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MD Research News

Issue 238

Monday 29 June, 2015

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Drug treatment

Am J Ophthalmol. 2015 Jun 23. [Epub ahead of print]

Intravitreal Anti-Vascular Endothelial Growth Factor Treatment and the Risk of Thromboembolism.

Schlenker MB, Thiruchelvam D, Redelmeier DA.

PURPOSE: To evaluate the subsequent risk of thromboembolic events in patients receiving intravitreal ranibizumab and bevacizumab for age-related macular degeneration or macular edema.

DESIGN: Population-based crossover analysis with self-matched historical control data.

METHODS: Setting: Ontario, Canada, between April 1, 2006, and March 31, 2013.

STUDY POPULATION: Consecutive patients 65 and older who initiated intravitreal treatment (N=57,919).

INTERVENTION: Intravitreal injection of ranibizumab or bevacizumab.

MAIN OUTCOME MEASURES: Emergency visits for thromboembolic events spanning one to four years before treatment were compared to one year after treatment. We also examined other secondary events including hip fractures, congestive heart failure, angina, falls, depression, and total emergencies, as well as a control group.

RESULTS: A total of 57,919 patients were included who accounted for 1,858 thromboembolic emergencies (48 per month) during the three-year Baseline interval and 1,077 thromboembolic emergencies (83 per month) during the one-year Subsequent interval after initiating treatment. The absolute change in risk equaled an increase from 10.7 to 18.6 per 1,000 patients annually after initiation of treatment (rate ratio 1.74; 95% confidence interval 1.58-1.92; p<0.0001). The relative increase was particularly pronounced for ischemic stroke (rate ratio 2.18; 95% confidence interval 1.94-2.46; p<0.0001). The observed increase exceeded trends due to aging, applied across patients with diverse characteristics, occurred with each medication (ranibizumab and bevacizumab), was not apparent for emergencies unrelated to thromboembolic events, and did not occur in a control group following cataract surgery.

CONCLUSIONS: Intravitreal anti-vascular endothelial growth factor medications ranibizumab and bevacizumab may contribute to systemic thromboembolic events in patients 65 years or older.

PMID: 26116264 [PubMed - as supplied by publisher]

Retina. 2015 Jun 23. [Epub ahead of print]

INFLUENCE OF VITREOMACULAR INTERFACE ON ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY USING TREAT AND EXTEND TREATMENT PROTOCOL FOR AGE-RELATED

MACULAR DEGENERATION (VINTREX).

Houston SK 3rd, Rayess N, Cohen MN, Ho AC, Regillo CD.

PURPOSE: To determine the influence of vitreomacular adhesion (VMA) on treatment outcomes in patients with neovascular age-related macular degeneration who were treated with anti-vascular endothelial growth factor agents using a treat and extend treatment regimen.

METHODS: A retrospective consecutive case series of 204 eyes from 181 patients with a minimum of 1 year of follow-up at Wills Eye Hospital Retina Service. Vitreomacular interface characteristics were determined by spectral domain optical coherence tomography. One hundred and fifty-three eyes (75%) had no signs of VMA (non-VMA), and 51 (25%) had VMA.

RESULTS: Baseline mean visual acuity was 20/133 with a mean central retinal thickness of 350.5 μm in the non-VMA group and was 20/145 with 371.8 μm in the VMA group. Mean visual acuity in the non-VMA group was 20/83 and 20/64 at Years 1 and 2, respectively ($P < 0.01$ to baseline). Mean visual acuity in the VMA group was 20/81 and 20/85 at Years 1 and 2, respectively ($P < 0.01$ to baseline). The central retinal thickness was 289.71 μm and 267 μm at Years 1 and 2, respectively ($P < 0.01$ to baseline) in the non-VMA group and was 305.3 μm and 289.24 μm ($P < 0.01$ to baseline) in the VMA group. The mean total number of injections at Year 1 for non-VMA was 7.4 compared with 8.4 in VMA ($P = 0.001$) and 5.5 versus 6.7 for the 2 groups in Year 2 ($P = 0.027$). The mean longest extension at Year 1 was 11.8 weeks compared with 10.1 week ($P = 0.005$) and for Year 2 was 14.1 weeks compared with 12 weeks ($P = 0.041$).

CONCLUSION: The vitreomacular interface seems to have a significant influence on anti-vascular endothelial growth factor treatment intervals but not visual acuity or exudative control outcomes. Eyes with VMA on spectral domain optical coherence tomography at baseline may require more intensive treatment with decreased ability to extend treatment intervals.

PMID: 26110596 [PubMed - as supplied by publisher]

Ophthalmologica. 2015 Jun 19. [Epub ahead of print]

Intravitreal Ranibizumab in Daily Clinical Practice for Age-Related Macular Degeneration: Treatment of Exudative Age-Related Macular Degeneration in Real Life.

Cazet-Supervielle A, Gozlan J, Cabasson S, Boissonnot M, Manic H, Leveziel N.

PURPOSE: To describe the anatomical and functional outcomes in patients with exudative age-related macular degeneration (AMD) undergoing ranibizumab therapy in real-life practice.

METHODS: This is a retrospective analysis of patients with exudative AMD treated with ranibizumab. Visual acuity (VA) and optic coherence tomography characteristics at baseline and at the end of the follow-up, clinical forms of the disease, delay between diagnosis and treatment as well as the number of follow-up visits and of intravitreal injections were collected.

RESULTS: One hundred and seventy-nine patients (220 eyes) were followed up during a mean of 24 months. The mean delay between diagnosis and treatment was 20.3 days (SD ±16.8). VA stabilization was observed in 46.4% of eyes, 21.7% of eyes gained ≥15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters and 31.9% lost ≥15 ETDRS letters. The mean central retinal thickness decreased from 380.6 μm at baseline to 295.6 μm at the final examination. A lower baseline VA score was associated with a greater gain of letters (OR 1.04, 95% CI 1.02-1.06; $p < 0.001$).

CONCLUSION: Shortening the delays in diagnosis appears to be a key point in real-life situations.

PMID: 26111575 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Jun 18. pii: S0161-6420(15)00458-3. doi: 10.1016/j.ophtha.2015.05.010. [Epub ahead of print]

Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study.

Gillies MC, Campain A, Barthelmes D, Simpson JM, Arnold JJ, Guymer RH, McAllister IL, Essex RW, Morlet N, Hunyor AP; Fight Retinal Blindness Study Group.

PURPOSE: To analyze the long-term outcomes of eyes with neovascular age-related macular degeneration (AMD) starting treatment with vascular endothelial growth factor (VEGF) inhibitors at least 5 years earlier.

DESIGN: Database observational study.

