that monomeric CRP (mCRP) but not the pentameric form (pCRP) upregulates IL-8 and CCL2 levels in retinal pigment epithelial cells. Further, we show that complement factor H (FH) binds mCRP to dampen its proinflammatory activity. FH from AMD patients carrying the "risk" His402 polymorphism displays impaired binding to mCRP, and therefore proinflammatory effects of mCRP remain unrestrained.

PMID: 26961257 [PubMed - in process]

Age (Dordr). 2016 Apr;38(2):35.

Aging of perennial cells and organ parts according to the programmed aging paradigm.

Libertini G, Ferrara N.

Abstract: If aging is a physiological phenomenon-as maintained by the programmed aging paradigm-it must be caused by specific genetically determined and regulated mechanisms, which must be confirmed by evidence. Within the programmed aging paradigm, a complete proposal starts from the observation that cells, tissues, and organs show continuous turnover: As telomere shortening determines both limits to cell replication and a progressive impairment of cellular functions, a progressive decline in age-related fitness decline (i.e., aging) is a clear consequence. Against this hypothesis, a critic might argue that there are cells (most types of neurons) and organ parts (crystalline core and tooth enamel) that have no turnover and are subject to wear or manifest alterations similar to those of cells with turnover. In this review, it is shown how cell types without turnover appear to be strictly dependent on cells subjected to turnover. The loss or weakening of the functions fulfilled by these cells with turnover, due to telomere shortening and turnover slowing, compromises the vitality of the served cells without turnover. This determines well-known clinical manifestations, which in their early forms are described as distinct diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, etc.). Moreover, for the two organ parts (crystalline core and tooth enamel) without viable cells or any cell turnover, it is discussed how this is entirely compatible with the programmed aging paradigm.

PMID: 26957493 [PubMed - in process]

PLoS One. 2016 Mar 7;11(3):e0150211. eCollection 2016.

microRNA-34a-Mediated Down-Regulation of the Microglial-Enriched Triggering Receptor and Phagocytosis-Sensor TREM2 in Age-Related Macular Degeneration.

Bhattacharjee S, Zhao Y, Dua P, Rogaev EI, Lukiw WJ.

Abstract: The aggregation of Aβ42-peptides and the formation of drusen in age-related macular degeneration (AMD) are due in part to the inability of homeostatic phagocytic mechanisms to clear self-aggregating Aβ42-peptides from the extracellular space. The triggering receptor expressed in myeloid/microglial cells-2 (TREM2), a trans-membrane-spanning, sensor-receptor of the immune-globulin/lectin-like gene superfamily is a critical component of Aβ42-peptide clearance. Here we report a significant deficit in TREM2 in AMD retina and in cytokine- or oxidatively-stressed microglial (MG) cells. RT-PCR, miRNA-array, LED-Northern and Western blot studies indicated up-regulation of a microglial-enriched NF-κB-sensitive miRNA-34a coupled to a down-regulation of TREM2 in the same samples. Bioinformatics/transfection-luciferase reporter assays indicated that miRNA-34a targets the 299 nucleotide TREM2-mRNA-3'UTR, resulting in TREM2 down-regulation. C8B4-microglial cells challenged with Aβ42 were able to phagocytose these peptides, while miRNA-34a down-regulated both TREM2 and the ability of microglial-cells to phagocytose. Treatment of TNFα-stressed MG cells with phenyl-butyl nitrone (PBN), caffeic-acid phenethyl ester (CAPE), the NF-B-inhibitor/resveratrol analog CAY10512 or curcumin abrogated these responses. Incubation of anti-miRNA-34a (AM-34a) normalized miRNA-34a abundance and restored TREM2 back to homeostatic levels. These data support five novel observations: (i) that a ROS- and NF-B-sensitive, miRNA -34a-mediated modulation of TREM2 may in part regulate the phagocytic response; (ii) that gene products encoded on two different chromosomes (miRNA-34a at chr1q36.22 and TREM2 at chr6p21.1) orchestrate a phagocytic-Aβ42-peptide clearance-system; (iii) that this NF-kB-mediated-miRNA-34a-TREM2 mechanism is inducible from outside of the cell; (iv) that when operating normally, this pathway can clear Aβ42 peptide monomers from the extracellular medium; and (v) that anti-NF-kB and/or anti-miRNA (AM)-based therapeutic strategies may be useful against deficits in TREM-2 receptor-based-sensing and -phagocytic signaling that promote pathogenic amyloidogenesis.

PMID: 26949937 [PubMed - in process]

Epidemiology

Ophthalmology. 2016 Mar 7. [Epub ahead of print]

Risk of Age-related Macular Degeneration 4 to 5 Years after Cataract Surgery.

