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MD Research News

Issue 301

Wednesday19 October, 2016

Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2016 Oct 14. [Epub ahead of print]

A modified treat-and-extend regimen of aflibercept for treatment-naïve patients with neovascular age-related macular degeneration.

Ohnaka M, Nagai Y, Sho K, Miki K, Kimura M, Chihara T, Takahashi K.

PURPOSE: To evaluate a modified treat-and-extend (TAE) regimen of intravitreal aflibercept injection (IAI) for treatment-naïve patients with neovascular age-related macular degeneration (AMD).

METHODS: Thirty-six eyes (36 patients) treated with the modified TAE regimen were evaluated at 12 months retrospectively. The modified TAE regimen consisted of three steps: 1) an induction phase, during which patients were treated with ≥ 3-monthly IAIs until exudative activity disappeared, 2) an observation phase, during which patients were monitored until exudative activity appeared, and 3) a TAE phase, for which the initial treatment interval was determined based on the disease recurrence interval, followed by treatment intervals changing by 2 weeks.

RESULTS: Mean logMAR BCVA improved significantly from 0.48 ± 0.51 at baseline to 0.40 ± 0.53 at 12 months ($P < 0.01$), and was maintained (losing <0.3 logMAR units) in 35 eyes (97.2 %). Mean central retinal thickness and central choroidal thickness decreased significantly after 12 months. In the TAE phase, the distribution of treatment intervals was ≥8 weeks in 64.7 % (11 eyes) at 12 months. The mean number of injections was 4.53.

CONCLUSION: A modified TAE regimen of IAI for neovascular AMD produced good functional outcomes over 12 months with the small number of injections.

PMID: 27743159

Ophthalmologe. 2016 Oct 14. [Epub ahead of print]

[Intravitreal ranibizumab for the treatment of retinal angiomatous proliferation].[Article in German]

Maaß J, Sandner D, Matthé E.

BACKGROUND: Retinal angiomatous proliferations (RAP) are a subgroup of exsudative or "wet" age-related macular degeneration (wAMD) with devastating reduction of visual acuity in later stages. Intravitreal ranibizumab provides good therapy, but is considered to be less effective than in other choroidal neovascularizations (CNV).

OBJECTIVE: We investigated the efficacy of ranibizumab in late-stage III RAP with retinochoroidal anastomosis compared to the outcome of other CNV lesions.

MATERIALS AND METHODS: The data of all patients with wAMD treated with ranibizumab were retrospectively analyzed. Patients were divided into groups depending on the lesion type into RAP (identified and selected clinically, proven by fluorescein angiography) and CNV lesions (identified by fluorescein angiography only) named occult, minimally and predominantly classic groups. The best-corrected visual acuity (BCVA) was obtained before (at the timepoint "diagnosis"), during (1st, 2nd, and 3rd injection), and after upload ("1st control").

RESULTS: Before first injection, visual acuity decreased in all groups (0.73 to 0.78 logMAR for all CNV, 0.95 to 1.02 logMAR for RAP). During upload there was no further decline in visual acuity but no improvement as well up to the 1st control visit in the RAP group (1.02 to 1.03 logMAR), but a statistically significant increase in all other groups (0.78 to 0.67 logMAR).

CONCLUSION: Treatment of late-stage III RAP with ranibizumab is effective. Stabiliziation of visual acuity can be achieved, but-in contrast to other forms of CNV lesions-no further improvement. Therefore, patients with this special form need to be identified and treated as early as possible.

PMID: 27743113

Eur J Ophthalmol. 2016 Oct 3:0. [Epub ahead of print]

Clinical experience of switching anti-VEGF therapy from ranibizumab to aflibercept in age-related choroidal neovascularization.

Van Lancker L, Petrarca R, Moutsouris K, Masaoutis P, Kampougeris G.

PURPOSE: To report the response of participants switching from ranibizumab to aflibercept treatment for neovascular age-related macular degeneration (nAMD) requiring further anti-vascular endothelial growth factor treatment.

METHODS: In this retrospective case review of 68 participants treated in a single hospital, all participants, prior to switching, received ranibizumab injections only. Best-corrected visual acuity (BCVA), clinical examination, and optical coherence tomography (OCT) were performed at each visit. Active nAMD was defined as persistent intraretinal or subretinal fluid on OCT. Participants had their first aflibercept injection at baseline and 2 more injections at 2 monthly intervals. Afterwards, they were followed up every 6-8 weeks and given injections as needed. The main outcome measures were visual acuity and the OCT central retinal thickness (CRT), average thickness (AT), and total macular volume (TMV).

