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MD Research News

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Drug treatment

Eye (Lond). 2015 Jul;29 Suppl 1:S1-S11.

Aflibercept in wet AMD beyond the first year of treatment: recommendations by an expert roundtable panel.

McKibbin M, Devonport H, Gale R, Gavin M, Lotery A, Mahmood S, Patel PJ, Ross A, Sivaprasad S, Talks J, Walters G.

Abstract: This paper provides expert recommendations on administration of aflibercept in wet age-related macular degeneration (AMD) after Year 1 (Y1), based on a roundtable discussion held in London, UK in November 2014. The goals of treatment after Y1 are to maintain visual and anatomical gains whilst minimising treatment burden and using resources effectively. The treatment decision should be made at the seventh injection visit (assuming the label has been followed) in Y1, and three approaches are proposed: (a) eyes with active disease on imaging/examination but with stable visual acuity (VA) at the end of Y1 should continue with fixed 8-weekly dosing; (b) eyes with inactive disease on imaging/examination and stable VA should be managed using a 'treat and extend' (T&E) regimen. T&E involves treating and then extending the interval until the next treatment, by 2-week intervals, to a maximum of 12 weeks, provided the disease remains inactive. If there is new evidence of disease activity, treatment is administered and the interval to the next treatment shortened; and (c) if there has been no disease activity for ≥3 consecutive visits, a trial of monitoring without treatment may be appropriate, initiated at the end of Y1 or at any time during Y2. Where possible, VA testing, OCT imaging and injection should be performed at the same visit. The second eye should be monitored to detect fellow eye involvement. In bilateral disease, the re-treatment interval should be driven by the better-seeing eye or, if the VA is similar, the eye with the more active disease.

PMID: 26156564 [PubMed - in process]

Br J Ophthalmol. 2015 Jun 29. [Epub ahead of print]

Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK.

Buckle M, Donachie PH, Johnston RL.

AIMS: To study long-term, whole population 'real-world' clinical outcomes of ranibizumab therapy in treatment-naïve eyes for neovascular age-related macular degeneration.

METHODS: Data collected prospectively from a single centre serving a defined population using an electronic medical record included: demographics, Early Treatment Diabetic Retinopathy Study visual acuity (ETDRS VA) at all visits, injection dates, central 1 mm retinal thickness, and operative and

postoperative complications.

RESULTS: 1483 eyes from 1278 patients were included in this study. The median age at the time of the patient's first injection was 82.5 years, 64.9% of patients were female, and another ocular pathology was present in 7.3% eyes. The baseline VA was 23-39, 40-54, 55-70 and >70 ETDRS letters for 17.3%, 23.1%, 42.7% and 16.9% of eyes, respectively. The median VA in all baseline VA groups improved after the loading phase but declined back to the baseline level by 2-5 years. The rate of endophthalmitis following intravitreal injection was 1 in 2124 injections.

CONCLUSIONS: These long-term real-world data demonstrate that in general VA increases during the loading phase but returns to near baseline levels after 2-5 years of treatment for each baseline VA category. Patients should be identified and treated as early as possible, since presenting VA predicts the VA maintained after 5 years of treatment. National Institute of Health and Care Excellence guidance advising treatment only for eyes with vision below 70 letters does not promote best long-term VA outcomes for patients.

PMID: 26124462 [PubMed - as supplied by publisher]

Saudi J Ophthalmol. 2015 Jul-Sep;29(3):187-91. Epub 2015 Mar 5.

Factors affecting visual acuity after one year of follow up after repeated intravitreal ranibizumab for macular degeneration.

Williams GS, Seow E, Evans H, Owoniyi M, Evans S, Blyth C.

AIM: Providing intravitreal ranibizumab therapy for neovascular age related macular degeneration (nARMD) is a source of increasing strain for many UK eye departments. Whilst most units attempt to adhere to the product licence of following up patients at four weekly intervals; delays in follow up appointments can and do occur. We aim to see if mean follow up intervals during the maintenance phase are correlated with visual outcomes at one year and perform a multivariate analysis of patient factors in a bit to understand the factors affecting visual acuity outcomes.

METHOD: A continuously updated prospective audit of patients receiving ranibizumab therapy at the Royal Gwent Hospital was accessed and a coefficient of determination and Spearman's rank test undertaken to see whether mean follow up delays resulted in visual acuity penalties after nine months of maintenance. Multivariate analysis using ANOVA was then undertaken to examine in more detail the various factors affecting visual acuity outcomes.

RESULTS: 805 eyes of 708 patients were included in the study. Mean follow up intervals varied between 28.0 and 96.3 days over the first six treatments of the maintenance phase (mean 49.2 - SD 10.7) with a mean change in visual acuity from baseline of +7.1 letters at 12 weeks and +4.6 letters at 52 weeks. There was a negative correlation seen between visual acuity gains after nine months of the maintenance phase and increasing clinic follow up times although Spearman's rank analysis demonstrated a correlation coefficient of only -0.078, which was not statistically significant. Variability in follow up appointments resulting in worse outcomes was however significant ($p < 0.01$), as was increasing age at presentation ($p = 0.04$). Smoking was found to decrease age of presentation by six years (74.2 years vs 80.0 years). The adjusted R (2) for the whole analysis was 0.44.

CONCLUSION: Wide variation in follow up intervals was associated with a worse visual acuity outcome although longer mean follow up interval was not. Smokers presented at a significantly younger age than non-smokers or ex-smokers. This was a large study with an adjusted R (2) of 0.44. The results are relevant to other macular degeneration service providers around the world.

PMID: 26155076 [PubMed] PMCID: PMC4487938

Saudi J Ophthalmol. 2015 Jul-Sep;29(3):182-6. Epub 2014 Dec 13.

Comparison of intravitreal ranibizumab between phakic and pseudophakic neovascular age-related macular degeneration patients: Two-year results.

Ozkaya A, Alkin Z, Yilmaz I, Yazici AT.

BACKGROUND AND OBJECTIVE: To compare the efficacy of intravitreal ranibizumab (IVR) for the treatment of neovascular age-related macular degeneration (nAMD) between phakic and pseudophakic eyes after a follow-up of two years.

MATERIALS AND METHODS: Data were analyzed retrospectively. The newly diagnosed and treatment naïve nAMD patients were included in the study. The patients were divided into two subgroups: phakic group, and pseudophakic. All patients received 3 consecutive monthly IVR injections, and then the treatment was continued on an as-needed regimen. Patients were examined monthly, and the data at the baseline, at month 6, 12, 18, and 24 were evaluated. The changes in best corrected visual acuity (BCVA), central retinal thickness (CRT), and the number of injections were compared between the two groups.

RESULTS: The study included 92 eyes of 87 patients (58 phakic, 34 pseudophakic). Mean logarithm of the minimal angle of resolution (LogMAR) VA at the baseline, and at month 6, 12, 18, and 24 was 0.89, 0.74, 0.75, 0.73, and 0.75, in the phakic group; and 0.79, 0.71, 0.66, 0.70, and 0.70 in the pseudophakic group, respectively. The change in mean BCVA from the baseline to month 6, 12, 18, and 24 was not statistically different between the two groups ($p = 0.4$, $p = 0.9$, $p = 0.5$, $p = 0.6$, respectively). Mean injection number at month 24 was 7.9 and 8.1 in the phakic and pseudophakic group, respectively ($p = 0.7$).

CONCLUSION: Intravitreal ranibizumab treatment on an as-needed treatment regimen is effective in preserving vision and improving central retinal thickness in both the phakic and pseudophakic group of nAMD patients. The functional and anatomical outcomes of the treatment, and the number of injections were similar in the phakic and pseudophakic nAMD patients after a follow-up time of 24 months.

PMID: 26155075 [PubMed] PMCID: PMC4487941

Case Rep Ophthalmol. 2015 Jun 2;6(2):170-5.

Foveal Exudative Macroaneurysm Treated with Intravitreal Ranibizumab.

Menezes C, Carvalho R, Teixeira C, Lemos JA, Gonçalves R, Coelho P, Lima A.

PURPOSE: We report a case of a foveal macroaneurysm with long-standing macular edema in a rare location, successfully treated with intravitreal ranibizumab.

METHODS: We report the case of a 52-year-old man with left eye long-term visual loss due to macular edema caused by a retinal macroaneurysm, localized about 400 μm from the center of the fovea, and its response to 6 monthly ranibizumab intravitreal injections. His best-corrected visual acuity and morphological data evaluated by optical coherence tomography and fluorescein angiography are presented.

RESULTS: His best-corrected visual acuity improved from 1/10 to 3/10 after the 3rd injection, and from 1/10 to 4/10 after the 6th one. The central retinal thickness was evaluated by optical coherence tomography and improved from 310 to 233 μm, with the resolution of both the associated serous detachments and the cystoid macular edema; an almost complete reabsorption of the hard exudates at the end of the treatment was also observed. The macroaneurysm lumen almost obliterated after the 3rd injection and completely collapsed at the end of treatment.

