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Drug treatment

Ophthalmology. 2016 Jun 28. [Epub ahead of print]

Visual Acuity of Eyes with Early Persistent Retinal Fluid from Neovascular Age-Related Macular Degeneration in the VIEW Studies.

Jaffe GJ, Kaiser PK, Thompson D, Gibson A, Saroj N, Vitti R, Berliner AJ, Heier JS.

PURPOSE: To compare the effect of intravitreal aflibercept or ranibizumab drug type and frequency on visual acuity outcomes in eyes with neovascular age-related macular degeneration (NVAMD) and early persistent retinal fluid after 3 initial monthly injections.

DESIGN: A post hoc analysis of eyes enrolled in VIEW 1 and VIEW 2, 2 similarly designed, randomized, phase 3 trials.

PARTICIPANTS: A total of 1815 eyes with NVAMD from VIEW 1 and VIEW 2.

METHODS: Analyses included patients with known fluid status at baseline and weeks 4, 8, and 12 in 3 treatment groups: ranibizumab 0.5 mg every 4 weeks (Rq4) (n = 595), intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4) (n = 613), and IAI 2 mg every 8 weeks (2q8) after 3 monthly injections (n = 607).

MAIN OUTCOME MEASURES: Mean best-corrected visual acuity (BCVA) change from baseline over weeks 16 to 52 and the proportion of eyes that gained ≥ 15 letters or lost ≥ 5 letters were evaluated in eyes with and without persistent fluid (cystic intraretinal or subretinal fluid at all 4 initial visits). Visual outcomes also were assessed in eyes with persistent fluid by fluid type (intraretinal and subretinal fluid).

RESULTS: The proportions of eyes with persistent fluid were 29.4%, 18.8%, and 20.3% in the Rq4, 2q4, and 2q8 groups, respectively. In these eyes, mean BCVA gain from baseline to week 52 was greater with 2q4 compared with Rq4 ($P < 0.01$) and 2q8 ($P < 0.05$), whereas it was similar with Rq4 and 2q8 ($P = 0.294$). At week 52, similar proportions of eyes gained ≥ 15 letters (31.5%-35.2%), whereas fewer eyes lost ≥ 5 letters with 2q4 compared with Rq4 and 2q8 (6.5% vs. 16.6% and 16.2%). The pattern of visual outcomes was similar regardless of fluid type. In eyes without persistent fluid, BCVA changes were similar across treatment groups.

CONCLUSIONS: In patients with early persistent fluid, 2q4 may provide additional clinical benefit over 2q8 or Rq4.

PMID: 27369111

Clin Ophthalmol. 2016 Jun 15;10:1117-22. eCollection 2016.

Macular morphology and response to ranibizumab treatment in patients with wet age-related macular degeneration.

Dervenis N, Younis S.

PURPOSE: The purpose of this study was to assess whether specific characteristics of spectral domain optical coherence tomography (SD-OCT) affect structural and functional outcomes and number of injections needed in ranibizumab (0.05 mL of 10 mg/mL Lucentis solution)-treated wet age-related macular degeneration (AMD) patients.

PATIENTS AND METHODS: This retrospective case series included 62 newly diagnosed wet AMD patients treated with three monthly intravitreal ranibizumab injections followed by monthly follow-up and pro re nata retreatment. The presence of dome-shaped pigment epithelial detachment (PED), disruption of the retinal pigment epithelium (RPE), and subretinal and intraretinal fluid was associated with changes in Early Treatment of Diabetic Retinopathy Study visual acuity, central macular thickness (CMT), and number of injections needed during the 6-month follow-up.

RESULTS: The presence of PED was associated with lower values of CMT at presentation (399 μm [$\pm 132 \mu\text{m}$] vs 310 μm [$\pm 51 \mu\text{m}$], $P=0.005$). The presence of RPE disruption was associated with worse visual acuity in month 6 (0.36 [± 0.22] vs 0.61 [± 0.45], $P=0.027$) and fewer injections (4.23 [± 0.92] vs 3.55 [± 0.60], $P=0.007$). The presence of intraretinal fluid at presentation was associated with worse visual acuity outcomes in month 4 ($P=0.045$) but not in month 6.

CONCLUSION: The dome-shaped PED was associated with lower CMT at presentation, but it did not affect response to treatment. RPE disruption was associated with worse functional outcomes with fewer injections. Intraretinal fluid at presentation may suggest delayed response to treatment. Individualized SD-OCT analysis could lead to individualized approach to wet AMD patients. SD-OCT can offer imaging biomarkers to assess the prognosis of anti-VEGF treatment in AMD patients.

PMID: 27366051 PMCID: PMC4914034

Clin Ophthalmol. 2016 Jun 14;10:1103-10. eCollection 2016.

Baseline visual acuity strongly predicts visual acuity gain in patients with diabetic macular edema following anti-vascular endothelial growth factor treatment across trials.

Dugel PU, Hillenkamp J, Sivaprasad S, Vögeler J, Mousseau MC, Wenzel A, Margaron P, Hashmonay R, Massin P.

OBJECTIVE: This study was designed to evaluate the correlation of baseline visual acuity (VA) with VA outcome in response to anti-vascular endothelial growth factor (VEGF) in diabetic macular edema using a retrospective analysis of nine clinical trials. The result will help assess the relevance of VA gain comparisons across trials.

METHODS: A correlation analysis was performed between mean baseline VA and VA gain at month 12 for 1,616 diabetic macular edema patients across nine randomized clinical trials (RESOLVE, RISE, RIDE, RESTORE, RETAIN, DRCR.net Protocol I, DA VINCI, VIVID, VISTA) with anti-VEGF treatment regimens ranibizumab 0.5 mg and aflibercept 2 mg.