PARTICIPANTS: Treatment-naïve eyes with neovascular AMD tracked by the Fight Retinal Blindness outcome registry that received at least 1 anti-VEGF injection.

METHODS: Locally weighted scatterplot smoothing curves were used to display visual acuity (VA) results.

MAIN OUTCOME MEASURES: Change in mean VA and number of injections and visits from baseline up to 7 years after initiating treatment.

RESULTS: The mean follow-up time of all 1212 identified eyes was 53.5 months, and 549 (45%) continued attending after 60 months. Mean VA improved from 55.1 to 61.4 letters after 6 months and remained above the mean presenting VA for approximately 6 years. After 7 years, mean VA was 2.6 letters lower than baseline for the 131 eyes still being followed; 40% had VA ≥70 (20/40) letters, and 18% had VA ≤35 letters (20/200). Of those with 20/40 VA before treatment, 40% had lost it after 7 years. Geographic atrophy affecting the fovea was thought to be the cause of a ≥10-letter loss after 6.5 years in 37% of a subset of such eyes that were retrospectively analyzed. A median of 6 injections and 9 visits were recorded over the first 12 months, and then 5 treatments and 7 to 9 visits per annum thereafter through 7 years. Treatment was discontinued for 663 eyes (53%) within the first 5 years. Despite initial gains in vision, the mean VA of these eyes had deteriorated to baseline or worse around the time treatment was discontinued. The rate of serious adverse events was low.

CONCLUSIONS: Good long-term outcomes of VEGF inhibition for neovascular AMD were found in this study. These results may be better than other reports because more injections were given to our patients, possibly associated with a greater incentive for the physician to treat. Further studies to determine how to maximize the proportion of eyes that retain the initial VA gains of anti-VEGF are warranted.

PMID: 26096346 [PubMed - as supplied by publisher]

Retina. 2015 Jul;35(7):1323-30.

SWITCHING TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION FROM BEVACIZUMAB TO RANIBIZUMAB: Who is Likely to Benefit From the Switch?

Moisseiev E, Katz G, Moisseiev J, Loewenstein A, Goldstein M, Lomnicky Y, Abend Y, Treister G, Goldenberg D, Levkovitch-Verbin H.

PURPOSE: To evaluate the safety and efficacy of switching from bevacizumab to ranibizumab in patients with neovascular age-related macular degeneration.

METHODS: Retrospective study of patients with neovascular age-related macular degeneration initially treated with bevacizumab and switched to ranibizumab. Visual acuity and central retinal thickness (CRT) were retrieved at four time points: before the last three bevacizumab injections, at the switch, after the first three ranibizumab injections, and at the end of follow-up.

RESULTS: One hundred and fourteen eyes of 110 patients were included. Switching from bevacizumab to ranibizumab did not achieve a significant change in visual acuity, and a significant reduction in CRT was achieved after the first three injections but was not maintained by the end of follow-up. Eyes that lost ≥0.1 logMAR before the switch were more likely to improve in visual acuity (P = 0.013), and eyes with ≥10% increase in CRT before the switch were more likely to improve anatomically (P = 0.0003). In 47.3% of the eyes, the CRT was reduced by ≥10% after the first 3 ranibizumab injections, and the reduction was maintained with additional injections.

CONCLUSION: Switching to ranibizumab should be considered in patients with visual acuity decrease or CRT increase, despite monthly bevacizumab injections. The response should be evaluated after the first three injections to guide future treatment.

PMID: 26102434 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jun 1;46(6):638-41.

Quantification of Change in Pigment Epithelial Detachment Volume and Morphology After Transition to Intravitreal Aflibercept in Eyes With Recalcitrant Neovascular AMD: 18-Month Results.

Kanesa-Thasan A, Grewal DS, Gill MK, Lyon AT, Mirza RG.

BACKGROUND AND OBJECTIVE: To quantitatively evaluate the change in pigment epithelial detachment (PED) morphology on spectral-domain optical coherence tomography (SD-OCT) 18 months after the transition to intravitreal aflibercept in patients with neovascular age-related macular degeneration (AMD) with PED recalcitrant to monthly intravitreal bevacizumab or ranibizumab.

PATIENTS AND METHODS: Retrospective case series examining patients with neovascular AMD who had a persistent fibrovascular or serous PED on SD-OCT. PED volume was calculated by manually outlining the PED on individual OCT slices of the raster scan and multiplying by the pixel dimensions.

RESULTS: Eleven eyes of 10 patients who had received an average of 25.7 ± 20.1 (range: 6 to 70) prior bevacizumab or ranibizumab injections over a period of 26.6 ± 19.8 months (range: 4 to 63) were included. PED volume decreased with aflibercept from 0.687 ± 0.837 mm(3) to 0.562 ± 0.705 mm(3) (P = .02), a decrease of 19% ± 12.27%.

CONCLUSION: After 18 months of aflibercept, recalcitrant PED volumes were reduced by 19% while preserving visual acuity in eyes with neovascular AMD.

PMID: 26114844 [PubMed - in process]

Ophthalmic Physiol Opt. 2015 Jul;35(4):450-4.

A survey of UK practice patterns in the delivery of intravitreal injections.

Samia-Aly E, Cassels-Brown A, Morris DS, Stancliffe R, Somner JE.

PURPOSE: To assess UK practice patterns related to the prescription of antibiotics before, during and after intravitreal injections, the location where injections are carried out and the qualifications of those administering the injections.

METHODS: Every ophthalmology unit featured in the Royal College of Ophthalmologists (UK) training directory was contacted. A healthcare professional involved in giving intravitreal injections at each institution completed a questionnaire regarding local practice patterns.

RESULTS: A response rate of 85% (115/136) was achieved. Seventy four percent of hospitals (85/115) gave take home antibiotics post intravitreal injection. Twenty three percent (26/115) of hospitals employed non-medical healthcare professionals to administer injections and 83% (96/115) administered intravitreal

injections in a dedicated clean room as opposed to an operating theatre.

CONCLUSION: Practice patterns for intravitreal injection vary considerably. Guidelines alone do not appear to be effective in reducing practices which are considered wasteful and other approaches need to be developed.

PMID: 26094833 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Jun 1;56(6):4129-4134.

Restoration of Outer Retinal Layers After Aflibercept Therapy in Exudative AMD: Prognostic Value.

Coscas F, Coscas G, Lupidi M, Dirani A, Srour M, Semoun O, Français C, Souied EH.

Purpose. To evaluate the outer retinal layer (ellipsoid zone [EZ] and external limiting membrane [ELM]) changes following intravitreal aflibercept injections in eyes with treatment-naïve exudative age-related macular degeneration (eAMD) and to correlate these changes with fluid response and visual improvement.