CONCLUSIONS: Intravitreal ranibizumab may be effective in the treatment of long-standing macular edema associated with foveal macroaneurysms. To the best of our knowledge, this is the first report of a retinal macroaneurysm located so close to the foveal avascular zone.

PMID: 26120315 [PubMed] PMCID: PMC4478313

J Ocul Pharmacol Ther. 2015 Jul-Aug;31(6):357-62. Epub 2015 Jun 3.

Choroidal Thickness Changes After Intravitreal Antivascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration: Ranibizumab Versus Aflibercept.

Gharbiya M, Cruciani F, Mariotti C, Grandinetti F, Marenco M, Cacace V.

PURPOSE: To compare the changes in subfoveal choroidal thickness (CT) in eyes with neovascular age-related macular degeneration (nAMD) treated with intravitreal ranibizumab or aflibercept.

METHODS: In this retrospective case series, the medical records of 28 patients with nAMD treated with at least 3 consecutive monthly injections of ranibizumab (0.5 mg/0.05 mL) or aflibercept (2 mg/0.05 mL) between December 2013 and June 2014 and who were followed up for at least 3 months were reviewed. Subfoveal choroidal thickness was measured using enhanced depth imaging optical coherence tomography.

RESULTS: Choroidal thickness decreased over time in the aflibercept group, but was unchanged throughout the study in the ranibizumab group. At each time point, the decrease was significantly greater in aflibercept-treated eyes compared with ranibizumab-treated eyes ($P<0.05$). No significant change in best-corrected visual acuity (BCVA) was seen in either group during follow-up. There was no correlation between change in choroidal thickness and age, sex, duration of previous antivascular endothelial growth factor treatment, number of previous injections, spherical equivalent, baseline choroidal thickness, and the BCVA outcome in either group.

CONCLUSIONS: Subfoveal choroidal thickness appeared to decrease significantly in eyes with nAMD during 3 months of aflibercept treatment. No corresponding decrease in choroidal thickness occurred in ranibizumab-treated eyes.

PMID: 26133059 [PubMed - in process]

Am J Ophthalmol. 2015 Jul 2. [Epub ahead of print]

Factors Influencing the Treatment Response of Pigment Epithelium Detachment in Age-Related Macular Degeneration.

Dirani A, Ambresin A, Marchionno L, Decugis D, Mantel I.

PURPOSE: To study the effect of various baseline factors, particularly the type of drug (ranibizumab vs. aflibercept), on the functional and anatomical response of treatment-naïve pigment epithelial detachment (PED) associated with neovascular age-related macular degeneration (neovascular AMD), after three intravitreal injections.

DESIGN: Retrospective consecutive case series.

METHODS: This study included 102 patients (n = 115 eyes) with treatment-naïve neovascular AMD and PED (>150 μm), who were treated with either ranibizumab (n = 68 eyes) or aflibercept (n = 47 eyes). A multivariate analysis using stepwise linear regression was performed in order to assess factors influencing visual acuity improvement, and treatment response of PED height after three monthly injections.

RESULTS: Multivariate analysis revealed that better visual improvement was associated with lower best corrected visual acuity (BCVA) at baseline ($p = 0.001$), presence of subretinal fluid ($p = 0.001$), and retinal angiomatous proliferation ($p = 0.001$); PED reduction was associated with higher PED at baseline ($p = 0.001$), predominantly serous PED ($p = 0.003$), and the use of aflibercept ($p = 0.022$). Drug type was not associated with change in BCVA at 3 months.

CONCLUSION: Eyes with neovascular AMD and PED showed significant functional and anatomical response after three monthly intravitreal anti-VEGF injections. The functional response depended on baseline BCVA, presence of subretinal fluid and retinal angiomatous proliferation, while anatomic response

was influenced by baseline PED height, degree of vascularization and drug type. Drug type was not associated with change in BCVA, but had a weak effect on anatomical response.

PMID: 26144701 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 Jul 3. [Epub ahead of print]

Anti-vascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy with polyps resembling grape clusters.

Lee JH, Lee WK.

PURPOSE: The objective of this study was to investigate the 2-year outcomes of treatment with anti-vascular endothelial growth factor (VEGF) in patients with polypoidal choroidal vasculopathy (PCV) with polyps resembling grape clusters.

METHODS: Twenty eyes in 20 patients were included. All patients initially received three consecutive anti-VEGF injections, followed by an as-needed re-injection schedule. Patients were followed regularly at 1- to 3 -month intervals. The primary outcome was change in best-corrected visual acuity (BCVA).

RESULTS: The mean number of injections administered over the course of 24 months was 12.50 ± 2.77 (range, 9-18). The logarithm of the minimum angle of resolution (logMAR) BCVA improved from 0.61 ± 0.28 to 0.42 ± 0.27 at 12 months (P = 0.015), and 0.44 ± 0.31 at 24 months (P = 0.056). At 24 months, BCVA had improved in 6 (30.0 %) eyes by 0.3 logMAR or more, was stable in 11 (55.0 %) eyes, and had decreased in 3 (15.0 %) eyes. Complete absorption of fluid was achieved with anti-VEGF treatment in 18 (90 %) eyes at least once during the 2-year follow-up period, and 10 (50 %) eyes revealed a dry macula at 24 months. Two eyes (10.0 %) received rescue photodynamic therapy because subfoveal fluid persisted despite six and seven consecutive anti-VEGF injections. Of 18 eyes treated only with anti-VEGF agents, 3 (16.7 %) revealed partial resolution of the polypoidal lesions at 24 months.

CONCLUSIONS: A treatment regimen with anti-VEGF effectively improved or maintained visual acuity over a 24-month period in patients with PCV with clusters of grape-like polyps, and required frequent injections, comparable to typical choroidal neovascularization in age-related macular degeneration.

PMID: 26138657 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Jul 7;15(1):71.

Comparing the effectiveness and costs of Bevacizumab to Ranibizumab in patients with Diabetic Macular Edema: a randomized clinical trial (the BRDME study).

Schauwvlieghe AM, Dijkman G, Hooymans JM, Verbraak FD, Hoyng CB, Dijkgraaf MG, Van Leeuwen R, Vingerling JR, Moll AC, Schlingemann RO.

BACKGROUND: The effectiveness of ranibizumab in the treatment of diabetic macular edema has been proven with large clinical trials. For bevacizumab only two clinical trials have been published and a head-to-head comparison is lacking to date. However, if proved non-inferior to ranibizumab, use of the off-label bevacizumab could reduce costs enormously without a loss in visual acuity. A cost-effectiveness study has been designed to substantiate this hypothesis.

AIM: To compare the effectiveness and costs of 1.25 mg of bevacizumab to 0.5 mg ranibizumab given as monthly intravitreal injections during 6 months in patients with diabetic macular edema. It is hypothesized that bevacizumab is non-inferior to ranibizumab regarding its effectiveness.

DESIGN: This is a randomized, controlled, double masked, clinical trial in 246 patients in seven academic trial centres in The Netherlands.

OUTCOMES: The primary outcome measure is the change in best-corrected visual acuity (BCVA) in the study eye from baseline to month 6. Secondary outcomes are the proportions of patients with a gain or loss of 15 letters or more or a BCVA of 20/40 or more at 6 months, the change in leakage on fluorescein angiography and the change in foveal thickness by optical coherence tomography at 6 months, the number of adverse events in 6 months, and the costs per quality adjusted life-year of the two treatments.

PMID: 26149170 [PubMed - in process] PMCID: PMC4491889

Pak J Med Sci. 2015;31(3):510-5.

Efficacy and safety of Pro Re Nata regimen without loading dose ranibizumab injections in retinal vein occlusion.

Unsal E, Eltutar K, Sultan P, Gungel H.

OBJECTIVES: To evaluate the effects and safety of intravitreal ranibizumab on visual acuity and anatomic results in the treatment of macular edema due to retinal vein occlusion (RVO).

METHODS: Forty Six eyes of 45 patients who were administered intravitreal ranibizumab because of macular edema due to Retinal Vein Occlusion (RVO) were included in this retrospective clinical study. During monthly follow-up, the best corrected visual acuity values in terms of LogMAR with The Early Treatment Diabetic Retinopathy Study (ETDRS) chart, central macular thickness (CMT), and complications were examined. Cases were classified as central retinal vein occlusion (CRVO), superotemporal branch retinal vein occlusion (BRVO), and inferotemporal BRVO. We only included RVO patients but using ETDRS chart for the vision measurement.

RESULTS: In all follow-up months, there was a significant increase in BCVA in all RVO cases and in superotemporal BRVO cases after the first injection of ranibizumab. Although there was no significant increase in the 1(st) month of follow-up period compared to pre-treatment, there was significant increase in 2-6 months in inferotemporal BRVO patients. There was no statistically significant increase in 1(st) and 2 (nd) month follow-up periods compared to pre-treatment; however there was a significant increase in 3-6 months in the CRVO patients. There was a significant decrease in average CMT measurements in all follow -up months compared to pre-treatment in all RVO cases, in superotemporal and inferotemporal BRVO cases. There was no significant decrease in average CMT measurements in the 1(st), 2nd, and 3(rd) months compared to pre-treatment although there was a significant decrease in 4-6 months in cases included in the CRVO patients.

