

Issue 325

Wednesday 26 April, 2017

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

If you have not already subscribed, please email Rob Cummins at research@mdfoundation.com.au with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request or by clicking on the link at the bottom of the email linking you to this page.

Drug treatment

Int Ophthalmol. 2017 Apr 18. [Epub ahead of print]

Effect of intravitreal aflibercept (Eylea®) on retrobulbar hemodynamics in patients with neovascular age-related macular degeneration.

Gok M, Kapti HB.

PURPOSE: To investigate the short-term effect of single intravitreal aflibercept injection on retrobulbar blood flow in patients with neovascular age-related macular degeneration (nAMD).

METHODS: Twenty eyes of 20 patients with nAMD scheduled for single intravitreal aflibercept (Eylea®) injection and 20 fellow eyes (uninjected) were enrolled in this prospective interventional study. The hemodynamic parameters of the ophthalmic artery (OA), central retinal artery (CRA) and posterior ciliary artery (PCA) comprising peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) were measured by using color Doppler ultrasonography (CDU) in both injected and uninjected fellow eyes at baseline and 1 week after the injection.

RESULTS: The measured first-week values of PSV and EDV in the CRA, OA and PCA showed a statistically significant reduction when comparing baseline values in both injected and uninjected fellow eyes ($p = 0.0001$). Also, it was found a significant increase in the post-injection RI values of all the CRA, OA, PCA in injected eye and OA in the uninjected eye ($p = 0.0001$). There was any significant difference between pre- and post-injection RI values of the CRA and PCA in the fellow eyes ($p = 0.137$, $p = 0.736$, respectively).

CONCLUSION: Single intravitreal administration of aflibercept alters retrobulbar blood flow velocities (BFVs) in both injected and uninjected fellow eyes in the short-term period.

PMID: 28421399

Ophthalmic Surg Lasers Imaging Retina. 2017 Apr 1;48(4):326-332.

Pre-Existing RPE Atrophy and Defects in the External Limiting Membrane Predict Early Poor Visual Response to Ranibizumab in Neovascular Age-Related Macular Degeneration.

Zandi S, Weisskopf F, Garweg JG, Pfister IB, Prunte C, Sutter F, Hatz K.

BACKGROUND AND OBJECTIVES: The aim of this study was to identify the rate of early visual acuity poor responders in patients with neovascular age-related macular degeneration (AMD) after the first intravitreal injection of ranibizumab (Lucentis; Genentech, South San Francisco, CA) and to determine potential predictors for early response.

PATIENTS AND METHODS: Patients with choroidal neovascularization secondary to AMD were evaluated

before and 1 month after their first ranibizumab treatment. Early poor responders were defined as eyes gaining less than five letters 1 month after the first injection.

RESULTS: Following the first ranibizumab injection, 58% of 84 patients gained five or more letters. Beyond 42% poor responders, 31% displayed foveal retinal pigment epithelium (RPE) atrophy and 89% a loss of the external limiting membrane (ELM) integrity at baseline. However, the amount of intra- and subretinal fluid, pigment epithelial detachment (PED), and subfoveal fibrosis showed a similar distribution between gainers and poor responders.

CONCLUSION: Early poor responders present with more RPE atrophy, as well as a loss of the ELM integrity at baseline optical coherence tomography.

PMID: 28419398

Br J Ophthalmol. 2017 Apr 21. [Epub ahead of print]

Early response to ranibizumab predictive of functional outcome after dexamethasone for unresponsive diabetic macular oedema.

Cicinelli MV, Cavalleri M, Querques L, Rabiolo A, Bandello F, Querques G.

PURPOSE: To analyse the effects of intravitreal dexamethasone implant in patients suffering from diabetic macular oedema (DME) on the basis of their visual and functional response to antivascular endothelial growth factor (VEGF) loading dose, in order to early shift to corticosteroids in poorly responding patients.

DESIGN: Retrospective monocentric study.

METHODS: Data of patients with diabetes shifted to 0.7 mg dexamethasone implant after three injections of ranibizumab (RNB) and followed-up to 12 months were reviewed. Main outcome was the evaluation of short-term changes after dexamethasone implant injection, stratifying patients on the basis of best-corrected visual acuity (BCVA) and central macular thickness (CMT) after RNB loading dose. Secondary outcome was to investigate clinical gain maintenance at long-term follow-up.

RESULTS: Overall, 45 eyes of 45 patients (23 males, 51.1%), mean age 69.7±9 years, were included in the analysis. After 3 injections of RNB, 30 eyes (66.7%) had a poor visual response (-4.3±10.7 letters), while 15 eyes (33.3%) disclosed good visual outcome (+13.9±9.2 letters). Patients with poor visual response were associated with limited morphological improvement (p=0.04). After 1 month from dexamethasone, only poor responders showed relevant increase in BCVA (p=0.006) and reduction in CMT (p=0.002), in comparison to good visual response patients, featuring only minor clinical effects (p=0.3). The same trend was maintained up to 12 months, after a mean of 1.9±1.1 dexamethasone administrations.

CONCLUSION: Visual and anatomical responses after RNB loading dose are significant predictors of both early term and long-term visual acuity improvement after switching to corticosteroids in patients with DME unresponsive to anti-VEGF.

PMID: 28432109

Dev Ophthalmol. 2017;60:131-142. Epub 2017 Apr 20.

Anti-Vascular Endothelial Growth Factor Injections: The New Standard of Care in Proliferative Diabetic Retinopathy?

Li X, Zarbin MA, Bhagat N.

