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MD Research News

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Drug treatment

Ophthalmology. 2016 Mar 17. [Epub ahead of print]

Fellow Eye Comparisons for 7-Year Outcomes in Ranibizumab-Treated AMD Subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP Study).

Bhisitkul RB, Desai SJ, Boyer DS, Sadda SR, Zhang K.

PURPOSE: To compare study and fellow eyes in subjects with age-related macular degeneration (AMD) for 7-year outcomes arising from contrasting treatment histories and disease statuses.

DESIGN: Multicenter cohort study, predetermined secondary analysis.

PARTICIPANTS: A total of 65 participants from the ranibizumab-treatment arms of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR), Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular AMD (MARINA), and Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON) trials, recruited for an update evaluation from 14 study sites.

METHODS: Seven-year visual outcomes and retinal imaging data were compared with the ANCHOR, MARINA, and HORIZON databases. Under the ANCHOR and MARINA protocols, study eyes had received monthly ranibizumab injections for the initial 2 years, during which fellow eyes were prohibited from anti-vascular endothelial growth factor (VEGF) treatments.

MAIN OUTCOME MEASURES: Percentage of subjects with study eye vision better than fellow eye, vision change from baseline to year 7, and mean area of macular atrophy (MA) were predetermined secondary end points.

RESULTS: Fellow eyes with exudative AMD had received a mean 7.3 total injections of anti-VEGF agents in the mean 3.4 years off-study. For the 35% of subjects with exudative AMD in both eyes at baseline, within-patient comparisons at year 7 showed better vision in the study eye in 82%, with better mean final vision in study eyes (54.7 vs. 27.3 letters in fellow eyes, $P < 0.001$). Also in this subgroup, study eyes, which had received 2 years of high-frequency ranibizumab, had less severe MA than the respective fellow eye at year 7 in 88% of patients (mean area ± standard deviation 2.8±2.2 mm2 vs. 5.8±2.5 mm2 in the fellow eyes, $P = 0.0013$). Final fellow eye vision outcome was significantly correlated with MA severity (coefficient -6.95, $P < 0.001$), and patients' inter-eye vision difference corresponded to the degree of MA asymmetry.

CONCLUSIONS: Exudative fellow eyes remained at risk for further vision decline in later years under management with low-frequency anti-VEGF therapy. In patients with bilateral exudative AMD at baseline, final vision at year 7 was significantly better in study eyes than in fellow eyes, and MA was less severe. Macular atrophy area correlated with final visual outcomes, determined inter-eye vision differences, and was not attributable to high-frequency ranibizumab therapy.

PMID: 26996339 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 Mar 18. [Epub ahead of print]

Effects of switching from ranibizumab to aflibercept in eyes with exudative age-related macular degeneration.

Barthelmes D, Campain A, Nguyen P, Arnold JJ, McAllister IL, Simpson JM, Hunyor AP, Guymer R, Essex RW, Morlet N, Gillies MC; Fight Retinal Blindness! Project Investigators.

AIMS: To examine 12-month outcomes of eyes switching from intravitreal ranibizumab to aflibercept for neovascular age-related macular degeneration (nAMD).

METHODS: Database observational study of eyes with nAMD tracked by the Fight Retinal Blindness outcome registry that received ranibizumab for at least 12 months before switching to aflibercept and followed for at least 12 months after the switch. Visual acuity (VA) recorded at 12 months after the switch was analysed using locally weighted scatterplot smoothing curves. Lesion activity was graded according to a prospectively identified definition. Main outcomes were change in VA and treatment intervals 12 months after the treatment switch. Secondary outcomes included change in activity grading, effect of duration of treatment before switching and analysis of eyes that switched back.

RESULTS: A total of 384 eyes switched from ranibizumab to aflibercept after a mean duration of 39.8 months on the original treatment. The mean VA did not change from the time of switching treatment (63.4, SD 15.9 logarithm of the minimum angle of resolution letters) to 12 months later (63.3, SD 16.7). While 10% of eyes gained 10 or more letters 12 months after the switch, 13% lost the same amount. The mean number of injections decreased by around one injection in the 12 months after switching ($p<0.001$), with a decrease in the proportion of choroidal neovascular membrane lesions that were graded as active. Eyes that had been treated for the longest time (49 or more months) before switching had worse vision at the point of switch but neither change in VA nor treatment interval was different between groups. The small proportion (6.9%) of eyes that switched back again to ranibizumab had already lost a mean of 5.2 letters from the first switch to the switch back and continued to lose vision at a similar rate for at least 6 months.

CONCLUSIONS: The mean VA of eyes that switched treatments from ranibizumab to aflibercept was not different 12 months later. There was a modest increase in treatment intervals and a somewhat greater proportion of eyes that were graded as inactive after the switch.

PMID: 26994110 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2016 Mar 1;47(3):238-44.

Effect of Fluid Status at Week 12 on Visual and Anatomic Outcomes at Week 52 in the VIEW 1 and 2 Trials.

Moshfeghi DM, Hariprasad SM, Marx JL, Thompson D, Soo Y, Gibson A, Saroj N, Vitti R, Heier JS.

BACKGROUND AND OBJECTIVE: To evaluate effect of retinal fluid status at week 12 on visual and anatomic outcomes at week 52 in patients with neovascular age-related macular degeneration from the VIEW studies.

PATIENTS AND METHODS: Post-hoc analysis included 1,465 eyes treated with intravitreal aflibercept (Eylea; Regeneron, Tarrytown, NY) 2 mg every 4 weeks (2q4) or every 8 weeks following three initial monthly injections (2q8) or ranibizumab (Lucentis; Genentech, South San Francisco, CA) 0.5 mg every 4 weeks (Rq4), which had known retinal fluid status at weeks 12 and 52.

RESULTS: At 12 weeks, 512 (35%) eyes had fluid and 953 (65%) were fluid-free. Two hundred three (41.5%), 148 (29.8%), and 161 (33.5%) eyes had fluid in Rq4, 2q4, and 2q8, respectively. Best-corrected visual acuity (BCVA) change at week 52 from baseline was independent of retinal fluid status at week 12 or treatment assignment. Eyes were more likely to remain fluid-free at week 52 if absent of fluid at week 12.