CONCLUSIONS: Intraocular ranibizumab injections provided rapid, effective treatment for macular edema due to RVO with low rates of ocular and nonocular safety events. However, repeated injections and frequent follow-up intervals may be required.

PMID: 26150834 [PubMed] PMCID: PMC4485261

Ophthalmology. 2015 Jul 3. [Epub ahead of print]

Ranibizumab 0.5 mg for Diabetic Macular Edema with Bimonthly Monitoring after a Phase of Initial Treatment: 18-Month, Multicenter, Phase IIIB RELIGHT Study.

Pearce I, Banerjee S, Burton BJ, Chakravarthy U, Downey L, Gale RP, Gibson J, Pagliarini S, Patel J, Sivaprasad S, Andrews C, Brittain C, Warburton J; RELIGHT Study Group.

PURPOSE: To evaluate ranibizumab 0.5 mg using bimonthly monitoring and individualized re-treatment after monthly follow-up for 6 months in patients with visual impairment due to diabetic macular edema (DME).

DESIGN: A phase IIIb, 18-month, prospective, open-label, multicenter, single-arm study in the United

Kingdom.

PARTICIPANTS: Participants (N = 109) with visual impairment due to DME.

METHODS: Participants received 3 initial monthly ranibizumab 0.5 mg injections (day 0 to month 2), followed by individualized best-corrected visual acuity (BCVA) and optical coherence tomography-guided re-treatment with monthly (months 3-5) and subsequent bimonthly follow-up (months 6-18). Laser was allowed after month 6.

MAIN OUTCOME MEASURES: Mean change in BCVA from baseline to month 12 (primary end point), mean change in BCVA and central retinal thickness (CRT) from baseline to month 18, gain of ≥10 and ≥15 letters, treatment exposure, and incidence of adverse events over 18 months.

RESULTS: Of 109 participants, 100 (91.7%) and 99 (90.8%) completed the 12 and 18 months of the study, respectively. The mean age was 63.7 years, the mean duration of DME was 40 months, and 77.1% of the participants had received prior laser treatment (study eye). At baseline, mean BCVA was 62.9 letters, 20% of patients had a baseline BCVA of >73 letters, and mean baseline CRT was 418.1 μm, with 32% of patients having a baseline CRT <300 μm. The mean change in BCVA from baseline to month 6 was +6.6 letters (95% confidence interval [CI], 4.9-8.3), and after institution of bimonthly treatment the mean change in BCVA at month 12 was +4.8 letters (95% CI, 2.9-6.7; P < 0.001) and +6.5 letters (95% CI, 4.2-8.8) at month 18. The proportion of participants gaining ≥10 and ≥15 letters was 24.8% and 13.8% at month 12 and 34.9% and 19.3% at month 18, respectively. Participants received a mean of 6.8 and 8.5 injections over 12 and 18 months, respectively. No new ocular or nonocular safety findings were observed during the study.

CONCLUSIONS: The BCVA gain achieved in the initial 6-month treatment period was maintained with an additional 12 months of bimonthly ranibizumab PRN treatment.

PMID: 26150052 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2015 Jul 2. [Epub ahead of print]

Subretinal Hyperreflective Material in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Willoughby AS, Ying GS, Toth CA, Maguire MG, Burns RE, Grunwald JE, Daniel E, Jaffe GJ; Comparison of Age-Related Macular Degeneration Treatments Trials Research Group.

PURPOSE: To evaluate the association of subretinal hyperreflective material (SHRM) with visual acuity (VA), geographic atrophy (GA), and scar in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: The 1185 CATT participants.

METHODS: Masked readers graded scar and GA on fundus photography and fluorescein angiography and graded SHRM on time-domain and spectral-domain (SD) optical coherence tomography (OCT) throughout 104 weeks. Measurements of SHRM height and width in the fovea, within the center 1 mm2, or outside the center 1mm2 were obtained on SD OCT images at 56 (n = 76) and 104 (n = 66) weeks.

MAIN OUTCOME MEASURES: Presence of SHRM, as well as location and size, and associations with VA, scar, and GA.

RESULTS: Among CATT participants, the percentage with SHRM at enrollment was 77%, decreasing to

68% at 4 weeks after treatment and to 54% at 104 weeks. At 104 weeks, scar was present more often in eyes with persistent SHRM than in eyes with SHRM that resolved (64% vs. 31%; P < 0.0001). Among eyes with detailed evaluation of SHRM at weeks 56 (n = 76) and 104 (n = 66), mean VA letter score was 73.5 (standard error [SE], 2.8), 73.1 (SE, 3.4), 65.3 (SE, 3.5), and 63.9 (SE, 3.7) when SHRM was absent, present outside the central 1 mm2, present within the central 1 mm2 but not the foveal center, or present at the foveal center (P = 0.02), respectively. When SHRM was present, the median maximum height under the fovea, within the central 1 mm2 including the fovea and anywhere within the scan, was 86 µm, 120 µm, and 122 µm, respectively. Visual acuity was decreased with greater SHRM height and width (P < 0.05).

CONCLUSIONS: In eyes with neovascular age-related macular degeneration (AMD), SHRM is common and often persists after anti-vascular endothelial growth factor treatment. At 2 years, eyes with scar were more likely to have SHRM than other eyes. Greater SHRM dimensions were associated with worse VA. In eyes with neovascular AMD, SHRM is an important morphologic biomarker.

PMID: 26143666 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Jun 30. [Epub ahead of print]

PROGRESSION OF AGE-RELATED MACULAR DEGENERATION OVERLYING A LARGE CHOROIDAL VESSEL.

Inoue M, Dansingani KK, Freund KB.

PURPOSE: To describe a patient who showed progression of age-related macular degeneration along the course of an underlying large choroidal vessel.

METHODS: Retrospective case report.

RESULTS: An 84-year-old woman was diagnosed with age-related macular degeneration and followed for more than 6 years. Retinal pigment epithelial changes were more advanced in her right eye which had a thinner choroid than the fellow left eye. Multimodal imaging with swept-source optical coherence tomography showed that the progression of outer retinal and retinal pigment epithelial changes appeared to follow the course of a large choroidal vessel.

CONCLUSION: The authors hypothesize that large choroidal vessels can compress the overlying choriocapillaris, possibly leading to outer retinal ischemia, which subsequently could focally accelerate the course of age-related macular degeneration.

PMID: 26132988 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jun 17;9:1099-107. eCollection 2015.

Long-term (60-month) results for the implantable miniature telescope: efficacy and safety outcomes stratified by age in patients with end-stage age-related macular degeneration.

Boyer D, Freund KB, Regillo C, Levy MH, Garg S.

BACKGROUND: The purpose of this study was to evaluate the long-term results of an implantable miniature telescope (IMT) in patients with bilateral, end-stage, age-related macular degeneration (AMD).

METHODS: A prospective, open-label, multicenter clinical trial with fellow eye controls enrolled 217 patients (mean age 76 years) with AMD and moderate-to-profound bilateral central visual acuity loss (20/80-20/800) resulting from untreatable geographic atrophy, disciform scars, or both. A subgroup analysis was performed with stratification for age (patient age 65 to <75 years [group 1; n=70] and patient age ≥75 years [group 2; n=127]), with a comparative evaluation of change in best-corrected distance visual acuity (BCDVA), quality of life, ocular complications from surgery, adverse events, and endothelial cell density (ECD). Follow-up in

an extension study was 60 months.

RESULTS: Data were available for 22, 38, and 31 patients in group 1 and 42, 46, and 32 patients in group 2 at 36, 48, and 60 months, respectively. Mean BCDVA improvement from baseline to 60 months was 2.41±2.69 lines in all patients (n=76), with 2.64±2.55 lines in group 1 and 2.09±2.88 lines in group 2. Quality of life scores were significantly higher in group 1. The most common significant surgery-related ocular complications in group 1 were iritis >30 days after surgery (7/70; 10%) and persistent corneal edema (3/70; 4.3%); and in group 2 were a decrease in BCDVA in the implanted eye or IMT removal (10/127 each; 7.9%), corneal edema >30 days after surgery (9/127; 7.1%), and persistent corneal edema (6/127; 4.7%). Significant adverse events included four corneal transplants, comprising two (2.9%) in group 1 and two (1.6%) in group 2. At 60 months, one patient in group 1 (3.2%) and three patients in group 2 (9.4%) had lost ≥2 lines of vision. The IMT was removed in one (1.4%) and ten (7.9%) patients in group 1 and group 2, respectively. Mean ECD loss was 20% at 3 months. Chronic loss was 3% per year. ECD loss was less in group 1 than in group 2 (35% versus 40%, respectively) at 60 months.

CONCLUSION: Long-term results show substantial retention of improvement in BDCVA. Chronic ECD loss was consistent with that reported for conventional intraocular lenses. The IMT performed as well in group 1 (the younger group) as it did in group 2 through month 60. Younger patients retained more vision than their older counterparts and had fewer adverse events. Although not a specified outcome for this study, patients younger than 65 years also fared better than those in group 2 and retained more vision with fewer adverse events through month 60.

