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MD Research News

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Drug treatment

Ophthalmology. 2014 Dec 24. [Epub ahead of print]

Growth of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials.

Grunwald JE, Pistilli M, Ying G, Maguire MG, Daniel E, Martin DF; Comparison of Age-related Macular Degeneration Treatments Trials Research Group.

PURPOSE: To evaluate the growth of geographic atrophy (GA) during anti-vascular endothelial growth factor (VEGF) therapy.

DESIGN: Cohort within a clinical trial.

PARTICIPANTS: Patients included in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

METHODS: Participants were randomly assigned to injections of ranibizumab or bevacizumab and to a 2-year dosing regimen of monthly or pro re nata (PRN) or to monthly for 1 year and PRN the following year. Digital color photographs and fluorescein angiograms at baseline and 1 and 2 years were evaluated for GA, and the total area of GA was measured by 2 graders masked to treatment; differences were adjudicated. Multivariate linear mixed models of the annual change in the square root of the area included baseline demographic, treatment, and ocular characteristics on imaging as candidate risk factors.

MAIN OUTCOME MEASURES: Geographic atrophy growth rate.

RESULTS: Among 1185 participants, 86 (7.3%) had GA at baseline, 120 (10.1%) developed GA during year 1, and 36 (3.0%) developed GA during year 2. Among 194 eyes evaluable for growth, the rate was 0.43 mm/yr (standard error [SE], ±0.03 mm/year). In multivariate analysis, the growth rate was 0.37 mm/year in eyes receiving bevacizumab and 0.49 mm/year in eyes receiving ranibizumab (difference, 0.11 mm/yr; 95% confidence interval [CI], 0.01-0.22; P = 0.03). Growth rate did not differ between eyes treated monthly and PRN (P = 0.85). Eyes with subfoveal choroidal neovascularization (CNV) lesions had a lower growth rate than eyes with nonsubfoveal CNV lesions (difference, 0.12; 95% CI, 0.01-0.22; P = 0.03). Eyes with GA farther from the fovea had higher growth rates by 0.14 (95% CI, 0.01-27) mm/year for every millimeter farther from the fovea. The growth rate was 0.58 mm/year for eyes with predominantly classic lesions, 0.41 mm/year for eyes with minimally classic lesions, and 0.30 mm/year for eyes with occult only lesions (P < 0.01). The growth rate in eyes having a fellow eye with GA was higher by 0.13 mm/year (95% CI, 0.01-0.24; P = 0.03) than in eyes without GA in the fellow eye. Eyes with epiretinal membrane had a higher growth rate than eyes without epiretinal membrane (difference, 0.16; 95% CI, 0.03-0.30; P = 0.02).

CONCLUSIONS: Geographic atrophy growth depends on several ocular factors. Ranibizumab may accelerate GA growth.

PMID: 25542520 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Dec 19;131C:29-41. [Epub ahead of print]

Intracellular pathways following uptake of bevacizumab in RPE cells.

Aboul Naga SH, Dithmer M, Chitadze G, Kabelitz D, Lucius R, Roider J, Klettner A.

Abstract: The anti-VEGF antibody bevacizumab is widely used off-label for the treatment of various ocular diseases, most commonly in age-related macular degeneration and diabetic macular edema. Bevacizumab is able to penetrate the retina and is found in the choroid after intravitreal injection in a time dependent manner. It has previously been shown to be taken up by the retinal pigment epithelium (RPE). In this study, we have investigated the intracellular pathway following uptake of bevacizumab in RPE cells, tested both in primary porcine RPE cells and in the human cell line ARPE19. Bevacizumab displays a characteristic, time-dependent pattern of intracellular distribution, as detected by immunofluorescence and pulse chase experiments. In both primary cells and the cell line, intracellular bevacizumab can be found after seven days, as detected by immunofluorescence and Western blotting. Immediately after application, bevacizumab partially colocalizes with Rab5, indicating some uptake in early endosomes. Intracellularly, bevacizumab is detected in the cytoskeletal fraction, aligning with actin filaments, as revealed by subcellular fractioning and immunofluorescence. Bevacizumab seems to travel along actin filaments by myosin7a, as determined by triple staining immunofluorescence. Interestingly, over a period of seven days, bevacizumab seems to accumulate in certain storage areas, as observed by immunofluorescence. Furthermore, results obtained with immunocytochemistry, Western blotting and flow cytometry indicate that bevacizumab may be released from the RPE cells via exosomes. In conclusion, bevacizumab is taken up by and transported in the retinal pigment epithelial cells in a characteristic, time-dependent manner, where it seems to move along actin filaments by myosin7a and seem to be partially released from the cells via exosomes.