CONCLUSION: At week 52, 2q4, 2q8, and Rq4 improved BCVA independent of fluid status at week 12.

PMID: 26985797 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2016 Mar 1;47(3):245-51.

Evaluating Efficacy of Aflibercept in Refractory Exudative Age-Related Macular Degeneration With OCT Segmentation Volumetric Analysis.

Choi CS, Zhang L, Abràmoff MD, Sonka M, Shifera AS, Kay CN.

BACKGROUND AND OBJECTIVE: To use automated segmentation software to analyze spectral-domain optical coherence tomography (SD-OCT) scans and evaluate the effectiveness of aflibercept (Eylea; Regeneron, Tarrytown, NY) in the treatment of patients with exudative age-related macular degeneration (AMD) refractory to other treatments.

PATIENTS AND METHODS: Retrospective chart review of 16 patients refractory to bevacizumab (Avastin; Genentech, South San Francisco, CA)/ranibizumab (Lucentis; Genentech, San Francisco, CA) treatment was conducted. Visual acuity, central foveal thickness (CFT), maximum fluid height, pigment epithelial detachment (PED) volume, sub-retinal fluid (SRF) volume, fluid-free time interval, and adverse effects were evaluated. Automated segmentation analysis was used to quantify improvement.

RESULTS: With aflibercept treatment, there was a statistically significant improvement in visual acuity by 1 line (P = .020), in CFT by 74.02 μm (P = .001), and in maximum fluid height by 31.9 μm (P= .011). Total PED and SRF volume also decreased significantly by 1.50 μm(3) × 10(8) μm(3) (P = .013). Anatomic improvement was confirmed by automated segmentation analysis.

CONCLUSION: This study demonstrates utility of automated segmentation software in quantifying anatomic improvement with aflibercept treatment in exudative AMD refractory to other anti-vascular endothelial growth factor treatments.

PMID: 26985798 [PubMed - in process]

Expert Opin Biol Ther. 2016 Mar 17. [Epub ahead of print]

Vascular endothelial growth factor inhibitor use and treatment approach for choroidal neovascularization secondary to pathologic myopia.

Pakzad-Vaezi K, Mehta H, Mammo Z, Tufail A.

Introduction - Myopic choroidal neovascularization (CNV) is the most common cause of CNV in those under 50 years of age. It is a significant cause of visual loss in those with pathologic myopia. The current standard of care involves therapy with intravitreal inhibitors of vascular endothelial growth factor (VEGF). Areas Covered - The epidemiology of myopia, high myopia, pathologic myopia, and myopic CNV is reviewed, along with a brief discussion of historical treatments. The pharmacology of the three most commonly used anti-VEGF agents is discussed, with an emphasis on the licensed drugs, ranibizumab and aflibercept. A comprehensive clinical approach to diagnosis and treatment of myopic CNV is presented. Expert Opinion - The current standard of care for myopic CNV is intravitreal inhibition of VEGF, with ranibizumab and aflibercept licensed for intraocular use. The diagnosis, OCT features of disease activity and retreatment algorithm for myopic CNV is different from wet age-related macular degeneration. In the long-term, myopic CNV may be associated with gradual, irreversible visual loss due to progressive chorioretinal atrophy, for which there is currently no treatment.

PMID: 26985834 [PubMed - as supplied by publisher]

Expert Opin Biol Ther. 2016 Mar 16. [Epub ahead of print]

The Role of Aflibercept in the Management of Age-Related Macular Degeneration.

Hassan M, Afridi R, Sadiq MA, Soliman MK, Agarwal A, Sepah YJ, Do DV, Nguyen QD.

INTRODUCTION: During the past decade, significant advances have occurred in the management of neovascular age-related macular degeneration (NV-AMD). The advent of anti-vascular endothelial growth factor (anti-VEGF) therapy has shifted the treatment goal of NV-AMD from merely salvaging vision to improving visual acuity and maintaining a good quality of life. Aflibercept (AFL) is a significant addition to the arsenal of anti-VEGF therapies against the NV-AMD. In the index review, pharmacology and efficacy of AFL has been reviewed. Areas Covered: An extensive literature search was performed to identify preclinical and clinical studies performed to illustrate the role of AFL in NV-AMD. Randomized clinical trials evaluating other anti-VEGF agents were also included for comparison. Additionally, studies where AFL was employed to treat anti-VEGF-resistant cases agents have been reviewed. Expert Opinion: AFL is an effective agent in the management of NV-AMD and its efficacy has been found to be comparable to ranibizumab (RBZ). Additionally, AFL is a good alternative agent in patients with NV-AMD resistant to RBZ and BVZ, and can potentially lessen the treatment burden. As more research is conducted, the role of AFL in varying dosing regimens, as monotherapy and in combination with other agents, will become further defined.

PMID: 26982640 [PubMed - as supplied by publisher]

Transl Vis Sci Technol. 2016 Mar 11;5(2):10. eCollection 2016.

VEGF and Intraocular Neovascularization: From Discovery to Therapy.

Ferrara N.

Abstract: I am honored and humbled to be one of the awardees of the 2014 A. Champalimaud Vision Award. I offer my heartfelt thanks to the Champalimaud Foundation President, Leonor Beleza, and to the Award Committee Members for this wonderful recognition. I feel especially fortunate to have had the opportunity to witness my scientific discoveries move from the bench to the clinic. Scientific discovery is hugely exciting, but the ability to translate that work into potentially helping someone lead a better life is even more fulfilling. This Award is dedicated to the patients.

PMID: 26981332 [PubMed] PMCID: PMC4790412

Transl Vis Sci Technol. 2016 Mar 11;5(2):9. eCollection 2016.

VEGF: From Discovery to Therapy: The Champalimaud Award Lecture.

Miller JW.