PMID: 26124633 [PubMed] PMCID: PMC4476474

J Med Imaging (Bellingham). 2015 Jan;2(1):014501. Epub 2015 Jan 12.

Automated segmentation of geographic atrophy in fundus autofluorescence images using supervised pixel classification.

Hu Z, Medioni GG, Hernandez M, Sadda SR.

Abstract: Geographic atrophy (GA) is a manifestation of the advanced or late stage of age-related macular degeneration (AMD). AMD is the leading cause of blindness in people over the age of 65 in the western world. The purpose of this study is to develop a fully automated supervised pixel classification approach for segmenting GA, including uni- and multifocal patches in fundus autofluorescene (FAF) images. The image features include region-wise intensity measures, gray-level co-occurrence matrix measures, and Gaussian filter banks. A [Formula: see text]-nearest-neighbor pixel classifier is applied to obtain a GA probability map, representing the likelihood that the image pixel belongs to GA. Sixteen randomly chosen FAF images were obtained from 16 subjects with GA. The algorithm-defined GA regions are compared with manual delineation performed by a certified image reading center grader. Eight-fold cross-validation is applied to evaluate the algorithm performance. The mean overlap ratio (OR), area correlation (Pearson's [Formula: see text]), accuracy (ACC), true positive rate (TPR), specificity (SPC), positive predictive value (PPV), and false discovery rate (FDR) between the algorithm- and manually defined GA regions are [Formula: see text], [Formula: see text], [Formula: see text], [Formula: see text], [Formula: see text], [Formula: see text], and [Formula: see text], respectively.

PMID: 26158084 [PubMed] PMCID: PMC4478845

Curr Stem Cell Rep. 2015 Jun;1(2):79-91.

Regenerating Retinal Pigment Epithelial Cells to Cure Blindness: A Road Towards Personalized Artificial Tissue.

Jha BS, Bharti K.

Abstract: Retinal pigment epithelium (RPE) is a polarized monolayer tissue that functions to support the health and integrity of retinal photoreceptors (PRs). RPE atrophy has been linked to pathogenesis of age-related macular degeneration (AMD), a leading cause of blindness in elderly in the USA. RPE atrophy in AMD leads to the PR cell death and vision loss. It is thought that replacing diseased RPE with healthy RPE tissue can prevent PR cell death. Retinal surgical innovations have provided proof-of-principle data that autologous RPE tissue can replace diseased macular RPE and provide visual rescue in AMD patients. Current efforts are focused on developing an in vitro tissue using natural and synthetic scaffolds to generate a polarized functional RPE monolayer. In the future, these tissue-engineering approaches combined with pluripotent stem cell technology will lead to the development of personalized and "off-the-shelf" cell therapies for AMD patients. This review summarizes the historical development and ongoing efforts in surgical and in vitro tissue engineering techniques to develop a three-dimensional therapeutic native RPE tissue substitute.

PMID: 26146605 [PubMed] PMCID: PMC4485455

Asia Pac J Ophthalmol (Phila). 2015 Jul 2. [Epub ahead of print]

Predictability of Recalcitrance in Neovascular Age-Related Macular Degeneration With Indocyanine Green Angiography.

Rush RB, Rush SW.

PURPOSE: This study aimed to evaluate the utility of indocyanine green (ICG) angiography in predicting recalcitrance in neovascular age-related macular degeneration (nAMD).

DESIGN: Retrospective case series.

METHODS: The charts of treatment-naive subjects with nAMD undergoing anti-vascular endothelial growth factor (VEGF) therapy during a 6-month period were retrospectively reviewed. The study group consisted of subjects with persistent retinal edema on optical coherence tomography (OCT) despite 6 consecutive monthly anti-VEGF injections. The control group was age-matched to the study group and consisted of subjects who demonstrated complete resolution of retinal edema on OCT after 3 or fewer monthly anti-VEGF injections.

RESULTS: There were 42 study cases and 42 controls included in the analysis. The baseline visual acuity, central macular thickness on OCT, and choroidal neovascularization (CNV) surface area on ICG angiography were statistically similar between the study and control groups. The CNV surface area on ICG angiography 2 months after starting consecutive monthly anti-VEGF injections increased from a baseline of 1.78 ± 0.86 to 2.66 ± 0.92 mm in the study group ($P = 0.008$) and decreased from a baseline of 1.94 ± 0.97 to 1.12 ± 0.05 mm in the control group ($P = 0.04$); this change in CNV size on ICG angiography from baseline to 2-month follow-up was statistically significant between the study and control groups ($P < 0.0001$).

CONCLUSIONS: Change in CNV surface area on ICG angiography can predict which subjects with nAMD are likely to have persistent retinal edema on OCT after 6 or more consecutive monthly anti-VEGF injections.

PMID: 26147016 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2015 May;63(5):384-90.

Clinical applications of choroidal imaging technologies.

Chhablani J, Barteselli G.

Abstract: Choroid supplies the major blood supply to the eye, especially the outer retinal structures. Its

understanding has significantly improved with the advent of advanced imaging modalities such as enhanced depth imaging technique and the newer swept source optical coherence tomography. Recent literature reports the findings of choroidal changes, quantitative as well as qualitative, in various chorioretinal disorders. This review article describes applications of choroidal imaging in the management of common diseases such as age-related macular degeneration, high myopia, central serous chorioretinopathy, chorioretinal inflammatory diseases, and tumors. This article briefly discusses future directions in choroidal imaging including angiography.

PMID: 26139797 [PubMed - in process]

Indian J Ophthalmol. 2015 May;63(5):378-83.

En-face optical coherence tomography in the diagnosis and management of age-related macular degeneration and polypoidal choroidal vasculopathy.

Lau T, Wong IY1, Iu L, Chhablani J, Yong T, Hideki K, Lee J, Wong R.

Abstract: Optical coherence tomography (OCT) is a noninvasive imaging modality providing high-resolution images of the central retina that has completely transformed the field of ophthalmology. While traditional OCT has produced longitudinal cross-sectional images, advancements in data processing have led to the development of en-face OCT, which produces transverse images of retinal and choroidal layers at any specified depth. This offers additional benefit on top of longitudinal cross-sections because it provides an extensive overview of pathological structures in a single image. The aim of this review was to discuss the utility of en-face OCT in the diagnosis and management of age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV). En-face imaging of the inner segment/outer segment junction of retinal photoreceptors has been shown to be a useful indicator of visual acuity and a predictor of the extent of progression of geographic atrophy. En-face OCT has also enabled high-resolution analysis and quantification of pathological structures such as reticular pseudodrusen (RPD) and choroidal neovascularization, which have the potential to become useful markers for disease monitoring. En-face Doppler OCT enables subtle changes in the choroidal vasculature to be detected in eyes with RPD and AMD, which has significantly advanced our understanding of their pathogenesis. En-face Doppler OCT has also been shown to be useful for detecting the polypoid lesions and branching vascular networks diagnostic of PCV. It may therefore serve as a noninvasive alternative to fluorescein and indocyanine green angiography for the diagnosis of PCV and other forms of the exudative macular disease.

PMID: 26139796 [PubMed - in process]

Int Ophthalmol. 2015 Jul 2. [Epub ahead of print]

Choroidal neovascularisation as an unusual ophthalmic manifestation of cat-scratch disease in an 8 -year-old girl.

Latanza L, Viscogliosi F, Solimeo A, Calabrò F, De Angelis V, De Rosa P.

Abstract: To report the first case of choroidal neovascularisation (CNV) that appeared during the primary Bartonella henselae infection in an 8-year-old girl. An 8-year-old girl was referred to our clinic complaining of a central scotoma in the right eye. Fundus examination revealed a bilateral disc oedema and in the right eye neuroretinitis with macular star and CNV, which was confirmed by fluorescein angiography. The optical coherence tomography revealed the presence of macular serous retinal detachment. Laboratory analysis showed rising IgM and IgG titres for B. henselae. Cat-scratch disease was diagnosed, and an 8-week treatment with azithromycin was initiated. In addition, an intravitreal injection of ranibizumab was performed in the right eye to treat the CNV. A month later, we decided to administer a systemic antibiotic again for an additional 5 months, due to the persistence of papillitis. Cat-scratch disease should be considered among the different causes of inflammatory CNV secondary to infectious uveitis. Our case was the first described in the literature in which a CNV appeared during the primary infection and not as a later complication. The

combination of systemic antibiotic treatment with intravitreal anti-VEGF therapy was a successful choice because it allowed us to obtain the complete resolution of neuroretinitis, associated with the scarring of the choroidal neovascular membrane, with a final visual acuity of 20/20 in both eyes.

PMID: 26135983 [PubMed - as supplied by publisher]

Doc Ophthalmol. 2015 Jul 2. [Epub ahead of print]

The value of multifocal electroretinography to predict progressive visual acuity loss in early AMD.

Ambrosio L, Ambrosio G, Nicoletti G, de Crecchio G, Falsini B.