Wang JJ, Fong CS, Burlutsky G, Cugati S, Tan AG, Rochtchina E, Arnold J, Smith W, Mitchell P.

PMID: 26965529 [PubMed - as supplied by publisher]

Retina. 2016 Mar 10. [Epub ahead of print]

RISK OF AGE-RELATED MACULAR DEGENERATION IN END-STAGE RENAL DISEASE PATIENTS RECEIVING LONG-TERM DIALYSIS.

Wang IK, Lin HJ, Wan L, Lin CL, Yen TH, Sung FC.

PURPOSE: This study investigated the risk of age-related macular degeneration (AMD) in patients with end -stage renal disease (ESRD) receiving long-term dialysis and compared the risk between various dialysis modalities using propensity score-matching methods.

METHODS: From the National Health Insurance Research Database of Taiwan, the authors identified 27,232 patients with ESRD newly diagnosed from 2000 to 2010, including 9,287 patients on peritoneal dialysis (PD) and 17,945 patients on hemodialysis (HD). A total of 108,928 controls without kidney disease were randomly selected and frequency matched by age, sex, and index year of ESRD patients. The authors established an additional HD cohort matched by propensity scores of PD patients (N = 9,256 each). All cohorts were followed up until the end of 2011 to measure the incidence of AMD.

RESULTS:

The incidences of AMD were 1.84, 4.03, 5.37, and 3.50 per 1,000 person-years in the control, ESRD (PD and HD), PD, and HD cohorts, respectively. The hazard ratios for AMD were 1.72, 2.47, and 1.43 for the ESRD, PD, and HD cohorts, with 95% confidence intervals of 1.50 to 1.97, 2.05 to 2.98, and 1.22 to 1.68, respectively, compared with the control cohort. The patients on PD exhibited a hazard ratio of 1.74 (95% confidence interval = 1.27-2.38) for developing AMD compared with propensity score-matched patients on HD.

CONCLUSION:

Patients with ESRD may exhibit a higher risk of AMD than people without kidney disease. Patients on PD may be more likely to develop AMD than patients on HD.

PMID: 26966867 [PubMed - as supplied by publisher]

Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):89-95.

National Burden of Eye Diseases in Iran, 1990-2010; Findings from the Global Burden of Diseases Study 2010.

Hatef E, Mohammadi SF, Alinia C, Ashrafi E, Mohammadi SM, Lashay A, Sadeghi-Tari A.

PURPOSE: The disability-adjusted life-years (DALYs) lost due to eye diseases and trends in DALYs in Iran has not been previously reported. The object of this study is to report the burden of eye diseases in Iran and to compare changes from 1990 to 2010 based on age and gender.

METHODS: Data from the Global Burden of Disease Study 2010 (GBD 2010) are used to report DALYs for cataract, refraction/accommodation (functional) disorders, macular degeneration, and glaucoma.

RESULTS: Cataract, refraction/accommodation (functional) disorders, macular degeneration, and glaucoma were the 84(th), 87(th), 138(th), and 151(st) causes of DALY in 1990 and the 89(th), 72(nd), 99 (th), and 137(th) in 2010, respectively. Cataract accounted for 0.085% of national DALY in 1990 and 0.09% in 2010, refraction/accommodation (functional) disorders accounted for 0.42% in 1990 and 0.47% in 2010, macular degeneration accounted for 0.017% in 1990 and 0.071% in 2010 and glaucoma accounted for 0.0099% in 1990 and 0.025% in 2010. There was a steady increase in DALY with age for each eye disease for both genders and dichotomized for males and females from 1990 to 2010.

CONCLUSIONS: Epidemiologic transition is reflected in major ophthalmic and blinding diseases in the GBD data for Iran. The burden of macular degeneration is rising, followed by glaucoma. The burden of presbyopia affected individuals past their middle age. The burden of cataract manifested as a slower increase that could be attributable to better access to treatment.

PMID: 26957846 [PubMed - in process] PMCID: PMC4759911

Ophthalmic Epidemiol. 2016 Mar 7:1-8. [Epub ahead of print]

Risk Factors for Progression of Early Age-Related Macular Degeneration in Koreans.

Shim SH, Kim SG, Bae JH, Yu HG, Song SJ.

PURPOSE: To identify risk factors for the progression of early age-related macular degeneration (AMD) in Koreans.

METHODS: This study was conducted at a health-screening center and followed a prospective cohort study design. Of 10,890 participants older than 50 years, 318 (2.92%) presented with early AMD. Among these 318 participants, we re-examined 172 participants after a mean duration of 4.4 years. Progression was defined by the Age-Related Eye Disease Study (AREDS) simplified AMD severity scale. Multivariable logistic regression was used to examine associations between AMD progression and baseline physical, demographic, behavioral, and ocular characteristics.