PMID: 25533679 [PubMed - as supplied by publisher]

PLoS One. 2014 Dec 26;9(12):e113981.

Comparative evaluation of combined navigated laser photocoagulation and intravitreal ranibizumab in the treatment of diabetic macular edema.

Liegl R, Langer J, Seidensticker F, Reznicek L, Haritoglou C, Ulbig MW, Neubauer AS, Kampik A, Kernt M.

OBJECTIVE: To evaluate if a standardized combination therapy regimen, utilizing 3 monthly ranibizumab injections followed by navigated laser photocoagulation, reduces the number of total ranibizumab injections required for treatment of diabetic macular edema (DME).

RESEARCH DESIGN AND METHODS: A 12-month, prospective comparison of 66 patients with center-involving DME: 34 patients with combination therapy were compared to 32 patients treated with ranibizumab monotherapy. All patients initially received 3 monthly ranibizumab injections (loading phase) and additional injections pro re nata (PRN). Combination therapy patients additionally received navigated laser photocoagulation after the loading phase. Main outcome measures were mean number of injections after the loading phase and change in BCVA from baseline to month 12.

RESULTS: Navigated laser combination therapy and ranibizumab monotherapy similarly improved mean BCVA letter score (+8.41 vs. +6.31 letters, p=0.258). In the combination group significantly less injections were required after the 3 injection loading phase (0.88±1.23 vs. 3.88±2.32, p<=0.001). By month 12, 84% of patients in the monotherapy group had required additional ranibizumab injections as compared to 35% in the combination group (p<=0.001).

CONCLUSIONS: Navigated laser combination therapy demonstrated significant visual gains in most patients. Retreatment rate and number of injections were significantly lower compared to ranibizumab monotherapy and compared to the results of conventional laser combination therapy previously reported in pivotal anti-VEGF studies.

PMID: 25541960 [PubMed - in process]

PLoS One. 2014 Dec 26;9(12):e115797.

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema: A Meta-Analysis of Randomized Controlled Trials.

Chen G, Li W, Tzekov R, Jiang F, Mao S, Tong Y.

OBJECTIVE: To evaluate the relative efficacy of ranibizumab (RBZ) monotherapy or combined with laser (RBZ + Laser) versus laser monotherapy for the treatment of diabetic macular edema (DME).

METHODS: A comprehensive literature search using PUBMED, ClinicalTrials.gov, and the Cochrane Library to identify randomized controlled trials (RCTs) comparing RBZ or RBZ + Laser to laser monotherapy in patients with DME. Efficacy estimates were determined by comparing weighted mean differences (WMD) in the change of best corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline, and the risk ratios (RR) for the proportions of patients with at least 15 letters change from baseline. Safety analysis estimated the RR of cardiac disorders at 6 to 12 months in RBZ therapy vs. laser monotherapy. Statistical analysis was performed using the RevMan 5.1 software.

RESULTS: Seven RCTs were selected for this meta-analysis, including 1749 patients (394 patients in the RBZ group, 642 patients in the RBZ + Laser group, and 713 patients in the laser group). RBZ and RBZ + Laser were superior to laser monotherapy in the mean change of BCVA and CMT from baseline (WMD= 5.65, 95% confidence interval (CI), 4.44-6.87, P<0.00001; WMD =5.02, 95% CI, 3.83-6.20, P<0.00001, and WMD =-57.91, 95% CI, -77.62 to -38.20, P<0.00001; WMD =-56.63, 95% CI, -104.81 to -8.44, P=0.02, respectively). The pooled RR comparing the proportions of patients with at least 15 letters improvement or deterioration were also in favor of RBZ and RBZ + Laser (RR=2.94, 95% CI, 1.82-4.77, P<0.00001; RR= 2.04, 95% CI, 1.50-2.78, P<0.00001, and RR=0.21, 95% CI, 0.06-0.71, P=0.01; RR=0.52, 95% CI, 0.29-0.95, P=0.03, respectively). There were no significant differences between RBZ and RBZ + Laser for any of the parameters. There were no difference in the safety profile between RBZ and laser.

CONCLUSION: RBZ and RBZ + Laser had better visual and anatomic outcomes than laser monotherapy in the treatment of DME. RBZ + Laser seemed to be equivalent to RBZ.

PMID: 25541937 [PubMed - in process]

Int J Ophthalmol. 2014 Dec 18;7(6):1017-21.

Bilateral same-session intravitreal injections of anti-vascular endothelial growth factors.

Abu-Yaghi NE, Shokry AN, Abu-Sbeit RH.

AIM: To document the indications, safety and possible complications of bilateral same-session intravitreal anti-vascular endothelial growth factor (VEGF) injections performed in the ophthalmic operating room.