BACKGROUND: To investigate, in a prospective study, the role of multifocal electroretinography (mfERG) for predicting visual acuity decline in early age-related macular degeneration (AMD) with time.

METHODS: Twenty-six early AMD patients (12 males and 14 females, mean age 66.9 ± 9.8; range 46-82 years) were included in the study. A complete ophthalmic examination and mfERG (Retiscan, Roland Germany, ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first-order kernel mfERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg2), the P1 amplitude (μV) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves.

RESULTS: The loss in the mfERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS visual acuity with time (P = 0.004). ROC analysis showed that, after 24 months, the average decline in visual acuity was greater (3 letters vs 0.4 letters, P = 0.0021) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg2, compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95 % confidence interval 0.50-0.92) with a sensitivity of 64.3 % (35.14-87.24 %) and a specificity of 91.7 % (61.52-99.79 %).

CONCLUSIONS: The present results indicate that mfERG P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD.

PMID: 26135127 [PubMed - as supplied by publisher]

Med Phys. 2015 Jun;42(6):3644.

TU-F-CAMPUS-T-02: Monte Carlo Evaluation of Kilovoltage Radiosurgery with AuNPs for Age Related Macular Degeneration (AMD).

Brivio D, Zygmanski P, Sajo E, Makrigiorgos G, Ngwa W.

PURPOSE: To evaluate the benefit of gold nanoparticles (AuNP) in radiosurgery of Age related Macular Degeneration (AMD) using Monte Carlo (MC) simulation. AMD disease causes vision loss due to a leaky vasculature of the endothelial cells. Radiosurgical therapy aims to destroy this vasculature while minimizing the delivered dose to healthy tissues of the eye. AuNP known to enhance local dose have been targeted to the macular choroidal endothelial cells to increase the therapeutic efficacy.

METHODS: Dose enhancement ratio (DER) in macula endothelial cells due to a thin layer of AuNP has been calculated by a MC radiation transport simulation. AuNP layer (10-100nm) has been placed on the bottom of the macula at 2.4cm depth in a water parallelepiped 3×3×6cm3. This layer has been modeled considering various concentrations of AuNP ranging from 5.5-200mg per gram of endothelial cell (volume 10×10×2um3). The x-ray source is 100kVp 4mm diameter beam tilted 0°-30° with respect to the lens.

RESULTS: DER in endothelial cell for AuNP concentration of 31mg/g (shown experimentally feasible) and 10-100nm sizes is about 1.8. Tilting 4mm-beam does not reduce the enhancement but allows to avoid the

surrounding tissues. Dose distribution in the AuNP vicinity has a significant increase within 30um, peaked at AuNP interface. DER inside and outside of the irradiation 4mm-field are the same while the actual delivered dose is more than one order of magnitude lower outside the field. Compared to 100kVp, usage of filtered spectra with enhanced flux in the region 20keV-40keV shows further increase of DER by about 20%. Dose to the neighboring organs such as retina/optic nerve are reduced accordingly.

CONCLUSION: The results of this MC simulation provide further confirmation of the potential to enhance DER with AuNP from previous analytical calculations. This study provides impetus to improve treatment effectiveness of AMD disease with radiotherapy.

PMID: 26129120 [PubMed - in process]

Med Phys. 2015 Jun;42(6):3334.

SU-E-T-16: A Comparison of Expected Dwell Times and Dose Variations for NAMD Patients Treated with An Episcleral Brachytherapy Device.

Hamilton R, Patel P, Balaggan K, Restori M, Ilginis T, Drew M, McGovern M, Vitali J, Marsteller L.

PURPOSE: To evaluate the variations in dwell times and doses expected when using an episcleral brachytherapy device for treatment of neovascular agerelated macular degeneration (n-AMD) based on accurate imaging modalities

METHODS: Data from 40 eyes from 40 subjects with known n- AMD acquired through the Distance of Choroid Study (DOCS) conducted at Moorfields Eye Hospital was used to determine the target depth; the distance from the outer scleral surface of the eye, through the choroid, to the apex of the choroidal neovascularization (CNV). Each subject underwent, in triplicate, enhanced-depth Spectral Domain Optical Coherence Tomography (SD-OCT), Swept Source Optical Coherence Tomography, (SS-OCT) and Ocular Ultrasound (O-US). These data are the most comprehensive and accurate measurements of the dimensions of the CNV and adjacent layers of the eye for this cohort of patients. During treatment of n-AMD, patients receive a dose of 24Gy to the apex at the target depth. Using the percentage depth dose for a Sr-90 episcleral brachytherapy device, dwell times and doses to the apex were computed to determine the expected variations.

RESULTS: The mean target depth and the 95% confidence interval (CI) determined by combining O-US with SD-OCT were 1326 (956,1696)µm and with SS-OCT were 1332 (970,1693)µm. The calculated corresponding mean dwell times and 95% (CI) were 334 (223,445)s and 335 (226,445)s for SD-OCT and SS-OCT determined depths, respectively. The corresponding mean apex dose and 95% (CI) were 24 (35.9,18.0)Gy (SD-OCT) and 24 (35.6,18.1)Gy (SS-OCT).

CONCLUSION: For episcleral brachytherapy treatment of n-AMD, using a patient population average target depth for treatment planning is inadequate, resulting in dose variations of a factor of approximately two over the 95% CI and larger variations for a nontrivial segment of the population. Each patient should have individualized imaging studies to determine the target depth for use in the dwell time calculation. Study was sponsored by Salutaris Medical Devices, Ltd., a subsidiary of Salutaris Medical Devices, Inc. Hamilton and Marsteller are founders of Salutaris Medical Devices, Inc. Drew, McGovern and Vitali are minor equity holders in Salutaris Medical Devices, Inc.

PMID: 26127684 [PubMed - in process]

Cardiovasc Hematol Disord Drug Targets. 2015 Jul 1. [Epub ahead of print]

VALIDITY OF OXYGEN-OZONE THERAPY AS INTEGRATED MEDICATION FORM IN CHRONIC INFLAMMATORY DISEASES.

Bocci V, Zanardi I, Valacchi G, Borrelli E, Travagli V.

Abstract: The state-of-the-art of oxygen-ozone therapy is now clarified and all the mechanisms of action of medical ozone are within classical biochemistry and molecular biology. The outcomes of standard treatments in peripheral arterial occlusive disease (PAOD) and dry-form of age-related macular degeneration (AMD) have been compared with the documented therapeutic results achieved with ozonated autohemotherapy (O-AHT). On the other hand, the clinical data of O-AHT on stroke remain indicative. As the cost of O-AHT is almost irrelevant, its application in all public hospitals, especially those of poor Countries, would allow two advantages: the first is for the patient, who will improve her/his conditions, and the second is for Health Authorities burdened with increasing costs. The aim of this paper is to report to clinical scientists that O-AHT is a scientific-based therapeutic approach without side effects. The integration of O-AHT with effective approved drugs is likely to yield the best clinical results in several chronic inflammatory diseases.

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Pathogenesis

Ophthalmic Res. 2015 Jul 9;54(2):64-73. [Epub ahead of print]

Age-Related Macular Degeneration: A Complementopathy?

Kijlstra A, Berendschot TT.

Abstract:Age-related macular degeneration (AMD) is a progressive eye disease affecting many elderly individuals. It has a multifactorial pathogenesis and is associated with numerous environmental (e.g. smoking, light and nutrition) and genetic risk factors. A breakthrough in the mechanisms causing AMD is emerging; the involvement of the alternative pathway of the complement system appears to play a pivotal role. This has led to the statement that AMD is a disease caused by a hyperactive complement system, allowing the term 'complementopathy' to define it more precisely. Abundant evidence includes: the identification of drusen components as activators of complement, immunohistochemical data showing the presence of many species of the complement system in the retinal pigment epithelium-Bruch's membrane-choroidocapillary region of AMD eyes, a strong association of AMD with certain genetic complement protein variants, raised complement levels in blood from AMD patients and the preliminary successful treatments of geographic atrophy with complement factor D (FD) inhibitors. FD is the rate-limiting enzyme of the alternative complement pathway, and is produced by adipose tissue. Recent findings suggest that nutrition may play a role in controlling the level of FD in the circulation. Addressing modifiable risk factors such as smoking and nutrition may thus offer opportunities for the prevention of AMD. © 2015 S. Karger AG, Basel.

PMID: 26159686 [PubMed - as supplied by publisher]

Ophthalmologe. 2015 Jul 4. [Epub ahead of print]

[The role of the vitreous body in diseases of neighboring structures].[Article in German]

Gekeler K, Priglinger S, Gekeler F, Priglinger C.

BACKGROUND: The vitreoretinal interface is not merely the space between the vitreous body and the retina but it is also a site for highly complex pathologies with the vitreous body exerting an influence on all the neighbouring structures.

