Drug treatment

Retina. 2014 Dec 18. [Epub ahead of print]

ELIMINATING ANTIBIOTIC PROPHYLAXIS FOR INTRAVITREAL INJECTIONS: A Consecutive Series of 18,839 Injections by a Single Surgeon.

Bhavsar AR1, Sandler DR.

PURPOSE: By optimizing the protocol for intravitreal injections, the risk of endophthalmitis can be minimized. This study assesses the incidence of endophthalmitis and other complications after a consecutive series of intravitreal injections where all antibiotics were excluded.

METHODS: Injections were performed from August 1, 1997 to October 31, 2012 in outpatient examination rooms at the Retina Center of Minnesota by a single retinal surgeon, the lead author. Most injections were performed to treat exudative age-related macular degeneration. Other reasons included diabetic macular edema, cystoid macular edema because of retinal vein occlusions, cytomegalovirus retinitis, and severe uveitis. Injections were given with topical povidone-iodine, proparacaine, and tetracaine, a sterile eyelid speculum, and clean nonsterile gloves, but without any antibiotics. Data were retrospectively analyzed using billing codes from a computer database system.

RESULTS: A total of 18,839 injections were given. Of these, the following injections were administered: bevacizumab, 15,479 (82.16%); ranibizumab, 1,669 (8.86%); triamcinolone acetonide (Kenalog-40), 1,014 (5.38%); pegaptanib sodium, 370 (1.96%); aflibercept, 148 (0.79%); dexamethasone implant, 88 (0.47%); triamcinolone acetonide (Triesence), 32 (0.17%); dexamethasone, 29 (0.15%); and ganciclovir, 10 (0.05%). There was one case of postinjection endophthalmitis. The incidence of endophthalmitis per injection was 0.0053%.

CONCLUSION: A low incidence of endophthalmitis can be achieved when topical antibiotics are omitted.

PMID: 25526099


Incidence of myocardial infarction, stroke and death in patients with age-related macular degeneration treated with intra-vitreal anti vascular endothelial growth factor therapy.

Ng WY, Tan GS, Ong PG, Cheng CY, Cheung CY, Wong DW, Mathur R, Chow KY, Wong TY, Cheung GC.

PURPOSE: To describe the rates of myocardial infarction (MI), stroke and mortality in patients who have treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections for age-related macular degeneration (AMD).
DESIGN: A retrospective population linkage study.

METHOD: We identified patients aged 40 years and above who received treatment with intravitreal anti-VEGF injections for AMD from 1 January 2008 to 31 December 2011 at the Singapore National Eye Centre. We used a national record linkage database to identify patients who developed MI, stroke and all-cause mortality after the first injection, excluding those with previous MI or stroke at baseline from the respective analysis. We compared rates of MI, stroke and mortality from the total Singapore population.

RESULTS: A total of 1182 individuals had an intravitreal anti-VEGF injection included in this analysis, with the majority receiving bevacizumab (n=1046). Overall, 19 patients developed MI, 16 developed stroke and there were 43 mortalities, giving age-adjusted incidence rate of 350.2 per 100,000 person-years for MI, 299.3 per 100,000 person-years for stroke and 778.9 per 100,000 person-years for mortality. This is comparable to the weighted incidence rates of the Singapore population (427.1 per 100,000 person-years for MI, 340.4 per 100,000 person-years for stroke and 921.3 per 100,000 person-years for mortality).

CONCLUSION: The incidence rate of MI, stroke and death in this cohort of AMD patients treated with anti-VEGF was low, and not significantly higher than the age-adjusted incidence rate of these events in the Singapore population.

PMID: 25497143


Intravitreal Aflibercept Outcomes in Patients with Persistent Macular Exudate Previously Treated with Bevacizumab and/or Ranibizumab for Neovascular Age-Related Macular Degeneration.

Griffin DR, Richmond PP, Olson JC.

Purpose. To assess whether intravitreal aflibercept (2.0 mg) can effectively reduce persistent macular exudate and enhance visual acuity in ranibizumab (0.5 mg) and/or bevacizumab (1.25 mg) treatment resistant patients with neovascular age-related macular degeneration.

Methods. This retrospective study included 47 treatment resistant eyes from 47 patients switched to intravitreal aflibercept injections after receiving a minimum of 3 injections with either ranibizumab or bevacizumab. Snellen visual acuity and optical coherence tomography were assessed just prior to the first injection (baseline) and prior to the fourth injection (final). Additionally, anatomical regions of persistent macular exudate were tracked to determine if these areas yielded varying responses to aflibercept.

Results. At baseline, patients had received an average of 11.3 injections with any prior anti-VEGF drug (SD 5.96). For whole group analysis, baseline and final central retinal thickness were 370.57 µm and 295.7 µm (P ≤ .001), respectively. Baseline and final retinal fluid volumes were 4.81 mm(3) and 4.37 mm(3) (P ≤ .001), respectively. Baseline and final logMAR were 0.56 and 0.53 (P = 0.301), respectively. Anatomic location of persistent exudate did not appreciably alter treatment outcome.

Conclusion. Central retinal thickness and total retinal fluid volume were reduced in ranibizumab and/or bevacizumab treatment resistant patients following three aflibercept injections. No appreciable change in visual acuity was noted.

PMID: 25505976  PMCID: PMC4258314


Relationship of Retinal Morphology and Retinal Sensitivity in the Treatment of Neovascular Age-related Macular Degeneration using aflibercept.


Purpose: To relate the functional response to distinct morphological features of the retina during aflibercept treatment for neovascular age-related macular degeneration (nAMD).
Methods: A total of 726 retinal locations in twenty-two consecutive eyes presenting with treatment-naive nAMD underwent a standardized examination with spectral domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg) and topographic microperimetry (MP) at baseline, after 3 and after 12 months of continuous intravitreal aflibercept therapy. The retinal sensitivity at each stimulus location was registered to the corresponding location on SD-OCT morphology. Subsequently, the microperimetric responses were evaluated with respect to the following underlying SD-OCT-features: Neovascular complex (NVC), subretinal fluid (SRF), intraretinal fluid (IRF), intraretinal cystoid space (IRC), serous pigment epithelium detachment (sPED) and fibrovascular pigment epithelium detachment (fPED).

