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MD Research News

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Drug treatment

Ophthalmology. 2014 Sep 13. [Epub ahead of print]

Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol.

Berg K, Pedersen TR, Sandvik L, Bragadóttir R.

PURPOSE: To compare the efficacy and safety of bevacizumab versus ranibizumab when administered according to a treat-and-extend protocol for the treatment of neovascular age-related macular degeneration (AMD).

DESIGN: Multicenter, randomized, noninferiority trial with a noninferiority limit of 5 letters.

PARTICIPANTS: Patients aged ≥50 years with previously untreated neovascular AMD in 1 eye and best-corrected visual acuity (BCVA) between 20/25 and 20/320.

METHODS: Patients were randomly assigned to receive ranibizumab 0.5 mg or bevacizumab 1.25 mg intravitreal injections. Monthly injections were given until inactive disease was achieved. The patients were then followed with a gradual extension of treatment interval by 2 weeks at a time up to a maximum of 12 weeks. If signs of recurrent disease appeared, the treatment interval was shortened by 2 weeks at a time.

MAIN OUTCOME MEASURES: Change in visual acuity at 1 year.

RESULTS: Between March 2009 and July 2012, 441 patients were randomized at 10 ophthalmological centers in Norway. The 1-year visit was completed by 371 patients. In the per protocol analysis at 1 year, bevacizumab was equivalent to ranibizumab, with 7.9 and 8.2 mean letters gained, respectively (95% confidence interval [CI] of mean difference, -2.4 to 2.9; P = 0.845). The intention-to-treat analysis was concordant. There was no significant difference in measured central retinal thickness (CRT), with a mean decrease of -112 μm for bevacizumab and -120 μm for ranibizumab (95% CI of mean difference, -13 to 28; P = 0.460). There was a statistically significant difference (P = 0.001) between the drugs regarding the number of treatments: 8.9 for bevacizumab and 8.0 for ranibizumab. There were fewer arteriothrombotic events in the bevacizumab group (1.4%) than in the ranibizumab group (4.5%) (P = 0.050) and significantly more cardiac events in the ranibizumab group (P = 0.036). However, patients treated with ranibizumab more often had a history of myocardial infarction (P = 0.021).

CONCLUSIONS: Bevacizumab and ranibizumab had equivalent effects on visual acuity at 1 year when administered according to a treat-and-extend protocol. The visual acuity results at 1 year were comparable to those of other clinical trials with monthly treatment. The numbers of serious adverse events were small.

PMID: 25227499 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2014 Sep 15;9:CD011230. [Epub ahead of print]

Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration.

Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, D'Amico R, Dickersin K, Kodjikian L, Lindsley K, Loke Y, Maguire M, Martin DF, Mugelli A, Mühlbauer B, Püntmann I, Reeves B, Rogers C, Schmucker C, Subramanian ML, Virgili G.

BACKGROUND: Neovascular age-related macular degeneration (AMD) is the leading cause of legal blindness in elderly populations of industrialised countries. Bevacizumab (Avastin®) and ranibizumab (Lucentis®) are targeted biological drugs (a monoclonal antibody) that inhibit vascular endothelial growth factor, an angiogenic cytokine that promotes vascular leakage and growth, thereby preventing its pathological angiogenesis. Ranibizumab is approved for intravitreal use to treat neovascular AMD, while bevacizumab is approved for intravenous use as a cancer therapy. However, due to the biological similarity of the two drugs, bevacizumab is widely used off-label to treat neovascular AMD.

OBJECTIVES: To assess the systemic safety of intravitreal bevacizumab (brand name Avastin®; Genentech/Roche) compared with intravitreal ranibizumab (brand name Lucentis®; Novartis/Genentech) in people with neovascular AMD. Primary outcomes were death and All serious systemic adverse events (All SSAEs), the latter as a composite outcome in accordance with the International Conference on Harmonisation Good Clinical Practice. Secondary outcomes examined specific SSAEs: fatal and non-fatal myocardial infarctions, strokes, arteriothrombotic events, serious infections, and events grouped in some Medical Dictionary for Regulatory Activities System Organ Classes (MedDRA SOC). We assessed the safety at the longest available follow-up to a maximum of two years.

SEARCH METHODS: We searched CENTRAL, MEDLINE, EMBASE and other online databases up to 27 March 2014. We also searched abstracts and clinical study presentations at meetings, trial registries, and contacted authors of included studies when we had questions.

SELECTION CRITERIA: Randomised controlled trials (RCTs) directly comparing intravitreal bevacizumab (1.25 mg) and ranibizumab (0.5 mg) in people with neovascular AMD, regardless of publication status, drug dose, treatment regimen, or follow-up length, and whether the SSAEs of interest were reported in the trial report.

DATA COLLECTION AND ANALYSIS: Two authors independently selected studies and assessed the risk of bias for each study. Three authors independently extracted data.We conducted random-effects meta-analyses for the primary and secondary outcomes. We planned a pre-specified analysis to explore deaths and All SSAEs at the one-year follow-up.