RESULTS: The BCVA at baseline visit was 0.57 ± 0.33 log MAR and the final BCVA was 0.54 ± 0.37 log MAR ($p = 0.215$). The CRT mean change was -75.6 ± 85.6 ($p = 0.001$), the AT mean change was -24.2 ± 27.2 ($p = 0.001$), and TMV mean change was -0.69 ± 0.78 ($p = 0.001$). There were no significant ophthalmic complications related to treatments.

CONCLUSIONS: Intravitreal aflibercept improved anatomic outcomes (as measured by OCT) in eyes with nAMD that were previously treated with intravitreal ranibizumab and were still active. There was no statistically significant difference in logMAR visual acuity in participants who switched to aflibercept with a follow-up of at least 6 months.

PMID: 27739561

Jpn J Ophthalmol. 2016 Oct 11. [Epub ahead of print]

Effect of leaking perifoveal microaneurysms on resolution of diabetic macular edema treated by combination therapy using anti-vascular endothelial growth factor and short pulse focal/grid laser photocoagulation.

Hirano T, Toriyama Y, Iesato Y, Imai A, Hirabayashi K, Nagaoka T, Takamura Y, Sugimoto M, Murata T.

PURPOSE: The effect of combination therapy using intravitreal ranibizumab (IVR) injections and short pulse focal/grid laser photocoagulation was evaluated for the treatment of diabetic macular edema (DME).

METHODS: The current investigation was a preliminary single-arm, open-label, prospective clinical study conducted on 21 eyes at 4 sites in Japan. Treatment protocol consisted of two phases. The induction IVR phase included two monthly IVRs followed by PRN IVR phase in which additional IVR was administered if the central macular thickness (CMT) exceeded 300 μm. One week after each IVR in both phases, short pulse focal/grid laser was delivered to treat residual leakage outside of the fovea (>500 μm) and reduce edema fluid influx. At the 6-month endpoint, the effects of treatment were examined in terms of best corrected visual acuity (BCVA), CMT, and required number of IVR injections in eyes with or without perifoveal leaking microaneurysms (MAs).

RESULTS: In eyes with initial BCVA ≤70 letters, mean BCVA was significantly ameliorated by 7.0 ± 7.4 letters (P = 0.0324) and mean CMT improved significantly by 174.8 ± 105.0 μm (P = 0.0005). Both BCVA improvement (P = 0.8693) and CMT reduction (P = 0.9336) were comparable between MA(-) and MA(+) groups. The MA(-) group required significantly fewer PRN-IVR injections than did the MA(+) group over the 6-month study period (mean 3.4 ± 1.6 vs. 5.3 ± 0.9, median 3.0 vs. 5.5; P = 0.0229).

CONCLUSIONS: Short pulse focal/grid laser photocoagulation could reduce the number of IVR injections required to resolve macular edema and increase BCVA in a possible mechanism of reduced influx of edema fluid into the foveal area in eyes without apparent perifoveal microaneurysms.

PMID: 27730425

Korean J Ophthalmol. 2016 Oct;30(5):369-376. Epub 2016 Sep 29.

The Efficacy of Intravitreal Aflibercept in Submacular Hemorrhage Secondary to Wet Age-related Macular Degeneration.

Shin KH, Lee TG, Kim JH, Kim JW, Kim CG, Lee DW, Han JI, Lew YJ, Cho HJ.

PURPOSE: To evaluate the efficacy of intravitreal aflibercept monotherapy in submacular hemorrhage (SMH) secondary to wet age-related macular degeneration (AMD).

METHODS: This study included 25 eyes in 25 patients with SMH involving the fovea secondary to wet-AMD. All patients were treated with three consecutive monthly intravitreal aflibercept (2.0 mg/0.05 mL) injections, followed by as-needed reinjection. They were followed for at least 6 months. Best-corrected visual acuity (BCVA), central foveal thickness (CFT), and area of SMH were measured at diagnosis, as well as at 3 and 6 months after treatment initiation.

RESULTS: The BCVA significantly improved from 0.79 ± 0.41 logarithm of the minimum angle of resolution (logMAR) at baseline to 0.54 ± 0.41 logMAR at 6 months ($p < 0.001$). BCVA ≥3 lines and stable vision were observed in 96% of the eyes. The CFT significantly decreased from 560.8 ± 215.3 μm at baseline to 299.8 ± 160.2 μm at 6 months ($p < 0.001$). The area of SMH significantly decreased from 10.5 ± 7.1 mm2 at baseline to 1.8 ± 6.5 mm2 at 6 months ($p < 0.001$). The BCVA, CFT, and area of SMH at baseline, as well as duration of symptoms, all correlated with BCVA at the 6-month follow-up.