RESULTS: Of the 172 participants with early AMD who were re-examined, 34 (19.8%) had progression. Multivariable analyses revealed that current smoking (odds ratio, OR, 7.0, 95% confidence interval, CI, 1.4-34.4, adjusted for age, alcohol consumption, body mass index, BMI, blood pressure, BP, total cholesterol, and high density lipoprotein, HDL, cholesterol) and hypertension (OR 10.3, 95% CI 1.9-55.7, adjusted for age, smoking status, alcohol consumption, BMI, total cholesterol, and HDL cholesterol) were independently associated with progression of early AMD. Additionally, the presence of a central drusen lesion within one-third disc diameter of the macula (age-adjusted OR 4.8, 95% CI 1.3-17.6) and 20 or more drusen (age adjusted OR 7.8, 95% CI 2.5-24.0) were independently associated with progression of early AMD Conclusion: Current smoking, hypertension, central drusen location, and increasing number of drusen were associated with an increased risk of early AMD progression in Koreans.

PMID: 26950426 [PubMed - as supplied by publisher]

Genetics

J Clin Med. 2016 Mar 4;5(3).

The Application of Genetic Risk Scores in Age-Related Macular Degeneration: A Review.

Cooke Bailey JN, Hoffman JD, Sardell RJ, Scott WK, Pericak-Vance MA, Haines JL.

Abstract: Age-related macular degeneration (AMD), a highly prevalent and impactful disease of aging, is inarguably influenced by complex interactions between genetic and environmental factors. Various risk scores have been tested that assess measurable genetic and environmental contributions to disease. We herein summarize and review the ability and utility of these numerous models for prediction of AMD and

suggest additional risk factors to be incorporated into clinically useful predictive models of AMD.

PMID: 26959068 [PubMed]

Indian J Ophthalmol. 2016 Jan;64(1):55-61.

Genetic components in diabetic retinopathy.

Mishra B, Swaroop A, Kandpal RP.

Abstract: Diabetic retinopathy (DR) is a serious complication of diabetes, which is fast reaching epidemic proportions worldwide. While tight glycemic control remains the standard of care for preventing the progression of DR, better insights into DR etiology require understanding its genetic basis, which in turn may assist in the design of novel treatments. During the last decade, genomic medicine is increasingly being applied to common multifactorial diseases such as diabetes and age-related macular degeneration. The contribution of genetics to the initiation and progression of DR has been recognized for some time, but the involvement of specific genes and genetic variants remains elusive. Several investigations are currently underway for identifying DR susceptibility loci through linkage studies, candidate gene approaches, and genome-wide association studies. Advent of next generation sequencing and high throughput genomic technologies, development of novel bioinformatics tools and collaborations among research teams should facilitate such investigations. Here, we review the current state of genetic studies in DR and discuss reported findings in the context of biochemical, cell biological and therapeutic advances. We propose the development of a consortium in India for genetic studies with large cohorts of patients and controls from limited geographical areas to stratify the impact of the environment. Uniform guidelines should be established for clinical phenotyping and data collection. These studies would permit identification of genetic loci for DR susceptibility in the Indian population and should be valuable for better diagnosis and prognosis, and for clinical management of this blinding disease.

PMID: 26953025 [PubMed - in process]

Int J Ophthalmol. 2016 Feb 18;9(2):298-305. eCollection 2016.

Association between complement factor I gene polymorphisms and the risk of age-related macular degeneration: a Meta-analysis of literature.

Wang Q, Zhao HS, Li L.

AIM: To systematically review the association between complement factors I (CFI) polymorphisms and age-related macular degeneration (AMD) and to explore whether CFI polymorphisms are associated with AMD.

METHODS: Meta-analysis of articles published from 1995 to January 2015 of articles involved with AMD and polymorphisms of the CFI gene. Eligible data were pooled in a Meta-analysis, analyzing using STATA software (version 12.0), Review Manager (version 5.2) and different models based on the heterogeneity of effect sizes. Egger's test, Begg's rank correlation methods were used to evaluate for publication bias.