Abstract: For decades, panretinal photocoagulation (PRP) has been the standard of care for the treatment of proliferative diabetic retinopathy (PDR). The relatively recent advent of anti-vascular endothelial growth factor (VEGF) formulations for intravitreal injection has provided a fresh perspective on PDR treatment,

especially in eyes with concurrent diabetic macular edema (DME). The anti-VEGF agent ranibizumab has demonstrated a potentially protective effect on eyes with DME in terms of progression to PDR in the RIDE/RISE trials, as has aflibercept in the VIVID/VISTA trials. In 2015, these 2 agents were approved by the Food and Drug Administration for the treatment of PDR with DME, though PRP still remains the standard of care for eyes without baseline DME. Published results from Protocol S illustrate the non-inferiority of ranibizumab versus PRP in the treatment of PDR, the first prospective study to do so in eyes with and without baseline DME. These results also reveal that treatment with ranibizumab, when compared to standard treatment with PRP, may also lead to less peripheral visual field loss, reduced need for vitrectomy, and reduced chance for developing DME. Both PRP and intravitreal ranibizumab have very low rates of adverse events. However, treatment with anti-VEGF agents generally is associated with higher costs, increased need for follow-up, and the risk of potentially catastrophic ocular complications (e.g., endophthalmitis) and systemic side effects. Anti-VEGF agents should be considered in cases of media opacity preventing completion of PRP in compliant patients without recent cerebrovascular accident or myocardial infarction, though the long-term efficacy of these agents remains to be studied, especially after the discontinuation of injections.

PMID: 28427072

Dev Ophthalmol. 2017;60:109-124. Epub 2017 Apr 20.

Practical Lessons from Protocol T for the Management of Diabetic Macular Edema.

Mukkamala L, Bhagat N, Zarbin M.

PURPOSE: To review the results of Diabetic Retinopathy Clinical Research Network Protocol T, as applied to clinical practice.

METHODS: Review of major publications reporting the results of Protocol T, a randomized single-masked (in year-1 only), multicenter clinical trial comparing aflibercept, bevacizumab, and ranibizumab as treatment option for center-involving diabetic macular edema (DME). The main outcome measures were change in visual acuity (VA), central subfield thickness (CST) on optical coherence tomography, cost effectiveness, burden of care, and safety.

RESULTS: A total of 660 participants (mean age 61 ± 10 years, 47% women, 65% Caucasian) were randomized to treatment with aflibercept ($n = 224$), ranibizumab ($n = 218$), or bevacizumab ($n = 218$). The majority of patients (90%) had type II diabetes, with an average duration of 17 ± 11 years. About half the patients had baseline ETDRS VA of 20/32 to 20/40, and half had ETDRS VA of 20/50 to 20/320 in all 3 cohorts. Patients in all 3 cohorts received a similar number of injections during the study period (9-10 in year-1; 5-6 in year-2). The year-1 improvement in ETDRS letters was significantly higher for aflibercept than for ranibizumab and bevacizumab in patients with baseline VA 20/50 or worse ($p = 0.003$ and $p < 0.001$, respectively), but was no different in patients with better baseline VA of 20/32 to 20/40 ($p = 0.69$). By year-2, among patients with poorer baseline VA, there was a difference in mean letters gained between aflibercept and bevacizumab ($p = 0.02$), but no difference between aflibercept and ranibizumab ($p = 0.18$). At year-2, there was no clinically meaningful difference in VA improvement (i.e., gain or loss of ≥ 10 or ≥ 15 letters) among any of the agents ($p > 0.74$). Bevacizumab was less effective than the other agents in decreasing CST at years-1 and -2 in the overall cohort of patients ($p < 0.001$). However, bevacizumab is substantially cheaper and much more cost-effective (when comparing expense and quality of life measures) than aflibercept and ranibizumab. The cost of other agents would have to decrease by 80-90% to be cost-effective relative to bevacizumab. Intravitreal administration of anti-VEGF therapy has relatively few ocular and systemic side effects, but caution may be warranted for patients with a recent history or high risk of myocardial infarction or stroke.

CONCLUSIONS: Aflibercept, bevacizumab, and ranibizumab are highly effective treatments for DME. Bevacizumab is more cost-effective than aflibercept and ranibizumab. Intravitreal administration of drugs is relatively safe; however, intravitreal administration may be associated with severe systemic side effects in a small percentage of patients, particularly in those with a prior history of or high risk of Anti-Platelet Trialists'

Collaboration events.

PMID: 28427070

Dev Ophthalmol. 2017;60:91-108. Epub 2017 Apr 20.

Practical Lessons from Protocol I for the Management of Diabetic Macular Edema.

Mukkamala L, Bhagat N, Zarbin MA.

Abstract: Protocol I, a multicenter randomized clinical trial, compared the visual outcomes of patients treated with 0.5 mg intravitreal ranibizumab with either prompt or deferred (by 24 weeks laser), 4 mg intravitreal triamcinolone with prompt laser, or sham injection with prompt laser for the treatment of center-involving diabetic macular edema (DME). A total of 854 adult patients with type I or II diabetes and any level of non-proliferative diabetic retinopathy or proliferative retinopathy with adequate panretinal photocoagulation, with best-corrected visual acuity (BCVA) of 78 to 24 ETDRS letters (Snellen equivalent of 20/32 to 20/320) and visual loss attributed to macular edema, or retinal thickening with central subfield thickness of at least 250 μ m by OCT were enrolled. The main outcomes relevant for practicing clinicians are as follows. (1) Intravitreal ranibizumab treatment provides superior visual outcomes compared to conventional laser treatment. (2) Adjunctive laser treatment does not appear to provide substantial visual benefit compared to ranibizumab treatment alone, but may reduce the number of injections required to resolve DME. Deferral of laser is likely beneficial in patients with worse initial visual acuity. (3) Intravitreal triamcinolone provides similar visual outcomes compared to intravitreal ranibizumab in pseudophakic patients but is associated with a clinically important increased risk of increased intraocular pressure (IOP), need for glaucoma medications, and need for glaucoma surgery. (4) Delayed initiation of intravitreal ranibizumab therapy provides improved visual outcome among patients initially treated with conventional laser photocoagulation or triamcinolone, but the magnitude of the benefit is not as great as is observed when ranibizumab treatment is initiated promptly. (5) The number of ranibizumab injections required to achieve the desired visual outcome decreases substantially after the first year, with the majority of patients not requiring further treatment after 3 years. (6) Patients who do not have a rapid response to ranibizumab still display long-term benefit to continued therapy, although perhaps less than those with immediate improvement. (7) Intravitreal ranibizumab is not only effective in reducing retinal edema and improving BCVA among patients with DME, it is also a disease modifying therapy and induces improvement of the diabetic retinopathy severity score by 2 or more steps in approximately one third of patients. Triamcinolone injection also induces improvement in diabetic retinopathy severity in DME patients, but perhaps to a lesser degree. (8) No increased risk of systemic adverse events was observed among patients treated with intravitreal ranibizumab compared to sham-injected controls or triamcinolone-treated patients, but the low frequency of adverse events, restrictive enrollment criteria, and specific dosology employed in this study limit the generalization of this conclusion to patients routinely encountered in clinical practice. (9) There was no clinically important increased risk of major ocular complications among patients treated with intravitreal ranibizumab (including the risk of glaucoma), although endophthalmitis is a potentially devastating outcome should it occur. In addition to the risk of endophthalmitis, intravitreal triamcinolone injection was associated with clinically important increased risk of cataract progression and increased IOP.