CONCLUSIONS: Intravitreal injection of aflibercept is an effective treatment option for patients with SMH secondary to wet-AMD; however, there may be limited efficacy in eyes with large SMH area and cases in which treatment is delayed.

PMID: 27729757

J Ocul Pharmacol Ther. 2016 Oct 11. [Epub ahead of print]

Short-Term Outcomes of Switching to Ranibizumab Therapy for Diabetic Macular Edema in Patients

with Persistent Fluid After Bevacizumab Therapy.

Lee JH, Lee WK, Kim SE.

PURPOSE: To evaluate the efficacy of switching from bevacizumab to ranibizumab in patients with diabetic macular edema (DME).

METHODS: Patients with DME who showed persistent fluid after at least 3 monthly bevacizumab injections were administered a single ranibizumab injection and were followed up after 1 month. Anatomic responders to ranibizumab were followed up monthly and administered ranibizumab injections on an as-needed basis for 3 months.

RESULTS: At the 1-month follow-up, mean central subfield foveal thickness (CSFT) decreased from 422 to 346 μm ($P < 0.001$) and mean best-corrected visual acuity (BCVA) improved from 20/49 to 20/46 ($P = 0.063$) in 62 enrolled eyes. Thirty-nine eyes (62.9%) were classified as anatomical responders and, after repeated ranibizumab injections (mean number: 2.6), mean CSFT improved (429-317 μm, $P < 0.001$) while BCVA was stabilized (20/52 to 20/48, $P = 0.066$) after 3 months, compared with baseline. The rate of patients who showed partial response to previous bevacizumab between anatomical responders and nonresponders to ranibizumab was compared. The results showed that the rate was significantly higher in the responder group than nonresponder group (76.9% vs. 43.5%, $P = 0.008$).

CONCLUSIONS: Switching patients to ranibizumab may present a suitable option for the treatment of DME with persistent fluid after repeated bevacizumab injections. This treatment switch was more effective in eyes that showed partial response to previous bevacizumab therapy, compared with nonresponsive eyes.

PMID: 27726477

Sci Rep. 2016 Oct 11;6:34631.

Detection of aqueous VEGF concentrations before and after intravitreal injection of anti-VEGF antibody using low-volume sampling paper-based ELISA.

Hsu MY, Hung YC, Hwang DK, Lin SC, Lin KH, Wang CY, Choi HY, Wang YP, Cheng CM.

Abstract: Intraocular vascular endothelial growth factor (VEGF) levels play an important role in the pathogenesis of blindness-related diseases, such as age-related macular degeneration (AMD). Here, we aimed to develop a paper-based enzyme-linked immunosorbent assay (P-ELISA) to analyze the suppression of aqueous VEGF concentrations following intravitreal injection (IVI) of anti-VEGF antibody (bevacizumab or ranibizumab). A total of 25 eyes with wet AMD, one with myopic neovascularization, and one with polypoidal choroidal vasculopathy were enrolled in this study. The limit of detection using P-ELISA was 0.03 pg/mL. Forty-six consecutive samples of aqueous humor were acquired. From all samples, 66.67% (10/15) achieved complete VEGF suppression (below the detection limit) within 5 weeks of receiving IVI of anti-VEGF antibody. Only 13.33% of samples (2/15) achieved complete VEGF suppression 5 weeks after receiving treatment. In some patients, elevated VEGF was still detected 5 weeks after receipt of anti-VEGF antibody, and all samples (10/10) were found to have elevated VEGF levels 49 days after treatment. Thus, we suggest that monthly IVI of anti-VEGF antibody may be required to ensure durable VEGF inhibition. Ultrasensitive P-ELISA can detect elevated VEGF at an earlier time point and may facilitate decision-making regarding appropriate treatment strategies.

PMID: 27725716

Case Rep Ophthalmol. 2016 Sep 7;7(2):389-397.

Treatment of Retinitis Pigmentosa-Associated Cystoid Macular Oedema Using Intravitreal Aflibercept (Eylea) despite Minimal Response to Ranibizumab (Lucentis): A Case Report.

Strong SA, Gurbaxani A, Michaelides M.

BACKGROUND: We present an interesting case of bilateral retinitis pigmentosa (RP)-associated cystoid macular oedema that responded on two separate occasions to intravitreal injections of aflibercept, despite previously demonstrating only minimal response to intravitreal ranibizumab. This unique case would support a trial of intravitreal aflibercept for the treatment of RP-associated cystoid macular oedema.