METHODS: A retrospective case series study. Consecutive records of seventy four patients receiving simultaneous bilateral intravitreal injections of either ranibizumab or bevacizumab, between September 2010 and September 2013, were reviewed and the outcomes were assessed. Data collected included number of injections, indications for injections, pre-injection and post-injection visual acuity (VA), pre-injection and post-injection intraocular pressure and ocular and systemic complications/complaints after each injection.

RESULTS: A total of 342 injections were administered to 74 patients, with a mean of 4.62 injections per patient. Seventy-three patients received bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA) alone, and only one patient received both bevacizumab and ranibizumab (Lucentis; Genentech Inc.) distributed between the injections. Pre- and post-injection VA follow-up measurements were available for 65 patients. Mean follow up period was 22mo. The indications for initiating therapy were choroidal neovascular membrane from age-related macular degeneration (3 patients) and diabetic macular edema (71 patients). The mean Snellen VA before each injection was 6/22. The next post-injection follow-up mean Snellen VA was 6/20. One patient had a painful, culture-positive endophthalmitis in one eye 3d after bilateral bevacizumab. Another patient had a painless subconjunctival hemorrhage in one eye. No other ocular or systemic adverse side effects/complaints have been registered in this study group.

CONCLUSION: Bilateral same-session intravitreal injections using a separate povidone-iodine preparation, speculum, needle, and syringe for each eye are well-tolerated. None of the subjects in this study requested to switch to alternating unilateral injections. Proper patient counseling as to the risk of complications with this procedure is necessary.

PMID: 25540758 [PubMed] PMCID: PMC4270969

Clin Experiment Ophthalmol. 2014 Dec 29. [Epub ahead of print]

Safety, sterility and stability of direct-from-vial multiple dosing intravitreal injection of bevacizumab.

Das T, Volety S, Ahsan SM, Thakur AK, Sharma S, Padhi TR, Basu S, Rao CM.

PURPOSE: To determine the stability, sterility and safety of bevacizumab multiple dosing from a single vial without prior aliquoting.

METHODS: In-vitro and human study. Six bevacizumab vials, used in multiple patients on a single day by direct withdrawal from the vial, and stored in 4O C up to a variable period, were tested for stability (High Performance Liquid Chromatography; HPLC), sterility (Culture), conformational stability by circular dichroism and fluorescence spectroscopy and the rubber cork structural integrity (Electron Microscopy; EM).

RESULTS: HPLC of all six samples of used bevacizumab and the control bevacizumab sample were similar; culture was negative; and the EM of rubber corks did not show an open communication. Spectroscopic studies indicated drug conformational stability. Further there was no infection or inflammation in 221 consecutive patients (973 injections) when bevacizumab was stored at 4O C and used for one week.

CONCLUSION: Bevacizumab does not lose stability when stored at 4O C. It may be used for a week by direct withdrawal from the vial without fear of infection or inflammation if all standard precautions related to intravitreal injection are adhered to.

PMID: 25545882 [PubMed - as supplied by publisher]

Turk J Med Sci. 2014;44(5):889-95.

Comparative study of photodynamic therapy monotherapy versus triple management in age-related macular degeneration.

Selım A, Koçak N, Aslankara H, Kaynak S.

AIM: To compare the effectiveness of photodynamic therapy (PDT) and PDT combined with intravitreal triamcinolone (IVTA) and vascular endothelial growth factor inhibition (anti-VEGF) in age-related macular degeneration (AMD).

MATERIALS AND METHODS: Eighty eyes of 80 patients diagnosed with choroidal neovascularization (CNV) caused by AMD were included in the study. PDT was carried out on 40 eyes in group I, and PDT combined with 4 mg IVTA and anti-VEGF (1.25 mg bevacizumab in 20 eyes, 0.3 mg pegaptanib sodium in 20 eyes) was carried out in group II. The primary efficacy endpoint was the mean change from baseline visual acuity at month 12.

RESULTS: Mean follow-up was 14.2 ± 2.18 months in group I and 12.45 ± 2.82 months in group II. In group I there was a 2.88 logMAR line decrease and 1.95 logMAR line increase in group II in vision between pretreatment and 12th month measurements ($P < 0.05$). Mean PDT session was 2.00 in group I and the mean combined treatment session was 1.15 in group II in the 12th month.

CONCLUSION: Combination of IVTA and anti-VEGF with PDT is more effective and safer than PDT monotherapy in the treatment of CNV secondary to AMD. Combination treatment decreases the frequency

and number of treatment sessions for an improved visual prognosis.

PMID: 25539563 [PubMed - in process]

Clin Ophthalmol. 2014 Dec 15;8:2529-32.