PMID: 28427069

Dev Ophthalmol. 2017;60:71-77. Epub 2017 Apr 20.

Intravitreal Aflibercept in Diabetic Macular Edema: Long-Term Outcomes.

Introini U, Casalino G.

Abstract: For decades, macular laser photocoagulation has been the standard of care in the treatment of diabetic macular edema (DME). With the relatively recent advent of anti-vascular endothelial growth factor (VEGF) agents, DME treatment has entered a new era. VEGF is a well-known pro-angiogenic and pro-

permeability factor involved in the pathogenesis of DME. VEGF blockade has proven remarkably effective at reducing DME and improving visual acuity (VA) in eyes with center involved DME causing VA loss in several randomized controlled trials (RCTs). Intravitreal aflibercept, ranibizumab, and bevacizumab (the latter used off-label) are 3 anti-VEGF molecules currently available for DME treatment. Aflibercept is a 115-kDa recombinant fusion protein consisting of VEGF binding domains of human VEGF receptors-1 and -2 fused to the Fc domain of human immunoglobulin-G1. The ability to bind placental growth factors 1 and 2 (which is another pro-permeability mediator) and a theoretically long half-life are potential advantages of aflibercept over other anti-VEGF agents. The use of intravitreal aflibercept in DME treatment has been investigated in several RCTs. The aim of this chapter is to briefly report on the current evidence for treating DME with intravitreal aflibercept.

PMID: 28427067

Dev Ophthalmol. 2017;60:63-70. Epub 2017 Apr 20.

Intravitreal Ranibizumab in Diabetic Macular Edema: Long-Term Outcomes.

Zucchiatti I, Bandello F.

Abstract: Intravitreal ranibizumab (RBZ) has been shown in multiple randomized clinical trials to be a valuable treatment for diabetic macular edema (DME), promoting a significant improvement in best-corrected visual acuity (BCVA) and in anatomic outcomes. Compared to sham (RISE and RIDE studies), RBZ rapidly and sustainably improved BCVA and decreased macular edema at 2 years, reducing the risk of further vision loss, with low rates of local or systemic side effects. Compared to macular laser photocoagulation (READ-2 study), RBZ provided a greater improvement in BCVA and regression in foveal thickness, but required a higher number of injections compared to patients treated with both RBZ and laser. In RESTORE trial, RBZ alone or combined with macular laser turned out to be superior to laser alone, without significant differences between the 2 RBZ groups. Compared to combined treatment (RBZ or triamcinolone associated with macular laser) or photocoagulation laser alone (Diabetic Retinopathy Clinical Research Network trial), RBZ with prompt or deferred laser was more effective than laser alone at 1-year follow-up. At 3 years, prompt laser was not better than deferring laser for 24 weeks or more. At 5 years, subjects treated with RBZ achieved better long-term visual outcomes than patients managed with triamcinolone or laser followed by very deferred RBZ. In conclusion, randomized clinical trials showed that RBZ was superior to laser in DME treatment, providing excellent long-term visual outcomes. Frequent injections were necessary in most of the patients to properly control DME and maximize the visual benefits.

PMID: 28427066

Ophthalmic Res. 2017 Apr 21. [Epub ahead of print]

Long-Term Anatomical and Functional Outcomes in Patients with Ischemic Central Retinal Vein Occlusion Treated with Anti-Vascular Endothelial Growth Factor Agents.

Chatziralli I, Theodossiadis G, Parikakis E, Mitropoulos PG, Theodossiadis P.

PURPOSE: To evaluate the anatomical and functional outcomes in patients with ischemic central retinal vein occlusion (CRVO) treated with intravitreal anti-vascular endothelial growth factor (VEGF) agents.

METHODS: This retrospective study included 15 treatment-naïve patients with ischemic CRVO and macular edema who were treated with intravitreal ranibizumab or aflibercept. The main outcomes were the evolution of retinal ischemia over time, as well as the change in best corrected visual acuity (BCVA) and in central subfield thickness (CST) at month 24.

RESULTS: At month 24, patients with ischemic CRVO gained +7.8 letters compared to baseline, while there was a significant decrease in CST by 243.7 µm. At baseline, ischemia was located mainly at the peripheral retina, while 6.6% of patients presented macular ischemia. At month 24, 20% of patients had

macular ischemia, which was found to be negatively correlated with BCVA. The patients with macular ischemia had very poor final visual outcome and were advised to discontinue treatment.

CONCLUSIONS: Our study showed that anti-VEGF treatment was effective in patients with ischemic CRVO, since it reduces macular edema and maintains or improves VA in the long term (24-month follow-up). It is worthy of note that in a small proportion of patients (13.3%) peripheral ischemia progressed to macular ischemia over time. In cases where macular ischemia is present, anti-VEGF treatment does not seem to offer any improvement in VA.