CASE PRESENTATION: A 38-year-old man from Dubai, United Arab Emirates, presented to the UK with a 3-year history of bilateral RP-associated cystoid macular oedema. Previous treatment with topical dorzolamide, oral acetazolamide, and intravitreal ranibizumab had demonstrated only minimal reduction of cystoid macular oedema. Following re-confirmation of the diagnosis by clinical examination and optical coherence tomography imaging, bilateral loading doses of intravitreal aflibercept were given. Central macular thickness reduced and the patient returned to Dubai. After 6 months, the patient was treated with intravitreal ranibizumab due to re-accumulation of fluid and the unavailability of aflibercept in Dubai. Only minimal reduction of central macular thickness was observed. Once available in Dubai, intravitreal aflibercept was administered bilaterally with further reduction of central macular thickness observed. Visual acuity remained stable throughout.

CONCLUSIONS: This is the first case report to demonstrate a reduction of RP-associated CMO following intravitreal aflibercept, despite inadequate response to ranibizumab on two separate occasions. Aflibercept may provide superior action to other anti-VEGF medications due to its intermediate size (115 kDa) and higher binding affinity. This is worthy of further investigation in a large prospective cohort over an extended time to determine the safety and efficacy of intravitreal aflibercept for use in this condition.

PMID: 27721789

EBioMedicine. 2016 Sep 30. [Epub ahead of print]

Fenofibrate Inhibits Cytochrome P450 Epoxygenase 2C Activity to Suppress Pathological Ocular Angiogenesis.

Gong Y, Shao Z, Fu Z, Edin ML, Sun Y, Liegl RG, Wang Z, Liu CH, Burnim SB, Meng SS, Lih FB, SanGiovanni JP, Zeldin DC, Hellström A, Smith LE.

Abstract: Neovascular eye diseases including retinopathy of prematurity, diabetic retinopathy and age-related-macular-degeneration are major causes of blindness. Fenofibrate treatment in type 2 diabetes patients reduces progression of diabetic retinopathy independent of its peroxisome proliferator-activated receptor (PPAR)α agonist lipid lowering effect. The mechanism is unknown. Fenofibrate binds to and inhibits cytochrome P450 epoxygenase (CYP)2C with higher affinity than to PPARα. CYP2C metabolizes ω-3 long-chain polyunsaturated fatty acids (LCPUFAs). While ω-3 LCPUFA products from other metabolizing pathways decrease retinal and choroidal neovascularization, CYP2C products of both ω-3 and ω-6 LCPUFAs promote angiogenesis. We hypothesized that fenofibrate inhibits retinopathy by reducing CYP2C ω-3 LCPUFA (and ω-6 LCPUFA) pro-angiogenic metabolites. Fenofibrate reduced retinal and choroidal neovascularization in PPARα-/-mice and augmented ω-3 LCPUFA protection via CYP2C inhibition. Fenofibrate suppressed retinal and choroidal neovascularization in mice overexpressing human CYP2C8 in endothelial cells and reduced plasma levels of the pro-angiogenic ω-3 LCPUFA CYP2C8 product, 19,20-epoxydocosapentaenoic acid. 19,20-epoxydocosapentaenoic acid reversed fenofibrate-induced suppression of angiogenesis ex vivo and suppression of endothelial cell functions in vitro. In summary fenofibrate suppressed retinal and choroidal neovascularization via CYP2C inhibition as well as by acting as an agonist of PPARα. Fenofibrate augmented the overall protective effects of ω-3 LCPUFAs on neovascular eye diseases.

PMID: 27720395

Other treatment & diagnosis

Medicine (Baltimore). 2016 Oct;95(41):e4907.

Optical coherence angiography: A review.

Wylęgała A1, Teper S, Dobrowolski D, Wylęgała E.

BACKGROUND: Retinal vascular diseases are one of the most common causes of blindness in the developed world. Optical Coherence Tomography Angiography (OCT-A) is a new noninvasive method that uses several algorithms to detect blood movement. This enables the creation of high-resolution vascular images with contrast depicting motionless tissue.

METHODS: This review presents the results of articles relevant to age-related macular degeneration (AMD), diabetic retinopathy (DR), and OCT-A. The OCT-A technique can successfully be used in the diagnosis of neovascularization, retinal vein occlusion (RVO) and retinal artery occlusion (RAO), vessel abnormalities and even anterior segment neovascularization. OCT-A can also be applied to compute data such as vessel density, and flow index in both superficial and deep plexuses.