PURPOSE: Intraocular vascular diseases are leading causes of adult vision loss, and in the mid-1900s, I. C. Michaelson postulated that the retina releases a soluble, diffusible factor that causes abnormal vascular growth and leakage. What became known as "Factor X" eluded investigators for decades.

METHODS: The field of cancer research, where Judah Folkman pioneered the concept of angiogenesis, provided the inspiration for the work honored by the 2014 Champalimaud Vision Award. Recognizing that tumors recruit their own blood supply to achieve critical mass, Dr Folkman proposed that angiogenic factors could be therapeutic targets in cancer. Napoleone Ferrara identified vascular endothelial growth factor (VEGF) as such an angiogenic agent: stimulated by hypoxic tumor tissue, secreted, and able to induce neovascularization. VEGF also was a candidate for Factor X, and the 2014 Champalimaud Laureates and colleagues worked individually and collaboratively to identify the role of VEGF in ocular disease.

RESULTS: The Champalimaud Laureates correlated VEGF with ocular neovascularization in animal models and in patients. Moreover, they showed that VEGF not only was sufficient, but it also was required to induce neovascularization in normal animal eyes, as VEGF inhibition abolished ocular neovascularization in key animal models.

CONCLUSIONS: The identification of VEGF as Factor X altered the therapeutic paradigms for age-related

macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, and other retinal disorders.

TRANSLATIONAL RELEVANCE:

The translation of VEGF from discovery to therapy resulted in the most successful applications of antiangiogenic therapy to date. Annually, over one million patients with eye disease are treated with anti-VEGF agents.

PMID: 26981331 [PubMed] PMCID: PMC4790434

Ophthalmic Surg Lasers Imaging Retina. 2016 Mar 1;47(3):224-31.

Predictors of Macular Atrophy Detected by Fundus Autofluorescence in Patients With Neovascular Age-Related Macular Degeneration After Long-Term Ranibizumab Treatment.

Kuehlewein L, Dustin L, Sagong M, Hariri A, Mendes TS, Rofagha S, Bhisitkul RB, Sadda SR.

BACKGROUND AND OBJECTIVE: To study the relationship between baseline morphologic characteristics of the choroidal neovascular (CNV) lesion and long-term development of macular atrophy in eyes with neovascular age-related macular degeneration (AMD) treated with ranibizumab (Lucentis; Genentech, South San Francisco, CA).

PATIENTS AND METHODS: Certified graders evaluated baseline and 7-year follow-up (SEVEN-UP study) images of 41 eyes from the MARINA/ANCHOR and HORIZON trials. Using GRADOR software and stepwise linear regression, graders correlated lesion characteristics on fluorescein angiography (FA) at both visits with areas of definite decreased autofluorescence (DDAF) on fundus autofluorescence (FAF) imaging at the SEVEN-UP visit.

RESULTS: Three of 41 eyes (7.3%) had macular atrophy on FA at baseline (mean ± standard deviation [SD] size: 0.29 mm(2) ± 1.50 mm(2)), 29 (70.7%) at SEVEN-UP (mean ± standard deviation [SD] area: 7.42 mm(2) ± 7.97 mm(2)). On FAF imaging at the SEVEN-UP visit, all 41 eyes (100%) had DDAF (mean ± SD size: 10.29 mm(2) ± 8.07 mm(2)). Variables significantly associated with area of DDAF at the SEVEN-UP visit were the area of leaking CNV lesion components (coefficient: 0.953; $P < .001$), the area of other lesion components (coefficient: 1.094; $P = .038$), and the area of retinal pigment epithelial (RPE) atrophy (coefficient: 1.334; $P = .040$) on baseline FA imaging.

CONCLUSION: The area of DDAF at more than 7 years after initiation of ranibizumab therapy was 35% larger than the original CNV lesion. The baseline area of leaking CNV and other components of the CNV lesion and the baseline area of RPE atrophy were important predictors of the area of definite decreased autofluorescence, presumably corresponding to areas of photoreceptor and RPE loss. The findings from this study may guide hypothesis generation for future AMD trials.

PMID: 26985795 [PubMed - in process]

Ophthalmology. 2016 Mar 15. [Epub ahead of print]

Visual and Anatomic Outcomes in Patients with Diabetic Macular Edema with Limited Initial Anatomic Response to Ranibizumab in RIDE and RISE.

Pieramici DJ, Wang PW, Ding B, Gune S.

PURPOSE: To explore the visual acuity and anatomic outcomes over 24 months of patients with diabetic macular edema (DME) who showed a delayed anatomic response after 3 ranibizumab injections in the RIDE and RISE trials.

DESIGN: Analysis of data from RIDE and RISE, 2 phase III, parallel, randomized, multicenter, double-masked trials (ClinicalTrials.gov identifiers, NCT00473382 and NCT00473330).

PARTICIPANTS: Patients with DME (n = 681) who received monthly intravitreal ranibizumab 0.3-mg injections, ranibizumab 0.5-mg injections, or sham injections.

METHODS: Patients were separated into 3 groups: delayed responders (ranibizumab-treated patients with ≤10% central foveal thickness [CFT] reduction after 3 injections), immediate responders (ranibizumab-treated patients with >10% CFT reduction after 3 injections), and sham recipients. Central foveal thickness was measured by time-domain optical coherence tomography, best-corrected visual acuity (BCVA) was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores, and diabetic retinopathy (DR) was measured by the standardized ETDRS severity scale (using fundus photographs).

MAIN OUTCOME MEASURES: Month-24 CFT, BCVA, and DR severity levels.

RESULTS: In RIDE and RISE, 9% to 10% of ranibizumab-treated eyes were delayed responders. At month 24, delayed responders had less CFT reduction (median, -102 μm) from baseline compared with immediate responders (median, -274 μm; P < 0.0001). Delayed responders gained a median of 10 letters at 24 months, similar to immediate responders (14 letters; P = 0.15). At month 24, DR improvement among the delayed responders (31% and 22% of patients with ≥2- or ≥3-step DR improvement, respectively) was comparable with that among immediate responders (42% and 17%, respectively; P = 0.21 and P = 0.48, respectively).