PMID: 28427057

Retina. 2017 Apr 19. [Epub ahead of print]

INTRAVITREAL DEXAMETHASONE IMPLANTATION IN PATIENTS WITH DIFFERENT MORPHOLOGICAL DIABETIC MACULAR EDEMA HAVING INSUFFICIENT RESPONSE TO RANIBIZUMAB.

Kaldırım H, Yazgan S, Atalay K, Gurez C, Savur F.

PURPOSE: To evaluate the effectiveness of a single intravitreal injection of dexamethasone implant in resistant diabetic macular edema that have different morphological types.

METHODS: In this retrospective study, 31 patients (35 eyes) with persistent diabetic macular edema, who underwent a single injection of dexamethasone implant, were evaluated. Diabetic macular edema was classified into three types: diffuse retinal thickening (n = 10), cystoid macular edema (n = 13), and serous retinal detachment (n = 12). Primary outcome measures were best corrected visual acuity, and central macular thickness.

RESULTS: The three subgroups were similar in terms of age and gender ($P > 0.05$). Total duration of diabetes was significantly less in the serous retinal detachment subgroup ($P = 0.01$). There were no differences in the best corrected visual acuity between the three subgroups until the sixth month. However, the best corrected visual acuity was significantly better in the diffuse retinal thickness subgroup at the sixth month ($P = 0.008$). Regarding the central macular thickness values, it was statistically better in serous retinal detachment than in diffuse retinal thickening and cystoid macular edema subgroups till the sixth month ($P = 0.001$). However, at the sixth month, there was not any statistical difference between subgroups regarding central macular thickness values. Antiglaucomatous agents were required in 4 (11.4%) patients throughout the study.

CONCLUSION: Treatment algorithms should differ according to the morphology of diabetic macular edema; however, more data is needed to give specific recommendations.

PMID: 28426623

Medicine (Baltimore). 2017 Apr;96(16):e6459.

Predictive factors of better outcomes by monotherapy of an antivascular endothelial growth factor drug, ranibizumab, for diabetic macular edema in clinical practice.

Sato S, Shinoda H, Nagai N, Suzuki M, Uchida A, Kurihara T, Kamoshita M, Tomita Y, Iyama C, Minami S, Yuki K, Tsubota K, Ozawa Y.

Abstract: Intravitreal ranibizumab (IVR) has been approved for treating diabetic macular edema (DME), and is used in daily clinical practice. However, the treatment efficacies of IVR monotherapy in real-world clinical settings are not well known. The medical records of 56 eyes from 38 patients who received their first IVR for DME between April 2014 and March 2015, and were retreated with IVR monotherapy as needed with no rescue treatment, such as laser photocoagulation, were retrospectively reviewed. The clinical course, best-

corrected visual acuity (BCVA), and fundus findings at baseline, before the initial IVR injection, and at 12 months, were evaluated. Twenty-five eyes from 25 patients (16 men; mean age 68.7 ± 9.8 years) who received IVR in the first eye, or unilaterally, without any other treatments during follow-up were included. After 12 months, mean central retinal thickness (CRT), which includes edema, was reduced ($P = .003$), although mean BCVA remained unchanged. There was a negative correlation between individual changes in BCVA ($r = -0.57$; $P = .003$) and CRT ($r = -0.60$; $P = .002$) at 12 months compared with baseline values. BCVA changes were greater in individuals with a history of pan-retinal photocoagulation at baseline ($P = .026$). After adjusting for age and sex, CRT improvement $>100 \mu\text{m}$ at 12 months was associated with a greater CRT at baseline (OR 0.87 per $10 \mu\text{m}$ [95% CI 0.72-0.97]; $P = .018$) according to logistic regression analyses; however, better BCVA and CRT at 12 months were associated with a better BCVA ($r = 0.77$; $P < .001$) and lower CRT ($r = 0.41$; $P = .039$) at baseline, respectively, according to linear regression analyses. IVR monotherapy suppressed DME, and the effects varied according to baseline conditions. Eyes that had poorer BCVA or greater CRT, or a history of pan-retinal photocoagulation at baseline, demonstrated greater improvement with IVR monotherapy. In contrast, to achieve better outcome values, DME eyes should be treated before the BCVA and CRT deteriorate. These findings advance our understanding of the optimal use of IVR for DME in daily clinical practice, although further study is warranted.

PMID: 28422835

Case Rep Ophthalmol. 2017 Feb 2;8(1):87-90.

Intravitreal Aflibercept in Recalcitrant Radiation Maculopathy due to External Beam Radiotherapy for Nasopharyngeal Cancer: A First Case Report.

Loukianou E, Loukianou G.

PURPOSE: To present the safety and efficacy of intravitreal aflibercept (Eylea) in a patient with radiation maculopathy secondary to external beam radiotherapy for nasopharyngeal cancer unresponsive to other therapeutic options.

METHODS: A 73-year-old female presented with decreased visual acuity in both eyes 18 months after completing 47 external beam cycles of radiation for nasopharyngeal cancer. On presentation, her best corrected visual acuity was 6/60 in the right eye and counting fingers from 1 meter in the left eye. She received 5 bevacizumab injections in the right eye and 7 bevacizumab injections in the left eye over the last year without any improvement. A treatment with intravitreal injections of aflibercept was recommended in both eyes.

RESULTS: The patient received 3 intravitreal aflibercept injections (2 mg/0.05 mL) in each eye every 4 weeks. The visual acuity improved from 6/60 to 6/12 in the right eye and from counting fingers to 6/36 in the left eye. Biomicroscopy showed less exudates, hemorrhages, and microaneurysms. Optical coherence tomography revealed reduced central retinal thickness in both eyes after 1-3 intravitreal aflibercept injections.