Results: Baseline sensitivity was reduced to mean values of 1.8dB in NVC, 2.2dB in IRC, 2.8dB in IRF, 2.6dB in sPED, 3.6dB in SRF and 4.6dB in fPED. Improvements in retinal sensitivity were most pronounced during the initial three month interval, when significant recovery was documented for SRF and sPED with +4.0/5.5dB (p<0.0001) and to a lesser extent for IRF, IRC, fPED with +1.1dB,1.7dB, 2.3dB respectively. From month 3 to 12, the additional benefit ranged from 0.3 to 1.0dB (p>0.05 for each category).

Conclusions: Significant functional benefits following intravitreal aflibercept treatment could be detected over all defined morphological pathologies. The level of improvement varied dependent on the associated feature with the best prognosis for visual improvement in SRF and sPED and least with intraretinal fluid and particularly intraretinal cysts.

PMID: 25503456


Changes in Clotting Time, Plasma Fibrinogen Levels, and Blood Viscosity After Administration of Ranibizumab for Treatment of Choroidal Neovascularization.

Yi Z, Chen C, Su Y, Li L, Zhou Y.

Abstract Purpose: To observe changes in clotting time, plasma fibrinogen levels, and blood viscosity after intravitreal ranibizumab (IVR) injection in patients with macular choroidal neovascularization (CNV).

Methods: A total of 77 patients were enrolled in the study. Patients were divided into a study group (n = 42 CNV patients) and a control group (n = 35 age- and gender-matched healthy subjects). Study group patients received IVR injections; control group patients received none. Clotting times, plasma fibrinogen levels and blood viscosity were evaluated before, and 1 week and 1 month after the first IVR injection, and again 1 month after the second injection in the study group, but only once in the control group. A paired-sample t-test was used to analyze data at four time points in the study group. Study group patients were further categorized as those with neovascular age-related macular degeneration (AMD subgroup) or CNV secondary to pathological myopia (PM subgroup). Indicators were also analyzed for each subgroup.

Results: There were no significant differences between study and control group patients in baseline values. Results showed that 1 week after the first IVR injection, the mean activated partial thromboplastin time (APTT) of study group patients was significantly reduced compared with baseline values (27.88 ± 4.00 versus 30.70 ± 5.56 s), respectively. Low-, median- and high-shear viscosity rates were increased significantly compared with baseline values. No statistically significant changes in tested indicators were found at other time points. In AMD subgroup patients, changes in all indicators were similar to those found overall. In contrast, only changes in median- and high-shear viscosity rates were statistically significant in PM subgroup patients.

Conclusion: IVR injection may cause short-term fluctuations in APTT and blood viscosity in AMD patients. Further studies are needed to establish the long-term safety of IVR treatment.

PMID: 25495575
Ophthalmologe. 2014 Dec 20. [Epub ahead of print]

[Change of therapy from ranibizumab to aflibercept for recurrent or persistent exudative age-related macular degeneration.] [Article in German]


BACKGROUND: Even during consistent anti-vascular endothelial growth factor (VEGF) therapy a reactivation of exudative age-related macular degeneration (AMD) lesions can be observed in many patients. The present case series examined whether a switch from ranibizumab to aflibercept is safe and whether differences in potency can be observed.

PATIENTS AND METHODS: In 56 consecutive patients with recurrent activity of AMD according to the morphological criteria of the spectral domain optical coherence tomography (SD-OCT) examination, a change to aflibercept was made after 6-41 (mean 18.9, SD 6.3) injections with ranibizumab. In all controls and before each injection logMAR visual acuity was measured and a SD-OCT (volume scan) was performed in addition to the clinical examination.

RESULTS: The mean visual acuity was stable under both therapies. The analysis of the morphological parameters showed a greater reduction of the retinal thickness after the change in therapy (mean retinal thickness within 1000 μm and central foveal thickness) compared to the initial treatment. The changes in the subretinal fluid as well as the height of an associated pigment epithelial detachment (PED) did not show any significant differences. The analysis of the morphological parameters at the level of the photoreceptors showed a decrease in discontinuity in the ellipsoid layer and also in the external limiting membrane (ELM).

CONCLUSION: In patients with recurrent or high SD-OCT-based activity of exudative AMD lesions, a switch of the treatment strategy from ranibizumab to aflibercept can achieve a new functional stability in spite of multiple pretreatment. We found morphological indications of a regression of intraretinal edema and improvement in the photoreceptor area. In the context of a well-defined treatment strategy, a switch from anti-VEGF therapy to a similar active substance is safe. Before a definitive evaluation can be made, prospective controlled conditions are required to verify the clinical benefits of the switch.

PMID: 25523611


Intravitreal Ranibizumab versus Isovolemic Hemodilution in the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion: Twelve-Month Results of a Prospective, Randomized, Multicenter Trial.


Purpose: This is a prospective, randomized, multicenter, investigator-initiated trial to evaluate the 12-month effectiveness of isovolemic hemodilution (IH) with prompt versus deferred intravitreal injections (IVI) of ranibizumab 0.5 mg for the treatment of macular edema secondary to early central retinal vein occlusion (CRVO).

Methods: Eyes with macular edema due to CRVO having occurred not more than 8 weeks previously received either monthly ranibizumab IVI in combination with IH (group I, n = 28) or IH alone (group II, n = 30). From month 2 to 12, the patients in both groups could be treated with monthly intravitreal ranibizumab. The main outcome variables were gain of visual acuity and the course of central retinal thickness as measured with optical coherence tomography.

Results: At 12 months, eyes in group I on average gained +28.1 (±19.3) letters compared to +25.2 (±20.9) letters in group II (p = 0.326). This result was achieved with significantly fewer injections in group II. Additionally, 30% of the eyes in group II did not need ranibizumab IVI during the 12 months of the trial.

Conclusion: Ranibizumab IVI in addition to IH proved to be highly effective in increasing visual acuity and
Reducing macular edema secondary to CRVO. Initial IH in early CRVO may be a first treatment option in patients anxious about IVI. © 2014 S. Karger AG, Basel.