RESULTS: Thirteen articles were eligible, describing two loci polymorphisms of the CFI gene (of which 12 articles focus on rs10033900T>C and 3 articles focus on rs2285714C>T). For rs10033900T>C, the results of our study revealed that having a mutant allele C, TC, CC and TC+CC was associated with a decreased risk of AMD in all population groups studied (C versus T models, OR=0.84, 95%CI: 0.72-0.99, P=0.04; TC versus TT models OR=0.89, 95%CI: 0.88-0.99, P=0.04; CC versus TT models, OR=0.76, 95%CI: 0.60-0.98, P=0.03; TC+CC versus TT models, OR=0.81, 95%CI:0.65-0.99, P=0.04). We found that C allele were related to lower AMD risk in the Caucasian population by subgroup analysis, but there was no association with AMD under the allele and genotypes comparison in Asian studies. For rs2285714 C>T, the TC, TT genotypes contributed to a higher risk of AMD, compared with the CC carriers and TC+CC (OR=1.34, 95% CI: 1.09-1.63, P=0.004; OR=1.50, 95%CI: 1.25-1.80, P<0.0001).

CONCLUSION: This Meta-analysis suggests that CFI rs10033900T>C and rs2285714C>T polymorphisms may contribute to AMD.

PMID: 26949655 [PubMed] PMCID: PMC4761747

Stem cells

Semin Ophthalmol. 2016;31(1-2):25-9.

Stem Cell-Based Therapy for Diseases of the Retinal Pigment Epithelium: From Bench to Bedside.

Sachdeva MM, Eliott D.

Abstract: Age-related macular degeneration (AMD) represents a leading cause of blindness in the elderly, and Stargardt's macular dystrophy (SMD) is the most common form of juvenile-onset macular degeneration. Dry AMD and SMD share an underlying pathophysiology, namely dysfunction and ultimately loss of the retinal pigment epithelium (RPE), suggesting that RPE transplantation may offer a potential treatment strategy for both patient populations. Stem cells have emerged as a promising source of replacement RPE. During the past 15 years, extraordinary strides have been made in the identification, characterization, and differentiation of stem cells. Recently, this large body of basic science and preclinical research has been translated to patient care with the publication of results from Phase 1/2 trials demonstrating safety of transplantation of human embryonic stem cell (hESC)-derived RPE into patients with AMD and SMD. While significant challenges remain before dry AMD and SMD become treatable diseases, the goal has become more tangible.

PMID: 26959126 [PubMed - in process]

Diet, lifestyle and low vision

Molecules. 2016 Mar 2;21(3).

Anti-Oxidant, Anti-Inflammatory and Anti-Angiogenic Properties of Resveratrol in Ocular Diseases.

Lançon A, Frazzi R, Latruffe N.

Abstract: Resveratrol (3,4',5 trihydroxy-trans-stilbene) is one of the best known phytophenols with pleiotropic properties. It is a phytoalexin produced by vine and it leads to the stimulation of natural plant defenses but also exhibits many beneficial effects in animals and humans by acting on a wide range of organs and tissues. These include the prevention of cardiovascular diseases, anti-cancer potential, neuroprotective effects, homeostasia maintenance, aging delay and a decrease in inflammation. Age-related macular degeneration (AMD) is one of the main causes of deterioration of vision in adults in developed countries This review deals with resveratrol and ophthalmology by focusing on the antioxidant, anti-inflammatory, and anti-angiogenic effects of this molecule. The literature reports that resveratrol is able to act on various cell types of the eye by increasing the level of natural antioxidant enzymatic and molecular defenses. Resveratrol anti-inflammatory effects are due to its capacity to limit the expression of pro-inflammatory factors, such as interleukins and prostaglandins, and also to decrease the chemo-attraction and recruitment of immune cells to the inflammatory site. In addition to this, resveratrol was shown to possess anti-VEGF effects and to inhibit the proliferation and migration of vascular endothelial cells. Resveratrol has the potential to be used in a range of human ocular diseases and conditions, based on animal models and in vitro experiments.

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Nippon Ganka Gakkai Zasshi. 2016 Jan;120(1):41-8.

[Effects of Constant Intake of Lutein-rich Spinach on Macular Pigment Optical Density: a Pilot Study].[Article in Japanese]

Ozawa Y, Nagai N, Suzuki M, Kurihara T, Shinoda H, Watanabe M, Tsubota K.

PURPOSE: Anti-oxidative nutrient supplements, including lutein, are an important preventive approach for age-related macular degeneration (AMD). In this pilot study, we obtained data required for planning a future dietary intervention study investigating the prevention of AMD progression with lutein-rich spinach.

METHODS: We examined 22 eyes from 11 healthy nonsmokers (ages 21-45 years) who ingested 75 g of frozen spinach containing 10 mg lutein every day for 2 months. Food frequency questionnaire, measurement of macular pigment optical density (MPOD), and eye and blood examinations were performed.