CONCLUSION: Intravitreal aflibercept should be regarded a safe and effective treatment in patients with recalcitrant macular edema due to radiation maculopathy.

PMID: 28413405 PMCID: PMC5346944

Eur J Ophthalmol. 2017 Apr 20:0. [Epub ahead of print]

Comments to: Visual and anatomic outcomes after conversion to aflibercept in neovascular age-related macular degeneration: 12-month results.

Călugăru D, Călugăru M.

PMID: 28430321

Ophthalmic Surg Lasers Imaging Retina. 2017 Apr 1;48(4):280.

Letter to the Editor: Short-Term Outcomes of Aflibercept Therapy for Diabetic Macular Edema in Patients With Incomplete Response to Ranibizumab and/or Bevacizumab.

Călugăru D, Călugăru M.

PMID: 28419391

Other treatment & diagnosis

Eye (Lond). 2017 Apr 21. [Epub ahead of print]

Supervised learning and dimension reduction techniques for quantification of retinal fluid in optical coherence tomography images.

Breger A, Ehler M, Bogunovic H, Waldstein SM, Philip AM, Schmidt-Erfurth U, Gerendas BS.

Purpose: The purpose of the present study is to develop fast automated quantification of retinal fluid in optical coherence tomography (OCT) image sets. **Methods:** We developed an image analysis pipeline tailored towards OCT images that consists of five steps for binary retinal fluid segmentation. The method is based on feature extraction, pre-segmentation, dimension reduction procedures, and supervised learning tools. **Results:** Fluid identification using our pipeline was tested on two separate patient groups: one associated to neovascular age-related macular degeneration, the other showing diabetic macular edema. For training and evaluation purposes, retinal fluid was annotated manually in each cross-section by human expert graders of the Vienna Reading Center. Compared with the manual annotations, our pipeline yields good quantification, visually and in numbers. **Conclusions:** By demonstrating good automated retinal fluid quantification, our pipeline appears useful to expert graders within their current grading processes. Owing to dimension reduction, the actual learning part is fast and requires only few training samples. Hence, it is well-suited for integration into actual manufacturer's devices, further improving segmentation by its use in daily clinical life.

PMID: 28430181

Ophthalmic Res. 2017 Apr 21. [Epub ahead of print]

Choroidal Thickness and Microperimetry Sensitivity in Age-Related Macular Degeneration.

Broadhead GK, Hong T, McCluskey P, Grigg JR, Schlub TE, Chang AA.

PURPOSE: To assess choroidal thickness (CT) and its relationship to retinal sensitivity in mild/moderate age-related macular degeneration (AMD).

METHODS: Seventy-two eyes of 51 participants with mild/moderate AMD and 36 eyes of 18 age-matched normal participants were prospectively recruited to undergo enhanced-depth imaging optical coherence tomography (EDI-OCT) imaging and microperimetry (MP) functional assessment. OCT-measured CT and retinal thickness (RT) were matched with MP sensitivity at 13 retinal loci, and correlations were analysed.

RESULTS: Patients with AMD had an average RT 56.5 μm greater than those without AMD ($p < 0.001$). There was no significant difference in CT between normal and AMD participants ($p = 0.36$). In patients without atrophy or pigment epithelial detachment, there was no correlation between MP sensitivity and CT ($p = 0.08$); however, a correlation between RT and MP was detected ($b = 0.006$, $p = 0.046$). Among patients without AMD, MP sensitivity was positively correlated with RT ($b = 0.007$, $p < 0.001$) and negatively correlated with CT ($b = 0.0046$, $p = 0.035$).

CONCLUSIONS: CT does not correlate with retinal sensitivity in AMD. Although choroidal damage and

impaired choroidal perfusion appear to be important concepts in AMD pathogenesis, increasing choroidal thinning may not be associated with worsening retinal function in AMD.

PMID: 28427081

Biomed Res Int. 2017;2017:7148245. Epub 2017 Mar 23.

Fully Automated Robust System to Detect Retinal Edema, Central Serous Chorioretinopathy, and Age Related Macular Degeneration from Optical Coherence Tomography Images.

Khalid S, Akram MU, Hassan T, Nasim A, Jameel A.

Abstract: Maculopathy is the excessive damage to macula that leads to blindness. It mostly occurs due to retinal edema (RE), central serous chorioretinopathy (CSCR), or age related macular degeneration (ARMD). Optical coherence tomography (OCT) imaging is the latest eye testing technique that can detect these syndromes in early stages. Many researchers have used OCT images to detect retinal abnormalities. However, to the best of our knowledge, no research that presents a fully automated system to detect all of these macular syndromes is reported. This paper presents the world's first ever decision support system to automatically detect RE, CSCR, and ARMD retinal pathologies and healthy retina from OCT images. The automated disease diagnosis in our proposed system is based on multilayered support vector machines (SVM) classifier trained on 40 labeled OCT scans (10 healthy, 10 RE, 10 CSCR, and 10 ARMD). After training, SVM forms an accurate decision about the type of retinal pathology using 9 extracted features. We have tested our proposed system on 2819 OCT scans (1437 healthy, 640 RE, and 742 CSCR) of 502 patients from two different datasets and our proposed system correctly diagnosed 2817/2819 subjects with the accuracy, sensitivity, and specificity ratings of 99.92%, 100%, and 99.86%, respectively.

PMID: 28424788 PMCID: PMC5382397

Ophthalmic Surg Lasers Imaging Retina. 2017 Apr 1;48(4):319-325.

Influence of Retinal Pathology on the Reliability of Macular Thickness Measurement: A Comparison Between Optical Coherence Tomography Devices.

Bahrami B, Ewe SYP, Hong T, Zhu M, Ong G, Luo K, Chang A.

BACKGROUND AND OBJECTIVE: To evaluate the repeatability, reliability, and comparability of macular thickness measurements between three optical coherence tomography (OCT) machines in healthy eyes, eyes with diabetic macular edema (DME), and eyes with neovascular age-related macular degeneration (nAMD).