CONCLUSIONS: With continued treatment, at month 24, patients with DME with delayed anatomic response (≤10% CFT reduction) after 3 ranibizumab injections had visual acuity gains and DR improvement similar to those of patients with DME who had immediate anatomic response.

PMID: 26992841 [PubMed - as supplied by publisher]

Retina. 2016 Mar 16. [Epub ahead of print]

INTRAVITREAL INJECTIONS OF ZIV-AFLIBERCEPT FOR DIABETIC MACULAR EDEMA: A Pilot Study.

Andrade GC, Dias JR, Maia A, Farah ME, Meyer CH, Rodrigues EB.

PURPOSE: Diabetic macular edema is the leading cause of blindness in young adults in developed countries. Beyond metabolic control, several therapies have been studied such as laser treatment and intravitreal injections of corticosteroids or anti-vascular endothelial growth factor drugs. In terms of public health the long-term treatment with the current available drugs is very expensive and new therapies with the same or better effect should be investigated. This study sought to evaluate the efficacy and safety of intravitreal injections of ziv-aflibercept for the treatment of diabetic macular edema.

METHODS: Seven consecutive patients with diabetic macular edema were enrolled. A complete examination, including full-field electroretinography, visual acuity, central retinal thickness, and evaluation of systemic and ocular complications, was performed before and at 24 weeks after intravitreal injections of ziv-aflibercept. The seven patients were submitted to six consecutive intravitreal injections of ziv-aflibercept with a 4-week interval.

RESULTS: No significant differences were found in the amplitude or implicit time of any electroretinography component after intravitreal injections of ziv-aflibercept, and no systemic or ocular complication was observed. The improvement of visual acuity was significant at 24 weeks (P < 0.05). The central retinal thickness significantly decreased during the course of 24 weeks.

CONCLUSION: Intravitreal injections of ziv-aflibercept seem to be a safe and effective treatment option for diabetic macular edema.

PMID: 26991646 [PubMed - as supplied by publisher]

Med Sci Monit. 2016 Mar 14;22:833-9.

Effectiveness of Intravitreal Injection of Ranibizumab for Neovascular Age-Related Macular Degeneration with Serous Pigment Epithelial Detachment.

Zhao C, Zhang Z, Chen L, Wang F, Xu D.

BACKGROUND: We sought to observe the effectiveness of intravitreal injection of ranibizumab in treating neovascular age-related macular degeneration (nAMD) with serous pigment epithelial detachment (sPED). MATERIAL AND METHODS A retrospective, noncomparative case series was performed. Twenty-3 eyes of 23 patients with sPED secondary to nAMD who had received intravitreal injections of ranibizumab were included in this study. All patients underwent best-corrected visual acuity (BCVA), synchronous fluorescein fundus angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) examinations. All patients were treated with pro re nata intravitreal injections after 3 loading doses of ranibizumab and were followed up for 12 months. The differences in the BCVAs, maximum PED heights, PED volumes and CFTs of the affected eyes were compared between the baseline and last visit. RESULTS Twelve months after the first injection, improved visual acuity was observed in 16 of the 23 eyes. 4 eyes exhibited stable visual acuity, and 3 eyes exhibited impaired visual acuity. The mean post-injection logMAR BCVA was 0.58±0.05, which was much better than that at baseline (0.76±0.08; t=1.751, P=0.0869). The mean maximum PED height at baseline was 350.17±35.73μm and it was decreased to 238.87±36.87μm (t=2.192, P=0.0337) at the last visit. The mean PED volume after injection was 0.34±0.1 mm3, which was significantly decreased compared with that at baseline (0.81±0.21 mm3; t=2.021, P=0.0494).The mean CFT decreased, but this difference was not statistically significant (t=1.003, P=0.3211). None of the patients exhibited endophthalmitis, uveitis or RPE tears. CONCLUSIONS Intravitreal injection of ranibizumab for the treatment of neovascular age-related macular degeneration with serous pigment epithelial detachment safely and effectively improved the patients' visual acuities and decreased their PED heights volumes.

PMID: 26972376 [PubMed - in process]

Nippon Ganka Gakkai Zasshi. 2016 Feb;120(2):91-100.

[Anti-vascular Endothelial Growth Factor Therapy on Exudative Age-related Macular Degeneration in Routine Clinical Practice of a Single Site the Effectiveness of Cases Followed for More than Two Years]. [Article in Japanese]

Obana A, Gohto Y, Seto T.

PURPOSE: To investigate the long-term effectiveness of as-needed anti-vascular endothelial growth factor therapy on age-related macular degeneration (AMD).

SUBJECTS AND METHODS: The number of treatments, treatment period, visual acuity and morphological changes were investigated retrospectively in 257 eyes of 248 patients (189 men and 59 women, mean age ± SD; 71.1 ± 9.2 years old) who were followed up for two years and more. Re-treatment was mainly decided based on patient's will.

RESULTS: The mean number of treatments was 6.4 3.8 in the observational period of 3.7 years. Exudative changes were resolved at least once in the observational period in 240 eyes, and 160 eyes had no exudative changes at the final visit. Type 2 neovascularization by Gass resulted in fibrotic scar more frequently than type 1. The mean decimal visual acuity was 0.36 before the initiation of treatment and 0.26 at the final visit. The treatment period was less than 100 days in 54 eyes, and multivariate analysis revealed that polypoidal choroidal vasculopathy (PCV) was a factor of prolonged treatment period. No severe adverse effects were admitted locally and systemically.

CONCLUSIONS: The deterioration of mean visual acuity was assumed to be due to the relatively small number of treatments. Twenty-one percent of all eyes preserved well without any recurrence of treatments for short periods, and PCV needed treatments for longer periods than typical AMD.

PMID: 26987207 [PubMed - in process]

J Fr Ophtalmol. 2016 Mar 16. [Epub ahead of print]

[Intravitreal bevacizumab in AMD complicated by submacular hemorrhage]. [Article in French]

Bouraoui R, Bouladi M, Kort F, Limaiem R, Mghaieth F, El Matri L.