Long-lasting effects of anti-VEGF/photodynamic combination therapy in the treatment of exudative age-related macular degeneration: a retrospective chart review.

Silva-Garcia R, McLellan C, Shaya FS, Small KW.

PURPOSE: To examine the potential long-term benefit of an anti-VEGF/photodynamic therapy (PDT) combination on patients treated for wet age-related macular degeneration (AMD).

METHODS: A retrospective chart review was conducted on 29 eyes (subjects) from 26 patients (eight male and 18 female) that showed sustained, positive response to combination therapy for exudative AMD for a minimum of 1 year. Collected data included: visual acuity, central retinal thickness, intraocular pressure and history of glaucoma, wet AMD onset and treatment history, concomitant use of anticoagulants and past history or development of cerebrovascular or cardiovascular disease while receiving combination therapy.

RESULTS: Subjects underwent an average of five injections and two PDT treatments in total over 16 months before the choroidal neovascular membrane (CNVM) stabilized and became inactive for at least 1 year. Prior to the effective anti-VEGF/PDT combination therapy the median Snellen visual acuity ranged from 20/200 to 20/250 and presented at no worse than 20/200 at 1 year after treatment. Some subjects were followed for up to 5 years and remained inactive.

CONCLUSION: Combination therapy can cause long-lasting closure of the CNVM, even with advanced disease resistant to anti-VEGF monotherapy.

PMID: 25548512 [PubMed]

BMC Med Res Methodol. 2014 Dec 22;14(1):140.

Indirect comparisons of ranibizumab and dexamethasone in macular oedema secondary to retinal vein occlusion.

Thom HH, Capkun G, Nixon RM, Ferreira A.

BACKGROUND: Two treatments, ranibizumab and dexamethasone implant, for visual impairment due to macular oedema (ME) secondary to retinal vein occlusion (RVO) have recently been studied in clinical trials. There have been no head to head comparisons of the two treatments, and improvement measured as gain in Best Corrected Visual Acuity (BCVA) was reported using different outcomes thresholds between trials. To overcome these limitations, and inform an economic model, we developed a combination of a multinomial model and an indirect Bayesian comparison model for multinomial outcomes.

METHODS: Outcomes of change from baseline in BCVA for dexamethasone compatible with those available for ranibizumab, reported by 4 randomised controlled trials, were estimated by fitting a multinomial distribution model to the probability of a patient achieving outcomes in a range of changes from baseline in BCVA (numbers of letters) at month 1. A Bayesian indirect comparison multinomial model was then developed to compare treatments in the Branch RVO (BRVO) and Central RVO (CRVO) populations.

RESULTS: The multinomial model had excellent fit to the observed results. With the Bayesian indirect comparison, the probabilities of achieving ≥20 letters, with 95% credible intervals, at month 1 in patients with BRVO were 0.191 (0.130, 0.261) with ranibizumab and 0.093 (0.027, 0.213) with dexamethasone. In patients with CRVO, probabilities were 0.133 (0.082, 0.195) (ranibizumab) and 0.063 (0.016, 0.153) (dexamethasone). Probabilities of a gain in ≥10 letters in BRVO patients were 0.500 (0.365, 0.650) v 0.459 (0.248, 0.724) and in CRVO patients 0.459 (0.332, 0.602) v 0.498 (0.263, 0.791) for ranibizumab and dexamethasone treatments respectively. The comparisons also favoured ranibizumab at month 6 although changes to therapies after month 3 may have introduced bias.

CONCLUSION: The newly developed combination of multinomial and indirect Bayesian comparison models indicated a trend for ranibizumab association with a greater percentage of ME patients achieving visual gains than dexamethasone at months 1 and 6 in a common clinical context, although results were not classically significant. The method was a useful tool for comparisons of probability distributions between clinical trials that reported events on different categorical scales and estimates can be used to inform economic models.

PMID: 25533265 [PubMed - in process]

J Med Case Rep. 2014 Dec 22;8(1):458. [Epub ahead of print]

Successful long-term management of choroidal neovascularization secondary to angioid streaks in a patient with pseudoxanthoma elasticum: a case report.

Savastano MC, Minnella AM, Zinzanella G, Falsini B, Caporossi A.

INTRODUCTION: We describe the long-term effectiveness and tolerability of intravitreal vascular endothelial growth factor inhibitor ranibizumab in a patient with pseudoxanthoma elasticum with bilateral macular choroidal neovascularization secondary to angioid streaks.