PATIENTS AND METHODS: Twenty-three eyes with DME, 26 eyes with nAMD, and 24 healthy eyes as controls were evaluated. Scans were performed using the swept-source Triton (Topcon, Tokyo, Japan), the spectral-domain Cirrus (Carl Zeiss Meditec, Dublin, CA), and the Spectralis (Heidelberg Engineering, Heidelberg, Germany) machines. Scans were evaluated for central macular thickness (CMT), presence of segmentation and fixation imaging artifacts (IA), re-scan reliability, and agreement between machines and groups.

RESULTS: Mean CMT was significantly different between all OCT machines in all groups ($P < .01$ for all comparisons). Manually correcting IA did not alter these results. There was good scan repeatability among healthy and DME eyes for each machine, but poor repeatability among the nAMD group with the Spectralis ($P = .038$). IA were significantly increased in the presence of pathology.

CONCLUSIONS: There is poor agreement of CMT measurement between OCT machines in healthy eyes and those with DME and nAMD. DME and nAMD have a significant effect on the rate of IA in scans. Care is required when interpreting measurements from different OCT devices in clinical practice and research settings.

PMID: 28419397

Ophthalmic Surg Lasers Imaging Retina. 2017 Apr 1;48(4):312-318.

Correlation Between Mesopic Retinal Sensitivity and Optical Coherence Tomographic Metrics of the Outer Retina in Patients With Non-Atrophic Dry Age-Related Macular Degeneration.

Tepelus TC, Hariri AH, Al-Sheikh M, Sadda SR.

BACKGROUND AND OBJECTIVE: To determine the correlation between mesopic retinal sensitivity and optical coherence tomographic metrics of the outer retina in patients with intermediate age-related macular degeneration (AMD).

PATIENTS AND METHODS: Participants with nonatrophic dry AMD underwent mesopic MP-3 microperimetry (Nidek, Padova, Italy) and both Nidek and Cirrus (Carl Zeiss Meditec, Dublin, CA) spectral-domain optical coherence tomography (SD-OCT). The volume of the outer retinal layers was measured on the Nidek SD-OCT scans using the automatic segmentation algorithm of Navis-EX software. In addition, drusen area and volume within a 5-mm circle centered on the fovea were determined using the Cirrus Advanced RPE Analysis Tool. The mean retinal sensitivity at 8° and 10° of fixation (5-mm and 6-mm circles) was calculated for every eye. The correlation between retinal sensitivity and patient age, outer retinal layer volume, drusen area, and drusen volume was assessed.

RESULTS: Thirty-seven eyes from 25 patients with non-atrophic dry AMD were included in the study. The mean age of the patients was 76 years $\pm$ 9 years. The mean sensitivity across the whole tested retinal area was 24.9 dB $\pm$ 2.4 dB, with a sensitivity of 25.1 dB $\pm$ 2.4 dB within the central 5-mm circle. Drusen area within the central 5-mm circle was 0.7 mm² $\pm$ 0.89 mm² with a drusen volume of 0.03 mm³ $\pm$ 0.04 mm³. Retinal pigment epithelium and photoreceptor outer segment (RPE + OS) volume was 1.96 mm³ $\pm$ 0.1 mm³, and outer nuclear layer (ONL) volume was 1.91 mm³ $\pm$ 0.17 mm³. There was a significant correlation between RPE + OS volume and retinal sensitivity, as well as between patients' age and retinal sensitivity. There was no significant correlation between drusen area or volume and retinal sensitivity, nor between ONL volume and retinal sensitivity.

CONCLUSION: In eyes with nonatrophic AMD, retinal sensitivity is correlated with the RPE + OS volume, but not the ONL volume or the area or volume of drusen. [

PMID: 28419396

Invest Ophthalmol Vis Sci. 2017 Apr 1;58(4):2198-2206.

Prevalence, Natural Course, and Prognostic Role of Refractile Drusen in Age-Related Macular Degeneration.

Oishi A, Thiele S, Nadal J, Oishi M, Fleckenstein M, Schmid M, Holz FG, Schmitz-Valckenberg S.

PURPOSE: To report prevalence, clinical characteristics, and prognostic significance of refractile drusen in eyes with intermediate age-related macular degeneration (AMD).

METHODS: Presence of refractile drusen by color fundus photography (CFP), corresponding findings by multimodal imaging, and longitudinal changes with annual examinations for up to 4 years were analyzed within a prospective natural history study of 98 eyes with non-late AMD of 98 patients (Age-Related Eye Disease Study [AREDS] stages 3 and 4).

RESULTS: A total of 115 refractile drusen were detected at baseline in 20 eyes (20.4%). Refractile drusen typically showed hyperreflectivity by infrared (80.9%) and blue (93.9%) reflectance imaging, appearing more distinct when compared to CFP. Lamellar intense hyperreflectivity of Bruch's membrane was detected in 31 lesions by spectral-domain optical coherence tomography and was strongly related to atrophy development (23 out of 31 lesions). Presence of refractile drusen at baseline was overall associated with later development of geographic atrophy (GA) (9/20 eyes versus 6/78 eyes, $P < 0.001$). Spontaneous regression without evident atrophy occurred in seven lesions.

CONCLUSIONS: Refractile drusen are a relative common phenotype in intermediate AMD and appear to confer risk for the development of late AMD. While not all lesions develop late AMD and regression may also occur, distinct subphenotypes as identified by multimodal imaging may not only be visible earlier but also be topographically associated with the risk for GA development. Recognizing the characteristic pattern on multimodal imaging would inform physicians for identification of the lesion and its clinical history.

PMID: 28418494

Graefes Arch Clin Exp Ophthalmol. 2017 Apr 15. [Epub ahead of print]

Massive subretinal and subretinal pigment epithelial hemorrhage displacement with perfluorocarbon liquid using a two-step vitrectomy technique.