MAIN RESULTS: We included data from nine studies (3665 participants), including six published (2745 participants) and three unpublished (920 participants) RCTs, none supported by industry. Three studies excluded participants at high cardiovascular risk, increasing clinical heterogeneity among studies. The studies were well designed, and we did not downgrade the quality of the evidence for any of the outcomes due to risk of bias. Although the estimated effects of bevacizumab and ranibizumab on our outcomes were similar, we downgraded the quality of the evidence due to imprecision. At the maximum follow-up (one or two years), the estimated risk ratio (RR) of death with bevacizumab compared with ranibizumab was 1.10 (95% confidence interval (CI) 0.78 to 1.57, P value = 0.59; eight studies, 3338 participants; moderate quality evidence). Based on the event rates in the studies, this gives a risk of death with ranibizumab of 3.4% and with bevacizumab of 3.7% (95% CI 2.7% to 5.3%). For all SSAEs, the estimated RR was 1.08 (95% CI 0.90 to 1.31, P value = 0.41; nine studies, 3665 participants; low quality evidence). Based on the event rates in the studies, this gives a risk of SSAEs of 22.2% with ranibizumab and with bevacizumab of 24% (95% CI 20% to 29.1%).For the secondary outcomes, we could not detect any difference between bevacizumab and ranibizumab, with the exception of gastrointestinal disorders MedDRA SOC where there was a higher risk with bevacizumab (RR 1.82; 95% CI 1.04 to 3.19, P value = 0.04; six studies, 3190 participants). Pre-specified analyses of deaths and all SSAEs at one-year follow-up did not substantially

alter the findings of our review. Fixed-effect analysis for deaths did not substantially alter the findings of our review, but fixed-effect analysis of All SSAEs showed an increased risk for bevacizumab (RR 1.12; 95% CI 1.00 to 1.26, P value = 0.04; nine studies, 3665 participants): the meta-analysis was dominated by a single study (weight = 46.9%). The available evidence was sensitive to the exclusion of CATT or unpublished results. For All SSAEs, the exclusion of CATT moved the overall estimate towards no difference (RR 1.01; 95% CI 0.82 to 1.25, P value = 0.92), while the exclusion of LUCAS yielded a larger RR, with more SSAEs in the bevacizumab group, largely driven by CATT (RR 1.19; 95% CI 1.06 to 1.34, P value = 0.004). The exclusion of all unpublished studies produced a RR of 1.12 for death (95% CI 0.78 to 1.62, P value = 0.53) and a RR of 1.21 for SSAEs (95% CI 1.06 to 1.37, P value = 0.004), indicating a higher risk of SSAEs in those assigned to bevacizumab than ranibizumab.

AUTHORS' CONCLUSIONS: This systematic review of non-industry sponsored RCTs could not determine a difference between intravitreal bevacizumab and ranibizumab for deaths, All SSAEs, or specific subsets of SSAEs in the first two years of treatment, with the exception of gastrointestinal disorders. The current evidence is imprecise and might vary across levels of patient risks, but overall suggests that if a difference exists, it is likely to be small. Health policies for the utilisation of ranibizumab instead of bevacizumab as a routine intervention for neovascular AMD for reasons of systemic safety are not sustained by evidence. The main results and quality of evidence should be verified once all trials are fully published.

PMID: 25220133 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2014 Sep 18. [Epub ahead of print]

Evaluation of Compounded Bevacizumab Prepared for Intravitreal Injection.

Yannuzzi NA, Klufas MA, Quach L, Beatty LM, Kaminsky SM, Crystal RG, D'Amico DJ, Kiss S.

Importance: Bevacizumab acquired from compounding pharmacies for intravitreal injection may cause infectious and noninfectious inflammation. In addition to safety issues, the drug itself may have variable efficacy associated with product aliquoting, handling, and distribution.

Objective: To conduct surveillance cultures, evaluate endotoxin levels, and assess protein concentrations of bevacizumab obtained from compounding pharmacies in the United States.

Design and Setting: Prospective in vitro study of syringes containing intravitreal preparations of bevacizumab from compounding pharmacies. This study was conducted at a university-based, good manufacturing practice facility and academic ophthalmology practice.

Main Outcomes and Measures: Microbial culture growth, endotoxin levels, and quantity and binding affinity of protein in each sample.

Results: There were no microbial contaminants or endotoxin detected in any of the samples. Of the 21 compounded samples of bevacizumab obtained from 11 pharmacies, 17 (81%) had lower protein concentrations (mean [SD], 22.2 [4.9] mg/mL; range, 19.2-24.5 mg/mL) compared with bevacizumab acquired directly from Genentech (25 mg/mL; P < .05). In 3 of 10 compounding pharmacies where more than 1 sample was available, there were statistically significant differences in the protein concentration between samples from the same compounding pharmacy.

Conclusions and Relevance: Test results from intravitreal preparations of bevacizumab acquired from compounding pharmacies were negative for microbial contaminants and endotoxin. However, there were significant variations in protein concentration that appear in general to be lower than bevacizumab acquired directly from Genentech. The clinical implications of these variable protein levels remain uncertain.

PMID: 25233052 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Sep 8. [Epub ahead of print]

Three Year Treatment Outcomes for Neovascular Age-Related Macular Degeneration using a "Treat and Extend" Regimen.

Rayess N, Houston SK 3rd, Gupta OP, Ho AC, Regillo CD.

PURPOSE: To determine three year treatment outcomes after 1 to 3 years of ranibizumab or bevacizumab therapy using a "treat and extend" regimen for patients with neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, interventional, consecutive case series.

METHODS: 212 eyes from 196 patients diagnosed with treatment naïve neovascular AMD between January 2009 till March 2013 and were treated with either ranibizumab or bevacizumab for a minimum of 1 year using a "treat and extend" regimen. Main outcome measures were change from baseline best-corrected Snellen visual acuity (BCVA), proportion of eyes losing <3 BCVA lines, proportion of eyes gaining ≥3 BCVA lines, change from baseline central retinal thickness and mean number of injections at 1, 2 and 3 years follow-up.