CASE PRESENTATION: A 54-year-old Caucasian man with history of heart disease presented with visual loss in his right eye. An examination revealed choroidal neovascularization and reduced visual acuity, while no abnormalities were seen in his left eye. He was diagnosed with angioid streaks associated with pseudoxanthoma elasticum. Off-label treatment with intravitreal bevacizumab once a month initiated in December 2007 was discontinued after 3 months due to lack of efficacy. In September 2008, the patient reported reduced visual acuity in his left eye and an examination revealed changes. Left eye treatment was initiated in October 2008 with a loading dose (three consecutive monthly intravitreal injections of ranibizumab 0.5mg/50muL) followed by 0.5mg/50muL followed by treatment as needed until May 2014. After 21 ranibizumab injections, an examination revealed angioid streaks and choroidal neovascularization in both eyes. His right eye showed retinal layer deterioration with outer limiting membrane and photoreceptor inner/outer segment junction involvement. His left eye had a smaller foveal scar, with other areas preserved. Visual acuity was stable in his treated left eye, but had deteriorated in his right eye. Ranibizumab treatment was well tolerated with no adverse events reported.

CONCLUSIONS: In the present case, an as-needed regimen of ranibizumab after an initial loading dose, achieved maintenance of visual function and was well tolerated over a period of almost 6 years in a patient with pseudoxanthoma elasticum and high cardiovascular risk. As anti-vascular endothelial growth factor agents are associated with increased risk of systemic effects, particularly arterial thromboembolic events, following intravenous administration, the absence of serious thromboembolic or cardiovascular adverse events throughout the 6-year treatment period is particularly encouraging considering our patient's high cardiovascular risk status.

PMID: 25529762 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Dec 24. [Epub ahead of print]

Reply to the Comment by Ilhan et al. on Our Paper Entitled 'Effect of Macular Ischemia on Intravitreal Ranibizumab Treatment for Diabetic Macular Edema'

Chatziralli I, Douvali M, Theodossiadis P, Rouvas AA.

PMID: 25547525 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Biomed Res Int. 2014;2014:671529. Epub 2014 Dec 9.

Scotopic microperimetry in the early diagnosis of age-related macular degeneration: preliminary study.

Nebbioso M, Barbato A, Pescosolido N.

Background: Recent clinical studies have shown that, in some degenerative retinal diseases, like age-related macular degeneration (AMD), the sensitivity of the rods decreases more rapidly than the sensitivity of the cones. The aim of this study was to evaluate if there is a correlation between the presence of hard drusen at the macular level and the rod damage responsible for the reduction in scotopic retinal sensitivity in subjects at risk for AMD.

Methods: The authors selected 24 subjects (14 men and 10 women) with an average age of 67.25 ± 5.7 years. Macular hard drusen were present in 50% of the subjects at the fundus oculi exam. The researchers evaluated the retinal sensitivity to light in mesopic and scotopic conditions of each subject with an MP-1 scotopic microperimeter (MP-1S).

Results: In subjects with hard drusen in the fundus oculi examination, there was a statistically significant reduction in scotopic retinal sensitivity, while the mesopic retinal sensitivity was not compromised.

Conclusion: This study revealed how the presence of hard drusen at the macular level is associated with a reduction in scotopic retinal sensitivity compared to a control group of healthy subjects. Retinal functionality in a scotopic setting examined with MP-1S could be useful in early diagnosis of AMD.

PMID: 25548774 [PubMed - in process]

Am J Ophthalmol. 2014 Dec 16. [Epub ahead of print]

Relationship of Central Choroidal Thickness with Age-Related Macular Degeneration Status.

Yiu G, Chiu SJ, Petrou PA, Stinnett S, Sarin N, Farsiu S, Chew EY, Wong WT, Toth CA.

PURPOSE: To compare choroidal thickness in patients with intermediate or advanced age-related macular degeneration (AMD) and control subjects using enhanced-depth imaging optical coherence tomography (EDI-OCT).

DESIGN: Retrospective cross-sectional study of 325 eyes from 164 subjects who underwent EDI-OCT for the Age-Related Eye Disease Study (AREDS) 2 Ancillary Spectral Domain OCT study.

METHODS: Choroidal thickness was measured by semi-automated segmentation of EDI-OCT images from 1.5mm nasal to 1.5mm temporal to the fovea. Multivariate linear regression was used to evaluate the association of subfoveal choroidal thickness or average choroidal thickness across the central 3mm segment with systemic and ocular variables. Choroidal thickness measurements were compared between eyes with no AMD (n = 154) (i.e. controls), intermediate AMD (n = 109), and advanced AMD (n = 62).