PMID: 25502833

BMJ. 2014 Dec 10;349:g7524.

Macular degeneration needs longer lasting treatments.

Talks SJ.

PMID: 25498117 [PubMed - in process]

Other treatment & diagnosis


Microperimetry of Nascent Geographic Atrophy in Age-Related Macular Degeneration.

Wu Z, Ayton LN, Luu CD, Guymer RH.

Purpose: To determine the microperimetric retinal sensitivity in areas with nascent geographic atrophy (nGA) compared to other pathological features in eyes with intermediate age-related macular degeneration (AMD).

Methods: Participants with bilateral intermediate AMD underwent microperimetry examinations and high-resolution spectral-domain optical coherence tomography (SD-OCT) scans in a prospective study. Twenty-two participants (24 eyes) identified as having a microperimetric stimulus sampling an atrophic area (nGA or drusen-associated atrophy detected on SD-OCT) in an eye were analyzed, using three neighboring non-atrophic regions (with or without AMD-associated features) in the same eye as reference areas.

Results: On average, the mean microperimetric retinal sensitivity was worse in areas with nGA than non-atrophic reference areas (P ≤ 0.008), but better than areas with drusen-associated atrophy (P = 0.008).

Considering all the microperimetry points in an eye, there were only 6 out of 16 eyes (37.5%) where the retinal sensitivity over nGA was the worst performing point in the eye, whilst all 8 out of 8 eyes (100.0%) with an area of drusen-associated atrophy detected on SD-OCT had the worst performing point over that area.

Conclusions: Areas of nGA were characterized by worse microperimetric retinal sensitivity compared to non-atrophic areas in eyes with intermediate AMD, but better retinal sensitivity compared to areas of drusen-associated atrophy detected on SD-OCT. Areas of nGA were also not always the worst performing point in an eye. These findings further our understanding of the functional changes occurring in novel SD-OCT identified pathological changes in intermediate AMD.

PMID: 25515578


Comparison of Retinal and Choriocapillaris Thicknesses Following Sitting to Supine Transition in Healthy Individuals and Patients With Age-Related Macular Degeneration.

Almeida DR, Zhang L, Chin EK, Mullins RF, Kucukevilioglu M, Critser DB, Sonka M, Stone EM, Folk JC, Abràmoff MD, Russell SR.

Importance: The effects of position on retinal and choroidal structure are absent from the literature yet may provide insights into disease states such as age-related macular degeneration (AMD).
Objective: To evaluate the effect of postural change on retinal and choroidal structures in healthy volunteers and patients with non-neovascular AMD.

Design, Setting, and Participants: Prospective observational case series at an academic tertiary care retina service from September 2013 to April 2014 involving 4 unaffected volunteers (8 eyes) and 7 patients (8 eyes) with intermediate AMD. Healthy volunteers selected for the study had no evidence of ocular disease. Patients with AMD were required to have at least 10 intermediate-sized drusen.

Exposures: Spectral-domain optical coherence tomography with enhanced depth imaging in upright (sitting) and supine positions. Stable imaging was achieved using a rotating adjustable mechanical arm that we constructed to allow the optical coherence tomography transducer to rotate 90°. The Iowa Reference Algorithms were used to quantify choroid and choriocapillaris thicknesses.

Main Outcomes and Measures: Changes in sitting and supine position central macular thickness (in micrometers), total macular volume (in cubic millimeters), choroidal thickness (in micrometers), and choriocapillaris-equivalent thickness (CCET, in micrometers).

Results: Choriocapillaris-equivalent thickness was thinner in healthy participants (9.89 μm; range, 7.15-12.5 μm) compared with patients with intermediate AMD (16.73 μm; range, 10.31-27.38 μm) (P = .02); there was no difference in overall choroidal thickness between the 2 groups (P = .38). There was a 15% CCET reduction among healthy participants when transitioning from a sitting (9.89 μm) to supine (8.4 μm; range, 6.92-10.7 μm) position (P = .02) vs a CCET reduction of 11.1% from sitting (16.73 μm) to supine (14.88 μm; range, 8.76-20.8 μm) positioning (P = .10) in patients with intermediate AMD.

Conclusions and Relevance: Intermediate AMD appears to be associated with an increase in CCET and with a lack of positional responses that are observed in the CCET of normal eyes. Our results suggest that although outer portions of the choroid do not appear to be responsive to modest positional or hydrostatic pressure, the choriocapillaris capacity is, and this is measurable in vivo. Whether this physiologic deviation that occurs in AMD is related to atrophy, inflammation, or changes in autoregulatory factors or growth factors remains to be determined.

PMID: 25521616


Gene Therapies for Neovascular Age-Related Macular Degeneration.

Pechan P, Wadsworth S, Scaria A.

Abstract: Pathological neovascularization is a key component of the neovascular form (also known as the wet form) of age-related macular degeneration (AMD) and proliferative diabetic retinopathy. Several preclinical studies have shown that antiangiogenesis strategies are effective for treating neovascular AMD in animal models. Vascular endothelial growth factor (VEGF) is one of the main inducers of ocular neovascularization, and several clinical trials have shown the benefits of neutralizing VEGF in patients with neovascular AMD or diabetic macular edema. In this review, we summarize several preclinical and early-stage clinical trials with intraocular gene therapies, which have the potential to reduce or eliminate the repeated intravitreal injections that are currently required for the treatment of neovascular AMD.

PMID: 25524721


Photoreceptor inner segment ellipsoid band integrity on spectral domain optical coherence tomography.

Saxena S, Srivastav K, Cheung CM, Ng JY, Lai TY.

Abstract: Spectral domain optical coherence tomography cross-sectional imaging of the macula has conventionally been resolved into four bands. However, some doubts were raised regarding authentication
of the existence of these bands. Recently, a number of studies have suggested that the second band appeared to originate from the inner segment ellipsoids of the foveal cone photoreceptors, and therefore the previously called inner segment-outer segment junction is now referred to as inner segment ellipsoid band. Photoreceptor dysfunction may be a significant predictor of visual acuity in a spectrum of surgical and medical retinal diseases. This review aims to provide an overview and summarizes the role of the photoreceptor inner segment ellipsoid band in the management and prognostication of various vitreoretinal diseases.