RESULTS: The mean follow-up period was 1.88 years (median, 2 years). At baseline, mean BCVA was 20/139 and improved to 20/79 (P<0.001) after 1 year of treatment and was maintained at 20/69 and 20/64 at 2 and 3 years follow-up (P<0.001), respectively. At baseline, mean central retinal thickness was 351 μm and significantly decreased to 285 μm, 275 μm and 276 μm at 1, 2 and 3 years follow-up (P<0.001), respectively. Patients received on average 7.6, 5.7 and 5.8 injections over years 1, 2 and 3 of treatment, respectively. At final follow-up, 94% of eyes lost <3 lines BCVA and 34.4% of eyes gained ≥3 lines BCVA.

CONCLUSIONS: The "treat and extend" regimen is effective at both achieving and maintaining visual and anatomical improvements in patients with neovascular AMD for up to 3 years of treatment.

PMID: 25217859 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Sep 8. [Epub ahead of print]

Regression of Choroidal Neovascularization Results in Macular Atrophy in Anti-Vascular Endothelial Growth Factor-Treated Eyes.

Channa R, Sophie R, Bagheri S, Shah SM, Wang J, Adeyemo O, Sodhi A, Wenick A, Ying H, Campochiaro PA.

PURPOSE: To determine the incidence and progression of macular atrophy in patients with neovascular age-related macular degeneration (AMD) treated with vascular endothelial growth factor (VEGF) antagonists.

DESIGN: Retrospective interventional case series METHODS: All patients with neovascular AMD treated by the same physician during a 12-month period of ascertainment had all images from their entire follow up period evaluated, and areas of retina that developed atrophy were compared to the same area prior to the onset of anti-VEGF treatment. Longitudinal measurements of retinal atrophy were made.

RESULTS: Thirty-nine patients (52 eyes) with neovascular AMD were identified. Five eyes were excluded from analysis (4 had retinal pigment epithelium tear and one had laser scar). Fundus photographs of the remaining eyes showed that 18/47 eyes (38%) contained hypopigmented areas suggestive of atrophy within the macula at some time during follow up. Spectral domain-optical coherence tomography (SD-OCT) confirmed that these areas had loss of RPE and ellipsoid zone with or without subretinal material suggestive of subretinal fibrosis. Comparison of fundus photographs with fluorescein angiograms showed that in 13/18 eyes (72%), atrophy developed in areas previously occupied by choroidal neovascularization

(CNV) and the other 5 eyes had atrophy prior to the onset of anti-VEGF treatment. The mean (±standard deviation) rate of increase in pure atrophic areas (no subretinal material) was 0.7± 0.8mm2 per year with a range of 0.01-2.6mm2/year.

CONCLUSION: Treatment of neovascular AMD with a VEGF-neutralizing protein can result in regression of CNV, which is sometimes associated with atrophy of overlying retina.

PMID: 25217857 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2014 Sep 17. [Epub ahead of print]

Serum D-Dimer Levels to Evaluate the Risk for Arterial Thromboembolism After Intravitreal Injection of Bevacizumab and Ranibizumab.

Jee D, Zako M, La TY.

Abstract Purpose: There are concerns about arterial thromboembolic event after intravitreal injection of bevacizumab or ranibizumab. Motivated by the fact that D-dimer was a sensitive biomarker for thromboembolism, we evaluated serum D-dimer levels in patients with age-related macular degeneration (AMD) after intravitreal injection of bevacizumab and ranibizumab.

Methods: In this prospective, nonrandomized, uncontrolled study, 122 patients (122 eyes) with AMD were enrolled. Sixty-two eyes received intravitreal injections of bevacizumab and 60 eyes received intravitreal injections of ranibizumab monthly for 3 months. Serum D-dimer levels were measured in patients before intravitreal injection and 1 day, 1 week, 1 month, and 3 months thereafter.

Results: Serum D-dimer levels were not significantly altered following injection of either bevacizumab or ranibizumab. Subgroup analysis for patients at risk for thromboembolic events revealed that serum D-dimer levels showed no significant change after injection of ranibizumab. However, D-dimer levels significantly increased at 1 day (P=0.041) and 1 week (P=0.022) after injection of bevacizumab.

Conclusions: Serum D-dimer levels were not changed after injection with either bevacizumab or ranibizumab. In subgroup analysis, bevacizumab injection in patients at risk of thromboembolism increased serum D-dimer levels.

PMID: 25229129 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2014 Sep 4;8:1711-6.

Intravitreal injection of ranibizumab using a pro re nata regimen for age-related macular degeneration and vision-related quality of life.

Inoue M, Arakawa A, Yamane S, Kadonosono K.

BACKGROUND: The purpose of this study was to assess visual function and vision-related quality of life after intravitreal injection of ranibizumab (IVR) using a pro re nata regimen for the treatment of age-related macular degeneration.

METHODS: A prospective study of 54 eyes in 54 patients scheduled to undergo IVR for the treatment of exudative age-related macular degeneration was performed. A self-administered, 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was completed before and 3 and 12 months after the initial IVR treatment. We evaluated logMAR visual acuity and NEI VFQ-25 scores preoperatively and postoperatively. Further, associations between the changes in NEI VFQ-25 scores and patient characteristics were investigated at 12 months.

RESULTS: Postoperative best-corrected visual acuity improved significantly when compared with the preoperative visual acuity throughout the 12-month period (P<0.05 at 3 and 12 months, respectively). On the other hand, IVR treatment significantly improved the postoperative NEI VFQ-25 mean composite score at both 3 and 12 months (P<0.05, respectively). Better visual acuity at 12 months was associated with a greater improvement in NEI VFQ-25 score at 12 months (P<0.05).

CONCLUSION: IVR was well tolerated and improved vision in these patients with age-related macular degeneration, as evaluated at one-year follow-up examinations. IVR also enabled good subjective perception, as indicated by higher composite NEI VFQ-25 scores. Maintaining good visual acuity may be an important factor for improving vision-related quality of life.