RESULTS: Both subfoveal and average choroidal thicknesses were associated with age ($P < 0.001$) and refractive error ($P < 0.001$), but not other variables tested. Mean average choroidal thickness was significantly reduced in advanced AMD as compared with control eyes ($P = 0.008$), with no significant difference between advanced and intermediate AMD eyes ($P = 0.152$) or between intermediate AMD and control eyes ($P = 0.098$). Choroidal thinning was also noted from 1.5 mm nasal to 1.5 mm temporal to the fovea when comparing advanced AMD with control eyes ($P < 0.05$ at all 0.5mm interval locations). After adjustment for age and refractive error, however, there was no significant difference in subfoveal ($p = 0.675$) or average choroidal thickness ($p = 0.746$) across all three groups.

CONCLUSIONS: When adjusted for age and refractive error, central choroidal thickness may not be significantly influenced by AMD status based on AREDS categorization.

PMID: 25526948 [PubMed - as supplied by publisher]

Int J Clin Exp Med. 2014 Nov 15;7(11):3843-52.

Stem cell-based therapies for age-related macular degeneration: current status and prospects.

Mu Y, Zhao M, Su G.

Abstract: Age-related macular degeneration (AMD) is one of the major causes of irreversible blindness both in developed and developing countries. During the past decades, the managements of neovascular AMD (wet AMD) have dramatically progressed. However, still no effective treatment for non-neovascular AMD (dry AMD) which was characterized by geographic macular atrophy. Recent advances in stem cell sciences have demonstrated that retinal pigment epithelium (RPE) cells can be generated from several types of stem cells (including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, et al) by cell co-culturing or defined factors. Additionally, studies also showed that visual function could be recovered by transplantation of these cells into subretinal space in vivo. Moreover, the United States Food and Drug Administration already approved several clinical trials to evaluate the efficiencies of stem cell based cell transplantation for dry AMD patients. Till now, a few patients enrolled in these studies achieved promising outcomes. This review will summarize recent advances in stem cell based RPE differentiation, transplantation, and the preliminary results of clinical trials. The obstacles and prospects in this field will also be discussed.

PMID: 25550892 [PubMed]

Retina. 2014 Dec 24. [Epub ahead of print]

AGREEMENT AND REPRODUCIBILITY OF RETINAL PIGMENT EPITHELIAL DETACHMENT VOLUMETRIC MEASUREMENTS THROUGH OPTICAL COHERENCE TOMOGRAPHY.

Ho J, Adhi M, Baumal C, Liu J, Fujimoto JG, Duker JS, Waheed NK.

PURPOSE: To assess the agreement and reproducibility of retinal pigment epithelial detachment (RPED) volumetric measurements using a commercially available optical coherence tomography software available for the Zeiss Cirrus HD-OCT.

METHODS: Twelve eyes of 10 patients with a diagnosis of neovascular age-related macular degeneration with RPED, seen at the New England Eye Center between October 2012 and December 2012, were enrolled in the study. Three separate scans per affected eye were obtained using the "Macular Cube 512 × 128" protocol. "Retinal pigment epithelial (RPE) elevation analysis" software was used to measure RPED volumes in the central 3-mm and 5-mm circles by calculating the volume between the "RPE fit" and "true RPE" lines. All 128 raster scans for each eye were exported into the AMIRA software for manual segmentation of RPED volumes in the central 3-mm and 5-mm circles. Interscan reproducibility and manual -to-automated agreement were assessed by intraclass correlation coefficient. Incidence of automated segmentation line error for both RPE fit and true RPE lines in the central 1 mm region was calculated.

RESULTS: Average RPED volumes through automated segmentation software were 0.14 mm and 0.21 mm in the central 3-mm and 5-mm circles, respectively. Manual segmentation yielded average RPED volumes of 0.50 mm in the 3-mm circles and 0.92 mm in the 5-mm circles. Manual segmentation yielded significantly greater RPED volumes compared with automated measurements ($P < 0.05$). Intraclass correlation coefficients across the 3 automated measurements were 0.954 and 0.983 for volume in the 3-mm and 5-mm circles, respectively. Intraclass correlation coefficients between the manual and automatic volumes were 0.296 and 0.337 for the 3-mm and 5-mm circles, respectively. In the central 1 mm region, 11 of the 12 scans had breakdown in RPE fit line, whereas 8 of the 12 scans showed true RPE line breakdown.

CONCLUSION: Automated "RPED elevation" software demonstrated high interscan reproducibility. However, it showed low agreement with manual measurements from high rates of segmentation line breakdown, especially at the level of the RPE fit line (91.7%). Manual measurements resulted in greater volumes compared with automated measurements.

PMID: 25545485 [PubMed - as supplied by publisher]

Nihon Ganka Gakkai Zasshi. 2014 Nov;118(11):927-42.

[Polypoidal choroidal vasculopathy: new observations and therapeutic implications]. [Article in Japanese]

Koizumi H.