RESULTS: The mean baseline VA ranged from 56.9 to 64.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The mean VA gain at month 12 ranged from 6.8 to 13.1 ETDRS letters across trials. There was a strong inverse correlation between mean baseline VA and VA gain at month 12 ($r=-0.85$). The mean VA at 12 months plateaued at ~ 70 (68.5-73.0) ETDRS letters (20/40 Snellen VA equivalent) for the anti-VEGF treatment groups from all trials, regardless of dosing regimens and agents.

CONCLUSION: Cross-trial comparisons based on changes in best-corrected visual acuity should be done cautiously and only after adjusting for best-corrected visual acuity at baseline. Furthermore, the total VA afforded by treatment appears to be subject to a plateau effect, which warrants further exploration.

PMID: 27366049 PMCID: PMC4913960

Drugs. 2016 Jun 30. [Epub ahead of print]

Management of Myopic Choroidal Neovascularization: Focus on Anti-VEGF Therapy.

Teo KY, Ng WY, Lee SY, Cheung CM.

Abstract: Myopic choroidal neovascularization (mCNV) is the second most common form of CNV after age-related macular degeneration (AMD). It is a sight-threatening complication of pathologic myopia (PM) and often affects patients in their working years causing significant impact on quality of life. Previous therapies such as photodynamic therapy with verteporfin have shown limited success. Due to the similarities in pathogenesis of mCNV and AMD CNV, anti-vascular endothelial growth factor therapy (anti-VEGF), which has so far been the mainstay of treatment for AMD CNV, has been shown to be effective in the treatment of mCNV and has become the first-line treatment of choice. This article aims to examine briefly the epidemiology and pathophysiology of mCNV, as well as review the evidence for efficacy, safety, and clinical use of anti-VEGF treatment for mCNV.

PMID: 27364753

Ophthalmologie. 2016 Jun 30. [Epub ahead of print]

[Atrophy of the macula in the context of its wet, age-related degeneration : An inescapable consequence of anti-VEGF therapy?] [Article in German]

Garweg JG.

BACKGROUND: Current understanding of the mechanisms that underlie the long-term consequences of anti-VEGF therapy in wet, age-related macular degeneration (AMD) is poor. Here, the impact of this treatment on the development of macular atrophy (MA) is discussed based on our current pathophysiological understanding.

METHODS: This review is based on a PubMed literature survey using the MeSH terms "wet AMD" and "macular atrophy" (151 hits) and limited to publications since 2013 (n = 90). Publications focussing on diagnostics and clinical course not in the context of therapy were excluded. Macular atrophy is defined herein as atrophy affecting the functionally relevant complex of photoreceptors, retinal pigmented epithelium (RPE), Bruch's membrane and choriocapillaris.

RESULTS: Experimentally, a primary complete suppression of local VEGF leads to evident changes in the choriocapillaris, whereas its incomplete suppression exacerbates cell death of RPE and photoreceptors. Since pre-existing atrophic changes are already present at diagnosis, the role of anti-VEGF treatment cannot be separated from the spontaneous progression of AMD. The progression of MA appears to be faster under ranibizumab than bevacizumab, and likewise on a monthly rather than as-needed basis. Although MA progresses more rapidly under consequent therapy, visual function remains better. Hence, a functionally relevant progression of atrophy during the first five years of treatment would only be expected in pre-existing advanced MA.

CONCLUSIONS: Despite doubts regarding the long-term safety of anti-VEGF therapy, it is the author's view that this is the only option to stabilise visual function. The impact of therapy-induced damage on the spontaneous progression of AMD and the biological status of the aging individual cannot be unequivocally assessed.

PMID: 27364637

Ophthalmologica. 2016 Jul 1. [Epub ahead of print]

Comparison of the Effectiveness of Intravitreal Ranibizumab for Diabetic Macular Edema in Vitrectomized and Nonvitrectomized Eyes.

Koyanagi Y, Yoshida S, Kobayashi Y, Kubo Y, Yamaguchi M, Nakama T, Nakao S, Ikeda Y, Ohshima Y,

Ishibashi T, Sonoda KH.

PURPOSE: To compare the effectiveness of intravitreal ranibizumab (IVR) for diabetic macular edema (DME) between eyes with and without previous vitrectomy.

PROCEDURES: We prospectively assessed the best-corrected visual acuity (BCVA) and central macular thickness (CMT) after IVR for 6 months.

RESULTS: There were no significant differences in the baseline BCVA and CMT between both groups. In the nonvitrectomized group ($n = 15$), the mean changes of BCVA and CMT from baseline to month 6 were significant ($p < 0.01$). In the vitrectomized group ($n = 10$), the improvement appeared to be slower, and the mean BCVA improvement was not significant ($p = 0.5$), although the mean CMT decrease was significant ($p < 0.05$). There were no significant differences in the mean changes of BCVA and CMT between both groups at 6 months.

CONCLUSIONS: The difference in the effectiveness of IVR between both groups was not significant. IVR can be a treatment option even for vitrectomized DME eyes.

PMID: 27362944

Ophthalmologica. 2016 Jul 1. [Epub ahead of print]

Genetic Risk Evaluation in Wet Age-Related Macular Degeneration Treatment Response.

Chaudhary V, Brent M, Lam WC, Devenyi R, Teichman J, Mak M, Barbosa J, Kaur H, Carter R, Farrokhyar F.

OBJECTIVE: To evaluate the pharmacogenetic relationship between CFH haplotypes and single nucleotide polymorphisms (SNPs) with response to ranibizumab treatment for neovascular age-related macular degeneration (nAMD).