Methods. A retrospective case series of 50 treatment-naïve eAMD eyes followed-up for 18 months. All patients underwent regular comprehensive ophthalmic examinations. The presence of EZ disruption, ELM disruption, EZ swelling, subretinal hyper-reflective exudation (SHE), central macular thickness (CMT), cystoid spaces, subretinal fluid, and pigmented epithelium detachment were evaluated by two different retinal specialists at baseline and final visits, and correlated with best corrected visual acuity (BCVA) improvement.

Results. At 18 months, BCVA, EZ disruption, ELM disruption, EZ swelling and SHE improved significantly (P = 0.001) at 18 months. Improvement of BCVA showed a statistically significant correlation with ELM restoration (P = 0.018), but not with EZ restoration (P = 0.581). Swelling of the EZ decreased from 72% of the cases at baseline to 30% in 18 months while SHE decreased from 52% to 6% in 18 months (P = 0.001). We observed a statistically significant (P = 0.001) reduction between the baseline and final value of CMT.

Conclusions. Aflibercept is safe and effective in treating exudative AMD with the restoration of the outer retinal layers. Restoration of the EZ is not statistically correlated with the final BCVA, even though persistent EZ changes could be associated with irreversible decrease in vision. On the contrary, the final status of the ELM is directly correlated with final BCVA. Also, baseline changes in outer retinal layers, especially the ELM, appear to predict photoreceptor restoration and final BCVA, and must be comprehensively analyzed to enable and determine a future prognosis.

PMID: 26114491 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Jun 26. [Epub ahead of print]

A review of therapies for diabetic macular oedema and rationale for combination therapy.

Amoaku WM, Saker S, Stewart EA.

Abstract: Diabetic macular oedema (DMO) is responsible for significant visual impairment in diabetic patients. The primary cause of DMO is fluid leakage resulting from increased vascular permeability through contributory anatomical and biochemical changes. These include endothelial cell (EC) death or dysfunction, pericyte loss or dysfunction, thickened basement membrane, loss or dysfunction of glial cells, and loss/change of EC Glycocalyx. The molecular changes include increased reactive oxygen species, pro-inflammatory changes: advanced glycation end products, intracellular adhesion molecule-1, Complement 5-9 deposition and cytokines, which result in increased paracellular permeability, tight junction disruption, and increased transcellular permeability. Laser photocoagulation has been the mainstay of treatment until recently when pharmacological treatments were introduced. The current treatments for DMO target reducing vascular leak in the macula once it has occurred, they do not attempt to treat the underlying

pathology. These pharmacological treatments are aimed at antagonising vascular endothelial growth factor (VEGF) or non-VEGF inflammatory pathways, and include intravitreal injections of anti-VEGFs (ranibizumab, aflibercept or bevacizumab) or steroids (fluocinolone, dexamethasone or triamcinolone) as single therapies. The available evidence suggests that each individual treatment modality in DMO does not result in a completely dry macula in most cases. The ideal treatment for DMO should improve vision and improve morphological changes in the macular (eg, reduce macular oedema) for a significant duration, reduced adverse events, reduced treatment burden and costs, and be well tolerated by patients. This review evaluates the individual treatments available as monotherapies, and discusses the rationale and potential for combination therapy in DMO. A comprehensive review of clinical trials related to DMO and their outcomes was completed. Where phase III randomised control trials were available, these were referenced, if not available, phase II trials have been included.Eye advance online publication, 26 June 2015; doi:10.1038/eye.2015.110.

PMID: 26113500 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2015 Jun 24. [Epub ahead of print]

Anti-VEGF treatment in branch retinal vein occlusion: a real-world experience over 4 years.

Rezar S, Eibenberger K, Bühl W, Georgopoulos M, Schmidt-Erfurth U, Sacu S; Macula Study Group Vienna.

PURPOSE: To determine long-term outcome of intraocular antagonism of vascular endothelial growth factor (VEGF) in macular oedema (ME) secondary to branch retinal vein occlusion (BRVO).

METHODS: A total of 28 consecutive patients were treated with either intravitreal bevacizumab (IVB) or intravitreal ranibizumab (IVR) in the first series and were evaluated after a mean follow-up of 5 years for their functional and anatomical outcome.

RESULTS: Time between onset of macular oedema and initial treatment was 5.2 ± 0.4/0.1 ± 0.1 (IVB/IVR) months. A mean of 4 intravitreal injections were given per patients in the first 6 months. In months 7-12 intravitreal injections decreased to 2 and further decreased in the second year (months 13-18: 1.14; months 19-24: 0.5) and third year (months 25-30: 0.4; months 31-36: 0.2). After the fourth year, only two of the 28 patients received further treatment. Average visual acuity (VA) increased by 16 letters after 1 year ($p < 0.01$) and although not statistically significantly, by a mean of 5 letters ($p = 0.3$) at long-term evaluation (IVB -group). However, after mean of 5 years, central retinal sensitivity (CRS) improved by 3.6 dB ($p = 0.01$) and central retinal thickness (CRT) decreased by 161 µm ($p = 0.02$). In the IVR-group, VA and CRS increased significantly (31 letters and respectively 4.4 dB, $p < 0.001$) and CRT decreased by 229 µm ($p < 0.001$) after long-term follow-up. Final functional results were significantly better in patients with treatment initiation <3 months (79 versus 55 letters, $p = 0.01$). Microvascular abnormalities were detected in 88% (21 of 24 patients), hyperfluorescence in 42% (10 of 24 patients) on wide-field fluorescein angiography in both groups.

CONCLUSIONS: Inhibition of VEGF provides substantial long-term benefits for patients with ME secondary to BRVO. Early treatment with anti-VEGF agents and extended therapeutic surveillance was associated with improved visual recovery.

PMID: 26109209 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2015 Jun 11:0. [Epub ahead of print]

Early results of dexamethasone implant, ranibizumab, and triamcinolone in macular edema due to branch retinal vein occlusion.

Yumusak E, Buyuktortop N, Ornek K.

PURPOSE: To compare the short-term results of the efficacy and safety of dexamethasone intravitreal implant (DEX), ranibizumab (RAN), and intravitreal triamcinolone acetonide (IVTA) in macular edema secondary to branch retinal vein occlusion (BRVO).

METHODS: One eye each of 32 patients who were treated with intravitreal injections for macular edema secondary to BRVO was studied. This retrospective study included 3 groups. The patients received DEX in group 1 (n = 11), RAN in group 2 (n = 11), and IVTA in group 3 (n = 10). Data were collected before and after the injections at the first and third months. Best-corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure (IOP) were analyzed statistically.