PMID: 25525329


A hyporeflective space between hyperreflective materials in pigment epithelial detachment and Bruch's membrane in neovascular age-related macular degeneration.

Mukai R, Sato T, Kishi S.

BACKGROUND: The purpose of this study was to investigate the clinical characteristics of a hyporeflective space between hyperreflective materials in pigment epithelial detachment (PED) and Bruch's membrane in neovascular age-related macular degeneration (AMD) using spectral-domain optical coherence tomography (SD-OCT) or swept source optical coherence tomography (SS-OCT).

METHODS: Among 223 patients with neovascular AMD, 227 eyes were studied retrospectively. Using SD-OCT or SS-OCT, we reviewed clinical characteristics of the space.

RESULTS: Twenty-two (10%) of the 227 eyes showed a space between hyperreflective materials in PED and Bruch's membrane. In all spaces, fibrovascular changes of the choroidal neovascularization (CNV) membrane were seen on funduscopy, with OCT images showing the retinal pigment epithelium (RPE) above the space adhering tightly and continuously to the CNV membranes. Nineteen (86%) of the 22 eyes with this cleft also had serous retinal detachment or cystoid macular edema. Five eyes (23%) had an RPE tear during follow-up.

CONCLUSIONS: A hyporeflective space between hyperreflective materials in PED and Bruch's membrane sometimes appears in neovascular AMD. The appearance of such a space may indicate residual activities of the hyporeflective materials.

PMID: 25515712


Preventive and Therapeutic Effects of SkQ1-Containing Visomitin Eye Drops against Light-Induced Retinal Degeneration.

Novikova YP, Gancharova OS, Eichler OV, Philippov PP, Grigoryan EN.

Abstract: The human retina is constantly affected by light of varying intensity, this being especially true for photoreceptor cells and retinal pigment epithelium. Traditionally, photoinduced damages of the retina are induced by visible light of high intensity in albino rats using the LIRD (light-induced retinal degeneration) model. This model allows study of pathological processes in the retina and the search for retinoprotectors preventing retinal photodamage. In addition, the etiology and mechanisms of retina damage in the LIRD model have much in common with the mechanisms of the development of age-related retinal disorders, in particular, with age-related macular degeneration (AMD). We have studied preventive and therapeutic effects of Visomitin eye drops (based on the mitochondria-targeted antioxidant SkQ1) on albino rat retinas damaged by bright light. In the first series of experiments, rats receiving Visomitin for two weeks prior to illumination demonstrated significantly less expressed atrophic and degenerative changes in the retina compared to animals receiving similar drops without SkQ1. In the second series, the illuminated rats were treated for two weeks with Visomitin or similar drops without SkQ1. The damaged retinas of the
experimental animals were repaired much more effectively than those of the control animals. Therefore, we conclude that Visomitin SkQ1-containing eye drops have pronounced preventive and therapeutic effects on the photodamaged retina and might be recommended as a photoprotector and a pharmaceutical preparation for the treatment of AMD in combination with conventional medicines.

PMID: 25519068

Pathogenesis


Henle Fiber Layer Phase Retardation Changes Associated with Age-related Macular Degeneration.


Purpose: To quantify and compare phase retardation amplitude and regularity associated with the Henle fiber layer between non-exudative age-related macular degeneration (AMD) patients and age-matched controls using scanning laser polarimetry (SLP) imaging.

Methods: A scanning laser polarimeter was used to collect 15 x 15 deg macular centered images in 25 patients with non-exudative AMD and 25 age-matched controls. Raw image data were used to compute macular phase retardation maps associated with the Henle fiber layer. Consecutive, annular regions of interest from 0.5 to 3.0 deg eccentricity, centered on the fovea, were used to generate intensity profiles from phase retardation data and analyzed with two complementary techniques: a normalized 2f FFT component analysis and a curve fitting analysis using a 2f sine function. Paired t-tests were used to compare the normalized 2f FFT magnitude at each eccentricity between the two groups, the eccentricity that yielded the maximum normalized 2f FFT between paired individuals across the two groups, and curve fitting RMS error at each eccentricity between the two groups.

Results: Normalized 2f FFT components were lower in the AMD group at each eccentricity, with no difference between the two groups in the maximum normalized 2f FFT component eccentricity. The RMS error from curve fitting was significantly higher in the AMD group.

Conclusions: Phase retardation changes in the central macula indicate loss and/or structural alterations to central cone photoreceptors in non-exudative AMD patients. SLP imaging is a non-invasive method for quantifying cone photoreceptor changes associated with central macular disease.

PMID: 25525166


CX3CL1/CX3CR1 and CCL2/CCR2 Chemokine/Chemokine Receptor Complex in Patients with AMD.

Falk MK, Singh A, Faber C, Nissen MH, Hviid T, Serensen TL.

PURPOSE: The chemokine receptors CX3CR1 and CCR2 have been implicated in the development of age-related macular degeneration (AMD). The evidence is mainly derived from experimental cell studies and murine models of AMD. The purpose of this study was to investigate the association between expression of CX3CR1 and CCR2 on different leukocyte subsets and AMD. Furthermore we measured the plasma levels of ligands CX3CL1 and CCL2.

METHODS: Patients attending our department were asked to participate in the study. The diagnosis of AMD was based on clinical examination and multimodal imaging techniques. Chemokine plasma level and chemokine receptor expression were measured by flow-cytometry.

RESULTS: A total of 150 participants were included. We found a significantly lower expression of CX3CR1
on CD8+ T cells in the neovascular AMD group compared to the control group (p=0.04). We found a
significant positive correlation between CCR2 and CX3CR1 expression on CD8+ cells (r=0.727, p=
0.0001). We found no difference in plasma levels of CX3CL1 and CCL2 among the groups.

CONCLUSIONS: Our results show a down regulation of CX3CR1 on CD8+ cells; this correlated to a low
expression of CCR2 on CD8+ cells. Further studies are needed to elucidate the possible role of this cell
type in AMD development.