PMID: 25228787 [PubMed] PMCID: PMC4160327

Ophthalmic Surg Lasers Imaging Retina. 2014 Sep 23:1-4. [Epub ahead of print]

Response to Aflibercept in Patients With Persistent Exudation Despite Prior Treatment With Bevacizumab or Ranibizumab for Age-Related Macular Degeneration.

Eadie JA, Gottlieb JL, Ip MS, Blodi BA, Danis RP, Chandra SR, Nork MM, Altaweel MM, Stern-Hogan BS.

BACKGROUND AND OBJECTIVE: This study examines the clinical response of patients transitioned to aflibercept, the newest anti-VEGF medication, due to persistent evidence of exudation on optical coherence tomography (OCT) despite regular treatment with bevacizumab and/or ranibizumab.

PATIENTS AND METHODS: Aflibercept was administered to 111 patients considered for study inclusion. Eyes were included if they were transitioned to aflibercept for treatment of persistent exudation on OCT despite regular treatment with at least three injections of ranibizumab or bevacizumab. Retrospective data were collected from medical records.

RESULTS: Complete resolution of exudation was seen in 34% of eyes at final follow-up. Clear improvement in exudation amount or severity without complete resolution was seen in 25%. No improvement was seen in 34%, and 6% demonstrated worsening of exudation. Snellen visual acuity at the time of transition versus final follow-up after aflibercept injection did not appreciably change (logMAR 0.494 to 0.505, Snellen equivalent 20/62 to 20/64; P = .84). The mean center point neurosensory retina thickness decreased from 228.6 to 176.9 µm (P = .001).

CONCLUSION: Aflibercept may decrease the amount of exudation in a significant number of patients. However, this reduction did not result in an improvement in Snellen visual acuity.

PMID: 25230402 [PubMed - as supplied by publisher]

Case Rep Ophthalmol. 2014 Aug 4;5(2):243-8.

Intravitreal injection of dexamethasone implant and ranibizumab in cystoid macular edema in the course of irvine-gass syndrome.

Fenicia V, Balestrieri M, Perdicchi A, MauriziEnrici M, DelleFave M, Recupero SM.

PURPOSE: To evaluate the efficacy of 2 dexamethasone intravitreal implants and 1 ranibizumab intravitreal injection after a bilateral postoperative complication of cataract surgery as pseudophakic cystoid macular edema.

PATIENTS AND METHODS: A 70-year-old male patient with systemic hypertension developed a progressive cystoid macular edema (CME) in both eyes starting between 10 and 20 days after cataract surgery. Two intravitreal dexamethasone implants and 1 ranibizumab injection were administered; first in

the right eye (RE) and then in the left eye (LE). The patient was checked for 1 whole week and then once a month for 5 months after the injections.

RESULTS: One month after the first dexamethasone implant in his RE, the spectral domain optical coherence tomography (SD-OCT) showed a progressive reduction of the foveal thickness until a complete resolution of the CME occurred, which was associated with an improvement of visual acuity. After 3 months, the SD-OCT showed a relapse of the CME, which was then treated with 1 injection of ranibizumab. One month after this injection, there was a complete resolution of the CME. A new CME in his RE was diagnosed 2 months after the last ranibizumab injection; it was treated with a new dexamethasone implant. A complete resolution of the CME was obtained; a normal foveal profile was still present 5 months after the last injection, and the best-corrected visual acuity was 20/20. His LE developed a CME 40 days after surgery. One intravitreal injection of ranibizumab was first administered in his LE, with a complete resolution of the CME at SD-OCT 2 weeks later. As observed in his RE, 40 days after the ranibizumab injection, there was a relapse of the CME that was treated with 1 intravitreal injection of dexamethasone implant. Five months later, the patient showed a worsening of the CME, but it was completely resolved with a second dexamethasone injection. After 3 months, the foveal thickness was back to normal with a BCVA of 20/20.

CONCLUSION: Treatment with dexamethasone implants (Ozurdex(®)) and ranibizumab injections (Lucentis(®)) induced a progressive reduction of our patient's CME after cataract surgery (Irvine-Gass syndrome) until a complete normal foveal thickness was restored and his visual function was improved despite the order of injections.

PMID: 25232337 [PubMed]

Case Rep Ophthalmol. 2014 Jul 30;5(2):231-8.

Bilateral Hypertensive Retinopathy Complicated with Retinal Neovascularization: Panretinal Photocoagulation or Intravitreal Anti-VEGF Treatment?

Georgiadis O, Kabanarou SA, Batsos G, Feretis E, Xirou T.

PURPOSE: To present the case of a patient with bilateral hypertensive retinopathy complicated with retinal neovascularization who received anti-VEGF intravitreal injection in one eye and panretinal photocoagulation (PRP) in the fellow eye.

METHODS: A 33-year-old male patient presented with gradual visual loss in both eyes for the last 5 months. At that time, he was examined by an ophthalmologist and occlusive retinopathy due to malignant systematic hypertension was diagnosed. He was put on antihypertensive treatment but no ophthalmic treatment was undertaken. At presentation, 5 months later, best-corrected visual acuity (BCVA) was 0.1 in the right eye (RE) and 0.9 in the left eye (LE). Fundus examination was compatible with hypertensive retinopathy complicated with retinal neovascularization. Fluorescein angiography (FFA) revealed macular ischemia mainly in the RE and large areas of peripheral retinal ischemia and neovascularization with vascular leakage in both eyes. The patient was treated with two anti-VEGF (ranibizumab) injections with 2 months interval in the RE and PRP laser in the LE.