RESULTS: The median duration of the follow-up was 3.0 months in overall groups. The BCVA increased significantly in all groups (p = 0.018, p = 0.034, p = 0.014, respectively). The CMT increased significantly in groups 1 and 3 (p = 0.02, p<0.001, respectively), but not in group 2 (p = 0.14). The IOP increased significantly in groups 1 and 3 (p = 0.05, p<0.001, respectively). Antiglaucomatous treatment was required only in group 3. Cataract developed in 2 patients (20%) in group 3 and surgery was required.

CONCLUSIONS: Although RAN was the safest among the 3 agents, DEX and IVTA reduced CMT more than RAN, while significant improvement was achieved in BCVA in all groups. All 3 agents can be effectively used in the treatment of macular edema due to BRVO.

PMID: 26109021 [PubMed - as supplied by publisher]

J Ophthalmol. 2015;2015:710324. Epub 2015 May 25.

Critical Appraisal of Clinical Practice Guidelines for Age-Related Macular Degeneration.

Wu AM, Wu CM, Young BK, Wu DJ, Margo CE, Greenberg PB.

Purpose: To evaluate the methodological quality of age-related macular degeneration (AMD) clinical practice guidelines (CPGs).

Methods: AMD CPGs published by the American Academy of Ophthalmology (AAO) and Royal College of Ophthalmologists (RCO) were appraised by independent reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, which comprises six domains (Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence), and an Overall Assessment score summarizing methodological quality across all domains.

Results: Average domain scores ranged from 35% to 83% for the AAO CPG and from 17% to 83% for the RCO CPG. Intraclass correlation coefficients for the reliability of mean scores for the AAO and RCO CPGs were 0.74 and 0.88, respectively. The strongest domains were Scope and Purpose and Clarity of Presentation. The weakest were Stakeholder Involvement (AAO) and Editorial Independence (RCO).

Conclusions: Future AMD CPGs can be improved by involving all relevant stakeholders in guideline development, ensuring transparency of guideline development and review methodology, improving guideline applicability with respect to economic considerations, and addressing potential conflict of interests within the development group.

PMID: 26106484 [PubMed] PMCID: PMC4461780

Ophthalmologica. 2015 Jun 20. [Epub ahead of print]

Comparison of the Effectiveness and Prognostic Factors of Intravitreal Ranibizumab between Typical Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy over 24 Months of Follow-Up.

Matsumiya W, Honda S, Otsuka K, Miki A, Nagai T, Imai H, Kusuhara S, Nakamura M.

PURPOSE: To compare the response to ranibizumab between patients with typical neovascular age-related macular degeneration (tAMD) and those with polypoidal choroidal vasculopathy (PCV), and to determine the predictors for the outcomes.

METHODS: Fifty-nine eyes from 59 consecutive patients (tAMD: 27 eyes, PCV: 32 eyes) were treated with three monthly ranibizumab injections followed by as-needed retreatment. Best-corrected visual acuity (BCVA) and morphological parameters were evaluated over 24 months of follow-up.

RESULTS: The mean BCVA in tAMD and PCV patients was significantly improved at 3 months (-0.22 and -0.09 logMAR units, respectively). The improvement in BCVA was sustained up to 24 months in tAMD ($p = 0.01$) but not in PCV patients. The significant predictor for good response to ranibizumab in tAMD patients was the improvement of BCVA at 3 months, whereas that in PCV patients was the anatomical resolution at 3 months.

CONCLUSIONS: Ranibizumab is an effective therapy for tAMD and PCV over 24 months. The predictors for good outcome might be different between tAMD and PCV.

PMID: 26112059 [PubMed - as supplied by publisher]

Retina. 2015 Jul;35(7):1429-35.

INTRAVITREAL DEXAMETHASONE IMPLANT IN PATIENTS WITH RANIBIZUMAB PERSISTENT DIABETIC MACULAR EDEMA.

Zhioua I, Semoun O, Lalloum F, Souied EH.

PURPOSE: To study the efficacy of intravitreal injection (IVI) of dexamethasone implant as second-line treatment in patients with resistant chronic diabetic macular edema nonresponsive to 6 monthly consecutive IVI of ranibizumab.

METHODS: A retrospective study was conducted over 9 months. Best-corrected visual acuity and central macular thickness were noted. Patients with best-corrected visual acuity ≤20/40 using Snellen chart, central macular thickness ≥300 μm, and poor response to 6 monthly consecutive IVI of ranibizumab were included. Patients received IVI of dexamethasone implant and were examined at 1, 3, 6, and 9 months.

RESULTS: Thirteen eyes of 12 patients were included (6 men and 6 women; mean age, 64 ± 7.8 years). Best-corrected visual acuity increased by a mean of 5.58 letters at Month 1 ($P = 0.017$), 4.61 at Month 3 ($P = 0.05$), 4.61 at Month 6 ($P = 0.042$), and 5.77 at Month 9 ($P = 0.017$). Central macular thickness decreased from 594 μm to 402 μm at Month 1 ($P = 0.0002$), 428 μm at Month 3 ($P = 0.002$), 459 μm at Month 6 ($P = 0.02$), and 489 μm at Month 9 ($P = 0.03$). Mean number of dexamethasone IVI was 1.07. Two patients (15.3%) developed elevated intraocular pressure, and 1 patient was operated for cataract at 6 months (9% of phakic patients).

CONCLUSION: Intravitreal injection of dexamethasone implant seems as an effective second-line treatment in diabetic macular edema persistent after 6 monthly consecutive intravitreal ranibizumab injections in real life.

PMID: 26102440 [PubMed - in process]

Other treatment & diagnosis

Acta Ophthalmol. 2015 Jun 24. [Epub ahead of print]

Clinical application of 3D display device in ophthalmology: measurement of metamorphopsia.

Kim JW, Kim YT.

PURPOSE: To develop a new tool for detecting metamorphopsia.

METHOD: Evaluation of diagnostic test. Novel tool for measuring metamorphopsia was developed using commercial 3D display. Fifty-eight patients diagnosed with macular disease, which included epiretinal membrane, age-related macular degeneration, central serous chorioretinopathy and macular hole, as confirmed by macular optical coherence tomography were tested with Amsler grid and novel method. The subjective perception of metamorphopsia and its effect on the lives of the participants with macular disease was also evaluated using a brief questionnaire. The sensitivity and specificity to subjective perception of metamorphopsia were compared.

RESULTS: The sensitivity and specificity were 66.7% and 97.7%, respectively, using the Amsler grid test, and 100% and 90.7%, respectively, using the 3D novel metamorphopsia test developed for this study.

CONCLUSIONS: The detection rate of metamorphopsia in macular disease using novel metamorphopsia test was significantly higher than that using the Amsler grid test. This novel approach to detecting for metamorphopsia can also be used at home for self-assessment.

PMID: 26109491 [PubMed - as supplied by publisher]

Comput Struct Biotechnol J. 2015 May 6;13:382-9. eCollection 2015.