Abstract: Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration characterized by peculiar polypoidal lesions seen on indocyanine green angiography (IA). However, precise pathogenesis of PCV has yet to be clearly elucidated. In addition to the conventional diagnostic tools, we evaluated the clinical characteristics of PCV by means of relatively new and noninvasive imaging methods, namely, fundus autofluorescence photography and enhanced depth imaging optical coherence tomography, and found novel observations. This article focuses especially on the relationship between the clinical characteristics of PCV and choroidal vascular hyperpermeability. Choroidal vascular hyperpermeability, which is visualized as multifocal hyperfluorescence in the middle and late phases on IA, was originally described as a characteristic finding in, central serous chorioretinopathy (CSC). Of the 89 patients with PCV in our case series, 31 patients (34.8%) demonstrated choroidal vascular hyperpermeability. The patients with PCV associated with choroidal vascular hyperpermeability demonstrated more frequently bilateral occurrence of neovascular membrane, a history of CSC, a thickened choroid and poor responses to ranibizumab therapy than those without choroidal vascular hyperpermeability. Our results provide further understanding of PCV and new therapeutic implications.

PMID: 25543384 [PubMed - in process]

Eur J Pharm Biopharm. 2014 Dec 20. [Epub ahead of print]

Treatment of ocular disorders by gene therapy.

Ángeles Solinís M, Del Pozo-Rodríguez A, Apaolaza PS, Rodríguez-Gascón A.

Abstract: Gene therapy to treat ocular disorders is still starting, and current therapies are primarily experimental, with most human clinical trials still in research state, although beginning to show encouraging results. Currently 33 clinical trials have been approved, are in progress, or have been completed. The most promising results have been obtained in clinical trials of ocular gene therapy for Leber Congenital Amaurosis, which have prompted the study of several ocular diseases that are good candidates to be treated with gene therapy: glaucoma, age-related macular degeneration, retinitis pigmentosa, or choroideremia. The success of gene therapy relies on the efficient delivery of the genetic material to target cells, achieving optimum long-term gene expression. Although viral vectors have been widely used, their potential risk associated mainly with immunogenicity and mutagenesis has promoted the design of non-viral vectors. In this review, the main administration routes and the most studied delivery systems, viral and non-viral, for ocular gene therapy are presented. The primary ocular disease candidates to be treated with gene therapy have been also reviewed, including the genetic basis and the most relevant preclinical and clinical studies.

PMID: 25536112 [PubMed - as supplied by publisher]

Sci China Life Sci. 2014 Dec 20. [Epub ahead of print]

Cell therapy for macular degeneration-first phase I/II pluripotent stem cell-based clinical trial shows promise.

Chen Z, Zhang YA.

PMID: 25528254 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Dec 29;55(12):8542.

Association of focal choroidal excavation with age-related macular degeneration.

Querques G.

PMID: 25548212 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2014 Dec 29;55(12):8543.

Author response: association of focal choroidal excavation with age-related macular degeneration.

Kuroda Y, Tsujikawa A, Yoshimura N.

PMID: 25548213 [PubMed - in process]

Am J Ophthalmol. 2015 Feb;159(2):404.

Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic displacement for age-related macular degeneration.

Schaal S, Apenbrinck E, Barr CC.

PMID: 25542553 [PubMed - in process]

Pathogenesis

PLoS One. 2014 Dec 30;9(12):e116423.

Expression of thrombospondin-1 modulates the angioinflammatory phenotype of choroidal endothelial cells.

Fei P, Zaitoun I, Farnoodian M, Fisk DL, Wang S, Sorenson CM, Sheibani N.

Abstract: The choroidal circulation plays a central role in maintaining the health of outer retina and photoreceptor function. Alterations in this circulation contribute to pathogenesis of many eye diseases including exudative age-related macular degeneration. Unfortunately, very little is known about the choroidal circulation and its molecular and cellular regulation. This has been further hampered by the lack of methods for routine culturing of choroidal endothelial cells (ChEC), especially from wild type and transgenic mice. Here we describe a method for isolation and culturing of mouse ChEC. We show that expression of thrombospondin-1 (TSP1), an endogenous inhibitor of angiogenesis and inflammation, has a significant impact on phenotype of ChEC. ChEC from TSP1-deficient (TSP1-/-) mice were less proliferative and more apoptotic, less migratory and less adherent, and failed to undergo capillary morphogenesis in Matrigel. However, re-expression of TSP1 was sufficient to restore TSP1-/- ChEC migration and capillary morphogenesis. TSP1-/- ChEC expressed increased levels of TSP2, phosphorylated endothelial nitric oxide synthase (NOS) and inducible NOS (iNOS), a marker of inflammation, which was associated with significantly higher level of NO and oxidative stress in these cells. Wild type and TSP1-/- ChEC produced similar levels of VEGF, although TSP1-/- ChEC exhibited increased levels of VEGF-R1 and pSTAT3. Other signaling pathways including Src, Akt, and MAPKs were not dramatically affected by the lack of TSP1. Together our results demonstrate an important autocrine role for TSP1 in regulation of ChEC phenotype.