PURPOSE: To evaluate functional and anatomic results of intravitreal bevacizumab as monotherapy at 12 and 24 months in patients with neovascular age-related macular degeneration (AMD) complicated by large submacular hemorrhage.

METHODS: Retrospective analysis of a total of 21 patients (22 eyes) with large submacular hemorrhage secondary to age-related macular degeneration between May 2008 and December 2011. Patients were treated with three monthly intravitreal bevacizumab injections (1.25mg/0.05mL) at a four to six week interval and then PRN. Retreatment was based on the presence of hemorrhage on fundus examination or signs of activity on optical coherence tomography. Changes from baseline best corrected visual acuity (BCVA) scores, central retinal thickness, volume of hemorrhage and number of injections were analyzed.

RESULTS: The mean patient age was 72 years (range, 60-89 years). All patients completed at least 12 months of follow-up, and 17 patients fulfilled 24 months. The size of hemorrhage varied from 3 to 9 disc areas with a mean duration of 12.8 days. At baseline, mean initial BCVA was 20/400 (1.3 LogMAR) and improved to 20/160 at 12 months (P<0.001) and 20/164 at 24 months (P<0.001). Mean central retinal thickness decreased significantly from 550µm to 255µm at 24 months (P<0.001). The mean number of injections was 3.87 during the first 12 months. No case of recurrent bleeding was detected during the second year.

CONCLUSION: Intravitreal bevacizumab may be a beneficial approach for the management of large submacular hemorrhage secondary to AMD.

PMID: 26995076 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2016 Mar 16. [Epub ahead of print]

[Evaluation of the efficacy of aflibercept in the treatment of neovascular age-related macular degeneration in treatment-naive and switched patients. Report of 86 cases].[Article in French]

Maringe E, Letesson E, Duncombe A, Muraine M, Genevois O.

INTRODUCTION: AMD (age-related macular degeneration) is the leading cause of legal blindness after age 50 in developed countries. Anti-VEGF therapy by intravitreal injection has become the standard for the treatment of neovascular AMD. Ranibizumab is the most currently used, but the arrival of aflibercept on the market 1 year ago is changing clinical practices in France.

METHODS: The objective of this study is to evaluate the efficacy of aflibercept in AMD. All patients with neovascular AMD undergoing IVT (intra-vitreal injection) of aflibercept were included. All patients had at baseline and on follow-up visits a measurement of best corrected visual acuity (ETDRS), a fundus examination and an OCT. For statistical analysis, we analyzed the data at 0, 3, 6 and 12 months. An induction phase was carried out for treatment-naive patients, and follow-up was performed according to the PRN method (Pro Re Nata). The total number of injections over the entire follow-up period was recorded.

RESULTS: Ninety-six eyes were included, with 17 treatment-naive patients and 69 patients who had previously received ranibizumab. At 1 year, all patients had a mean improvement of 5.4 ETDRS letters (P=0.0026). The OCT data showed a rapid decline in retinal thickness, from baseline to the third month, of 143 microns on average (P=5.6×10-15); between the 3rd and 6th month, this was slower, with an average decrease of 4.6 microns, and between the 6th and the 12th month, the difference was significant, with an average decrease of 36 microns (P=0.003). The number of injections over one year was 5.7 on average.

CONCLUSION: The efficacy of aflibercept with a PRN protocol provides interesting results, with an improvement in visual acuity and central retinal thickness in all treated groups, and with fewer injections

than advocated.

PMID: 26995074 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2016 Apr;23(2):69-70.

Intraocular Inflammation Following Intravitreal Injection of Anti-VEGF Medications for Neovascular Age-Related Macular Degeneration.

Knickelbein JE, Chew EY, Sen HN.

PMID: 26996429 [PubMed - in process]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):1310-1316.

Reticular Pseudodrusen in Intermediate Age-Related Macular Degeneration: Prevalence, Detection, Clinical, Environmental, and Genetic Associations.

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

PURPOSE: To determine the prevalence of reticular pseudodrusen (RPD) and their detection using multimodal imaging in patients with bilateral large drusen, and examine their clinical, demographic, environmental, and genetic associations.

METHODS: Three hundred participants with bilateral large drusen (>125 μm) underwent color fundus photography (CFP), near-infrared reflectance (NIR), fundus autofluorescence (FAF), and spectral-domain optical coherence tomography (SD-OCT) imaging. Demographic information, smoking, and medical history were recorded, and a blood sample was obtained and genotyped to identify the risk alleles of the CFH and ARMS2 genes.

RESULTS: Reticular pseudodrusen were detected in 28.2% eyes of 29.0% participants using NIR and SD-OCT combined, but CFP and FAF detected only 42% and 89%, respectively, of these eyes with RPD. Participants with RPD were significantly older than those without ($P < 0.001$), but there was no significant difference in sex distribution, smoking history, cardiovascular factors, and minor allele frequency of the CFH gene ($P > 0.173$). However, the minor allele frequency of the ARMS2 gene was significantly higher in participants with RPD ($P = 0.002$). The presence of RPD was also independently associated with the presence of atrophic changes (including nascent geographic atrophy and drusen-associated atrophy detected on SD-OCT; $P = 0.043$).

CONCLUSIONS: Reticular pseudodrusen were detected on NIR and SD-OCT in more than a quarter of participants with bilateral large drusen, being often overlooked with CFP. Those with RPD had a higher frequency of the ARMS2 risk variant, and eyes with RPD were more likely to have atrophic changes. These findings are important to consider when managing patients with intermediate AMD.

PMID: 26998717 [PubMed - as supplied by publisher]

Surv Ophthalmol. 2016 Mar 16. [Epub ahead of print]

Perspectives on Reticular Pseudodrusen in Age-Related Macular Degeneration.

Sivaprasad S, Bird A, Nitiahpapand R, Nicholson L, Hykin P, Chatziralli I; Moorfields UCL AMD Consortium.

Abstract: Drusen have been considered the clinical hallmark of age-related macular degeneration (AMD).