PMID: 25503251


Enhanced differentiation and delivery of mouse retinal progenitor cells using a micropatterned
biodegradable thin-film polycaprolactone scaffold.

Yao J, Ko CW, Baranov PY, Regatiere CV, Redenti S, Tucker BA, Mighty J, Tao SL, Young MJ.

Abstract: The deterioration of retinal tissue in advanced stages of retinitis pigmentosa and age-related
macular degeneration and the lack of signaling cues for laminar regeneration are significant challenges
highlighting the need for a tissue-engineering approach to retinal repair. In this study, we fabricated a
biodegradable thin-film polycaprolactone (PCL) scaffold with varying surface topographies using
microfabrication techniques. Mouse retinal progenitor cells (mRPC) cultured on PCL scaffolds exhibited
enhanced potential to differentiate towards a photoreceptor fate in comparison to mRPCs cultured on
control substrates, suggesting that PCL scaffolds are promising as substrates to guide differentiation of
mRPCs towards a photoreceptor fate in vitro prior to transplantation. When co-cultured with the retinal
explants of rhodopsin null mice, mRPC/PCL constructs showed increased mRPC integration rates
compared to directly applied dissociated mRPCs. Moreover, these mRPC/PCL constructs could be
delivered into the sub-retinal space of rhodopsin null mice with minimal disturbance of the host retina.
Whether co-cultured with retinal explants or transplanted into the sub-retinal space, newly integrated
mRPCs localized to the outer nuclear layer and expressed appropriate markers of photoreceptor fate. Thus,
the PCL scaffold provides a platform to guide differentiation and organized deliver of mRPCs as a practical
strategy to repair damaged retina.

PMID: 25517296


Simultaneous targeting of two ligand-binding sites on VEGFR2 using biparatopic Affibody
molecules results in dramatically improved affinity.

Fleetwood F, Klint S, Hanze M, Gunneriusson E, Frejd FY, Ståhl S, Löffblom J.

Abstract: Angiogenesis plays an important role in cancer and ophthalmic disorders such as age-related
macular degeneration and diabetic retinopathy. The vascular endothelial growth factor (VEGF) family and
corresponding receptors are regulators of angiogenesis and have been much investigated as therapeutic
targets. The aim of this work was to generate antagonistic VEGFR2-specific affinity proteins having
adjustable pharmacokinetic properties allowing for either therapy or molecular imaging. Two antagonistic
Affibody molecules that were cross-reactive for human and murine VEGFR2 were selected by phage and
bacterial display. Surprisingly, although both binders independently blocked VEGF-A binding, competition
assays revealed interaction with non-overlapping epitopes on the receptor. Biparatopic molecules,
comprising the two Affibody domains, were hence engineered to potentially increase affinity even further
through avidity. Moreover, an albumin-binding domain was included for half-life extension in future in vivo
experiments. The best-performing of the biparatopic constructs demonstrated up to 180-fold slower
dissociation than the monomers. The new Affibody constructs were also able to specifically target VEGFR2
on human cells, while simultaneously binding to albumin, as well as inhibit VEGF-induced signaling. In
summary, we have generated small antagonistic biparatopic Affibody molecules with high affinity for
VEGFR2, which have potential for both future therapeutic and diagnostic purposes in angiogenesis-related
Protoporphyrins Enhance Oligomerization and Enzymatic Activity of HtrA1 Serine Protease.

Jo H, Patterson V, Stoessel S, Kuan CY, Hoh J.

Abstract: High temperature requirement protein A1 (HtrA1), a secreted serine protease of the HtrA family, is associated with a multitude of human diseases. However, the exact functions of HtrA1 in these diseases remain poorly understood. We seek to unravel the mechanisms of HtrA1 by elucidating its interactions with chemical or biological modulators. To this end, we screened a small molecule library of 500 bioactive compounds to identify those that alter the formation of extracellular HtrA1 complexes in the cell culture medium. An initial characterization of two novel hits from this screen showed that protoporphyrin IX (PPP-IX), a precursor in the heme biosynthetic pathway, and its metalloporphyrin (MPP) derivatives fostered the oligomerization of HtrA1 by binding to the protease domain. As a result of the interaction with MPPs, the proteolytic activity of HtrA1 against Fibulin-5, a specific HtrA1 substrate in age-related macular degeneration (AMD), was increased. This physical interaction could be abolished by the missense mutations of HtrA1 found in patients with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Furthermore, knockdown of HtrA1 attenuated apoptosis induced by PPP-IX. These results suggest that PPP-IX, or its derivatives, and HtrA1 may function as co-factors whereby porphyrins enhance oligomerization and the protease activity of HtrA1, while active HtrA1 elevates the pro-apoptotic actions of porphyrin derivatives. Further analysis of this interplay may shed insights into the pathogenesis of diseases such as AMD, CARASIL and protoporphyria, as well as effective therapeutic development.

Inhibition of choroidal fibrovascular membrane formation by new class of RNA interference therapeutic agent targeting periostin.


Abstract: Age-related macular degeneration (AMD) is a vision-threatening disease characterized by choroidal fibrovascular membrane (FVM) formation, choroidal neovascularization (CNV) and choroidal fibrosis. No safe and effective therapeutic method has been developed for the choroidal fibrosis, although anti-vascular endothelial growth factor therapy can partially shrink the CNV. We recently reported that periostin (POSTN), which is produced by retinal pigment epithelial cells, has an important role in the formation of preretinal FVMs, but its role in choroidal FVMs has not been determined. In this study, we used Postn knockout mice to investigate the role played by POSTN in choroidal FVM formation. In addition, we used a new class of RNA interference (RNAi) agent (NK0144) that targets POSTN and determined its effect on choroidal FVM development. Genetic ablation of Postn had an inhibitory effect not only on CNV formation but also on choroidal fibrosis in a mouse CNV model. NK0144 also had a greater inhibitory effect on both the CNV and choroidal fibrosis than control RNAi with no apparent adverse effects. These findings suggest a causal relationship between POSTN and choroidal FVM formation, and also a potential therapeutic role of intravitreal NK0144 for AMD.Gene Therapy advance online publication, 11 December 2014; doi:10.1038/gt.2014.112.
A zebrafish in vivo phenotypic assay to identify 3-aminothiophene-2-carboxylic Acid-based angiogenesis inhibitors.