Fleissig E, Barak A, Goldstein M, Loewenstein A, Schwartz S.

PURPOSE: The purpose of this study was to evaluate the efficacy and visual outcome of massive submacular hemorrhage (SMH) displacement with a planned two-step pars plana vitrectomy (PPV) using tissue plasminogen activator (tPA) and perfluorocarbon liquid (PFCL) tamponade.

METHODS: A retrospective case series of patients with age related macular degeneration and SMH was used. All patients underwent a 23G PPV, subretinal tPA injection and a medium term PFCL tamponade. A second stage PPV for PFCL removal was performed 7-17 days later. The main outcome was the change in macular and sub-RPE thickness after 6 months. Secondary outcomes were visual acuity and complications.

RESULTS: Seven patients (seven eyes) with mean age of 79.85 years were enrolled. The average SMH size was 17.5 disc area (range 4.5-33) with mean symptoms of a duration of 9.5 days (range: 2-21). SMH was successfully displaced in six eyes. Mean macular and sub-RPE thickness decreased from 1505 μ to 711.3 μ and 900 μ to 457 μ , respectively. Visual acuity (VA) remained stable in five eyes. Complications included corneal edema and transient intraocular pressure elevation in three patients.

CONCLUSIONS: SMH displacement using subretinal tPA injection and medium term PFCL tamponade is an effective alternative treatment option. In our experience, it can be safely performed, avoiding complications commonly attributed to other techniques.

PMID: 28412773

Pathogenesis

Curr Mol Med. 2017 Mar 31. [Epub ahead of print]

What can pharmacological models of retinal degeneration tell us?

Reisenhofer MH, Balmer J, Enzmann V.

Abstract: Animal models with pharmacologically induced retinal degeneration including sodium iodate (NaIO₃) and N-methyl-N-nitrosourea (MNU) have been extensively used in ophthalmic research to investigate retinal degeneration. NaIO₃ induces degeneration of the retinal pigment epithelium (RPE) followed by photoreceptor (PRC) cell death, mimicking features of age-related macular degeneration. In contrast, MNU leads to rapid destruction of the PRCs only, enabling the use of the MNU model to investigate degeneration induced in retinitis pigmentosa. It has been shown that multiple cell death pathways are involved in the cell-specific effects of the toxins. Necrosis has been identified as the cause of the NaIO₃-induced RPE loss. PRC degeneration in the described models is mainly induced by programmed cell death, indicated by the upregulation of conventional apoptosis initiator and effector caspases. However, recent research points to the additional involvement of caspase-independent processes as endoplasmic reticulum stress and calpain activation. Since there is still a substantial amount of contradictory hypotheses concerning triggers of cell death, the use of pharmacological models is

controversial. Thereby, the advantages of such models like the application reaching across species and strains as well as modulation of onset and severity of damage are not exploited to a full extent. Thus, the present review aims to give more insight into the involved cell death pathways and discusses recent findings in the most widely used retinal degeneration models. It might facilitate further studies aiming to develop putative therapeutic approaches for retinal degenerative diseases including combinatory treatment with cell death inhibitors and cell transplantation therapy.

PMID: 28429669

Front Pharmacol. 2017 Mar 30;8:168. eCollection 2017.

Retinal and Circulating miRNAs in Age-Related Macular Degeneration: An In vivo Animal and Human Study.

Romano GL, Platania CBM, Drago F, Salomone S, Ragusa M, Barbagallo C, Di Pietro C, Purrello M, Reibaldi M, Avitabile T, Longo A, Bucolo C.

Abstract: Age related macular degeneration (AMD) is the leading cause of blindness among people aged 50 and over. Retinal deposition of amyloid- β (A β) aggregates in AMD patients has suggested a potential link between AMD and Alzheimer's disease (AD). We have evaluated the differential retinal expression profile of miRNAs in a rat model of AMD elicited by A β . A serum profile of miRNAs in AMD patients has been also assessed using single TaqMan assay. Analysis of retina from rats intravitreally injected with A β revealed that miR-27a, miR-146a, and miR-155 were up-regulated in comparison to control rats. Seven miRNA (miR-9, miR-23a, miR-27a, miR-34a, miR-126, miR-146a, and miR-155) have been found to be dysregulated in serum of AMD patients in comparison to control group. Analysis of pathways has revealed that dysregulated miRNAs, both in the AMD animal model and in AMD patients, can target genes regulating pathways linked to neurodegeneration and inflammation, reinforcing the hypothesis that AMD is a protein misfolding disease similar to AD. In fact, miR-9, miR-23a, miR-27a, miR-34a, miR-146a, miR-155 have been found to be dysregulated both in AMD and AD. In conclusion, we suggest that miR-9, miR-23a, miR-27a, miR-34a, miR-146a, miR-155 represent potential biomarkers and new pharmacological targets for AMD.

PMID: 28424619 PMCID: PMC5371655

Oncotarget. 2017 Mar 10. [Epub ahead of print]

Wogonin induces retinal neuron-like differentiation of bone marrow stem cells by inhibiting Notch-1 signaling.

Shu Q, Zhuang H, Fan J, Wang X, Xu G.

Abstract: Age-related macular degeneration and retinitis pigmentosa are major causes of irreversible vision loss in the elderly and, despite sustained efforts, current treatments are largely ineffective. Wogonin is a bioactive plant flavonoid possessing a range of beneficial properties, including neuroprotective effects. We investigated the ability of wogonin to promote retinal neuron-like differentiation of bone marrow stem cells (BMSCs) and assessed the involvement of Notch-1 signaling in this process. Cultured mouse BMSCs were left untreated or exposed to neurotrophic factors in the presence or absence of wogonin, and western blotting, RT-PCR and immunofluorescence were used to identify changes in molecular markers of stemness and neuroretinal differentiation. Proteins in the Notch-1 signaling pathway, a main negative regulator of neurogenesis, were also examined by western blotting. We found that expression of stem cell markers was reduced, while markers of mature retinal neurons, bipolar cells and photoreceptors were increased in wogonin-treated BMSCs. Wogonin also dose-dependently decreased expression of Notch-1 signaling proteins. Moreover, blockade of Notch-1 both mimicked and enhanced the effect of wogonin to facilitate BMSC differentiation into retinal neuron-like cells. Wogonin thus appears to promote retinal neuron-like differentiation of BMSCs by antagonizing the inhibitory actions of Notch-1 signaling on neurogenesis

and may be useful in the treatment of retinal degenerative diseases.