PATIENTS AND METHODS: This was a prospective cohort study involving 70 treatment-naïve nAMD patients. Patients were genotyped for CFH haplotypes and SNPs in the C3, ARMS2, and mtDNA genes. Visual acuity and central macular thickness were assessed at baseline and during 6 monthly follow-up visits. Multivariate logistic regression was used to determine the association between genotypes and a gain of ≥ 15 letters at the 6-month endpoint after adjusting for potential confounders.

RESULTS: CFH haplotypes were associated with a gain of ≥ 15 letters at the 6-month endpoint ($p = 0.046$). Patients expressing protective haplotypes were more likely to achieve a gain of ≥ 15 letters relative to the greatly increased risk haplotypes [OR 6.58 (95% CI: 1.37, 31.59)].

CONCLUSION: CFH is implicated in nAMD patient treatment response to ranibizumab.

PMID: 27362858

Proc (Bayl Univ Med Cent). 2016 Jul;29(3):335-6.

Bevacizumab-induced pityriasis rubra pilaris-like eruption.

Brown S, Fletcher JW, Fiala KH.

Abstract: Pityriasis rubra pilaris is a rare inflammatory disorder characterized by follicular papules on an erythematous base often exhibiting islands of unaffected skin, follicular plugging, and palmoplantar hyperkeratosis. While vitamin A deficiency and autoimmune reactions have been hypothesized as possible etiologies of this condition, pityriasis rubra pilaris-like eruptions secondary to medications are extremely rare. To our knowledge, only three other cases have been reported, and pityriasis rubra pilaris has never been reported in association with bevacizumab. We present a 70-year-old man who developed erythroderma both clinically and histologically consistent with pityriasis rubra pilaris 10 days after intravitreal

injection of bevacizumab for age-related macular degeneration. As immune-modulating drugs grow in their application for a host of diseases, recognition of associated medication complications is important.

PMID: 27365893 PMCID: PMC4900791

Ophthalmic Surg Lasers Imaging Retina. 2016 Jun;47(6 Suppl):S4-S14.

The Role of Anti-VEGF Therapy in the Treatment of Diabetic Macular Edema.

Moshfeghi DM, Kaiser PK, Michels S, Midena E, Kitchens JW, Prenner JL, Regillo CD, Reichel E.

Abstract: Diabetic retinopathy (DR) is the leading cause of blindness among working-age adults. DR often leads to diabetic macular edema (DME), which often goes unnoticed until a patient presents with vision loss. However, treatment options and data for DME are continually improving. We know that vascular endothelial growth factor (VEGF) plays a key role in DME progression; therapies that act by inhibiting VEGF production seem to improve visual acuity in patients with DME. Of the anti-VEGF therapies available, two have been approved by the U.S. Food and Drug Administration to treat DME: ranibizumab (Lucentis; Genentech, South San Francisco, CA) and aflibercept (Eylea; Regeneron, Tarrytown, NY). Bevacizumab (Avastin; Genentech, South San Francisco, CA), which is approved for the treatment of certain types of cancer, is occasionally used off-label to treat DME. Anti-VEGF therapy can stop vision loss and even improve visual acuity. Other treatments remain effective, and these various treatment options fuel a need for new data and discussion. This roundtable discussion, which took place during the 2015 annual meeting of the American Academy of Ophthalmology, outlines the current protocols used to treat DME and provides clinical opinions about selecting and treating with an appropriate anti-VEGF therapy.

PMID: 27348433

Int J Ophthalmol. 2016 Jun 18;9(6):858-62. eCollection 2016.

Peripheral retinal non-perfusion and treatment response in branch retinal vein occlusion.

Abri Aghdam K, Reznicek L, Soltan Sanjari M, Framme C, Bajor A, Klingenstein A, Kernt M, Seidensticker F.

AIM: To evaluate the association between the size of peripheral retinal non-perfusion and the number of intravitreal ranibizumab injections in patients with treatment-naïve branch retinal vein occlusion (BRVO) and macular edema.

METHODS: A total of 53 patients with treatment-naïve BRVO and macular edema were included. Each patient underwent a full ophthalmologic examination including optical coherence tomography (OCT) imaging and ultra wide-field fluorescein angiography (UWFA). Monthly intravitreal ranibizumab injections were applied according to the recommendations of the German Ophthalmological Society. Two independent, masked graders quantified the areas of peripheral retinal non-perfusion.

RESULTS: Intravitreal injections improved best-corrected visual acuity (BCVA) significantly from 22.23 ± 16.33 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters to 36.23 ± 15.19 letters ($P < 0.001$), and mean central subfield thickness significantly reduced from $387 \pm 115 \mu\text{m}$ to $321 \pm 115 \mu\text{m}$ ($P = 0.01$). Mean number of intravitreal ranibizumab injections was 3.61 ± 1.56 . The size of retinal non-perfusion correlated significantly with the number of intravitreal ranibizumab injections ($R = 0.724$, $P < 0.001$).

CONCLUSION: Peripheral retinal non-perfusion in patients with BRVO associates significantly with intravitreal ranibizumab injections in patients with BRVO and macular edema.

PMID: 27366688 PMCID: PMC4916143

Ophthalmologica. 2016 Jun 28. [Epub ahead of print]

Aflibercept as First-Line Therapy in Patients with Treatment-Naïve Neovascular Age-Related Macular Degeneration: Prospective Case Series Analysis in Real-Life Clinical Practice.

Udaondo P, Salom D, García-Delpech S, Cisneros-Lanuza Á.

PURPOSE: To assess the 13-month effectiveness and safety of aflibercept in naïve patients with neovascular age-related macular degeneration (nvAMD) in a real-life clinical setting.

METHODS: Thirty-two treatment-naïve patients with nvAMD participated in a prospective two-center study. Patients received intravitreal injections of aflibercept (Eylea®), a loading dose of three monthly injections (2 mg/0.05 ml) every 4 weeks for the first 3 months, followed by intravitreal injections every 2 months.