METHODS: A literature search was performed in Pubmed and current book articles

RESULTS: This review article highlights the role of the vitreous body in vitreomacular adhesion and traction, in the development of macular holes and epiretinal membranes as well as its role in age-related macular degeneration. In the retinal periphery the vitreous structures play a pivotal role in retinal tears and detachment as well as in diabetic and other proliferative vitreoretinopathies. The role of the vitreous bodyin

the emergence of various forms of cataract is often underestimated.

DISCUSSION: Vitreo-etinal surgeons should thoroughly understand the pathophysiological relationship between the vitreous body and the neighboring structures, especially in the era of medical vitreolysis.

PMID: 26142226 [PubMed - as supplied by publisher]

Genome Med. 2015 Jun 19;7(1):58. eCollection 2015.

Restoration of mesenchymal retinal pigmented epithelial cells by TGFβ pathway inhibitors: implications for age-related macular degeneration.

Radeke MJ, Radeke CM, Shih YH, Hu J, Bok D, Johnson LV, Coffey PJ.

BACKGROUND: Age-related macular degeneration (AMD) is a leading cause of blindness. Most vision loss occurs following the transition from a disease of deposit formation and inflammation to a disease of neovascular fibrosis and/or cell death. Here, we investigate how repeated wound stimulus leads to seminal changes in gene expression and the onset of a perpetual state of stimulus-independent wound response in retinal pigmented epithelial (RPE) cells, a cell-type central to the etiology of AMD.

METHODS: Transcriptome wide expression profiles of human fetal RPE cell cultures as a function of passage and time post-plating were determined using Agilent 44 K whole genome microarrays and RNA-Seq. Using a systems level analysis, differentially expressed genes and pathways of interest were identified and their role in the establishment of a persistent mesenchymal state was assessed using pharmacological-based experiments.

RESULTS: Using a human fetal RPE cell culture model that considers monolayer disruption and subconfluent culture as a proxy for wound stimulus, we show that prolonged wound stimulus leads to terminal acquisition of a mesenchymal phenotype post-confluence and altered expression of more than 40 % of the transcriptome. In contrast, at subconfluence fewer than 5 % of expressed transcripts have two-fold or greater expression differences after repeated passage. Protein-protein and pathway interaction analysis of the genes with passage-dependent expression levels in subconfluent cultures reveals a 158-node interactome comprised of two interconnected modules with functions pertaining to wound response and cell division. Among the wound response genes are the TGFβ pathway activators: TGFB1, TGFB2, INHBA, INHBB, GDF6, CTGF, and THBS1. Significantly, inhibition of TGFBR1/ACVR1B mediated signaling using receptor kinase inhibitors both forestalls and largely reverses the passage-dependent loss of epithelial potential; thus extending the effective lifespan by at least four passages. Moreover, a disproportionate number of RPE wound response genes have altered expression in neovascular and geographic AMD, including key members of the TGFβ pathway.

CONCLUSIONS: In RPE cells the switch to a persistent mesenchymal state following prolonged wound stimulus is driven by lasting activation of the TGFβ pathway. Targeted inhibition of TGFβ signaling may be an effective approach towards retarding AMD progression and producing RPE cells in quantity for research and cell-based therapies.

PMID: 26150894 [PubMed] PMCID: PMC4491894

Biochim Biophys Acta. 2015 Jul 1. [Epub ahead of print]

Alpha-crystallin-derived peptides as therapeutic chaperones.

Raju M, Santhoshkumar P, Krishna Sharma K.

BACKGROUND: The demonstration of chaperone-like activity in peptides (mini-chaperones) derived from α -crystallin's chaperone region has generated significant interest in exploring the therapeutic potential of peptide chaperones in diseases of protein aggregation. Recent studies in experimental animals show that

mini-chaperones could reach intended targets and alter the disease phenotype. Although mini-chaperones show potential benefits against protein aggregation diseases, they do tend to form aggregates on storage. There is thus a need to fine-tune peptide chaperones to increase their solubility, pharmacokinetics, and biological efficacy.

SCOPE OF REVIEW: This review summarizes the properties and the potential therapeutic roles of mini-chaperones in protein aggregation diseases and highlights some of the refinements needed to increase the stability and biological efficacy of mini-chaperones while maintaining or enhancing their chaperone-like activity against precipitation of unfolding proteins.

MAJOR CONCLUSIONS: Mini-chaperones suppress the aggregation of proteins, block amyloid fibril formation, stabilize mutant proteins, sequester metal ions, and exhibit antiapoptotic properties. Much work must be done to fine-tune mini-chaperones and increase their stability and biological efficacy. Peptide chaperones could have a great therapeutic value in diseases associated with protein aggregation and apoptosis.

GENERAL SIGNIFICANCE: Accumulation of misfolded proteins is a primary cause for many age-related diseases, including cataract, macular degeneration, and various neurological diseases. Stabilization of native proteins is a logical therapeutic approach for such diseases. Mini-chaperones, with their inherent antiaggregation and antiapoptotic properties, may represent an effective therapeutic molecule to prevent the cascade of protein conformational disorders. Future studies will further uncover the therapeutic potential of mini-chaperones.

PMID: 26141743 [PubMed - as supplied by publisher]

J Ophthalmol. 2015;2015:275435. Epub 2015 Jun 4.

Role of Peroxisome Proliferator-Activated Receptor γ in Ocular Diseases.

Zhang S, Gu H, Hu N.

Abstract: Peroxisome proliferator-activated receptor γ (PPAR γ), a member of the nuclear receptor superfamily, is a ligand-activated transcription factor that plays an important role in the control of a variety of physiological processes. The last decade has witnessed an increasing interest for the role played by the agonists of PPAR γ in antiangiogenesis, antifibrosis, anti-inflammation effects and in controlling oxidative stress response in various organs. As the pathologic mechanisms of major blinding diseases, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), keratitis, and optic neuropathy, often involve neoangiogenesis and inflammation- and oxidative stress-mediated cell death, evidences are accumulating on the potential benefits of PPAR γ to improve or prevent these vision threatening eye diseases. In this paper we describe what is known about the role of PPAR γ in the ocular pathophysiological processes and PPAR γ agonists as novel adjuvants in the treatment of eye diseases.

PMID: 26146566 [PubMed] PMCID: PMC4471377

Biol Pharm Bull. 2015;38(7):1076-80.

Deferiprone Protects against Photoreceptor Degeneration Induced by Tunicamycin in the Rat Retina.

Shirai Y, Mori A, Nakahara T, Sakamoto K, Ishii K.

Abstract: Endoplasmic reticulum stress has been reported to be involved in the pathogenesis of retinitis pigmentosa, macular degeneration and diabetic retinopathy. In the present study, we examined the effects of deferiprone, an iron chelator, on photoreceptor degeneration induced by tunicamycin (300 nmol/eye), an endoplasmic reticulum stress inducer, in the rat retina. Scotopic electroretinogram measurement and

morphometric evaluation were done 7 d after the injection of tunicamycin. In the scotopic electroretinogram, intravitreal deferiprone (5 nmol/eye) injected simultaneously with tunicamycin significantly reduced the decreases in a- and b-wave amplitudes induced by tunicamycin. Morphometric evaluation showed that deferiprone significantly reduced thinning of the outer nuclear layer, the inner segment and the outer segment. These results suggest that iron chelation therapy may be a good candidate for the treatment of eye diseases related to endoplasmic reticulum stress.

PMID: 26133718 [PubMed - in process]

J Ophthalmol. 2015;2015:309510. Epub 2015 Jun 1.

Histological Characterization of the Dicer1 Mutant Zebrafish Retina.

Akhtar S, Patnaik SR, Kotapati Raghupathy R, Al-Mubrad TM, Craft JA, Shu X.

Abstract: DICER1, a multidomain RNase III endoribonuclease, plays a critical role in microRNA (miRNA) and RNA-interference (RNAi) functional pathways. Loss of Dicer1 affects different developmental processes. Dicer1 is essential for retinal development and maintenance. DICER1 was recently shown to have another function of silencing the toxicity of Alu RNAs in retinal pigment epithelium (RPE) cells, which are involved in the pathogenesis of age related macular degeneration. In this study, we characterized a Dicer1 mutant fish line, which carries a nonsense mutation (W1457Ter) induced by N-ethyl-N-nitrosourea mutagenesis. Zebrafish DICER1 protein is highly conserved in the evolution. Zebrafish Dicer1 is expressed at the earliest stages of zebrafish development and persists into late developmental stages; it is widely expressed in adult tissues. Homozygous Dicer1 mutant fish (DICER1(W1457Ter/W1457Ter)) have an arrest in early growth with significantly smaller eyes and are dead at 14-18 dpf. Heterozygous Dicer1 mutant fish have similar retinal structure to that of control fish; the retinal pigment epithelium (RPE) cells are normal with no sign of degeneration at the age of 20 months.

PMID: 26124959 [PubMed] PMCID: PMC4466466

Neurobiol Aging. 2015 Jun 15. [Epub ahead of print]

Mitochondrial decline precedes phenotype development in the complement factor H mouse model of retinal degeneration but can be corrected by near infrared light.

Calaza KC, Kam JH, Hogg C, Jeffery G.