RESULTS: Many studies have compared fluorescein angiography with OCT-A. Other studies have reported differences in vascular density in AMD patients and have compared them with people having healthy eyes. Although OCT-A offers rapid picture acquisition, high repeatability and resolution, it also has many drawbacks. The most common are: motion artifacts, projections from overlying vessels and limited field of view.An interesting new application is the possibility to assess changes during antivascular endothelial growth factor (anti-VEGF) therapy. Another function of OCT-A is the possible application in the study of choriocapillaries in many fields of ocular pathology.

CONCLUSION: OCT-A is a new promising method that allows the visualization of the retinal vascular network and the counting of blood flow parameters. This technique provides reliable images useful in clinical routines.

PMID: 27741104

Pathogenesis

EMBO Mol Med. 2016 Oct 14. [Epub ahead of print]

Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases.

Regula JT, Lundh von Leithner P, Foxton R, et al

Abstract: Anti-angiogenic therapies using biological molecules that neutralize vascular endothelial growth factor-A (VEGF-A) have revolutionized treatment of retinal vascular diseases including age-related macular degeneration (AMD). This study reports preclinical assessment of a strategy to enhance anti-VEGF-A monotherapy efficacy by targeting both VEGF-A and angiopoietin-2 (ANG-2), a factor strongly upregulated in vitreous fluids of patients with retinal vascular disease and exerting some of its activities in concert with VEGF-A. Simultaneous VEGF-A and ANG-2 inhibition was found to reduce vessel lesion number, permeability, retinal edema, and neuron loss more effectively than either agent alone in a spontaneous choroidal neovascularization (CNV) model. We describe the generation of a bispecific domain-exchanged (crossed) monoclonal antibody (CrossMAb; RG7716) capable of binding, neutralizing, and depleting VEGF-A and ANG-2. RG7716 showed greater efficacy than anti-VEGF-A alone in a non-human primate laser-induced CNV model after intravitreal delivery. Modification of RG7716's FcRn and FcγR binding sites disabled the antibodies' Fc-mediated effector functions. This resulted in increased systemic, but not ocular, clearance. These properties make RG7716 a potential next-generation therapy for neovascular indications of the eye.

PMID: 27742718

Int Ophthalmol. 2016 Oct 12. [Epub ahead of print]

Comparison of serum thiol-disulphide homeostasis and total antioxidant-oxidant levels between exudative age-related macular degeneration patients and healthy subjects.

Elbay A, Ozer OF, Akkan JC, Celik U, Kutlutürk I, Koytak A, Ozdemir H.

PURPOSE: The purpose of the study was to calculate serum total oxidant status (TOS), total antioxidant status (TAS), and dynamic thiol-disulphide (T-D) homeostasis in patients with age-related macular degeneration (AMD), and compare the results with healthy individuals.

METHODS: Thirty-three exudative AMD patients and 33 healthy controls were included in this case-control study. Participants' serum TAS and TOS levels were measured. In addition, total thiol (TT), native thiol (NT), and disulphide (DS) concentrations were assessed using a novel automated method of measurement.

RESULTS: In comparison with the control group, serum TAS, TT, and NT levels were found to be significantly lower ($p < 0.0001$, $p = 0.004$, $p = 0.003$, respectively) and TOS levels were detected higher ($p = 0.032$) in AMD patients. Serum DS levels were elevated in the AMD patient group, but the difference was not statistically significant ($p = 0.219$). DS/TT and DS/NT ratios were significantly higher ($p = 0.012$, $p = 0.013$, respectively) in AMD patients. A positive correlation was found between TT and NT ($p < 0.0001$) in AMD group.

CONCLUSIONS: Serum TOS levels are higher, TAS levels are lower, and the T-D balance is shifted to the DS bond side in AMD patients. These results suggest that increased oxidative stress and decreased antioxidant levels may play a role in AMD progression. Further studies are needed to confirm the pathophysiologic role of T-D homeostasis in AMD.

PMID: 27734243

Mol Vis. 2016 Oct 8;22:1156-1168. eCollection 2016.

Proinflammatory cytokines decrease the expression of genes critical for RPE function.

Kutty RK, Samuel W, Boyce K, Cherukuri A, Duncan T, Jaworski C, Nagineni CN, Redmond TM.

PURPOSE: Proinflammatory cytokines interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin-1 beta (IL-1β) secreted by infiltrating lymphocytes or macrophages may play a role in triggering RPE dysfunction associated with age-related macular degeneration (AMD). Binding of these proinflammatory cytokines to their specific receptors residing on the RPE cell surface can activate signaling pathways that, in turn, may dysregulate cellular gene expression. The purpose of the present study was to investigate whether IFN-γ, TNF-α, and IL-1β have an adverse effect on the expression of genes essential for RPE function, employing the RPE cell line ARPE-19 as a model system.