RESULTS: Follow-up examination after 12 months showed mild improvement in BCVA, and FFA documented regression of retinal neovascularization in both eyes.

CONCLUSION: Hypertensive retinopathy can be rarely complicated with retinal neovascularization. Treatment with PRP can be undertaken. In our case, the use of an intravitreal anti-VEGF agent seemed to halt its progression satisfactorily.

PMID: 25232335 [PubMed]

Cornea. 2014 Sep 12. [Epub ahead of print]

Marginal Keratitis After Intravitreal Injection of Ranibizumab.

Aslan Bayhan S, Bayhan HA, Adam M, Gürdal C.

PURPOSE: To report a case of marginal keratitis that developed after intravitreal ranibizumab injection.

METHODS: A 56-year-old man with diffuse diabetic macular edema received intravitreal injection of ranibizumab into his right eye.

RESULTS: One day after injection, the patient presented with pain, redness, tearing, and discomfort in his right eye. Anterior segment examination of the right eye revealed subconjunctival hemorrhage, 3 corneal subepithelial peripheral infiltrates separated from the limbus by a clear zone, and mild anterior chamber reaction. Examination of the eyelids was remarkable for mild blepharitis. Fungal and bacterial cultures were negative. The condition resolved with topical corticosteroids and antibiotics.

CONCLUSIONS: Intravitreal ranibizumab injection may trigger hypersensitivity reaction in the form of marginal keratitis in patients with mild blepharitis.

PMID: 25222003 [PubMed - as supplied by publisher]

Biomed Mater Eng. 2014 Jan 1;24(6):1941-50.

Controlled release bevacizumab in thermoresponsive hydrogel found to inhibit angiogenesis.

Hu CC, Chaw JR, Chen CF, Liu HW.

Abstract: Age-related macular degeneration (ARMD) and intraocular neovascular diseases have been treated clinically by anti-VEGF antibody drug bevacizumab. However, the use of bevacizumab in the treatment of retinal neovascular diseases has been limited due to the short half-life and frequent injections. In this research, novel amphiphilic hydrophilic-hydrophobic block copolymers of methoxy-poly (ethylene glycol)-block-poly (lactic-co-glycolic acid) were synthesized with ring-opening polymerization, and cross-linked with 2,2-bis (2-oxazoline) (BOX). The aqueous solution of the block copolymers can reverse the sol-gel-sol phase transition. After 1 month of intravitreal injection, the histomorphology of a rabbit's retina was preserved, which indicated the mPEG-PLGA-BOX hydrogel had no cytotoxicity in vivo. Released bevacizumab from the mPEG-PLGA-BOX hydrogel inhibited the RF/6A (Maraca mulatta retina epithelial cell) and HUVEC cell growth, and anti-angiogenesis in 3-D cultures, which showed the bioactivity of the anti -VEGF agent, were maintained in the hydrogel within the release process. In conclusion, the mPEG-PLGA-BOX hydrogel had a sol-gel behavior phase transition, and its intraocular biocompatibility and the characteristics of biodegradability and bioactivity appear to be a promising intravitreal injection carrier for bevacizumab delivery.

PMID: 25226890 [PubMed - in process]

Cochrane Database Syst Rev. 2014 Sep 15;9:ED000090.

A clearer view of evidence in treating macular degeneration: off-label policies and independent research.

Formoso G, Marata AM, Magrini N, Bero L.

PMID: 25228121 [PubMed - in process]

BMJ. 2014 Sep 14;349:g5618.

Cheaper alternative for macular degeneration is as safe as licensed drug, review finds.

Kmietowicz Z.

PMID: 25224545 [PubMed - in process]

Other treatment & diagnosis

Ophthalmic Physiol Opt. 2014 Sep 16. [Epub ahead of print]

Ophthalmic digital image transfer: benefits to triage, patient care and resource.

Goudie C, Lunt D, Reid S, Sanders R.

PURPOSE: Hospital capacity in the UK is currently significantly challenged due to new treatments, targets and resource limitations. There have been significant improvements in training, equipment and shared care services in community primary care optometry services. Despite this the challenges to ophthalmic service delivery are considerable. One area of potential benefit is the effect on outcome when a clinical image is attached to a referral. We aimed to quantify the effect of attaching digital images to ophthalmic referrals.

METHODS: Retrospective analysis of 358 consecutive optometry referrals to the Hospital Eye Service in Dunfermline, Scotland using electronic referral with digital images. All images were screened by consultant ophthalmologists.

RESULTS: The patients were aged between 9 and 100 years (mean age 63.6 years). Sixty four (18%) referrals were deemed urgent (requiring appointment within 24-60 h), with the majority, 28 (8%) being wet macular degeneration. One hundred and seventy (48%) were deemed routine (appointment within 2-6 weeks), with categories including macular disease, glaucoma, cataract, optic disc and retinal abnormalities. Twenty seven (8%) patients were already attending the hospital eye service, or had been referred previously for the same condition. Categories were mainly glaucoma, diabetic retinopathy and cataract. Ninety-five (25%) were 'e-diagnosed' based on image and referral information (i.e. with no secondary eye care appointment). Diagnosis included glaucoma suspect (22, 6%), macular pathology (12, 3%), abnormal looking discs (9, 2.5%) and cataract (9, 2.5%). The overall 'did not attend' rate for those patients seen in the hospital eye service (254) was <1% (two patients).

CONCLUSIONS: The attachment of digital images improved the quality of referral triaging from optometry to secondary eye care in the hospital eye service. It allowed detection of sight threatening disease early and more appropriate allocation of patients to specific specialist clinics at first visit. They allowed safe and speedy 'e-diagnosis' of a subgroup, saving hospital capacity and minimising patient inconvenience. Indirectly the service also reduced the 'did not attend' rate. With recent improvements in camera and internet technology digital images will have an ever increasing role in secondary eye care as it continues to adapt to meet modern demands.