Reticular pseudodrusen (RPD), although first described about twenty-five years ago, have only been recently recognised as an additional clinical phenotype of AMD with distinct characteristics on multimodal imaging and significant impact on visual function. Eyes with RPD are at greater risk of progression to advanced AMD when compared with eyes with drusen only. RPD can also occur in the absence of drusen. Unlike features external to the retinal pigment epithelium that have received most attention in AMD, evidence suggests that RPD are associated with changes internal to the RPE. Therefore, new avenues regarding the pathogenesis of AMD are highlighted by these recent observations. We summarize the current knowledge regarding the histology, imaging and functional changes in eyes with RPD in AMD and offer concepts of future research for the AMD community to discuss.

PMID: 26994868 [PubMed - as supplied by publisher]

Med J Malaysia. 2015 Dec;70(6):358-60.

Recalcitrant cystoid macular oedema in an eye with ischaemic central retinal vein occlusion - what's next?

Yong MH, Amin A, Mushawiahti M, Bastion ML.

Abstract: We report a case of a middle-aged gentleman with recalcitrant macular oedema (RMO) secondary to ischaemic central retinal vein occlusion (CRVO). He was given six injections of intravitreal ranibizumab (anti-VEGF) monthly. However, his visual acuity (VA) deteriorated and the macular oedema worsened. He then received an intravitreal dexamethasone implant eight months post-CRVO. His VA and macular oedema improved dramatically and significantly at first follow-up and remained stable at six months after implant. This case can be a reference for those who treating recalcitrant macular oedema. It shows the effect of an intravitreal dexamathasone implant might have in a patient with RMO due to CRVO. The patient enjoyed improvement of vision, with clinical evidence of reduction in central macular thickness (CMT) and with no serious adverse events after a single injection up to six months post implant.

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Telemed J E Health. 2016 Mar 17. [Epub ahead of print]

Snapshot of Teleretinal Screening for Diabetic Retinopathy at the West Los Angeles Medical Center.

Tsui I, Havunjian MA, Davis JA, Giaconi JA.

INTRODUCTION: The West Los Angeles Veterans Affairs Medical Center is a large urban facility with a robust teleretinal screening program in primary care clinic, established in 2006. The purpose of this article is to provide a snapshot of teleretinal screening at this site.

METHODS: Diabetic patients from 2012 were analyzed with a prospective cohort study. Demographic information, results of teleretinal screening, referral to eye clinic, and loss to follow-up (defined as no eye care within 2 years) were collected.

RESULTS: Of 516 patients with diabetes screened with teleretinal imaging, 120 patient charts were reviewed for data analysis. Teleretinal imaging diagnosed 15% (18/120) of patients with varying stages of nonproliferative diabetic retinopathy (DR). Of patients screened, 55.8% (67/120) of the patients were referred to an eye clinic for further ophthalmic evaluation. Nondiabetic retinopathy reasons for eye clinic referral included glaucoma suspect (13.3%, 16/120) and age-related macular degeneration (10.0%, 12/120). Of all patients screened, 37.5% (45/120) of them were lost to follow-up, defined as no teleretinal screening or eye clinic appointment within 2 years. Patients who lived farther away from clinic had a higher risk of loss to follow-up ($p = 0.04$).

DISCUSSION: We found, although only 15% of patients were diagnosed with DR from teleretinal screening, more than 50% of patients were referred to eye clinic. In addition, of all screened patients, there

was a high rate of not returning to the Veterans Affairs (VA) for eye care.

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Non-photoinduced biological properties of Verteporfin.

Gibault F, Corvaisier M, Bailly F, Huet G, Melnyk P, Cotelle P1.

BACKGROUND: Verteporfin is a porphyrinic photosensitizer clinically used for the photodynamic treatment of age-related macular degeneration. It has been identified almost simultaneously as a YAP/TEAD and an autophagosome inhibitor. Over the last past years, YAP (and TAZ), the downstream effectors of the Hippo pathway, have emerged as a promising anticancer target, as shown by several experimental lines of evidence, which reveal showing the overproduction of YAP in several cancers. However, YAP was also found to be closely connected to autophagy, mitochondria and reactive oxygen/nitrogen species. We herein, review the recent studies where VP was used without photoactivation as a YAP/TEAD inhibitor or protein oligomerization promoter, focusing on its effects on the YAP/TEAD gene targets and other biomarkers related to autophagy.

RESULTS: Since the identification of VP as YAP/TEAD inhibitor, several in vitro and in vivo studies have revealed the new potential of this molecule in different cancers where YAP is overexpressed. However, detailed structural information about its interaction with YAP is still lacking. Concomitantly, VP was identified as autophagosome inhibitor by promoting oligomerization of p62. Moreover, VP proves to be tumor-selective proteotoxic (by oligomerization of p62, STAT3) in colorectal cancer. Knowledges on the biological properties of this only YAP inhibitor available to date are capital for its pharmacological use on cellular and animal models.

CONCLUSION: VP is a multi-target drug interacting with several proteins implicated in major cellular processes. Although this does not impact its clinical use, VP does not seem to be the ideal drug for pharmacological inhibitions of YAP/TEAD.

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Automated geographic atrophy segmentation for SD-OCT images using region-based C-V model via local similarity factor.

Niu S, de Sisternes L, Chen Q, Leng T, Rubin DL.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among elderly individuals. Geographic atrophy (GA) is a phenotypic manifestation of the advanced stages of non-exudative AMD. Determination of GA extent in SD-OCT scans allows the quantification of GA-related features, such as radius or area, which could be of important value to monitor AMD progression and possibly identify regions of future GA involvement. The purpose of this work is to develop an automated algorithm to segment GA regions in SD-OCT images. An en face GA fundus image is generated by averaging the axial intensity within an automatically detected sub-volume of the three dimensional SD-OCT data, where an initial coarse GA region is estimated by an iterative threshold segmentation method and an intensity profile set, and subsequently refined by a region-based Chan-Vese model with a local similarity factor. Two image data sets, consisting on 55 SD-OCT scans from twelve eyes in eight patients with GA and 56 SD-OCT scans from 56 eyes in 56 patients with GA, respectively, were utilized to quantitatively evaluate the automated segmentation algorithm. We compared results obtained by the proposed algorithm, manual segmentation by graders, a previously proposed method, and experimental commercial software. When compared to a manually determined gold standard, our algorithm presented a mean overlap ratio

(OR) of 81.86% and 70% for the first and second data sets, respectively, while the previously proposed method OR was 72.60% and 65.88% for the first and second data sets, respectively, and the experimental commercial software OR was 62.40% for the second data set.