RESULTS: At 3 and 13 months, the mean best-corrected visual acuity improved significantly as compared with baseline (logMAR 0.53 ± 0.30 and 0.55 ± 0.32 vs. 0.30 ± 0.24 , respectively, $p < 0.001$). At 3 and 13 months, 46.8% of patients (15/32) gained ≥ 15 ETDRS letters. The mean decrease in central macular thickness was also significant at 3 months ($252 \pm 35 \mu\text{m}$) and at 13 months ($249 \pm 38 \mu\text{m}$) as compared with pretreatment values ($383 \pm 76 \mu\text{m}$) ($p < 0.01$). Also, 50% resolution of pigment epithelial detachment (PED) was observed in 8 out of 9 eyes (88.9%) with PED at baseline. Intravitreal injections were well tolerated and no adverse events were recorded.

CONCLUSION: Aflibercept was effective and safe for treating nvAMD in naïve patients in routine daily practice.

PMID: 27348231

Clin Ophthalmol. 2016 Jun 8;10:1047-51. eCollection 2016.

Ranibizumab in neovascular age-related macular degeneration: a 5-year follow-up.

Cvetkova NP, Hölldobler K, Prahs P, Radeck V, Helbig H, Märker D.

PURPOSE: Our aim was to evaluate an optical coherence tomography (OCT) and visual acuity (VA)-guided, variable-dosing regimen with intravitreal ranibizumab injection for treating patients with neovascular age-related macular degeneration (AMD) from 2007 to 2012.

DESIGN: This was a retrospective clinical study of 5 years follow-up in a tertiary eye center.

PATIENTS AND METHODS: In this study, 66 patients with neovascular AMD (mean age of 74 years, SD 8.7 years) were included. We investigated the development of best-corrected visual acuity (BCVA), the number of intravitreal injections, and the central retinal thickness measured with OCT (OCT Spectralis) over 5 years of intravitreal treatment.

RESULTS: The mean number of intravitreal ranibizumab injections over 5 years was 8.8. The mean BCVA before therapy was 0.4 logarithm of the minimum angle of resolution (logMAR). After 5 years of therapy, the mean BCVA was 0.6 logMAR. In all, 16% of treated patients had stable VA over 5 years and 10% of study eyes approved their VA. The mean OCT-measured central retinal thickness at the beginning of this study was $295 \mu\text{m}$; after 5 years of treatment, the mean central retinal thickness was $315 \mu\text{m}$. There was an increase in central retinal thickness in 47.5% of examined eyes.

CONCLUSION: Other studies showed VA improvement in OCT-guided variable-dosing regimens. Our study revealed a moderate decrease in VA after a total mean injection number as low as 8.8 injections over 5 years. In OCT, an increase in central retinal thickness over 5 years could be observed. Probably, this is due to deficient treatment when comparing the total injection number to other treatment regimens. Anti-VEGF therapy helps to keep the VA stable for a period of time, but cannot totally stop the progression of the disease completely. Patients with late stages of neovascular AMD can maintain VA even if they are relatively undertreated.

PMID: 27354758 PMCID: PMC4907736

Clin Ophthalmol. 2016 Jun 8;10:1053-7. eCollection 2016.

Worsening anatomic outcomes following aflibercept for neovascular age-related macular degeneration in eyes previously well controlled with ranibizumab.

Nudleman E, Wolfe JD, Woodward MA, Yonekawa Y, Williams GA, Hassan TS.

PURPOSE: Antivascular endothelial growth factor injection is the mainstay of treating neovascular age-related macular degeneration (AMD). Previous studies have shown that switching treatment from ranibizumab to aflibercept led to an improvement in eyes with recalcitrant activity. Herein, we identify a unique subset of patients whose eyes with neovascular AMD were previously well controlled with ranibizumab injections were then worsened after being switched to aflibercept.

METHODS: This is a retrospective interventional case series. Eyes with neovascular AMD, previously well controlled with monthly injections of ranibizumab, which then developed worsening of subretinal fluid after being switched to aflibercept were included.

RESULTS: A total of 17 eyes were included. All eyes developed increased subretinal fluid when switched from ranibizumab to aflibercept. Fourteen patients were switched back to ranibizumab after a single injection of aflibercept and had subsequent rapid resolution of subretinal fluid. Three patients continued with monthly aflibercept injections for two subsequent months and demonstrated the persistence of the increased subretinal fluid until they were switched back to treatment with ranibizumab at which time the fluid resolved. No eye had persistent decline in visual acuity.

CONCLUSION: Switching from intravitreal ranibizumab to aflibercept in eyes with well-controlled neovascular AMD may result in worsening in a subset of patients and resolves when therapy is switched back to ranibizumab.

PMID: 27354759 PMCID: PMC4907716

Patient Prefer Adherence. 2016 Jun 3;10:993-1002. eCollection 2016.

Using qualitative research to facilitate the interpretation of quantitative results from a discrete choice experiment: insights from a survey in elderly ophthalmologic patients.

Vennedey V, Danner M, Evers SM, Fauser S, Stock S, Dirksen CD, Hiligsmann M.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in industrialized countries. Currently, mainly three treatment options are available, which are all intravitreal injections, but differ with regard to the frequency of injections needed, their approval status, and cost. This study aims to estimate patients' preferences for characteristics of treatment options for neovascular AMD.

METHODS: An interviewer-assisted discrete choice experiment was conducted among patients suffering from AMD treated with intravitreal injections. A Bayesian efficient design was used for the development of 12 choice tasks. In each task patients indicated their preference for one out of two treatment scenarios described by the attributes: side effects, approval status, effect on visual function, injection and monitoring frequency. While answering the choice tasks, patients were asked to think aloud and explain the reasons for choosing or rejecting specific characteristics. Quantitative data were analyzed with a mixed multinomial logit model.