PMID: 28415701

Epidemiology

Ophthalmic Epidemiol. 2017 Apr 19:1-7. [Epub ahead of print]

Rapid Assessment of Avoidable Blindness and Diabetic Retinopathy in Gilan Province, Iran.

Katibeh M, Behboudi H, Moradian S, Alizadeh Y, Beiranvand R, Sabbaghi H, Ahmadi H.

PURPOSE: To conduct an assessment of avoidable blindness and diabetic retinopathy (DR) in Gilan, 2014.

METHODS: A cross-sectional population-based survey was performed on a representative sample of urban and rural individuals aged ≥ 50 years of the province. Blindness was defined as presenting visual acuity (PVA) $< 3/60$ in the better eye. Moderate visual impairment (MVI) and severe visual impairment (SVI) were defined as $6/60 \leq PVA < 6/18$ and $3/60 \leq PVA < 6/60$ in the better eye, respectively. Diabetes mellitus (DM) was determined based on random blood sugar (RBS) levels ≥ 200 mg/dL or a previous diagnosis. We used the Scottish grading system to grade DR.

RESULTS: We invited 2975 individuals from 85 clusters. Age- and sex-adjusted prevalence and 95% confidence interval (CI) of blindness, SVI, MVI, and DM in 2587 participants (response rate: 86.9%) were 1.5% (95% CI: 1.1-2.0), 1.5% (95% CI: 0.9-2.0), 11.3% (95% CI: 9.9-12.7) and 21.4% (95% CI: 19.2-23.7), respectively. The leading causes of blindness were cataract (47.1%), age-related macular degeneration (14.7%) and DR (8.8%). Cataract surgery (CS) coverage was 69.3%. The main challenges for CS were cost and unawareness. The outcome of CS was good in 66.9% of operated eyes. Any DR and/or maculopathy were observed in 25.3% (95% CI: 21.0-29.5) of subjects including 12.6% (95% CI: 9.7-15.6) sight-threatening DR. In previously known DM cases, 215 (41.7%) had never undergone an eye examination for DR.

CONCLUSION: The proportion of avoidable blindness and DR is considerable in Gilan Province.

PMID: 28422552

Stem cells

Am J Ophthalmol. 2017 Apr 17. [Epub ahead of print]

Stem cells for retinal disease: a perspective on the promise and perils.

Rao RC, Dedania VS, Johnson MW.

PURPOSE: To summarize key concepts, and early safety and efficacy signals from clinical trials for stem/progenitor cell-based interventions for retinal disease.

DESIGN: Interpretive essay.

METHODS: Review and synthesis of selected recent reports of stem/progenitor cell-based approaches for retinal disease, with interpretation and perspective.

RESULTS: Stem/progenitor cell-based interventions represent a novel class of potential therapies for retinal diseases, such as age-related macular degeneration, inherited retinal dystrophies, and others. Sources include pluripotent stem cells, fetal and postnatal tissues. Two mechanisms of "rescue" have been proposed: regenerative or trophic. While pluripotent and fetal sourced-cell types have been tested in preclinical animal models of retinal disease, many postnatal stem/progenitor cell populations currently in trial do not have preclinical safety or efficacy data. Some early phase trials of cell therapies suggest

acceptable safety profiles. Other reports, involving some types of autologous, non-ocular cell sources, have been linked to severe, blinding complications. Larger trials will be needed to determine short and long-term safety and efficacy of these cell-based interventions.

CONCLUSIONS: Stem/progenitor cell-based interventions have the potential to address blinding retinal diseases that affect hundreds of millions worldwide. Yet no FDA-approved stem cell therapies for retinal disease exist. While some early phase trial data are promising, reports of blinding complications from cell interventions remain troubling. It is paramount to apply a strong level of scientific rigor toward a well-planned, step-wise sequence of preclinical and clinical studies, to determine whether this class of potential therapies will be safe and effective for individuals with retinal diseases.

PMID: 28428049

Diet, lifestyle & low vision

Molecules. 2017 Apr 20;22(4).

The Pharmacological Effects of Lutein and Zeaxanthin on Visual Disorders and Cognition Diseases.

Jia YP, Sun L, Yu HS, Liang LP, Li W, Ding H, Song XB, Zhang LJ.

Abstract: Lutein (L) and zeaxanthin (Z) are dietary carotenoids derived from dark green leafy vegetables, orange and yellow fruits that form the macular pigment of the human eyes. It was hypothesized that they protect against visual disorders and cognition diseases, such as age-related macular degeneration (AMD), age-related cataract (ARC), cognition diseases, ischemic/hypoxia induced retinopathy, light damage of the retina, retinitis pigmentosa, retinal detachment, uveitis and diabetic retinopathy. The mechanism by which they are involved in the prevention of eye diseases may be due their physical blue light filtration properties and local antioxidant activity. In addition to their protective roles against light-induced oxidative damage, there are increasing evidences that L and Z may also improve normal ocular function by enhancing contrast sensitivity and by reducing glare disability. Surveys about L and Z supplementation have indicated that moderate intakes of L and Z are associated with decreased AMD risk and less visual impairment. Furthermore, this review discusses the appropriate consumption quantities, the consumption safety of L, side effects and future research directions.

PMID: 28425969

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.