Using Stem Cells to Model Diseases of the Outer Retina.

Yvon C, Ramsden CM, Lane A, Powner MB, da Cruz L, Coffey PJ, Carr AJ.

Abstract: Retinal degeneration arises from the loss of photoreceptors or retinal pigment epithelium (RPE). It is one of the leading causes of irreversible blindness worldwide with limited effective treatment options. Generation of induced pluripotent stem cell (IPSC)-derived retinal cells and tissues from individuals with retinal degeneration is a rapidly evolving technology that holds a great potential for its use in disease modelling. IPSCs provide an ideal platform to investigate normal and pathological retinogenesis, but also deliver a valuable source of retinal cell types for drug screening and cell therapy. In this review, we will provide some examples of the ways in which IPSCs have been used to model diseases of the outer retina including retinitis pigmentosa (RP), Usher syndrome (USH), Leber congenital amaurosis (LCA), gyrate atrophy (GA), juvenile neuronal ceroid lipofuscinosis (NCL), Best vitelliform macular dystrophy (BVMD) and age related macular degeneration (AMD).

PMID: 26106463 [PubMed] PMCID: PMC4477013

Comput Biol Med. 2015 Jun 4;63:208-218. [Epub ahead of print]

Local configuration pattern features for age-related macular degeneration characterization and classification.

Mookiah MR, Acharya UR, Fujita H, Koh JE, Tan JH, Noronha K, Bhandary SV, Chua CK, Lim CM, Laude A, Tong L.

Abstract: Age-related Macular Degeneration (AMD) is an irreversible and chronic medical condition characterized by drusen, Choroidal Neovascularization (CNV) and Geographic Atrophy (GA). AMD is one of the major causes of visual loss among elderly people. It is caused by the degeneration of cells in the macula which is responsible for central vision. AMD can be dry or wet type, however dry AMD is most common. It is classified into early, intermediate and late AMD. The early detection and treatment may help one to stop the progression of the disease. Automated AMD diagnosis may reduce the screening time of the clinicians. In this work, we have introduced LCP to characterize normal and AMD classes using fundus images. Linear Configuration Coefficients (CC) and Pattern Occurrence (PO) features are extracted from fundus images. These extracted features are ranked using p-value of the t-test and fed to various supervised classifiers viz. Decision Tree (DT), Nearest Neighbour (k-NN), Naive Bayes (NB), Probabilistic

Neural Network (PNN) and Support Vector Machine (SVM) to classify normal and AMD classes. The performance of the system is evaluated using both private (Kasturba Medical Hospital, Manipal, India) and public domain datasets viz. Automated Retinal Image Analysis (ARIA) and STructured Analysis of the Retina (STARE) using ten-fold cross validation. The proposed approach yielded best performance with a highest average accuracy of 97.78%, sensitivity of 98.00% and specificity of 97.50% for STARE dataset using 22 significant features. Hence, this system can be used as an aiding tool to the clinicians during mass eye screening programs to diagnose AMD.

PMID: 26093788 [PubMed - as supplied by publisher]

Retina. 2015 Jul;35(7):1303-14.

IDENTIFICATION OF FLUID ON OPTICAL COHERENCE TOMOGRAPHY BY TREATING OPHTHALMOLOGISTS VERSUS A READING CENTER IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS.

Toth CA, Decroos FC, Ying GS, Stinnett SS, Heydary CS, Burns R, Maguire M, Martin D, Jaffe GJ.

PURPOSE: To examine treatment decisions by ophthalmologists versus reading center fluid identification from optical coherence tomography in Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

METHODS: Fluid in 6,210 optical coherence tomography scans (598 patients) in "as needed treatment" arm of CATT Year 1 was compared with ophthalmologist's treatment: positive fluid agreement (PFA, fluid+, treatment+) and positive fluid discrepancy (PFD, fluid+, treatment-), negative fluid agreement (fluid-, treatment-) and negative fluid discrepancy (fluid-, treatment+). For PFDs, fluid location and visual acuity were characterized.

RESULTS: Treatment and reading center fluid determination agreed in 72.1% (53.0% PFA, 19.1% negative fluid agreement) and disagreed in 27.9% (25.7% PFD, 2.2% negative fluid discrepancy) of visits, with no discrepancies for 20.9% of patients. Compared with PFA, PFD occurred more commonly with lower total foveal thickness (mean ± SD: 265 ± 103 PFD, 366 ± 151 μm PFA), presence of intraretinal fluid only, smaller fluid areas (PFA areas greater than twice those of PFD, $P < 0.001$), and greater decrease in retinal and lesion thickness. Mean acuities before, at, and after PFD were 65.8, 66.9, and 66.3 letters.

CONCLUSION: Treatment decisions by ophthalmologists matched reading center fluid determination in the majority of visits. More pronounced response to treatment and smaller foci of fluid likely contributed to PFD. Positive fluid discrepancy did not have substantial impact on subsequent visual acuity.

PMID: 26102433 [PubMed - in process] PMCID: PMC4479420

Graefes Arch Clin Exp Ophthalmol. 2015 Jun 23. [Epub ahead of print]

Influence of macular oedema on the measurement of macular pigment optical density.

Thiele S, Rauscher FG, Wiedemann P, Dawczynski J.

INTRODUCTION: The purpose of this study was to determine macular pigment optical density (MPOD) in patients with macular degeneration as well as in patients with non-proliferative diabetic retinopathy.

METHODS: Fifty-one phakic patients with either age-related macular degeneration (60 eyes of 30 patients; average age, 70.9 years) or non-proliferative diabetic retinopathy (42 eyes of 21 patients; average age, 61.7 years) were included in this cross-sectional study. Within the groups, patients were divided into those suffering from macular oedema and those with no oedema. An intra-subject comparison between eyes was carried out in both groups. Data were investigated on the basis of the coefficient of determination (R 2). Macular pigment optical density was measured by fundus reflectometry using the one-wavelength reflection

method (Visucam 500; Carl Zeiss Meditec AG, Jena, Germany), in conformity with the method described by Schweitzer et al. (2010). We evaluated the maximum optical density in the measurement area (max OD) and the average optical density across the reference area in the measurement area (mean OD). Specifically, the influence of macular oedema on macular pigment optical density was examined. The subsequent measurement of retinal thickness was carried out by spectral-domain optical coherence tomography (Spectralis SD-OCT, Heidelberg Engineering GmbH, Heidelberg, Germany).