Abstract: Small molecules that inhibit angiogenesis are attractive drug candidates for cancer, retinopathies, and age-related macular degeneration. In vivo, phenotypic screening in zebrafish (Danio rerio) emerges as a powerful methodology to identify and optimize novel compounds with pharmacological activity. Zebrafish provides several advantages for in vivo phenotypic screening especially for angiogenesis, since it develops rapidly, externally, and does not rely on a functional cardiovascular system to survive for several days during development. In this study, we utilize a transgenic line that allows the noninvasive monitoring of angiogenesis at a cellular level. The inhibition of angiogenesis can be observed under a fluorescent stereoscope and quantified. To exemplify the versatility and robustness of the zebrafish screen, we have employed a series of 60 novel compounds that were designed based on a potent VEGFR2 inhibitor. Herein, we report their structure-based design, synthesis, and in vivo zebrafish screening for optimal activity, toxicity, and off-target effects, which revealed six reversible inhibitors of angiogenesis.

PMID: 25506802

TGF-β2 secretion from RPE decreases with polarization and becomes apically oriented.


Abstract: Retinal pigmented epithelium (RPE) secretes transforming growth factor beta 1 and 2 (TGF-β1 and -β2) cytokines involved in fibrosis, immune privilege, and proliferative vitreoretinopathy (PVR). Since RPE cell polarity may be altered in various disease conditions including PVR and age-related macular degeneration, we determined levels of TGF-β from polarized human RPE (hRPE) and human stem cell derived RPE (hESC-RPE) as compared to nonpolarized cells. TGF-β2 was the predominant isofrom in all cell culture conditions. Nonpolarized cells secreted significantly more TGF-β2 supporting the contention that loss of polarity of RPE in PVR leads to rise of intravitreal TGF-β2. Active TGF-β2, secreted mainly from apical side of polarized RPE, represented 6-10% of total TGF-β2. In conclusion, polarity is an important determinant of TGF-β2 secretion in RPE. Low levels of apically secreted active TGF-β2 may play a role in the normal physiology of the subretinal space. Comparable secretion of TGF-β from polarized hESC-RPE and hRPE supports the potential for hESC-RPE in RPE replacement therapies.

PMID: 25496702

Modeling the response of ON and OFF retinal bipolar cells during electric stimulation.

Werginz P, Benav H, Zrenner E, Rattay F.

Abstract: Retinal implants allowing blind people suffering from diseases like retinitis pigmentosa and macular degeneration to regain rudimentary vision are struggling with several obstacles. One of the main problems during external electric stimulation is the co-activation of the ON and OFF pathways which results in mutual impairment. In this study the response of ON and OFF cone retinal bipolar cells during extracellular electric stimulation from the subretinal space was examined. To gain deeper insight into the behavior of these cells sustained L-type and transient T-type calcium channels were integrated in the synaptic terminals of reconstructed 3D morphologies of ON and OFF cone bipolar cells. Intracellular calcium concentration in the synaptic regions of the model neurons was investigated as well since calcium influx is a crucial parameter for cell-to-cell activity between bipolar cells and retinal ganglion cells. It was
shown that monophasic stimulation results in significant different calcium concentrations in the synaptic terminals of ON and OFF bipolar cells. Intracellular calcium increased to values up to fourfold higher in the OFF bipolar model neuron in comparison to the ON bipolar cell. Furthermore, geometric properties strongly influence the activation of bipolar cells. Monophasic, biphasic, single and repetitive pulses with similar lengths, amplitudes and polarities were applied to the two model neurons.

PMID: 25499837

Epidemiology


The First Rapid Assessment of Avoidable Blindness (RAAB) in Thailand.


BACKGROUND: The majority of vision loss is preventable or treatable. Population surveys are crucial for planning, implementation, and monitoring policies and interventions to eliminate avoidable blindness and visual impairments. This is the first rapid assessment of avoidable blindness (RAAB) study in Thailand.

METHODS: A cross-sectional study of a population in Thailand age 50 years old or over aimed to assess the prevalence and causes of blindness and visual impairments. Using the Thailand National Census 2010 as the sampling frame, a stratified four-stage cluster sampling based on a probability proportional to size was conducted in 176 enumeration areas from 11 provinces. Participants received comprehensive eye examination by ophthalmologists.

RESULTS: The age and sex adjusted prevalence of blindness (presenting visual acuity (VA) <20/400), severe visual impairment (VA <20/200 but ≥20/400), and moderate visual impairment (VA <20/70 but ≥20/200) were 0.6% (95% CI: 0.5-0.8), 1.3% (95% CI: 1.0-1.6), 12.6% (95% CI: 10.8-14.5). There was no significant difference among the four regions of Thailand. Cataract was the main cause of vision loss accounted for 69.7% of blindness. Cataract surgical coverage in persons was 95.1% for cut off VA of 20/400. Refractive errors, diabetic retinopathy, glaucoma, and corneal opacities were responsible for 6.0%, 5.1%, 4.0%, and 2.0% of blindness respectively.

CONCLUSION: Thailand is on track to achieve the goal of VISION 2020. However, there is still much room for improvement. Policy refinements and innovative interventions are recommended to alleviate blindness and visual impairments especially regarding the backlog of blinding cataract, management of non-communicative, chronic, age-related eye diseases such as glaucoma, age-related macular degeneration, and diabetic retinopathy, prevention of childhood blindness, and establishment of a robust eye health information system.

PMID: 25502762  PMCID: PMC4263597


Retinal vascular caliber, iris color and age-related macular degeneration in the Irish Nun Eye Study.

McGowan AJ, Silvestri G, Moore E, Silvestri V, Patterson CC, Maxwell AP, McKay GJ.

PURPOSE. To evaluate the relationship between retinal vascular caliber (RVC), iris color and age-related macular degeneration (AMD) in elderly Irish nuns.