RESULTS: Eighty-six patients completed the questionnaire. Patients significantly preferred treatments that improve visual function, are approved, are administered in a pro re nata regimen (as needed), and are accompanied by bimonthly monitoring. Patients significantly disliked less frequent monitoring visits (every 4 months) and explained this was due to fear of deterioration being left unnoticed, and in turn experiencing disease deterioration. Significant preference heterogeneity was found for all levels except for bimonthly monitoring visits and severe, rare eye-related side effects. Patients gave clear explanations of their individual preferences during the interviews.

CONCLUSION: Significant preference trends were discernible for the overall sample, despite the preference heterogeneity for most treatment characteristics. Patients like to be monitored and treated regularly, but not too frequently or infrequently. The results of our qualitative research facilitated the interpretation of the quantitative data collected in this study.

PMID: 27350743 PMCID: PMC4902149

Adv Ophthalmol Vis Syst. 2016;4(3). Epub 2016 Jun 6.

Three-Month Outcome of Ziv-Aflibercept for Diabetic Macular Edema.

Marashi A.

PURPOSE: Is to show the 3-month efficacy and safety of treatment diabetic macular edema treated with intravitreal ziv-aflibercept as studies have shown that Ziv-aflibercept does not cause retinal pigment epithelial toxicity and to study its cost effectiveness.

METHODS: Ten eyes in eight patients diagnosed with central diabetic macular edema were enrolled for three consecutive intravitreal injections of ziv-aflibercept 1.25 mg every 4 weeks, a complete exam including BCVA and CRT at baseline and 12 weeks with evaluation of ocular and systemic complications.

RESULTS: Improvement of best corrected visual acuity was clinically significant from baseline LogMAR 0.77 and 0.35 at 12 weeks and statistically significant ($P < 0.05$) along with reduction of central retinal thickness from 562.4 μm and 317.7 μm at 12 weeks follow up ($P < 0.05$) with no signs of ocular nor systemic complications.

CONCLUSION: Ziv aflibercept is a safe and effective in diabetic macular edema treatment for 12 weeks follow up with cost effectiveness especially in countries where aflibercept is not available.

PMID: 27347566 PMCID: PMC4917211

Acta Ophthalmol. 2016 Jun 27. [Epub ahead of print]

Switching to aflibercept in patients with neovascular age-related macular degeneration not responding to bevacizumab: a pilot study.

van Asten F, Klevering BJ, Hoyng CB.

PMID: 27350361

Clin Interv Aging. 2016 Jun 14;11:775.

Erratum: Effects of intravitreal ranibizumab on the untreated eye and systemic gene expression profile in age-related macular degeneration [Corrigendum].

Abstract: [This corrects the article on p. 357 in vol. 11, PMID: 27069359].

PMID: 27358559 PMCID: PMC4912323

Other treatment & diagnosis

Retina. 2016 Jun 24. [Epub ahead of print]

CHANGES OF OUTER RETINAL THICKNESS WITH INCREASING AGE IN NORMAL EYES AND IN NORMAL FELLOW EYES OF PATIENTS WITH UNILATERAL AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To test the hypothesis that the thickness of outer retinal layers will change with increasing age in normal eyes and in the normal fellow eyes of patients with unilateral age-related macular degeneration.

METHODS: Spectral domain optical coherence tomography images of 127 normal eyes of 127 subjects and 58 normal fellow eyes of 58 patients with unilateral age-related macular degeneration were studied. The thickness between the retinal pigment epithelium line and the cone outer segment tips line, between the cone outer segment tips line and the photoreceptor inner segment/outer segment line, and between the inner segment/outer segment line and the external limiting membrane line were measured at the fovea in both groups.

RESULTS: The thickness between retinal pigment epithelium line and the cone outer segment tips line, and between inner segment/outer segment line and the external limiting membrane line were significantly and negatively associated with age in the normal group. Cone outer segment tips line and the photoreceptor inner segment/outer segment thickness was not significantly associated with age. Retinal pigment epithelium line and the cone outer segment tips line was thinner in the fellow eyes of patients with unilateral age-related macular degeneration than in the age-matched normal eyes. Cone outer segment tips line and the photoreceptor inner segment/outer segment and inner segment/outer segment line and the external limiting membrane line thicknesses in the fellow eyes were not significantly different from that of normal eyes.

CONCLUSION: The tissue between the retinal pigment epithelium line and the cone outer segment tips line may become atrophic in older eyes and in the normal fellow eyes of patients with unilateral age-related macular degeneration.

PMID: 27347643

Am J Ophthalmol. 2016 Jun 24. [Epub ahead of print]

Subretinal hyperreflective material imaged with optical coherence tomography angiography.

Dansingani KK, Tan A, Gilani F, Phasukkijwatana N, Novais E, Querques L, Waheed NK, Duker JS, Querques G, Yannuzzi LA, Sarraf D, Freund KB.

PURPOSE: The range of subretinal hyperreflective material (SHRM) seen in macular disease includes type 2 macular neovascularization, fibrosis, exudation, vitelliform material and hemorrhage. The prognostic significance of SHRM has been evaluated retrospectively in clinical trials but discriminating SHRM subtypes traditionally requires multiple imaging modalities. The purpose of this study is to describe optical coherence tomography angiography (OCTA) flow characteristics and artifacts which might help to distinguish SHRM subtypes.

DESIGN: Validity analysis.