RESULTS: Mean lutein ± SD intake from food was 0.87 ± 0.76 mg/1,000 kcal at baseline. Mean MPOD, best corrected visual acuity, and serum lutein concentrations were increased at 1 and 2 months compared with baseline.

CONCLUSION: Constant intake of lutein-rich spinach increased both MPOD and serum lutein concentrations. These data are important for planning of a future interventional study examining the effects of dietary lutein.

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Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: a prospective cohort study.

Merle BM, Silver RE, Rosner B, Seddon JM.

BACKGROUND: There is growing evidence of the importance of nutrition in age-related macular degeneration (AMD), but few studies have explored associations with folate and B vitamins. No effective therapeutic strategy for geographic atrophy (GA) is available, and prevention could be of great value.

OBJECTIVE: We investigated associations between dietary folate, B vitamins, and progression to GA and whether these associations might be modified by genetic susceptibility.

DESIGN: Among 2525 subjects (4663 eyes) in the Age-Related Eye Disease Study, 405 subjects (528 eyes) progressed to GA over 13 y. Folate and B vitamins were log transformed and calorie adjusted separately for men and women. Ten loci in 7 AMD genes [complement factor H, age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase 1, complement component 2, complement component 3, complement factor B, collagen type VIII α 1, and RAD51 paralog B] were examined. Survival analysis was used to assess associations between incident GA and dietary intake of folate and B vitamins. Interaction effects between these nutrients and genetic variation on AMD risk were also evaluated. Subjects with at least one eye free of advanced AMD at baseline were included in these analyses.

RESULTS: There was a reduced risk of progression to GA with increasing intake of thiamin, riboflavin, and folate after adjusting for age, sex, and total energy intake (P-trend = 0.01, 0.03, and 0.001, respectively). After adjustment for demographic, behavioral, ocular, and genetic covariates, trends remained statistically significant for folate (P-trend = 0.007) and were borderline for thiamin (P-trend = 0.05). Riboflavin did not retain statistical significance (P-trend = 0.20). Folate was significantly associated with lower risk of incident GA among subjects homozygous for the complement component 3 (C3) R102G rs2230199 nonrisk genotype (CC) (HR = 0.43; 95% CI: 0.27, 0.70; P = 0.0005) but not subjects carrying the risk allele (G) (P = 0.76). Neither folate nor any B vitamin was significantly associated with neovascular AMD.

CONCLUSIONS: High folate intake was associated with a reduced risk of progression to GA. This relation could be modified by genetic susceptibility, particularly related to the C3 genotype. This trial was registered at clinicaltrials.gov as NCT00594672.

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Lower cognitive function in patients with age-related macular degeneration: a meta-analysis.

Zhou LX, Sun CL, Wei LJ, Gu ZM, Lv L, Dang Y.

OBJECTIVE: To investigate the cognitive impairment in patients with age-related macular degeneration (AMD).

METHODS: Relevant articles were identified through a search of the following electronic databases through October 2015, without language restriction: 1) PubMed; 2) the Cochrane Library; 3) EMBASE; 4) ScienceDirect. Meta-analysis was conducted using STATA 12.0 software. Standardized mean differences with corresponding 95% confidence intervals were calculated. All of the included studies met the following four criteria: 1) the study design was a case-control or randomized controlled trial (RCT) study; 2) the study investigated cognitive function in the patient with AMD; 3) the diagnoses of AMD must be provided; 4) there were sufficient scores data to extract for evaluating cognitive function between cases and controls. The Newcastle-Ottawa Scale criteria were used to assess the methodological quality of the studies.

RESULTS: Of the initial 278 literatures, only six case-control and one RCT studies met all of the inclusion criteria. A total of 794 AMD patients and 1,227 controls were included in this study. Five studies were performed with mini-mental state examination (MMSE), two studies with animal fluency, two studies with trail making test (TMT)-A and -B, one study with Mini-Cog. Results of the meta-analysis revealed lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test ($P \leq 0.001$ for all). The results also showed that differences in the TMT-A (except AMD [total] vs controls) and TMT-B test had no statistical significance ($P > 0.01$). The Newcastle-Ottawa Scale score was ≥5 for all of the included studies. Based on the sensitivity analysis, no single study influenced the overall pooled estimates.

CONCLUSION: This meta-analysis suggests lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test. The other cognitive impairment screening tests, such as animal fluency test and TMT, need more studies to assess.

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JAMA. 2016 Mar 1;315(9):875-6.

Visual Acuity Screening Among Asymptomatic Older Adults.

Lee P.

Comment on:

Screening for Impaired Visual Acuity in Older Adults: US Preventive Services Task Force Recommendation Statement. [JAMA. 2016]

Screening for Impaired Visual Acuity in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. [JAMA. 2016]

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