PMID: 25223370 [PubMed - as supplied by publisher]

J Pharmacol Exp Ther. 2014 Sep 17. [Epub ahead of print]

Complement Inhibition in Cynomolgus Monkey by Anti-Factor D Antigen-Binding Fragment for the Treatment of an Advanced Form of Dry Age-Related Macular Degeneration.

Loyet KM, Good J, Davancaze T, Sturgeon L, Wang X, Yang J, Le K, Wong M, Hass PE, van Lookeren Campagne M, Haughney P, Morimoto A, Damico-Beyer LA, DeForge LE.

Abstract: Anti-factor D (AFD) (FCFD4514S, lampalizumab) is a humanized IgG Fab fragment directed against factor D (fD), a rate-limiting serine protease in the alternative complement pathway (AP). Evaluation of AFD as a potential intravitreal (IVT) therapeutic for dry age-related macular degeneration patients with geographic atrophy (GA) is ongoing. However, it is unclear whether IVT administration of AFD can affect systemic AP activation and potentially compromise host-immune responses. Here we characterize the pharmacological properties of AFD and assess the effects of AFD administered IVT (2 or 20 mg) or IV (0.2, 2, or 20 mg) on systemic complement activity in cynomolgus monkeys. For the IVT groups, serum AP activity was reduced for the 20 mg dose between 2-6 hours post-injection. For the IV groups, AFD inhibited systemic AP activity for periods of time ranging from 5 minutes (0.2 mg group) to 3 hours (20 mg group). Interestingly, the concentrations of total serum fD increased up to 10-fold relative to predose levels following administration of AFD. Furthermore, AFD was found to inhibit systemic AP activity only when the molar concentration of AFD exceeded that of fD. This occurred in the cynomolgus monkeys at serum AFD levels ≥ 2 μg/mL, a concentration 8-fold greater than the serum Cmax observed following a single 10 mg IVT dose in a clinical investigation in patients with GA. Based on these findings, the low levels of serum AFD resulting from IVT administration of a clinically relevant dose are not expected to appreciably affect systemic AP activity.

PMID: 25232192 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Sep 17. [Epub ahead of print]

Current knowledge on reticular pseudodrusen in age-related macular degeneration.

Alten F, Eter N.

Abstract: Drusen are focal deposits of extracellular material located between the retinal pigment epithelium (RPE) and Bruch's membrane and represent the major phenotypic characteristic of age-related macular degeneration (AMD). Due to evolving imaging techniques and recent histological studies, reticular pseudodrusen (RPD) have received increasing attention and have been recently identified as an additional phenotypic entity in AMD. In contrast to conventional drusen, RPD proved to be located internal to the RPE. In the past few years, numerous studies collected new findings on RPD related to their pathogenesis, imaging properties and impact on retinal function. While most former natural history studies as well as interventional studies in early AMD did not include imaging RPD beyond colour fundus photography, this phenotype must be included in every future large-scale study on AMD. This review summarises the current knowledge on RPD.

PMID: 25232026 [PubMed - as supplied by publisher]

Ophthalmic Res. 2014 Sep 11;52(3):107-115. [Epub ahead of print]

Treatment of Dry Age-Related Macular Degeneration.

Querques G, Rosenfeld PJ, Cavallero E, Borrelli E, Corvi F, Querques L, Bandello FM, Zarbin MA.

Abstract: A number of different approaches are under development for treating nonexudative manifestations of age-related macular degeneration (AMD). Some interventions target specific pathways that are believed to play a role in AMD pathogenesis, e.g. oxidative damage, lipofuscin accumulation, chronic inflammation (including complement activation), extracellular matrix changes (e.g. β-amyloid accumulation), impaired choroidal blood flow, and apoptosis. In principle, these therapies can be combined ('combination therapy'), which may lead to synergistic effects that include better visual outcome, less likelihood for 'escape' (i.e. drug resistance), and less frequent treatment.

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Pathogenesis

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Evaluation of circulating miRNAs in wet age-related macular degeneration.

Ertekin S, Yıldırım O, Dinç E, Ayaz L, Fidancı SB, Tamer L.

PURPOSE: In the present study, we aimed to investigate the changes in plasma miRNA in patients with wet age-related macular degeneration.

METHODS: The expression profiles of 384 miRNAs in plasma from 33 patients (22 male, 11 female) who were diagnosed with wet age-related macular degeneration with fundus examination, fundus fluorescein angiography, and optical coherence tomography and 31 controls (17 male, 14 female) were evaluated using high-throughput quantitative real-time PCR.

RESULTS: Our results demonstrated that the expression level of five miRNAs (miR-17-5p, miR-20a-5p, miR-24-3p, miR-106a-5p, and miR-223-3p) was significantly upregulated in patients with age-related macular degeneration when compared to the control group ($p<0.05$). The expression level of 11 miRNAs (miR-21-5p, miR-25-3p, miR-140-3p, miR-146b-5p, miR-192-5p, miR-335-5p, miR-342-3p, miR-374a-5p, miR-410, miR-574-3p, and miR-660-5p) was significantly downregulated in patients ($p<0.05$). In addition, ten miRNAs (miR-26b-5p, miR-27b-3p, miR-29a-3p, miR-139-3p, miR-212-3p, miR-324-3p, miR-324-5p, miR-532-3p, miR-744-5p, and miR-Let-7c) were expressed only in the patient group.