METHODS: Patients with age-related macular degeneration (AMD), myopia, pachychoroid disease and macular dystrophy, manifesting SHRM on optical coherence tomography (OCT), were recruited. Clinical chart review and multimodal imaging established the SHRM subtype. All patients underwent OCTA (RTVue XR, Optovue). OCT and OCTA images were examined together for i) intrinsic flow, ii) retinal projection onto the anterior SHRM surface (strong, weak, absent), iii) retinal projection through SHRM onto retinal pigment epithelium (RPE), iv) masking of choriocapillaris flow.

RESULTS: Thirty-three eyes of 25 patients were included (type 2 neovascularization×3; fibrosis×4; exudation×10; hemorrhage×5; vitelliform×17). Mean age per eye was 76 years (SD: 12). Intrinsic flow was strongest in type 2 neovascularization. Subretinal fibrosis showed limited flow in residual large caliber vessels and branches. Flow was not detected within foci of exudation, hemorrhage or vitelliform lesions. Retina-SHRM surface projection was strongest onto smooth surfaced SHRM and weaker onto exudation. Retinal projection was weakest on the surface of vitelliform lesions. Retina-RPE projection was masked by dense hemorrhage and vitelliform material. In compound SHRM, OCTA distinguished between vascular and avascular components.

CONCLUSION: Optical coherence tomography angiography can distinguish vascular from avascular SHRM components. OCTA artifacts may distinguish certain avascular SHRM components.

PMID: 27349411

Retina. 2015 Dec 22. [Epub ahead of print]

DIAGNOSIS OF TYPE 3 NEOVASCULARIZATION BASED ON OPTICAL COHERENCE TOMOGRAPHY IMAGES.

Kim JH, Chang YS, Kim JW, Lee TG, Kim HS.

PURPOSE: To evaluate the concordance of an optical coherence tomography (OCT)-based diagnosis of Type 3 neovascularization and an indocyanine green angiography (ICGA)-based diagnosis in neovascular age-related macular degeneration (AMD).

METHODS: This observational case series includes 263 eyes from 263 patients who were diagnosed with treatment-naïve neovascular AMD. Patients exhibiting at least three of the following OCT features were diagnosed with Type 3 neovascularization: subfoveal choroidal thickness <200 µm, presence of intraretinal fluid accumulation, absence of subretinal fluid, gently-sloping dome-shaped retinal pigment epithelial detachment or trapezoid-shaped retinal pigment epithelial detachment without an obvious peak, and intraretinal mass lesion. The incidence of cases exhibiting three or more OCT features was compared among different subtypes of neovascular AMD. Additionally, the concordance of OCT-based diagnosis and ICGA-based diagnosis was evaluated.

RESULTS: Three or more OCT features were noted in 8 of 82 (9.8%) eyes with typical neovascular AMD, 4 of 147 (2.7%) eyes with polypoidal choroidal vasculopathy, and 30 of 34 (88.2%) eyes with Type 3 neovascularization, respectively. The incidence was significantly greater in Type 3 neovascularization than in the other subtypes of neovascular AMD ($P < 0.001$). Of patients diagnosed with Type 3 neovascularization using ICGA-based methods, 88.2% were also diagnosed with Type 3 neovascularization using OCT-based methods. Only 5.2% of patients diagnosed with other subtypes of neovascular AMD using ICGA-based methods were diagnosed with Type 3 neovascularization using OCT-based methods.

CONCLUSION: Optical coherence tomography-based diagnosis of Type 3 neovascularization showed relatively high concordance compared with ICGA-based diagnosis. This method may be useful in clinical practice.

PMID: 27359259

Invest Ophthalmol Vis Sci. 2016 Jun 1;57(7):3323-3330.

Frequency, Phenotypic Characteristics and Progression of Atrophy Associated With a Diseased Bruch's Membrane in Pseudoxanthoma Elasticum.

Gliem M, Müller PL, Birtel J, Hendig D, Holz FG, Charbel Issa P.

PURPOSE: To characterize atrophy of the outer retina and the retinal pigment epithelium in patients with pseudoxanthoma elasticum (PXE).

METHODS: In this retrospective cross-sectional study, the frequency and phenotypic characteristics of manifest atrophy were investigated in 276 eyes of 139 patients using color fundus photography, fundus autofluorescence (AF) imaging, and spectral domain optical coherence tomography. Progression rates of atrophy were quantified in eyes with longitudinal AF recordings.

RESULTS: Atrophy was present in 90 eyes (32%; mean age, 60; range, 32-88 years). In 19 eyes (7%; mean age, 56; range, 37-77 years) atrophy occurred without any signs for an active or fibrotic choroidal neovascularization (CNV). The frequency of both, atrophy and CNV, increased with age. In those > 60

years of age, atrophy and/or CNV were almost universally present but varied considerably in severity. Eyes with emerging pure atrophy (n = 13, no signs of CNV) showed pattern dystrophy-like changes (100%), reticular pseudodrusen (82%), and reduced choroidal thickness. Advanced atrophy was multifocal, reached beyond the arcades, and was present nasal to the optic disc. The average expansion rate of atrophy was 3.3 ± 1.3 and 1.6 ± 1.1 mm²/year (mean $\pm$ SD), in those without or with signs for CNV, respectively.

CONCLUSIONS: Atrophy of the outer retina and the retinal pigment epithelium is a common finding in PXE patients characterized by early onset and fast progression with subsequent visual loss independent from CNV. This suggests that atrophy is the natural endpoint of Bruch's membrane disease. Phenotypic similarities with multifactorial geographic atrophy in age-related macular degeneration suggest common pathogenic pathways at the level of Bruch's membrane.

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Pathogenesis

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Retinal Pigment Epithelium Responses to Selective Retina Therapy in Mouse Eyes.

Kim HD, Jang SY, Lee SH, Kim YS, Ohn YH, Brinkmann R, Park TK.