METHODS: ARPE-19 cells were cultured for 3-4 months until they exhibited epithelial morphology and expressed mRNAs for visual cycle genes. The differentiated cells were treated with IFN-γ, TNF-α, and/or IL-1β, and gene expression was analyzed with real-time PCR analysis. Western immunoblotting was employed for the detection of proteins.

RESULTS: Proinflammatory cytokines (IFN-γ + TNF-α + IL-1β) greatly increased the expression of chemokines and cytokines in cultured ARPE-19 cells that exhibited RPE characteristics. However, this response was accompanied by markedly decreased expression of genes important for RPE function, such as CDH1, RPE65, RDH5, RDH10, TYR, and MERTK. This was associated with decreased expression of the genes MITF, TRPM1, and TRPM3, as well as microRNAs miR-204 and miR-211, which are known to regulate RPE-specific gene expression. The decreased expression of the epithelial marker gene CDH1 was associated with increased expression of mesenchymal marker genes (CDH2, VIM, and CCND1) and epithelial-mesenchymal transition (EMT) promoting transcription factor genes (ZEB1 and SNAI1).

CONCLUSIONS: RPE cells exposed to proinflammatory cytokines IFN-γ, TNF-α, and IL-1β showed decreased expression of key genes involved in the visual cycle, epithelial morphology, and phagocytosis. This adverse effect of proinflammatory cytokines, which could be secreted by infiltrating lymphocytes or macrophages, on the expression of genes indispensable for RPE function may contribute to the RPE dysfunction implicated in AMD pathology.

PMID: 27733811

Korean J Ophthalmol. 2016 Oct;30(5):377-381. Epub 2016 Sep 29.

The Relationship between Neutrophil-to-lymphocyte Ratio and Age-related Macular Degeneration.

Kurtul BE, Ozer PA.

PURPOSE: To investigate the possible associations of neutrophil-to-lymphocyte ratio (NLR) and high sensitivity C-reactive protein (hs-CRP) level with age-related macular degeneration (ARMD).

METHODS: Patients were divided to three groups of 40 patients with non-neovascular ARMD (group 1), 40 patients with neovascular ARMD (group 2), and 40 healthy control subjects (group 3). The neutrophil and lymphocyte counts were evaluated using an ABX Pentra DF120/USA biochemical analyzer, and hs-CRP levels were measured using a Beckman Coulter Immage 800. The NLR was measured by dividing neutrophil count by lymphocyte count.

RESULTS: The patients in group 2 were older and more often diabetic than the patients in groups 1 and 3 ($p < 0.001$ and $p < 0.001$, respectively). The NLR level was 1.65 ± 0.71 in group 1, 1.98 ± 0.84 in group 2, and 1.46 ± 0.44 in group 3. The hs-CRP value was 1.98 ± 0.251 mg/L in group 1, 3.242 ± 0.211 mg/L in group 2, and 1.145 ± 0.193 mg/L in group 3. Both NLR and hs-CRP values were significantly higher in group 2 compared to group 3 ($p = 0.002$ and $p = 0.002$, respectively). In multivariate analysis, NLR remained an independent predictor of neovascular ARMD (odds ratio, 3.882; 95% confidence interval, 1.574 to 9.576; $p = 0.003$) together with age ($p < 0.001$), diabetes mellitus ($p = 0.041$), and hs-CRP ($p = 0.018$).

CONCLUSIONS: Our study suggests that increased NLR value is independently associated with neovascular ARMD.

PMID: 27729758

Exp Eye Res. 2016 Oct 7. [Epub ahead of print]

A SEMA3E mutant resistant to cleavage by furins (UNCL-SEMA3E) inhibits choroidal neovascularization.

Toledano S, Lu H, Palacio A, Kigel B, Kessler O, Allon G, Barak Y, Neufeld G, Schaal S.

Abstract: Abnormal subretinal choroidal neovascularization (CNV) is a major cause of blindness in exudative age-related macular degeneration (AMD). Current anti-angiogenic treatments by VEGF sequestering agents have been successful, but a significant proportion of patients do not respond well to these treatments, and the response of others diminishes over time, suggesting that additional anti-angiogenic agents that function by separate mechanisms may be of use to such patients. We have previously found that a point mutated form of semaphorin-3E resistant to cleavage by furin like pro-protein convertases (UNCL-Sema3E) displays potent anti-angiogenic properties. We therefore determined if UNCL-Sema3E has potential as an inhibitor of CNV formation. We chose to study UNCL-Sema3E rather than wild type sema3E because unlike full length sema3E, the major p61-Sema3E peptide that is produced by cleavage of sema3E with furin like pro-protein convertases activates signal transduction mediated by the ErbB2 receptor and can promote tumor metastasis in addition to its anti-angiogenic activity. UNCL-Sema3E inhibited efficiently vascular endothelial growth factor-A (VEGF), platelet derived growth factor (PDGF) and