METHODS. Data from 1233 participants in the cross-sectional observational Irish Nun Eye Study were assessed from digital photographs with a standardized protocol using computer-assisted software. Macular images were graded according to the modified Wisconsin age-related maculopathy grading system.
Regression models were used to assess associations, adjusting for age, mean arterial blood pressure, body mass index, refraction and fellow RVC.

RESULTS. In total, 1122 (91%) participants had gradable retinal images of sufficient quality for vessel assessment (mean age: 76.3 years [range: 56-100 years]). In an unadjusted analysis, we found some support for a previous finding that individuals with blue iris color had narrower retinal venules compared to those with brown iris color (P<0.05) but this was no longer significant after adjustment. AMD status was categorized as no AMD, any AMD and late AMD only. Individuals with any AMD (early or late AMD) had significantly narrower arterioles and venules compared to those with no AMD in an unadjusted analysis but this was no longer significant after adjustment. A non-significant reduced risk of any AMD or late AMD only was observed in association with brown compared to blue iris color, in both unadjusted and adjusted analyses.

CONCLUSIONS. RVC was not significantly associated with iris color or early/late AMD after adjustment for confounders. A lower but non-significant AMD risk was observed in those with brown compared to blue iris color.

PMID: 25525170

**Genetics**


High-Temperature Requirement A Serine Peptidase 1 Gene is Transcriptionally Regulated by Insertion/Deletion Nucleotides Located at the 3 Prime End of Age-Related Maculopathy Susceptibility 2 Gene in Patients with Age-Related Macular Degeneration.


Abstract: Dry age-related macular degeneration (AMD) accounts for over 85% of AMD cases in the United States, while Japanese AMD patients predominantly progress to wet AMD or polypoidal choroidal vasculopathy. Recent genome-wide association studies have revealed a strong association between AMD and an insertion/deletion sequence between the ARMS2 and HTRA1 genes. Transcription regulator activity was localized in mouse retinas using heterozygous HtrA1 knockout mice in which HtrA1 exon 1 was replaced with beta-galactosidase cDNA, thereby resulting in dominant expression of the photoreceptors. The insertion/deletion sequence significantly induced HTRA1 transcription regulator activity in photoreceptor cell lines, but not in retinal pigmented epithelium or other cell types. A deletion construct of the HTRA1 regulatory region indicated that potential transcriptional suppressors and activators surround the insertion/deletion sequence. Ten double-stranded DNA probes for this region were designed, three of which interacted with nuclear extracts from 661W cells in EMSA. Liquid chromatography-mass spectrometry (LC-MS/MS) of these EMSA bands subsequently identified a protein which bound the insertion/deletion sequence, lysine-rich, CEACAM1 co-isolated protein (LYRIC). In addition, induced pluripotent stem cells from wet AMD patients carrying the insertion/deletion sequence showed significant upregulation of the HTRA1 transcript compared with controls. These data suggest that the insertion/deletion sequence alters the suppressor and activator cis-elements of HTRA1 and triggers sustained upregulation of HTRA1. These results are consistent with a transgenic mouse model that ubiquitously overexpresses HtrA1 and exhibits characteristics similar to those of wet AMD patients.

PMID: 25519903


Prognostic phenotypic and genotypic factors associated with photodynamic therapy response in patients with age-related macular degeneration.

Tsuchihashi T, Mori K, Horie-Inoue K, Okazaki Y, Awata T, Inoue S, Yoneya S.
BACKGROUND: This study aimed to demonstrate the phenotypic and genotypic factors associated with photodynamic therapy (PDT) for age-related macular degeneration (AMD).

METHODS: The study included 149 patients with exudative AMD treated by PDT. Eight phenotypic factors and ten genotypic factors for three single nucleotide polymorphisms (SNPs; rs800292, rs1061170, rs1410996) in the complement factor H (CFH) gene, rs 11200638-SNP in the high temperature requirement A-1 (HTRA1) gene, two SNPs (rs699947, rs2010963) in the vascular endothelial growth factor (VEGF) gene, and four SNPs (rs12948385, rs12150053, rs9913583, rs1136287) in the pigment epithelium-derived factor (PEDF) gene were evaluated.

RESULTS: A significant association with best-corrected visual acuity change was demonstrated in the greatest linear dimension, presence or absence of pigment epithelial detachment, and HTRA1-rs11200638 genotype statistically (P=3.67×10(-4), 1.95×10(-2), 1.24×10(-3), respectively). Best-corrected visual acuity in patients with AA genotype of HTRA1-rs11200638 significantly decreased compared with that in patients with GG genotype (P=1.33×10(-3)). Logistic regression analyses demonstrated HTRA1-rs11200638 genotype was most strongly associated with best-corrected visual acuity outcome from baseline at 12 months after photodynamic therapy (P=4.60×10(-3); odds ratio 2.363; 95% confidence interval 1.303-4.285).

CONCLUSION: The HTRA1-rs11200638 variant showed the most significant association. Therefore, this variant may be used as a prognostic factor to estimate the PDT response with significant predictive power.

PMID: 25525324


Complement regulators in human disease: lessons from modern genetics.

Liszewski MK, Atkinson JP.

Abstract: First identified in human serum in the late 19th century as a 'complement' to antibodies in mediating bacterial lysis, the complement system emerged more than a billion years ago probably as the first humoral immune system. The contemporary complement system consists of nearly 60 proteins in three activation pathways (classical, alternative and lectin) and a terminal cytolytic pathway common to all. Modern molecular biology and genetics have not only led to further elucidation of the structure of complement system components, but have also revealed function-altering rare variants and common polymorphisms, particularly in regulators of the alternative pathway, that predispose to human disease by creating 'hyper-inflammatory complement phenotypes'. To treat these 'complementopathies', a monoclonal antibody against the initiator of the membrane attack complex, C5, has received approval for use. Additional therapeutic reagents are on the horizon. This article is protected by copyright. All rights reserved.

PMID: 25495259


Stem Cells as Tools for Studying the Genetics of Inherited Retinal Degenerations.