PURPOSE: To investigate the characteristics of retinal pigment epithelium (RPE) and retinal damage induced by selective retina therapy (SRT) in mice, and to elucidate longitudinal changes in RPE cells.

METHODS: C57BL/6J mice received SRT and continuous-wave laser photocoagulation (cwPC). The cell death pattern was evaluated using TUNEL assay, and proliferative potential of the RPE cells was evaluated using 5-ethynyl-2'-deoxyuridine (EdU) assay. To investigate the cell-cell integrity of RPE cells, β -catenin staining was performed. The number and hexagonality of RPE cells in the SRT-treated area were estimated using a Voronoi diagram with time periods of 3 hours to 14 days. Antibodies to microphthalmia-associated transcription factor (MITF) and orthodenticle homeobox 2 (Otx2) were used to confirm the specific characteristics of RPE cells in the SRT-treated area.

RESULTS: The number of TUNEL-positive cells located in the neural retina was significantly lower in lesions treated with SRT compared to those treated with cwPC. EdU-positive RPE cells were first detected 3 to 12 hours after SRT, and increased until 3 to 7 days after SRT. β -catenin staining showed that hexagonality was compromised and subsequently, RPE cells expanded in size within the targeted location. The number of RPE cells in SRT lesions decreased gradually until 12 hours after SRT and recovered by 14 days. Upregulated expression of MITF and Otx2 was observed for 2 weeks in the SRT lesions.

CONCLUSIONS: Selective retina therapy seems to induce selective RPE damage without collateral thermal injury in the neural retina. Furthermore, SRT-treated lesions recovered by proliferation of RPE cells that were present in the treated lesions and by expansion of adjacent RPE cells.

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Innate sensing of oxidation-specific epitopes in health and disease.

Binder CJ, Papac-Milicevic N, Witztum JL.

Abstract: Ageing, infections and inflammation result in oxidative stress that can irreversibly damage cellular structures. The oxidative damage of lipids in membranes or lipoproteins is one of these deleterious consequences that not only alters lipid function but also leads to the formation of neo-self epitopes - oxidation-specific epitopes (OSEs) - which are present on dying cells and damaged proteins. OSEs represent endogenous damage-associated molecular patterns that are recognized by pattern recognition receptors and the proteins of the innate immune system, and thereby enable the host to sense and remove

dangerous biological waste and to maintain homeostasis. If this system is dysfunctional or overwhelmed, the accumulation of OSEs can trigger chronic inflammation and the development of diseases, such as atherosclerosis and age-related macular degeneration. Understanding the molecular components and mechanisms that are involved in this process will help to identify individuals with an increased risk of developing chronic inflammation, and will also help to indicate novel modes of therapeutic intervention.

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miRNA involvement in angiogenesis in age-related macular degeneration.

Wang L, Lee AY, Wigg JP, Peshavariya H, Liu P, Zhang H.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. Late-stage AMD is characterized by choroidal neovascularization (CNV). miR-93 appears to play a role in regulating vascular endothelial growth factor-A (VEGF-A), a known factor involved in neovascularization. Understanding its biological significance might enable development of therapeutic interventions for diseases like AMD. We aimed to determine the role of miR-93 in AMD using a laser-induced CNV mouse model. CNV was induced by laser photocoagulation in C57BL/6 mice. The CNV mice were transfected with scrambled miR or miR-93 mimic. The treatment effect was assessed by fundus photography and fluorescein angiography and confirmed by choroidal flatmount. The expression of miR-93 and VEGF-A in ocular tissues was analysed by quantitative polymerase chain reaction (qPCR) and Western blot. The overexpression effects of miR-93 were also proved on human microvascular endothelial cells (HMECs). Significantly decreased expression of miR-93 was observed by qPCR analysis in CNV mice compared to untreated mice ($p < 0.05$). VEGF-A messenger RNA (mRNA) and protein expression were upregulated with CNV; these changes were ameliorated by restoration of miR-93 ($p < 0.05$). CNV was reduced after miR-93 transfection. Transfection of miR-93 reduced the proliferation of HMECs ($p < 0.01$), but no significant changes were observed in 2D capillary-like tube formation ($p > 0.05$) and migration ($p > 0.05$) compared with that in the untreated cells. miR-93 has been shown to be a negative modulator of angiogenesis in the eye. All together, these results highlight the therapeutic potential of miR-93 and suggest that it may contribute as a putative therapeutic target for AMD in humans.

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A novel AhR ligand, 2AI, protects the retina from environmental stress.

Gutierrez MA, Davis SS, Rosko A, Nguyen SM, Mitchell KP, Mateen S, Neves J, Garcia TY, Mooney S, Perdew GH, Hubbard TD, Lamba DA, Ramanathan A.

Abstract: Various retinal degenerative diseases including dry and neovascular age-related macular degeneration (AMD), retinitis pigmentosa, and diabetic retinopathy are associated with the degeneration of the retinal pigmented epithelial (RPE) layer of the retina. This consequently results in the death of rod and cone photoreceptors that they support, structurally and functionally leading to legal or complete blindness. Therefore, developing therapeutic strategies to preserve cellular homeostasis in the RPE would be a favorable asset in the clinic. The aryl hydrocarbon receptor (AhR) is a conserved, environmental ligand-dependent, per ARNT-sim (PAS) domain containing bHLH transcription factor that mediates adaptive response to stress via its downstream transcriptional targets. Using in silico, in vitro and in vivo assays, we identified 2,2'-aminophenyl indole (2AI) as a potent synthetic ligand of AhR that protects RPE cells in vitro from lipid peroxidation cytotoxicity mediated by 4-hydroxynonenal (4HNE) as well as the retina in vivo from light-damage. Additionally, metabolic characterization of this molecule by LC-MS suggests that 2AI alters the lipid metabolism of RPE cells, enhancing the intracellular levels of palmitoleic acid. Finally, we show that, as a downstream effector of 2AI-mediated AhR activation, palmitoleic acid protects RPE cells from 4HNE-mediated stress, and light mediated retinal degeneration in mice.