basic fibroblast growth factor (bFGF) signaling in human umbilical vein derived endothelial cells (HUVEC) and to a lesser extent hepatocyte growth factor (HGF) signal transduction. CNV that was induced in the eyes of C57 black mice by laser photocoagulation was inhibited by 65% (P < 0.01) following a single bolus intra-vitreal injection of 5 µg UNCL-Sema3E. This inhibitory effect was similar to the inhibition produced by a single bolus intra-vitreal injection of 5 µg aflibercept. A similar inhibition of CNV was observed following the injection of UNCL-Sema3E into the eyes of Long-Evans rats. However, a higher dose of UNCL-Sema3E (125 µg), partially due to the larger volume of the vitreous cavity of rats, was required to achieve maximal inhibition of CNV. Injection of UNCL-Sema3E into eyes of healthy mice did not have any adverse effect on retinal function as assessed by optic kinetic reflex (OKR) or by electroretinogram (ERG) assays nor did UNCL-Sema3E injection affect the structure of the retina as determined using histology. To conclude, our results suggest that UNCL-Sema3E may be useful for the treatment of exudative AMD, which does not respond well to conventional anti-VEGF therapy.

PMID: 27725196

Epidemiology

Ophthalmology. 2016 Oct 6. [Epub ahead of print]

Associations with Retinal Pigment Epithelium Thickness Measures in a Large Cohort: Results from the UK Biobank.

Ko F, Foster PJ, Strouthidis NG, Shweikh Y, Yang Q, Reisman CA, Muthy ZA, Chakravarthy U, Lotery AJ, Keane PA, Tufail A, Grossi CM, Patel PJ; UK Biobank Eye & Vision Consortium.

PURPOSE: To describe associations of ocular and systemic factors with retinal pigment epithelium (RPE)-Bruch's membrane (BM) complex thickness as measured by spectral-domain (SD) optical coherence tomography (OCT).

DESIGN: Multisite community-based study. This research has been conducted using the UK Biobank Resource.

PARTICIPANTS: Sixty-seven thousand three hundred eighteen people 40 to 69 years old received questionnaires, physical examination, and eye examination, including macular SD OCT. Systematic selection process identified 34 652 eyes with high-quality SD OCT images from normal individuals for analysis.

METHODS: We included people with no self-reported ocular disease, diabetes, or neurologic disorders; visual acuity of ≥20/25 or better; refraction between -6 diopters (D) to 6 D, and IOP of 6 to 21 mmHg. Only high-quality, well-centered SD OCT images with central, stable fixation were included. Descriptive statistics, t tests, and regression analyses were performed. Multivariate regression modeling was used to adjust for covariates and to identify relationships between RPE-BM thickness and ocular and systemic features.

MAIN OUTCOME MEASURES: Retinal pigment epithelium-BM thickness, as measured by SD OCT segmentation using Topcon Advanced Boundary Segmentation at 9 Early Treatment of Diabetic Retinopathy Study subfields.

RESULTS: Mean RPE-BM thickness was 26.3 µm (standard deviation, 4.8 µm) at central subfield. Multivariate regression with age stratification showed that RPE thinning became apparent after age 45 years. Among those aged ≤45, RPE-BM was significantly thicker among those of black or mixed/other race (+3.61 µm and +1.77 µm vs. white, respectively; P < 0.001) and higher hyperopia (+0.4 µm/D; P < 0.001), but not for other variables considered. Among those age >45, RPE-BM was significantly thinner with older age (-0.10 µm/year; P < 0.001), Asian ethnicity (-0.45 µm vs. white; P = 0.02), taller height (-0.02 µm/cm; P < 0.001), higher IOP (-0.03 µm/mmHg; P < 0.001), and regular smoking (-0.27 µm vs. nonsmokers; P = 0.02). In contrast, RPE-BM was significantly thicker among black or mixed/other race (+3.29 µm and +0.81 µm vs. white, respectively; P < 0.001) and higher hyperopia (+0.28 µm/D; P < 0.001). There was no significant association with sex or Chinese ethnicity.

CONCLUSIONS: We describe novel findings of RPE-BM thickness in normal individuals, a structure that varies with age, ethnicity, refraction, IOP, and smoking. The significant association with IOP is especially interesting and may have relevance for the etiology of glaucoma, while the association between age and smoking may have relevance for the etiology of age-related macular degeneration.