Wiley LA, Burnight ER, Mullins RF, Stone EM, Tucker BA.

Abstract: The ability to provide early clinical intervention for inherited disorders is heavily dependent on knowledge of a patient's disease-causing mutations and the resultant pathophysiologic mechanism(s). Without knowing a patient's disease-causing gene, and how gene mutations alter the health and functionality of affected cells, it would be difficult to develop and deliver patient-specific molecular or small molecule therapies. Many believe that the field of stem cell biology holds the keys to the future development of disease-, patient-, and cell-specific therapies. In the case of the eye, which is susceptible to an extremely common late-onset degenerative disease known as age-related macular degeneration, stem
cell-based therapies could increase the quality of life for millions of patients worldwide. Furthermore, autologous, patient-specific induced pluripotent stem cells could be a viable source to treat rare Mendelian retinal degenerative diseases such as retinitis pigmentosa, Stargardt disease, and Best disease, to name a few.

PMID: 25502747

**Diet & lifestyle**


Lutein and Zeaxanthin Supplementation and Association with Visual Function in Age-related Macular Degeneration: a Meta-Analysis.

Liu R, Wang T, Zhang B, Qin L, Wu C, Li Q, Ma L.

**PURPOSE:** To evaluate the effects of lutein and zeaxanthin on visual function in randomized controlled trials (RCTs) of age-related macular degeneration (AMD) patients.

**METHODS:** Relevant studies were identified by searches on PubMed, EMBASE, Web of Science and Cochrane Library database up to April 2014. Three investigators independently determined the eligibility of RCTs which compared lutein and zeaxanthin intervention with placebo. The adjusted weighted mean differences (WMDs) from each study were extracted to calculate a pooled estimate with its corresponding 95% confidence interval (CI). The main outcome measurements included visual acuity (VA), contrast sensitivity (CS), glare recovery time (GRT), and subjective perception of visual quality.

**RESULTS:** Eight RCTs involving 1176 AMD patients were included in the meta-analysis. Xanthophyll carotenoids supplementation was associated with significant decrease in logMAR levels compared with the placebo group (WMD, -0.04; 95% CI, -0.06 to -0.03), and during intervention, each 1 mg/day-increase in these carotenoids supplementation was related to a 0.003 reduction in logMAR level of VA. Remarkable benefit was also observed at all four spatial frequencies of CS (WMD ranging from 0.08 to 0.18; all P<0.05) in contrast to placebo. Furthermore, association was observed between the postintervention increase in macular pigment optical density and improvements in VA (r = -0.58; P =0.02), and in CS at 12cycles/degree as well (r = 0.94; P< 0.001).

**CONCLUSIONS:** Lutein and zeaxanthin supplementation is a safe strategy for improving visual performance of AMD patients, which mainly showed in a dose-response relationship.

PMID: 25515572


The Effect of Intensive Education on Concordance with the Age-Related Eye Disease Study (AREDS) Recommendations in a Tertiary Referral Practice.

Weaver TR, Beaumont PE.

**Background/Aims:** The Age-Related Eye Disease Study (AREDS) showed that supplementation with their formula led to a significant decrease in progression of age-related macular degeneration (AMD). This study aims to assess the effect of different education protocols on concordance with the trial recommendations in two retinal clinics.

**Methods:** A prospective controlled survey of concordance with the AREDS recommendations in two retinal clinics was administered to 330 patients with AREDS category 3 or 4 AMD. The results were evaluated to assess the effect of differing levels of patient education. In clinic 1, there was a formal policy of giving the patient both verbal and written instructions and verbal repetition of these instructions from each staff member.
member on each patient visit; in clinic 2, there was no specific education policy.

Results: Clinic 1 had a concordance rate of 81.6% and clinic 2 of 44.1%. There were no significant differences in the patient demographics between the two clinics.

Conclusion: A high concordance rate can be achieved in clinical practice with rigorous patient education that includes a policy of having continual repetition of instructions.

PMID: 25503414

Psychogeriatrics. 2014 Dec 17.

Seeing the unseen: Charles Bonnet syndrome revisited.

Nair AG, Nair AG, Shah BR, Gandhi RA.

Abstract: Charles Bonnet syndrome (CBS) is a rare condition that encompasses three clinical features: complex visual hallucinations, ocular pathology causing visual deterioration, and preserved cognitive status. Common associated ocular pathologies include age-related macular degeneration, glaucoma, and cataracts. Several theories have been proposed to try to explain the visual hallucinations. However, the pathophysiology remains poorly understood, and treatment is largely based on anecdotal data. The lack of awareness of CBS among medical professionals often leads to inappropriate diagnosis and medication. In a country like India, where awareness of mental health is not widespread, cultural myths and stigma prevent patients from seeking professional help. Here we describe two cases of CBS and revisit different ocular morbidities that have been reported to occur in conjunction with CBS. Psychiatrists and ophthalmologists alike must be sensitive to this clinical condition to ensure prompt diagnosis and treatment.

PMID: 25515178


Morphologic and physiologic retinal degeneration induced by intravenous delivery of vitamin A dimers in the leporid retina.

Penn J, Mihai DM, Washington I.

Abstract: The eye uses vitamin A as a cofactor to sense light, during this process a fraction of vitamin A dimerizes forming vitamin A dimers. A striking chemical signature of retinas undergoing degeneration in major eye diseases such as age-related macular degeneration (AMD) and Stargardt disease, is the accumulation of these dimers in the retinal pigment epithelium (RPE) and Bruch’s membrane (BM). However, it is not known whether dimers of vitamin A are merely secondary symptoms or primary insults that drive degeneration. Here, we present a chromatography free method to prepare gram quantities of the vitamin A dimer, A2E, and show that intravenous administration of A2E to the rabbit results in retinal degeneration. A2E damaged photoreceptors and RPE cells, triggered inflammation, induced remodeling of the choroidal vasculature, and triggered a decline in the retina's response to light. Data suggest that vitamin A dimers are not bystanders, but can be primary drivers of retinal degeneration. Thus, preventing dimer formation could be a preemptive strategy to address serious forms of blindness.

PMID: 25504631

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