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Pathogenesis

Sci Rep. 2016 Mar 16;6:22375.

Simultaneous determination of 8-oxo-2'-deoxyguanosine and 8-oxo-2'-deoxyadenosine in human retinal DNA by liquid chromatography nanoelectrospray-tandem mass spectrometry.

Ma B, Jing M, Villalta PW, Kapphahn RJ, Montezuma SR, Ferrington DA, Stepanov I.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among older adults in the developed world. Oxidative damage to mitochondrial DNA (mtDNA) in the retinal pigment epithelium (RPE) may play a key role in AMD. Measurement of oxidative DNA lesions such as 8-oxo-2'-deoxyguanosine (8-oxo-dG) and 8-oxo-2'-deoxyadenosine (8-oxo-dA) in diseased RPE could provide important insights into the mechanism of AMD development. We have developed a liquid chromatography-nanoelectrospray ionization-tandem mass spectrometry method for simultaneous analysis of 8-oxo-dG and 8-oxo-dA in human retinal DNA. The developed method was applied to the analysis of retinal DNA from 5 donors with AMD and 5 control donors without AMD. In mtDNA, the levels of 8-oxo-dG in controls and AMD donors averaged 170 and 188, and 8-oxo-dA averaged 11 and 17 adducts per 10(6) bases, respectively. In nuclear DNA, the levels of 8-oxo-dG in controls and AMD donors averaged 0.54 and 0.96, and 8-oxo-dA averaged 0.04 and 0.05 adducts per 10(6) bases, respectively. This highly sensitive method allows for the measurement of both adducts in very small amounts of DNA and can be used in future studies investigating the pathophysiological role of 8-oxo-dG and 8-oxo-dA in AMD and other oxidative damage-related diseases in humans.

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Hypoxia-induced metabolic stress in retinal pigment epithelial cells is sufficient to induce photoreceptor degeneration.

Kurihara T, Westenskow PD, Gantner ML, Usui Y, Schultz A, Bravo S, Aguilar E, Wittgrove C, Friedlander MS, Paris LP, Chew E, Siuzdak G, Friedlander M.

Abstract: Photoreceptors are the most numerous and metabolically demanding cells in the retina. Their primary nutrient source is the choriocapillaris, and both the choriocapillaris and photoreceptors require trophic and functional support from retinal pigment epithelium (RPE) cells. Defects in RPE, photoreceptors, and the choriocapillaris are characteristic of age-related macular degeneration (AMD), a common vision-threatening disease. RPE dysfunction or death is a primary event in AMD, but the combination(s) of cellular stresses that affect the function and survival of RPE are incompletely understood. Here, using mouse models in which hypoxia can be genetically triggered in RPE, we show that hypoxia-induced metabolic stress alone leads to photoreceptor atrophy. Glucose and lipid metabolism are radically altered in hypoxic RPE cells; these changes impact nutrient availability for the sensory retina and promote progressive photoreceptor degeneration. Understanding the molecular pathways that control these responses may provide important clues about AMD pathogenesis and inform future therapies.

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Int J Mol Sci. 2016 Mar 11;17(3).

Molecular Selection, Modification and Development of Therapeutic Oligonucleotide Aptamers.

Yu Y, Liang C, Lv Q, Li D, Xu X, Liu B, Lu A, Zhang G.

Abstract: Monoclonal antibodies are the dominant agents used in inhibition of biological target molecules for disease therapeutics, but there are concerns of immunogenicity, production, cost and stability. Oligonucleotide aptamers have comparable affinity and specificity to targets with monoclonal antibodies whilst they have minimal immunogenicity, high production, low cost and high stability, thus are promising inhibitors to rival antibodies for disease therapy. In this review, we will compare the detailed advantages and disadvantages of antibodies and aptamers in therapeutic applications and summarize recent progress in aptamer selection and modification approaches. We will present therapeutic oligonucleotide aptamers in preclinical studies for skeletal diseases and further discuss oligonucleotide aptamers in different stages of clinical evaluation for various disease therapies including macular degeneration, cancer, inflammation and coagulation to highlight the bright commercial future and potential challenges of therapeutic oligonucleotide aptamers.

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Nat Med. 2016 Mar 14. [Epub ahead of print]

Retinal lipid and glucose metabolism dictates angiogenesis through the lipid sensor Ffar1.

Joyal JS, Sun Y, Gantner ML, et al.

Abstract: Tissues with high metabolic rates often use lipids, as well as glucose, for energy, conferring a survival advantage during feast and famine. Current dogma suggests that high-energy-consuming photoreceptors depend on glucose. Here we show that the retina also uses fatty acid β-oxidation for energy. Moreover, we identify a lipid sensor, free fatty acid receptor 1 (Ffar1), that curbs glucose uptake when fatty acids are available. Very-low-density lipoprotein receptor (Vldlr), which is present in photoreceptors and is expressed in other tissues with a high metabolic rate, facilitates the uptake of triglyceride-derived fatty acid. In the retinas of Vldlr-/- mice with low fatty acid uptake but high circulating lipid levels, we found that Ffar1 suppresses expression of the glucose transporter Glut1. Impaired glucose entry into photoreceptors results in a dual (lipid and glucose) fuel shortage and a reduction in the levels of the Krebs cycle intermediate α-ketoglutarate (α-KG). Low α-KG levels promotes stabilization of hypoxia-induced factor 1a (Hif1a) and secretion of vascular endothelial growth factor A (Vegfa) by starved Vldlr-/- photoreceptors, leading to neovascularization. The aberrant vessels in the Vldlr-/- retinas, which invade normally avascular photoreceptors, are reminiscent of the vascular defects in retinal angiomatous proliferation, a subset of neovascular age-related macular degeneration (AMD), which is associated with high vitreous VEGFA levels in humans. Dysregulated lipid and glucose photoreceptor energy metabolism may therefore be a driving force in macular telangiectasia, neovascular AMD and other retinal diseases.