Abstract: Mitochondria produce adenosine triphosphate (ATP), critical for cellular metabolism. ATP declines with age, which is associated with inflammation. Here, we measure retinal and brain ATP in normal C57BL/6 and complement factor H knockout mice (Cfh-/-), which are proposed as a model of age-related macular degeneration. We show a significant premature 30% decline in retinal ATP in Cfh-/- mice and a subsequent shift in expression of a heat shock protein that is predominantly mitochondrial (Hsp60). Changes in Hsp60 are associated with stress and neuroprotection. We find no differences in brain ATP between C57BL/6 and Cfh-/- mice. Near infrared (NIR) increases ATP and reduces inflammation. ATP decline in Cfh-/- mice was corrected with NIR which also shifted Hsp60 labeling patterns. ATP decline in Cfh-/- mice occurs before inflammation becomes established and photoreceptor loss occurs and may relate to disease etiology. However, ATP levels were corrected with NIR. In summary, we provide evidence for a mitochondrial basis for this disease in mice and correct this with simple light exposure known to improve mitochondrial function.

PMID: 26149919 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 Jul 7. [Epub ahead of print]

Abundance of infiltrating CD163+ cells in the retina of postmortem eyes with dry and neovascular age-related macular degeneration.

Lad EM, Cousins SW, Van Arnam JS, Proia AD.

PURPOSE: Prior research in animal models has suggested that retinal macrophages play an important role in age-related macular degeneration (AMD), but studies have insufficiently characterized the distribution of retinal macrophages in various stages of human AMD.

METHODS: In this case series, we analyzed H&E, periodic acid-Schiff, and CD163 and CD68 immunostained slides from 56 formaldehyde-fixed, paraffin-embedded autopsy eyes of patients over age 75: 11 age-matched, normal eyes, and 45 AMD eyes.

RESULTS: Qualitative analysis of the macula and retinal periphery revealed that all eyes contained a significant number of CD163+ cells but a negligible number of CD68+ cells. In normal eyes and eyes with thin or infrequent basal laminar deposits, CD163+ cells were restricted to the inner retina. In contrast, in AMD eyes with thick basal deposits, choroidal neovascular membranes, and geographic atrophy, qualitatively there was a marked increase in the number and size of the CD163+ cells in the outer retina, sub-retinal, and sub-retinal pigment epithelium space in the macula.

CONCLUSIONS: The changes in number and localization of retinal CD163+ cells in eyes with intermediate-severe AMD support a key role for macrophages in the pathogenesis and progression of the disease. A larger, quantitative study evaluating the distribution of macrophage subpopulations in postmortem AMD eyes is warranted.

PMID: 26148801 [PubMed - as supplied by publisher]

Sci Rep. 2015 Jul 7;5:11872.

Intravitreal TSG-6 suppresses laser-induced choroidal neovascularization by inhibiting CCR2(+) monocyte recruitment.

Jin Kim S, Ju Lee H, Yun JH, Hwa Ko J, Choi da Y, Youn Oh J.

Abstract: Choroidal neovascularization (CNV) is the hallmark of wet age-related macular degeneration (AMD), one of the leading causes of blindness in the elderly. Although the pathogenesis of CNV is not clear, a number of studies show that ocular-infiltrating macrophages and inflammation play a critical role in the development of CNV. TNFα-stimulated gene/protein (TSG)-6 is a multifunctional endogenous protein that has anti-inflammatory activities partly by regulating macrophage activation. Therefore, we here investigated the therapeutic potential of TSG-6 in a rat model of CNV induced by laser photocoagulation. Time course analysis showed that the expression of VEGF and pro-inflammatory cytokines in the choroid was up-regulated early after laser injury, and gradually decreased to baseline over 14 days. An intravitreal injection of TSG-6 suppressed the expression of VEGF and pro-inflammatory cytokines including CCL2, and reduced the size of CNV. Also, the number of Iba(+) and CCR2(+) cells including infiltrating macrophages was markedly lower in the CNV lesion of TSG-6-treated eyes. Further analysis identified CCR2(+) CD11b(+) CD11c(+) cells and CCR2(+) CD11b(-)CD11c(+) cells as the cell populations that were increased by laser injury and reduced by TSG-6 treatment. Together, the results demonstrate that TSG-6 inhibits inflammation and CCR2(+) monocyte recruitment into the choroid, and suppresses the development of CNV.

PMID: 26149224 [PubMed - in process] PMCID: PMC4493567

Epidemiology

Ophthalmology. 2015 Jun 25. [Epub ahead of print]

Fundus Tessellation: Prevalence and Associated Factors: The Beijing Eye Study 2011.

Yan YN, Wang YX, Xu L, Xu J, Wei WB, Jonas JB.

PURPOSE: To examine the prevalence of fundus tessellation and its associated factors.

DESIGN: Population-based study.

PARTICIPANTS: The Beijing Eye Study 2011 included 3468 individuals with a mean age of 64.6±9.8 years (range, 50-93 years).

METHODS: Participants underwent a comprehensive ophthalmic examination. By using 45° color fundus photographs of the macula and optic disc, fundus tessellation, defined as variation in the visibility of the large choroidal vessels, was differentiated into 3 grades.

MAIN OUTCOME MEASURES: Fundus tessellation.

RESULTS: Assessment of fundus tessellation was available for 3442 individuals (99.6%) or 6789 eyes (98.6%). In multivariate analysis, a higher degree of fundus tessellation (mean, 0.84±0.79) was associated with older age (P < 0.001; standardized correlation coefficient beta, 0.14), male sex (P < 0.001; beta, -0.08), lower body mass index (P = 0.04; beta, 0.03), worse best-corrected visual acuity (P < 0.001; beta, 0.05), thinner subfoveal choroidal thickness (P < 0.001; beta, -0.51), longer axial length (P < 0.001; beta, 0.11), larger parapapillary beta zone (P < 0.001; beta, 0.08), lower prevalence of intermediate age-related macular degeneration (AMD) (P = 0.02; beta, -0.04), and lower prevalence of late AMD (P = 0.007; beta, -0.04). If parapapillary beta zone was dropped, higher glaucoma prevalence (P = 0.003) was associated with a higher degree of fundus tessellation. Prevalence of diabetes mellitus and retinal vein occlusions, mean blood pressure, and intraocular pressure were not (P > 0.10) associated with fundus tessellation. In a reverse manner, thinner subfoveal choroidal thickness was associated with a higher degree of fundus tessellation (P < 0.001; beta, -0.49) in the multivariate analysis. Subfoveal choroidal thickness decreased from 322±90 µm (95% confidence interval [CI], 317-327) in eyes without fundus tessellation to 229±80 µm in eyes with grade 1, to 122±52 µm in eyes with grade 2, and to 81±37 µm in eyes with grade 3 of fundus tessellation.

CONCLUSIONS: Fundus tessellation is a surrogate for choroidal thinness and may be a clinical sign for a leptochoroid. After adjusting for ocular and systemic parameters, fundus tessellation also is associated with a larger parapapillary beta zone and higher glaucoma prevalence, and a lower prevalence of intermediate and late AMD. Its association with lower visual acuity warrants further investigation.

PMID: 26119000 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Jul 1. [Epub ahead of print]

Disease Burden in the Treatment of Age-Related Macular Degeneration: Findings From a Time-and-Motion Study.

Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Z, Seibert R.

PURPOSE: To examine the time burden of managing neovascular age-related macular degeneration (AMD) imposed on physicians, staff, patients, and caregivers.

DESIGN: Mixed-methods, prospective, observational, time-and-motion study.

METHODS: The multicenter study was conducted from March 2011 through August 2012. Retina specialists administering ? 50 vascular endothelial growth factor (VEGF)-inhibitor injections monthly were

surveyed and completed records for ? 5 patients scheduled for office visits within 3 weeks for anti-VEGF injection or monitoring. A survey was administered to 75 neovascular AMD patients aged ? 50 years who received ? 1 anti-VEGF injection in the past 6 months. Telephone interviews were conducted with 13 neovascular AMD patient caregivers.

RESULTS: 56 physicians provided data for 221 patients with neovascular AMD. Patients accounted for 20% of the health care staff's time per week, with an average of 23 staff members. An average patient visit for neovascular AMD was 90 minutes (range: 13 minutes to > 4 hours). Patients reported an average time per visit of almost 12 hours, including preappointment preparation (16 minutes), travel (66 minutes), waiting time (37 minutes), treatment time (43 minutes), and postappointment recovery (9 hours). Patients stated that caregivers took time away from work (22%) and personal activities (28%) to provide transportation to appointments.

CONCLUSIONS: Neovascular AMD management imposes a substantial time burden on physicians, staff, patients, and caregivers. There may be a need for additional support and/or reimbursement for services required by patients and caregivers and provided by physicians.

Genetics

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The genetic variant rs4073 A→T of the Interleukin-8 promoter region is associated with the earlier onset of exudative age-related macular degeneration.

Hautamäki A, Seitsonen S, Holopainen JM, Moilanen JA, Kivioja J, Onkamo P, Järvelä I, Immonen I.