RESULTS: The current study included two groups. The first group consisted of patients with non-proliferative diabetic retinopathy, as follows: no macular oedema on either side (max OD: R 2 = 43.2 %, p = 0.16; mean OD: R 2 = 68.7 %, p = 0.04); one-sided macular oedema (max OD: R2 = 16 %, p = 0.60; mean OD: R2 = 100 %, p = 0.04); or macular oedema in both eyes (max OD: R2 = 79.7 %, p < 0.01; mean OD: R2 = 81.4 %, p < 0.01). The second group comprised patients with age-related macular degeneration (AMD), as follows: non-exudative changes on both sides (max OD: R2 = 64.0 %, p = 0.20; mean OD: R 2 = 16 %, p = 0.60); one-sided exudative macular changes (max OD: R 2 = 50.6 %, p < 0.01; mean OD: R 2 = 20.8 %, p = 0.04); or exudative macular degeneration on both sides (max OD: 3 R 2 = 6.0 %, p = 0.29; mean OD: R 2= 81.0 %, p = 0.04). The data available presented a correlation of MPOD values of both eyes of an individual within the groups investigated. In this respect, the data of the partner eyes within the group of patients with diabetic retinopathy were more highly correlated with each other than the values of both eyes of patients suffering from age-related macular degeneration.

CONCLUSIONS: The present study showed that macular oedema did not seem to have an influence on a valid measurement of MPOD by one-wavelength fundus reflectometry. Thus, meaningful data could also be obtained on patients with exudative retinal changes.

PMID: 26100452 [PubMed - as supplied by publisher]

F1000Res. 2013 May 23;2:131. eCollection 2013.

Reliability and reproducibility of spectral and time domain optical coherence tomography images before and after correction for patients with age-related macular degeneration.

Rashid A, Sepah YJ, Channa R, Hatef E, Shulman M, Do DV, Nguyen QD.

PURPOSE: To evaluate the reproducibility and reliability of Optical Coherence Tomography scans (OCT) obtained using the Time Domain (TD-OCT) StratusTM OCT, and the Spectral Domain (SD-OCT) SpectralisTM and CirrusTM OCT devices before and after manual correction in eyes with either Neovascular (NV-AMD) or Non-Neovascular (NNV-AMD) Age-related Macular Degeneration.

METHODS: We conducted a prospective observational study of 36 patients (50 eyes) with NV-AMD or NNV-AMD at a university-based retina practice. OCT scans were taken simultaneously using one TD-OCT and two SD-OCT devices. Macular thickness measurements were assessed before and after correction of the OCT algorithm by constructing Bland-Altman plots for agreement and calculating intraclass correlation coefficients (ICCs) and coefficients of repeatability (COR) to evaluate intraclass repeatability.

RESULTS: The Spectralis device had the highest number of images needing manual correction. All machines had high ICCs, with Spectralis having the highest. Bland-Altman plots indicated that there was low agreement between both Cirrus™ and Stratus™ and Spectralis™ and Stratus™, while there was good agreement between the Cirrus™ and Spectralis™ devices. The CORs were lowest for SpectralisTM and similar with each other and had higher values for CirrusTM and StratusTM. Agreement, CORs, and ICCs generally improved after manual correction, but only minimally.

CONCLUSION: Agreement is low between devices, except between both SD-OCT machines. Manual correction tends to improve results.

PMID: 26097682 [PubMed]

Prog Retin Eye Res. 2015 Jun 22. [Epub ahead of print]

Stem cell based therapies for age-related macular degeneration: the promises and the challenges.

Nazari H, Zhang L, Zhu D, Chader GJ, Falabella P, Stefanini F, Rawland T, Clegg DO, Kashani AH, Hinton DR, Humayun MS.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in developed countries. AMD is classified as either neovascular (NV-AMD) or non-neovascular (NNV-AMD). Cumulative damage to the retinal pigment epithelium, Bruch's membrane, and choriocapillaris leads to dysfunction and loss of RPE cells. This causes degeneration of the overlying photoreceptors and consequential vision loss in advanced NNV-AMD (Geographic Atrophy). In NV-AMD, abnormal growth of capillaries under the retina and RPE, which leads to hemorrhage and fluid leakage, is the main cause of photoreceptor damage. Although a number of drugs (e.g., anti-VEGF) are in use for NV-AMD, there is currently no treatment for advanced NNV-AMD. However, replacing dead or dysfunctional RPE with healthy RPE has been shown to rescue dying photoreceptors and improve vision in animal models of retinal degeneration and possibly in AMD patients. Differentiation of RPE from human embryonic stem cells (hESC-RPE) and from induced pluripotent stem cells (iPSC-RPE) has created a potentially unlimited source for replacing dead or dying RPE. Such cells have been shown to incorporate into the degenerating retina and result in anatomic and functional improvement. However, major ethical, regulatory, safety, and technical challenges have yet to be overcome before stem cell-based therapies can be used in standard treatments. This review outlines the current knowledge surrounding the application of hESC-RPE and iPSC -RPE in AMD. Following an introduction on the pathogenesis and available treatments of AMD, methods to generate stem cell-derived RPE, immune reaction against such cells, and approaches to deliver desired cells into the eye will be explored along with broader issues of efficacy and safety. Lastly, strategies to improve these stem cell-based treatments will be discussed.

PMID: 26113213 [PubMed - as supplied by publisher]

Retina. 2015 Jul;35(7):1375-80.

IMPROVED SPECIFICITY OF POLYPOIDAL CHOROIDAL VASCULOPATHY DIAGNOSIS USING A MODIFIED EVEREST CRITERIA.

Gemmy Cheung CM, Laude A, Wong W, Mathur R, Chan CM, Wong E, Wong D, Wong TY, Lim TH.

PURPOSE: To evaluate the performance of polypoidal choroidal vasculopathy (PCV) diagnosis using fundus camera-based indocyanine green angiography, comparing a single sign of "subretinal focal hyperfluorescence" on indocyanine green angiography with a modification of the EVEREST criteria.

METHODS: Color fundus photograph, flash fundus camera-based fluorescein angiography, and indocyanine green angiography of 241 eyes of 230 consecutive patients with exudative maculopathy due to PCV or typical age-related macular degeneration were graded independently by 2 retinal specialists using a modified EVEREST criteria, which requires the presence of subretinal focal hyperfluorescence plus any 1 of 5 additional criteria. Discordant cases were adjudicated by a senior retinal specialist to arrive at the final diagnosis. Sensitivity, specificity, and area under the receiver operating curve of subretinal focal hyperfluorescence versus the EVEREST criteria and combinations of individual EVEREST criteria were compared.

RESULTS: Among the 241 eyes with exudative maculopathy, 131 eyes had PCV and 110 eyes had typical age-related macular degeneration. Using a single sign of subretinal focal hyperfluorescence alone for the diagnosis of PCV, sensitivity was 85.3% and specificity was 80.9%, with an area under the receiver operating curve of 83.1%. When applying the EVEREST definition, sensitivity was reduced to 78.4% but specificity improved to 87.1% with a similar area under the receiver operating curve of 82.8%. The frequency of individual criteria was highly variable, with stereo nodular appearance (73.7%) and orange nodule (55.0%) being the most common and branching vascular network, massive hemorrhage, and

hypofluorescent halo in the presence of subretinal focal hyperfluorescence being less common (21.5%-28.1%).