PMID: 27720551

Ophthalmic Res. 2016 Oct 13. [Epub ahead of print]

Risk Prediction Model for Progression of Age-Related Macular Degeneration.

Shin KU1, Song SJ, Bae JH, Lee MY.

AIMS: The aim of this paper was to develop a risk prediction model for the progression of age-related macular degeneration (AMD) in Koreans using systemic and environmental factors.

METHODS: The study sample included 10,890 individuals 50 years of age or older; 318 (2.92%) presented with early AMD findings in baseline examinations. Re-examinations were performed in 157 (49.37%) who were followed up for 4.4 years. The multivariate analysis of covariates included demographic and environmental factors. After using these data to develop a risk prediction model, the individual algorithm was made, and receiver operating characteristic curves were calculated to assess the predictive ability of the risk model for AMD progression.

RESULTS: The individual algorithm to predict the AMD progression risk based on systemic and ocular factors was as follows: Y = -9.565 + 1.709 (drusen locationcenter) + 0.795 (drusen locationparacentral) + 1.074 (both eyes) + 0.094 (drusen sizeintermediate) + 0.034 (drusen sizelarge) + 0.614 (drusen number10-20) + 2.278 (drusen number>20) + 0.577 (hyperpigmentation) + 0.725 (hypopigmentation) + 0.079 (male) - 0.025 (age) - 0.921 (SMKex) + 1.574 (SMKcurrent) + 0.363 (total protein) + 1.626 (globulin), where SMK means smoking status. The C statistics for the model was 0.84 (0.75-0.92) indicating a good predictive power.

CONCLUSION: A comprehensive risk prediction model for AMD progression was made to calculate the individual AMD progression risk using personal systemic and environmental factors.

PMID: 27732974

Genetics

Sci Rep. 2016 Oct 14;6:35414.

Clinical and genetic analyses reveal novel pathogenic ABCA4 mutations in Stargardt disease families.

Lin B, Cai XB, Zheng ZL, Huang XF, Liu XL, Qu J, Jin ZB.

Abstract: Stargardt disease (STGD1) is a juvenile macular degeneration predominantly inherited in an autosomal recessive pattern, characterized by decreased central vision in the first 2 decades of life. The condition has a genetic basis due to mutation in the ABCA4 gene, and arises from the deposition of lipofuscin-like substance in the retinal pigmented epithelium (RPE) with secondary photoreceptor cell death. In this study, we describe the clinical and genetic features of Stargardt patients from four unrelated Chinese cohorts. The targeted exome sequencing (TES) was carried out in four clinically confirmed patients and their family members using a gene panel comprising 164 known causative inherited retinal dystrophy (IRD) genes. Genetic analysis revealed eight ABCA4 mutations in all of the four pedigrees, including six mutations in coding exons and two mutations in adjacent intronic areas. All the affected individuals showed typical manifestations consistent with the disease phenotype. We disclose two novel ABCA4 mutations in Chinese patients with STGD disease, which will expand the existing spectrum of disease-causing variants

and will further aid in the future mutation screening and genetic counseling, as well as in the understanding of phenotypic and genotypic correlations.

PMID: 27739528

Diet, lifestyle and low vision

Clin Ophthalmol. 2016 Sep 29;10:1899-1903. eCollection 2016.

Tolerability in the elderly population of high-dose alpha lipoic acid: a potential antioxidant therapy for the eye.

Sarezky D, Raquib AR, Dunaief JL, Kim BJ.

PURPOSE: Alpha lipoic acid (ALA) is an antioxidant and iron-chelating supplement that has potential benefits for geographic atrophy in dry age-related macular degeneration as well as other eye diseases. The purpose of this study was to determine the tolerability of ALA in the elderly population.

PATIENTS AND METHODS: Fifteen subjects, age ≥65 years, took sequential ALA doses of 600, 800, and 1,200 mg. Each dose was taken once daily with a meal for 5 days. After each dose was taken by the subjects for 5 days, the subjects were contacted by phone, a review of systems was performed, and they were asked if they thought they could tolerate taking that dose of ALA for an extended period of time.

RESULTS: The 600 mg dose was well tolerated. At the 800 mg dose, one subject had an intolerable flushing sensation. At the 1,200 mg dose, two subjects had intolerable upper gastrointestinal side effects and one subject had an intolerable flushing sensation. Subjects taking gastrointestinal prophylaxis medications had no upper gastrointestinal side effects.

CONCLUSION: High-dose ALA is not completely tolerated by the elderly. These preliminary data suggest that gastrointestinal prophylaxis may improve tolerability. (ClinicalTrials.gov, NCT02613572).

PMID: 27729766