PURPOSE: To study the association of the single nucleotide polymorphism (SNP) rs4073 in the interleukin-8 (IL-8) promoter region with the diagnosis and age of onset of exudative age-related macular degeneration (AMD) in association with the known genetic risk factors for AMD and tobacco smoking.

METHODS: Medical records, smoking history and angiograms or fundus photographs of 301 patients with exudative AMD, 72 patients with dry AMD and 119 control subjects were analysed retrospectively. The associations of IL-8 rs4073 A→T, CFH rs1061170 T→C, ARMS2 rs10490924 G→T and C3 rs2230199 C→G SNPs with the presence of AMD and with the age of onset of exudative AMD were analysed.

RESULTS: Younger age of exudative AMD onset was associated with the homozygous AA genotype of IL-8 rs4073 ($p = 0.009$, Mann-Whitney U-test), CC genotype of CFH rs1061170 ($p = 0.016$), TT genotype of ARMS2 rs10490924 ($p = 0.001$) and with current smoking ($p = 0.002$). The risk alleles C in CFH rs1061170 ($p < 0.0001$, Pearson chi-square) and T in ARMS2 rs10490924 ($p < 0.0001$), as well as smoking ($p < 0.0001$), were more prevalent in AMD patients compared with controls. No association was found between the IL-8 rs4073 genotype and the presence of AMD.

CONCLUSION: Out of the factors associated with the earlier onset of exudative AMD, only the genotype of IL-8 rs4073 did not appear as a risk factor for AMD in general. IL-8 may have a role in accelerating the development of the choroidal neovascularization in exudative AMD.

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CFH polymorphisms in a Northern Spanish population with neovascular and dry forms of age-related macular degeneration.

García M, Álvarez L, Nogacka AM, González-Iglesias H, Escribano J, Fernández-Vega B, Fernández-Vega Á, Fernández-Vega L, Coca-Prados M.

PURPOSE: To elucidate the potential role of single-nucleotide polymorphisms (SNPs) in complement factor H (CFH) gene in Northern Spanish patients with age-related macular degeneration (AMD).

METHODS: A case-control study of 130 unrelated native Northern Spanish diagnosed with AMD (46 dry, 35 neovascular and 49 mixed) and 96 healthy controls matched by age and ethnicity were enrolled. DNA was isolated from peripheral blood and genotyped for AMD-associated SNPs (rs3753394, rs529825, rs800292, rs3766404, rs203674, rs10671170, rs3753396 and rs1065489) using TaqMan probes and restriction fragment length polymorphism (RFLP). The association study was performed using the HaploView 4.0 software.

RESULTS: The allelic frequency analysis revealed that rs529825, rs800292, rs203674 and rs10671170 were significantly associated with an increased risk for AMD. The haplotypes CGG (rs3753394, rs529825 and rs800292) and GCAG (rs203674, rs1061170, rs3753396 and rs1065489) were significantly associated with AMD while the haplotypes CAA (rs3753394, rs529825 and rs800292) and TTAG (rs203674, rs1061170, rs3753396 and rs1065489) were found to be protective. Small differ-ences in allelic frequencies were found between dry and neovascular cases; however, these differences were not significant and did not distinguish one form the other.

CONCLUSIONS: This study found significant association of SNPs rs529825, rs800292, rs203674 and rs1061170 in the CFH gene with susceptibility to AMD. We identified haplotypes that confer protection or increased risk of AMD but not specific genetic variants in CFH capable to distinguish the different clinical forms of AMD in this cohort. Collectively, our results confirmed that CFH represents a strong genetic risk factor for this disease in the Northern Spanish population.

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Highly efficient retinal gene delivery with helper-dependent adenoviral vectors.

Lam S, Cao H, Wu J, Duan R, Hu J.

Abstract: There have been significant advancements in the field of retinal gene therapy in the past several years. In particular, therapeutic efficacy has been achieved in three separate human clinical trials conducted to assess the ability of adeno-associated viruses (AAV) to treat of a type of Leber's congenital amaurosis caused by RPE65 mutations. However, despite the success of retinal gene therapy with AAV, challenges remain for delivering large therapeutic genes or genes requiring long DNA regulatory elements for controlling their expression. For example, Stargardt's disease, a form of juvenile macular degeneration, is caused by defects in ABCA4, a gene that is too large to be packaged in AAV. Therefore, we investigated the ability of helper dependent adenovirus (HD-Ad) to deliver genes to the retina as it has a much larger transgene capacity. Using an EGFP reporter, our results showed that HD-Ad can transduce the entire retinal epithelium of a mouse using a dose of only 1 × 105 infectious units and maintain transgene expression for at least 4 months. The results demonstrate that HD-Ad has the potential to be an effective vector for the gene therapy of the retina.

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Diet, lifestyle & low vision

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CFH Y402H and ARMS2 A69S Polymorphisms and Oral Supplementation with Docosahexaenoic Acid in Neovascular Age-Related Macular Degeneration Patients: The NAT2 Study.

Merle BM, Richard F, Benlian P, Puche N, Delcourt C, Souied EH.

PURPOSE: Genetic susceptibility could be modified by environmental factors and may also influence differential responses to treatments for age-related macular degeneration (AMD). We investigated whether genotype could influence response to docosahexaenoic acid (DHA)-supplementation in the occurrence of choroidal new vessels (CNV).

METHODS: The Nutritional AMD Treatment 2 (NAT2) study was a randomized, placebo-controlled, double-blind, parallel, comparative study, including 250 patients aged 55 to 85 years with early lesions of age-related maculopathy, visual acuity better than 0.4 Logarithm of Minimum Angle of Resolution units in the study eye and neovascular AMD in the fellow eye. Patients were randomized at baseline to receive either 3 daily fish-oil capsules, each containing 280 mg DHA, 90 mg EPA and 2 mg Vitamin E, or placebo.

RESULTS: Patients carrying the risk allele (C) for CFH Y402H had no statistically significant increased risk for developing CNV in the study eye (Hazard Ratio (HR)=0.97; 95% Confidence Interval (CI): 0.54-1.76 for heterozygous and HR=1.29; 95%CI: 0.69-2.40 for homozygous). Patients carrying the risk allele (T) for ARMS2 A69S had no statistically significant increased risk for developing CNV in the study eye (HR=1.68; 95%CI: 0.91-3.12) for heterozygous and HR=1.78; 95%CI: 0.90-3.52 for homozygous). A significant interaction was observed between CFH Y402H and DHA-supplementation (p=0.01). We showed a protective effect of DHA-supplementation among homozygous non-risk patients. Among these patients, occurrence of CNV was 38.2% in placebo group versus 16.7% in DHA group (p=0.008).

CONCLUSIONS: These results suggest that a genetic predisposition to AMD conferred by the CFH Y402H variant limits the benefit provided by DHA supplementation.

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Proc Biol Sci. 2015 Jul 22;282(1811).

Perceiving polarization with the naked eye: characterization of human polarization sensitivity.

Temple SE, McGregor JE, Miles C, Graham L, Miller J, Buck J, Scott-Samuel NE, Roberts NW.

Abstract: Like many animals, humans are sensitive to the polarization of light. We can detect the angle of polarization using an entoptic phenomenon called Haidinger's brushes, which is mediated by dichroic carotenoids in the macula lutea. While previous studies have characterized the spectral sensitivity of Haidinger's brushes, other aspects remain unexplored. We developed a novel methodology for presenting gratings in polarization-only contrast at varying degrees of polarization in order to measure the lower limits of human polarized light detection. Participants were, on average, able to perform the task down to a threshold of 56%, with some able to go as low as 23%. This makes humans the most sensitive vertebrate tested to date. Additionally, we quantified a nonlinear relationship between presented and perceived polarization angle when an observer is presented with a rotatable polarized light field. This result confirms a previous theoretical prediction of how uniaxial corneal birefringence impacts the perception of Haidinger's brushes. The rotational dynamics of Haidinger's brushes were then used to calculate corneal retardance. We suggest that psychophysical experiments, based upon the perception of polarized light, are amenable to the production of affordable technologies for self-assessment and longitudinal monitoring of visual dysfunctions such as age-related macular degeneration.

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Retinal prostheses in degenerative retinal diseases.

Lin TC, Chang HM, Hsu CC, Hung KH, Chen YT, Chen SY, Chen SJ.

Abstract: Degenerative retinal diseases may lead to significant loss of vision. Age-related macular

degeneration (AMD) and retinitis pigmentosa (RP), which eventually affect the photoreceptors, are the two most common retinal degenerative diseases. Once the photoreceptorcells are lost, there are no known effective therapies for AMD or RP. The concept of retinal prosthesis is to elicit neural activity in the remaining retinal neurons by detecting light and converting it into electrical stimuli using artificial devices. Subretinal, epiretinal, and other retinal prostheses implants are currently designed to restore functional vision in retinal degenerative diseases. In this review, we have summarized different types of retinal prostheses, implant locations, and visual outcomes. Our discussions will further elucidate the results from clinical trials, and the challenges that will need to be overcome to more efficaciously assist patients with AMD and RP in the future.

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