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Neurobiol Aging. 2016 Apr;40:110-9. Epub 2016 Jan 4.

Enhanced Ccl2-Ccr2 signaling drives more severe choroidal neovascularization with aging.

Robbie SJ, Georgiadis A, Barker SE, Duran Y, Smith AJ, Ali RR, Luhmann UF, Bainbridge JW.

Abstract: The impact of many inflammatory diseases is influenced by age-related changes in the activation of resident and circulating myeloid cells. In the eye, a major sight-threatening consequence of age-related macular degeneration is the development of severe choroidal neovascularization (CNV). To identify the molecular pathways and myeloid cell populations involved in this increased neovascular response, we characterized the immune status of murine choroid and retina during aging and in the context of

experimental CNV. In the choroid, but not in the retina, advancing age is associated with proinflammatory upregulation of CCL2-CCR2 signaling. Genetic excision of CCL2 diminishes age-related inflammatory changes in the choroid, with reduced recruitment of proinflammatory myeloid cells and attenuation of CNV. These findings indicate that CCL2-driven recruitment of myeloid cells contributes to increased severity of CNV with age. Similar mechanisms may be involved in other age-related inflammatory diseases.

PMID: 26973110 [PubMed - in process]

Mol Immunol. 2016 Mar 9;72:65-73. [Epub ahead of print]

Rapid isolation of pure Complement Factor H from serum for functional studies by the use of a monoclonal antibody that discriminates FH from all the other isoforms.

Berra S, Clivio A.

Abstract: Several mutations have been identified in the gene coding for Complement Factor H (FH) from patients with atypical Hemolytic Uraemic Syndrome (aHUS), Age-related Macular Degeneration (AMD) and Membranoproliferative Glomerulonephritis (MPGN). These data allow for a precise description of the structural changes affecting FH, but a simple test for specifically assessing FH function routinely is not yet of common use. We have produced and characterised a monoclonal antibody (5H5) which discriminates between FH and the smaller FH-like 1 and FH-related proteins and show here that it specifically binds to FH without detecting the smaller isoforms. We therefore used this mAb for a quick, one-step micro-purification of FH directly from control sera and showed that this affinity chromatography procedure is not disruptive of its cofactor function. We also developed a modified sheep erythrocytes haemolysis test using our antibody and affinity-purified FH. These tests can be used in conjunction for assessing the function of FH purified from patients affected by FH-related diseases. Moreover we used this mAb to develop a FH-specific ELISA test.

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Genetics

Rep Biochem Mol Biol. 2015 Oct;4(1):43-9.

Association of Htra1 gene polymorphisms with the risk of developing AMD in Iranian population.

Askari M, Nikpoor AR, Gorjipour F, Mazidi M, Sanati MH, Aryan H, Irani A, Ghasemi Falavarjani K, Nazari H, Mousavizadeh K.

BACKGROUND: Half of the cases of vision loss in people under 60 years of age have been attributed to age-related macular degeneration (AMD). This is a multifactorial disease with late onset. It has been demonstrated that many different genetic loci are implicated in the risk of developing AMD in different populations. In the current study, we investigated the association of high-temperature requirement A-1 (HTRA1) gene polymorphisms with the risk of developing AMD in the Iranian population.

METHODS: Genomic DNA samples were extracted from 120 patients with AMD and 120 healthy age- and sex-matched controls. A 385 base-pair fragment of the HTRA1 gene promoter region was amplified using the polymerase chain reaction (PCR) technique and sequenced. The frequencies of the alleles were calculated and statistical analysis was performed using SPSS software.

RESULTS: Our study demonstrated that the rate of polymorphisms rs11200638 -625 G>A and rs2672598 -487T>C were significantly greater in AMD patients than in healthy controls from the Iranian population.

CONCLUSIONS: The results of our study indicate that HTRA1 gene promoter region polymorphisms are associated with the risk of developing AMD in the Iranian population.

PMID: 26989749 [PubMed] PMCID: PMC4757096

Diet, lifestyle & low vision

Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):1276-1283.

Overweight, Obesity, and Risk of Age-Related Macular Degeneration.

Zhang QY, Tie LJ, Wu SS, Lv PL, Huang HW, Wang WQ, Wang H, Ma L.

PURPOSE: The aim of this study was to quantify the relationship between categories of body mass index (BMI) and age-related macular degeneration (AMD) risk in different stages.

METHODS: MEDLINE, EMBASE, and ISI Web of Science were searched for all eligible studies on the relationship between BMI and incident early or late AMD. The analyses were based on data extracted from study reports. The pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of this association, and dose-response relationship was assessed by restricted cubic spline.

RESULTS: Seven prospective cohort studies with 1613 cases identified among 31,151 subjects were included. For overweight, the relationship remained insignificant for its association with both early AMD (RR = 0.92, 95% CI: 0.68-1.15; P = 0.54) and late AMD (RR = 1.09, 95% CI: 0.93-1.25; P = 0.18). A marked 32% increase in the risk of developing late AMD was noted among obese individuals (RR = 1.32, 95% CI: 1.11-1.53, P < 0.01), while obesity showed no significant association with early AMD (RR = 0.91, 95% CI: 0.74-1.08; P = 0.67). Furthermore, elevated BMI showed a linear dose-response relation with AMD risk (Pnonlinearity = 0.17), and the AMD risk increased by 2% (RR = 1.02, 95% CI: 1.01-1.04) for each 1 kg/m2 increase in BMI within the overweight and obese BMI ranges.

CONCLUSIONS: Excess body weight was weakly associated with increase in the risk of AMD in a dose-dependent fashion, especially for its late stage, indicating that keeping normal body weight and avoiding further weight gain may confer potential protection against this disease.

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