CONCLUSION: The EVEREST criteria have a higher specificity for the diagnosis of PCV than subretinal focal hyperfluorescence alone and may be applied to flash fundus camera-based indocyanine green angiography in a clinical setting. Stereo nodular appearance is the most important additional criterion.

PMID: 26102436 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Jun 1;56(6):3998.

Two Subtypes of Polypoidal Choroidal Vasculopathy: Idiopathic Disease or Age-Related Macular Degeneration.

Yuzawa M.

PMID: 26098466 [PubMed - in process]

Pathogenesis

Prog Retin Eye Res. 2015 Jun 23. [Epub ahead of print]

Molecular pathogenesis of retinal and choroidal vascular diseases.

Campochiaro PA.

Abstract: There are two major types of ocular neovascularization that affect the retina, retinal neovascularization (NV) and subretinal or choroidal NV. Retinal NV occurs in a group of diseases referred to as ischemic retinopathies in which damage to retinal vessels results in retinal ischemia. Most prevalent of these are diabetic retinopathy and retinal vein occlusions. Subretinal and choroidal NV occur in diseases of the outer retina and Bruch's membrane, the most prevalent of which is age-related macular degeneration. Numerous studies in mouse models have helped to elucidate the molecular pathogenesis underlying retinal, subretinal, and choroidal NV. There is considerable overlap because the precipitating event in each is stabilization of hypoxia inducible factor-1 (HIF-1) which leads to upregulation of several hypoxia-regulated gene products, including vascular endothelial growth factor (VEGF), angiopoietin 2, vascular endothelial-protein tyrosine phosphatase (VE-PTP), and several others. Stimulation of VEGF signaling and suppression of Tie2 by angiopoietin 2 and VE-PTP are critical for sprouting of retinal, subretinal, and choroidal NV, with perturbation of Bruch's membrane also needed for the latter. Additional HIF-1-regulated gene products cause further stimulation of the NV. It is difficult to model macular edema in animals and therefore proof-of-concept clinical trials were done and demonstrated that VEGF plays a central role and that suppression of Tie2 is also important. Neutralization of VEGF is currently the first line therapy for all of the above disease processes, but new treatments directed at some of the other molecular targets, particularly stabilization of Tie2, are likely to provide additional benefit for subretinal/choroidal NV and macular edema. In addition, the chronicity of these diseases as well as the implication of VEGF as a cause of retinal nonperfusion and progression of background diabetic retinopathy make sustained delivery approaches for VEGF antagonists a priority.

PMID: 26113211 [PubMed - as supplied by publisher]

J Neuroinflammation. 2015 Jun 24;12(1):121. [Epub ahead of print]

Age-related increases in amyloid beta and membrane attack complex: evidence of inflammasome activation in the rodent eye.

Zhao T, Gao J, Van J, To E, Wang A, Cao S, Cui JZ, Guo JP, Lee M, McGeer PL, Matsubara JA.

BACKGROUND: The membrane attack complex (MAC) is a key player in the pathogenesis of age-related macular degeneration (AMD) and is a putative activator of the NLRP3 inflammasome. Amyloid beta (Aβ), a component of drusen deposits, has also been implicated in inflammasome activation by our work and those of others. However, the interactions of MAC and Aβ are still poorly understood, especially their roles in aging and retinal degenerative pathologies. Since inflammasome activation may represent a key cellular pathway underlying age-related chronic inflammation in the eye, the purpose of this study is to identify the effects associated with MAC and inflammasome activation in the retinal pigment epithelium (RPE)/choroid and to evaluate the therapeutic merits of MAC suppression.

METHODS: Adult Long-Evans rats were divided into treatment and control groups. Treatment groups received oral aurin tricarboxylic acid complex (ATAC), a MAC inhibitor, in drinking-water, and control groups received drinking-water alone (No ATAC). Groups were sacrificed at 7.5 or 11.5 months, after approximately 40 days of ATAC treatment. To study age-related changes of Aβ and MAC in RPE/choroid, naive animals were sacrificed at 2.5, 7.5, and 11.5 months. Eye tissues underwent immunohistochemistry and western blot analysis for MAC, Aβ, NF-κB activation, as well as cleaved caspase-1 and IL-18. Vitreal samples were collected and assessed by multiplex assays for secreted levels of IL-18 and IL-1β. Statistical analyses were performed, and significance level was set at $p \leq 0.05$.

RESULTS: In vivo studies demonstrated an age-dependent increase in MAC, Aβ, and NF-κB activation in the RPE/choroid. Systemic ATAC resulted in a prominent reduction in MAC formation and a concomitant reduction in inflammasome activation measured by cleaved caspase-1 and secreted levels of IL-18 and IL-1β, but not in NF-κB activation. In vitro studies demonstrated Aβ-induced MAC formation on RPE cells.

CONCLUSIONS: Age-dependent increases in Aβ and MAC are present in the rodent outer retina. Our results suggest that suppressing MAC formation and subsequent inflammasome activation in the RPE/choroid may reduce chronic low-grade inflammation associated with IL-18 and IL-1β in the outer retina.

PMID: 26104676 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2015 Jun 18. [Epub ahead of print]

The Effects of Cataract Surgery on Patients with Wet Macular Degeneration.

Saraf SS, Ryu CL, Ober MD.

PURPOSE: To explore whether cataract surgery contributes to the progression of wet age-related macular degeneration (wet AMD).

DESIGN: Retrospective cohort study.

METHODS: Retrospective review was performed of consecutive patients with wet AMD who underwent cataract surgery at the midpoint of a one-year study window. A control arm included wet AMD eyes treated with anti-vascular endothelial growth factor (VEGF) injections that did not undergo cataract surgery for a one year period. Best corrected visual acuity (BCVA), number of anti-VEGF injections, and optical coherence tomography (OCT) features were compared between the two arms.

RESULTS: 40 eyes in the surgical group and 42 in the non-surgical group were included. BCVA was equivalent in the first half of the study, and became significantly better in the surgical group versus the non-surgical group (0.23 ± 0.65 versus 0.11 ± 0.59 logMAR improvement, p=0.049). There was no change in the number of injections given 6 months before versus after the midpoint in the surgical group (p=0.921). The mean OCT central retinal thickness became greater in post-surgical eyes compared to nonsurgical eyes (265.4 ± 98.4 μm versus 216.4 ± 58.3 μm, p=0.011). Surgical eyes were more likely to develop new or worse cystoid changes after the study midpoint, (13 surgical eyes [54.2%] versus 9 non-surgical eyes [28.1%], p=0.048).