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Metabolism of 4-Hydroxy-7-oxo-5-heptenoic Acid (HOHA) Lactone by Retinal Pigmented Epithelial Cells.

Wang H, Linetsky MD, Guo J, Yu AO, Salomon RG.

Abstract: 4-Hydroxy-7-oxo-5-heptenoic acid (HOHA)-lactone is a biologically active oxidative truncation product released ($t_{1/2} = 30$ min at 37 °C) by non-enzymatic transesterification/deacylation from docosahexaenoate lipids. We now report that HOHA-lactone readily diffuses into retinal pigmented epithelial (RPE) cells where it is metabolized. A reduced glutathione (GSH) Michael adduct of HOHA-lactone is the most prominent metabolite detected by LC-MS in both the extracellular medium and cell lysates. This molecule appeared inside of ARPE-19 cells within seconds after exposure to HOHA-lactone. The intracellular level reached a maximum concentration at 30 min and then decreased with concomitant increases in its level in the extracellular medium, thus revealing a unidirectional export of the reduced GSH-HOHA-lactone adduct from the cytosol to extracellular medium. This metabolism is likely to modulate the involvement of HOHA-lactone in the pathogenesis of human diseases. HOHA-lactone is biologically active, e.g., low concentrations (0.1-1 μ M) induce secretion of vascular endothelial growth factor (VEGF) from ARPE-19 cells. HOHA-lactone is also a precursor of 2-(ω -carboxyethyl)pyrrole (CEP) derivatives of primary amino groups in proteins and ethanolamine phospholipids that have significant pathological and physiological relevance to age-related macular degeneration (AMD), cancer and wound healing. Both HOHA-lactone and the derived CEP can contribute to the angiogenesis that defines the neovascular "wet" form of AMD and that promotes the growth of tumors. While GSH depletion can increase the lethality of radiotherapy, because it will impair the metabolism of HOHA-lactone, the present study suggests that GSH depletion will also increase levels of HOHA-lactone and CEP that may promote recurrence of tumor growth.

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Stem cells

Nature. 2016 Jun 15;534(7607):310-2.

How iPS cells changed the world.

Scudellari M.

PMID: 27306170

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Human neural progenitor cells decrease photoreceptor degeneration, normalize opsin distribution and support synapse structure in cultured porcine retina.

Mollick T, Mohlin C, Johansson K.

Abstract: Retinal neurodegenerative disorders like retinitis pigmentosa, age-related macular degeneration, diabetic retinopathy and retinal detachment decrease retinal functionality leading to visual impairment. The pathological events are characterized by photoreceptor degeneration, synaptic disassembly, remodeling of postsynaptic neurons and activation of glial cells. Despite intense research, no effective treatment has been found for these disorders. The current study explores the potential of human neural progenitor cell (hNPC) derived factors to slow the degenerative processes in adult porcine retinal explants. Retinas were cultured for 3 days with or without hNPCs as a feeder layer and investigated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), immunohistochemical, western blot and quantitative real time -polymerase chain reaction (qRT-PCR) techniques. TUNEL showed that hNPCs had the capacity to limit photoreceptor cell death. Among cone photoreceptors, hNPC coculture resulted in better maintenance of cone outer segments and reduced opsin mislocalization. Additionally, maintained synaptic structural

integrity and preservation of second order calbindin positive horizontal cells was also observed. However, Müller cell gliosis only seemed to be alleviated in terms of reduced Müller cell density. Our observations indicate that at 3 days of coculture, hNPC derived factors had the capacity to protect photoreceptors, maintain synaptic integrity and support horizontal cell survival. Human neural progenitor cell applied treatment modalities may be an effective strategy to help maintain retinal functionality in neurodegenerative pathologies. Whether hNPCs can independently hinder Müller cell gliosis by utilizing higher concentrations or by combination with other pharmacological agents still needs to be determined.

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Diet, lifestyle & low vision

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Machine Learning Techniques in Clinical Vision Sciences.

Caixinha M, Nunes S.

Abstract: This review presents and discusses the contribution of machine learning techniques for diagnosis and disease monitoring in the context of clinical vision science. Many ocular diseases leading to blindness can be halted or delayed when detected and treated at its earliest stages. With the recent developments in diagnostic devices, imaging and genomics, new sources of data for early disease detection and patients' management are now available. Machine learning techniques emerged in the biomedical sciences as clinical decision-support techniques to improve sensitivity and specificity of disease detection and monitoring, increasing objectively the clinical decision-making process. This manuscript presents a review in multimodal ocular disease diagnosis and monitoring based on machine learning approaches. In the first section, the technical issues related to the different machine learning approaches will be present. Machine learning techniques are used to automatically recognize complex patterns in a given dataset. These techniques allows creating homogeneous groups (unsupervised learning), or creating a classifier predicting group membership of new cases (supervised learning), when a group label is available for each case. To ensure a good performance of the machine learning techniques in a given dataset, all possible sources of bias should be removed or minimized. For that, the representativeness of the input dataset for the true population should be confirmed, the noise should be removed, the missing data should be treated and the data dimensionally (i.e., the number of parameters/features and the number of cases in the dataset) should be adjusted. The application of machine learning techniques in ocular disease diagnosis and monitoring will be presented and discussed in the second section of this manuscript. To show the clinical benefits of machine learning in clinical vision sciences, several examples will be presented in glaucoma, age-related macular degeneration, and diabetic retinopathy, these ocular pathologies being the major causes of irreversible visual impairment.

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