CONCLUSIONS: Our results suggest that plasma miRNA levels may change in wet age-related macular degeneration. These molecules may have an important therapeutic target in patients who are unresponsive to antivascular endothelial growth factor therapy. However, further studies must be conducted for possible effects of miRNAs in vascular disorders of eye such as age-related macular degeneration.

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Effects of Multifunctional Antioxidants on Mitochondrial Dysfunction and Amyloid-β Metal Dyshomeostasis.

Kawada H, Blessing K, Kiyota T, Woolman T, Winchester L, Kador PF.

Background: Redox-active metal dyshomeostasis and oxidative stress are associated with mitochondrial dysfunction and amyloid-β (Aβ) neurotoxicity that are linked to both the development of age-related macular degeneration (AMD) and Alzheimer's disease (AD). As potential therapeutic agents, orally active multifunctional antioxidants (MFAOs) possessing two independent functional groups capable of binding redox-active metals and scavenging free radicals have been synthesized. Objective: To determine whether MFAOs affect mitochondrial function and reduce the presence of Aβ plaque formation.

Methods: The MFAOs were evaluated in cultured SH-SY5Y cells and ARPE-19 cells. MFAO effects on mitochondrial function were investigated using rhodamine 123 staining after 2 hour exposure to MnCl2. MFAO effects on Aβ:Zn complex formation were evaluated with Zinquin staining and the ability of the Aβ:Zn complex to be degraded by matrix metalloproteinase-2 (MMP-2). The ability of MFAOs to reduce Aβ plaque in the brain was determined by orally feeding MFAO for one year to B6;129-Psen1tm1Mpm Tg (AβPPSwe,tauP301L) 1Lfa/Mmjax transgenic mice. Aβ levels were determined by ELISA.

Results: MFAOs neither adversely affected mitochondrial signaling nor labile cytoplasmic zinc levels. MFAOs protected cells against Mn2+-induced mitochondrial dysfunction. MFAOs also removed zinc from the Aβ:Zn complex so that Aβ plaque could be degraded by MMP-2. Zinquin staining indicated that the removed zinc was present in the cytoplasm as labile zinc. Orally administered MFAOs reduced the brain levels of both Aβ40 and Aβ42 isoforms of Aβ.

Conclusion: These studies demonstrate that these MFAOs have metal attenuating properties with therapeutic potential in the treatment of both AMD and AD.

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Interleukin-17 Induces Angiogenesis in Human Choroidal Endothelial Cells in vitro.

Chen Y, Zhong M, Liang L, Gu F, Peng H.

Purpose: The proinflammatory cytokine, interleukin-17 (IL-17), has recently been shown to promote angiogenesis. Additionally, a receptor for IL-17, the IL-17 receptor C (IL-17RC), has also been shown to be enriched in patients afflicted with wet age-related macular degeneration (AMD), a disease characterized by the formation of choroidal neovascularization. However, the role of IL-17 on choroidal endothelial cells (CECs) angiogenesis has not been defined. This study was conducted to determine the effect of IL-17 on proliferation, migration, and tube formation of human CECs.

Methods: The expression patterns of IL-17 receptor A (IL-17RA) and IL-17RC on isolated human CECs were analyzed by flow cytometry and immunofluorescent staining. Proangiogenic effects of IL-17 on CECs was determined by proliferation assays with WST-1, wound healing migration assays, and tube formation assays with Matrigel matrix. Cytoskeletal changes were observed by F-actin immunofluorescent staining. Activated Rac1 and RhoA levels were analyzed by pull-down assays.

Results: IL-17RA and IL-17RC were present on human CECs. IL-17 was chemotactic for CECs and enhanced migration and tube formation but did not affect proliferation. Moreover, IL-17 induced rearrangement of the actin cytoskeleton and upregulated activated Rac1 and RhoA in CECs. The PI3K inhibitor, wortmannin, suppressed CEC migration, cytoskeleton rearrangement, and upregulation of activated Rac1and RhoA induced by IL-17.

Conclusions: IL-17 elicits a proangiogenesis effect on human CECs in vitro by promoting migration and tube formation. The promoted migration effect was dependent on PI3K-Rac1 and RhoA-mediated actin cytoskeleton remodeling.

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Epidemiology

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Global Burden of Eye and Vision Disease as Reflected in the Cochrane Database of Systematic Reviews.

Boyers LN, Karimkhani C, Hilton J, Richheimer W, Dellavalle RP.

Importance: Eye and vision disease burden should help guide ophthalmologic research prioritization. The Global Burden of Disease (GBD) Study 2010 compiled data from 1990 to 2010 on 291 diseases and injuries, 1160 disease and injury sequelae, and 67 risk factors in 187 countries. The Cochrane Database of Systematic Reviews (CDSR) is a resource for systematic reviews in health care, with peer-reviewed systematic reviews that are published by Cochrane Review Groups.

Objective: To determine whether systematic review and protocol topics in the CDSR reflect disease burden, measured by disability-adjusted life-years (DALYs), from the GBD 2010 project. This is one of a series of projects mapping GBD 2010 medical field disease burdens to corresponding systematic reviews in the CDSR.

Design and Setting: Two investigators independently assessed 8 ophthalmologic conditions in the CDSR for systematic review and protocol representation according to subject content. The 8 diseases were matched to their respective DALYs from the GBD 2010 project.

Main Outcomes and Measures: Cochrane Database of Systematic Reviews systematic review and protocol representation and percentage of total 2010 DALYs.