CONCLUSIONS: Cataract surgery leads to vision improvement and does not appear to contribute to worsening of wet AMD. However, anatomic changes based upon OCT analysis suggest a susceptibility to subclinical postoperative cystoid macular edema or exacerbation of choroidal neovascularization.

PMID: 26095263 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Jun 1;56(6):4045-4052.

Peripapillary Choroidal Thickness in Adult Chinese: The Beijing Eye Study.

Jiang R, Wang YX, Wei WB, Xu L, Jonas JB.

Purpose. To measure peripapillary choroidal thickness (PPCT) and to assess its associations.

Methods. The population-based cross-sectional Beijing Eye Study 2011 included 3468 participants. Detailed medical and ophthalmic examinations were performed. We measured PPCT by spectral-domain optical coherence tomography (SD-OCT) with a 3.4-mm scan circle centered on the optic nerve head.

Results. Peripapillary choroidal thickness measurements were available for 3060 (88.2%) study participants with a mean age of 64.4 ± 9.6 years (range, 50-93 years). Mean global PPCT was 134 ± 53 μm (range, 35-348 μm). Peripapillary choroid was thickest in the superior region (155 ± 60 μm), followed by the temporal region (144 ± 75 μm; P < 0.001); nasal region (139 ± 55 μm; P < 0.001); and inferior region (110 ± 45 μm; P < 0.001). In multivariate analysis, thicker PPCT was associated with younger age (P < 0.001; standardized coefficient β: -0.33; correlation coefficient B: -1.95; 95% confidence interval (CI): -2.25, -1.65); shorter axial length (P < 0.001; β: -0.11; B: -5.39; 95% CI: -7.85, -2.93); smaller parapapillary α zone (P = 0.01; β: -0.06; B: -5.46; 95% CI: -9.73, -1.19); and smaller β zone (P < 0.001; β: -0.14; B: -8.29; 95% CI: -11.12, -5.46); better best corrected visual acuity (logMAR; P = 0.002; β: -0.05; B: -14.75; 95% CI: -28.59, -0.91), and higher prevalence of early age-related macular degeneration (P = 0.04; β: 0.05; B: 9.11; 95% CI: 0.42, 17.80) and intermediate age-related macular degeneration (P = 0.001; β: 0.08; B: 10.90; 95% CI: 4.46, 17.33). It was not significantly (all P > 0.05) associated with blood pressure, blood concentration of lipids, intraocular pressure and prevalence of glaucoma, diabetic retinopathy, and retinal vein occlusions. The decrease of PPCT with longer axial length occurred predominantly in the temporal region.

Conclusions. Peripapillary choroidal thickness is thickest superiorly and thinnest inferiorly. It decreases by 2 μm per year of life and by 5 μm per diopter of myopia. Thinner PPCT is correlated with larger parapapillary α and β zones. The association of thinner PPCT with lower best corrected visual acuity may warrant further study.

PMID: 26114482 [PubMed - as supplied by publisher]

Genetics

Front Physiol. 2015 Jun 9;6:177. eCollection 2015.

Inherited macular degeneration-associated mutations in CNGB3 increase the ligand sensitivity and spontaneous open probability of cone cyclic nucleotide-gated channels.

Meighan PC, Peng C, Varnum MD.

Abstract: Cyclic nucleotide gated (CNG) channels are a critical component of the visual transduction cascade in the vertebrate retina. Mutations in the genes encoding these channels have been associated with a spectrum of inherited retinal disorders. To gain insight into their pathophysiological mechanisms, we have investigated the functional consequences of several CNGB3 mutations, previously associated with macular degeneration (Y469D and L595F) or complete achromatopsia (S156F, P309L, and G558C), by expressing these subunits in combination with wild-type CNGA3 in Xenopus oocytes and characterizing them using patch-clamp recordings in the inside-out configuration. These mutations did not prevent the

formation of functional heteromeric channels, as indicated by sensitivity to block by L-cis-diltiazem. With the exception of S156F, each of the mutant channels displayed electrophysiological properties reflecting enhanced channel activity at physiological concentrations of cGMP (i.e., a gain-of-function phenotype). The increased channel activity produced by these mutations resulted from either increased functional expression levels, or increased sensitivity to cyclic nucleotides. Furthermore, L595F increased the spontaneous open probability in the absence of activating ligand, signifying a ligand independent gain-of-function change. In addition to the CNGB3 disease-associate mutations, we characterized the effects of several common CNGB3 and CNGA3 single-nucleotide polymorphisms (SNPs) on heteromeric CNGA3+CNGB3 channel function. Two of the SNPs examined (A3-T153M, and B3-W234C) produced decreased ligand sensitivity for heteromeric CNG channels. These changes may contribute to background disease susceptibility when combined with other genetic or non-genetic factors. Together, these studies help to define the underlying molecular phenotype for mutations relating to CNG channel disease pathogenesis.

PMID: 26106334 [PubMed] PMCID: PMC4460308

Proc Natl Acad Sci U S A. 2015 Jun 23. [Epub ahead of print]

Rescue of the Stargardt phenotype in Abca4 knockout mice through inhibition of vitamin A dimerization.

Charbel Issa P, Barnard AR, Herrmann P, Washington I, MacLaren RE.

Abstract: Stargardt disease, an ATP-binding cassette, subfamily A, member 4 (ABCA4)-related retinopathy, is a genetic condition characterized by the accelerated accumulation of lipofuscin in the retinal pigment epithelium, degeneration of the neuroretina, and loss of vision. No approved treatment exists. Here, using a murine model of Stargardt disease, we show that the propensity of vitamin A to dimerize is responsible for triggering the formation of the majority of lipofuscin and transcriptional dysregulation of genes associated with inflammation. Data further demonstrate that replacing vitamin A with vitamin A deuterated at the carbon 20 position (C20-D3-vitamin A) impedes the dimerization rate of vitamin A-by approximately fivefold for the vitamin A dimer A2E-and subsequent lipofuscinogenesis and normalizes the aberrant transcription of complement genes without impairing retinal function. Phenotypic rescue by C20-D3-vitamin A was also observed noninvasively by quantitative autofluorescence, an imaging technique used clinically, in as little as 3 months after the initiation of treatment, whereas upon interruption of treatment, the age-related increase in autofluorescence resumed. Data suggest that C20-D3-vitamin A is a clinically amiable tool to inhibit vitamin A dimerization, which can be used to determine whether slowing the dimerization of vitamin A can prevent vision loss caused by Stargardt disease and other retinopathies associated with the accumulation of lipofuscin in the retina.

PMID: 26106163 [PubMed - as supplied by publisher]