Results: All 8 ophthalmologic conditions were represented by at least 1 systematic review in the CDSR. A total of 91.4% of systematic reviews and protocols focused on these conditions were from the Cochrane Eyes and Vision Group. Comparing the number of reviews and protocols with disability, only cataract was well matched; glaucoma, macular degeneration, and other vision loss were overrepresented. In comparison, trachoma, onchocerciasis, vitamin A deficiency, and refraction and accommodation disorders were underrepresented.

Conclusions and Relevance: These results prompt further investigation into why certain diseases are overrepresented or underrepresented in the CDSR relative to their DALY. With regard to ophthalmologic conditions, this study encourages that certain conditions get more focus to create a better representation of what is causing the most disability and mortality within this research database. These results provide high-quality and transparent data to inform future prioritization decisions.

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Five Heavy Metallic Elements and Age-Related Macular Degeneration: Korean National Health and Nutrition Examination Survey, 2008-2011.

Park SJ, Lee JH, Woo SJ, Kang SW, Park KH; the Epidemiologic Survey Committee of the Korean Ophthalmologic Society.

OBJECTIVE: To investigate the association between age-related macular degeneration (AMD) and 5 heavy metallic elements (lead, mercury, cadmium, manganese, and zinc).

DESIGN: A cross-sectional study using a complex, stratified, multistage, probability cluster survey.

PARTICIPANTS: Participants of the Korean National Health and Nutrition Examination Survey from 2008 to 2011.

METHODS: Using a standardized protocol, AMD was determined by fundus photograph grading. Blood concentrations of lead, mercury, cadmium, manganese, and zinc were measured. Associations between AMD and these 5 elements were estimated using logistic regression analyses (LRAs). The distributions of the 5 metallic elements in blood were analyzed, and the same set of LRAs estimating the association between AMD and logarithmic-transformed blood concentrations of the 5 elements were also conducted.

MAIN OUTCOME MEASURES: Association between AMD and 5 heavy metals.

RESULTS: Lead was positively associated with both early AMD and late AMD in all LRAs. Mercury and cadmium also had a positive association with late AMD in all LRAs, but not with early AMD. In contrast, manganese and zinc had an inverse association with late AMD in all LRAs. Manganese and zinc were not associated with early AMD. Using logarithmic-transformed blood concentrations for each metallic element, the LRAs showed similar results compared with those of the LRAs using nontransformed blood concentrations, despite the skewed distribution of these metallic elements in the blood.

CONCLUSIONS: This study suggests that the toxic heavy metals (lead, mercury, and cadmium) may negatively influence late AMD, whereas essential heavy metals (manganese and zinc) may favorably influence late AMD. Lead may widely affect the pathogenesis of both early and late AMD.

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rs4711751 and rs1999930 Are Not Associated with Neovascular Age-Related Macular Degeneration or Polypoidal Choroidal Vasculopathy in the Chinese Population.

Huang L, Li M, Ma X, Li Y, Zhang C, Sun Y, Bai Y, Wang B, Yu W, Zhao M, Khor CC, Li X.

Purpose: rs1999930 and rs4711751 have recently been identified as novel variants associated with advanced age-related macular degeneration (AMD) in populations of European ancestry. We aimed to investigate whether these two single nucleotide polymorphisms (SNPs) were associated with neovascular AMD (nAMD) or with polypoidal choroidal vasculopathy (PCV), a variant of AMD in Asians, using a Chinese case-control study.

Methods: A total of 900 subjects, including 300 controls, 300 cases with nAMD and 300 cases with PCV, were included in the present study. Genomic DNA was extracted from venous blood leukocytes. The allelic variants of rs1999930 and rs4711751 were determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The differences in allele distribution between cases and controls were tested by a $\chi 2$ test, with additional adjustments for age and gender using logistic regression. The statistical power was also calculated. Values of $p < 0.05$ were considered statistically significant.

Results: No statistically significant association was observed between the two polymorphisms of nAMD or PCV phenotype ($p > 0.05$ for all comparisons). The difference remained insignificant after correction for age and gender ($p > 0.05$ for all comparisons). The statistical powers to detect the association between these two SNPs and nAMD or PCV range from 0.05 to 0.36, assuming conventional levels of statistical significance.

Conclusions: In the present study, we could not replicate the reported association of these two SNPs and either nAMD or PCV in a Chinese population, suggesting that they are unlikely to be a major AMD and PCV susceptibility gene locus in the Chinese population. Considering the low power value, a large sample size is required to draw more reliable conclusions.

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Diet & lifestyle

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Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: a randomised, double-blind, placebo-controlled trial.

Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lu XR, Lin XM.

AIMS: To investigate functional and macular pigment (MP) changes in patients with early age-related macular degeneration (AMD) after multiple supplementation with lutein and zeaxanthin.

METHODS: 112 patients with early AMD were randomly (1:1:1:1) assigned to receive 10 mg lutein, 20 mg lutein, lutein (10 mg)+zeaxanthin (10 mg), or placebo daily for 2 years. MP optical density (MPOD) was recorded at baseline, 48 weeks and 2 years. Retinal sensitivities were measured by multifocal electroretinogram for peak-to-trough amplitude (N1P1) at baseline and at 48 weeks, and in terms of microperimeter-determined mean retinal sensitivity (MRS) at 48 weeks and 2 years.

RESULTS: Supplementation with lutein and zeaxanthin augmented MPOD significantly in active treatment groups (all $p<0.05$). N1P1 response densities showed significant increases in ring 1 and ring 2 after 48 weeks of supplementation, while no significant changes were seen in rings 3-6. Significant increases in MRS were detected after supplementation with either 10 or 20 mg lutein, whereas no such increases were seen in the placebo arm.

CONCLUSIONS: Supplementation with lutein and/or zeaxanthin increases MPOD, and supplemental lutein enhances retinal sensitivity, in patients with early AMD.

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