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Pathway activation profiling reveals new insights into Age-related Macular Degeneration and provides avenues for therapeutic interventions.

Makarev E, Cantor C, Zhavoronkov A, Buzdin A, Aliper A, Csoka AB.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in older people and is caused by loss of the central region of the retinal pigment epithelium (RPE). Conventional methods of gene expression analysis have yielded important insights into AMD pathogenesis, but the precis molecular pathway alterations are still poorly understood. Therefore we developed a new software program, "AMD Medicine", and discovered differential pathway activation profiles in samples of human RPE/choroid from AMD patients and controls. We identified 29 pathways in RPE-choroid AMD phenotypes: 27 pathways were activated in AMD compared to controls, and 2 pathways were activated in controls compared to AMD. In AMD, we identified a graded activation of pathways related to wound response, complement cascade, and apoptosis. Furthermore, significant activation of pro-mitotic pathways is consistent with dediffentiation and cell proliferation events, which occur early in the pathogenesis of AMD. Significantly, we discovered new global pathway activation signatures of AMD involved in the cell-based inflammatory response: IL-2, STAT3, and ERK. The ultimate aim of our research is to achieve a better understanding of signaling pathways involved in AMD pathology, which will eventually lead to better treatments.

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The Unfolded Protein Response in Retinal Vascular Diseases: Implications and Therapeutic Potential Beyond Protein Folding.

Zhang SX, Ma JH, Bhatta M, Fliesler SJ, Wang JJ.

Abstract: Angiogenesis is a complex, step-wise process of new vessel formation that is involved in both normal embryonic development as well as postnatal pathological processes, such as cancer, cardiovascular disease, and diabetes. Aberrant blood vessel growth, also known as neovascularization, in the retina and the choroid is a major cause of vision loss in severe eye diseases, such as diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, and central and branch retinal vein occlusion. Yet, retinal neovascularization is causally and dynamically associated with vasodegeneration, ischemia, and vascular remodeling in retinal tissues. Understanding the mechanisms of retinal neovascularization is an urgent unmet need for developing new treatments for these devastating diseases. Accumulating evidence suggests a vital role for the unfolded protein response (UPR) in regulation of angiogenesis, in part through coordinating the secretion of pro-angiogenic growth factors, such as VEGF, and modulating endothelial cell survival and activity. Herein, we summarize current research in the context of endoplasmic reticulum (ER) stress and UPR signaling in retinal angiogenesis and vascular remodeling, highlighting potential implications of targeting these stress response pathways in the prevention and treatment of retinal vascular diseases that result in visual deficits and blindness.

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Preliminary study on electrophysiological changes after cellular autograft in age-related macular degeneration.

Limoli PG, Vingolo EM, Morales MU, Nebbioso M, Limoli C.

Abstract: Evolving atrophic macular degeneration represents at least 80% of all macular degenerations and is currently without a standardized care. Autologous fat transplantation efficacy was demonstrated by several studies, as these cells are able to produce growth factors. The aim of the work was to demonstrate possible therapeutic effect of the joined suprachoroidal graft of adipocytes, adipose-derived stem cells

(ADSCs) in stromal vascular fractions (SVFs) of adipose tissue, and platelet-rich plasma (PRP).Twelve eyes in 12 dry age-related macular degeneration (AMD) patients, aged 71.25 (SD±6.8) between 62 and 80 years, were analyzed. A complete ocular evaluation was performed using best corrected visual acuity (BCVA), retinographic analysis, spectral-domain optical coherence tomography, microperimetry, computerized visual field, and standard electroretinogram (ERG). Each eye received a cell in graft between choroid and sclera of mature fat cells and ADSCs in SVF enriched with PRP by means of the variant second Limoli (Limoli retinal restoration technique [LRRT]). In order to test if the differences pre- and post-treatment were significant, the Wilcoxon signed-rank test has been performed.Adverse effects were not reported in the patients. After surgery with LRRT, the most significant increase in the ERG values was recorded by scotopic rod-ERG (answer coming from the rods), from 41.26 to 60.83 μV with an average increase of 47.44% highly significant ($P<0.05$). Moderately significant was the one recorded by scotopic maximal ERG (answer coming from the rods and cones), from 112.22 to 129.68 μV with an average increase of 15.56% ($P<0.1$).Cell-mediated therapy based on growth factors used appears interesting because it can improve the retinal functionality responses in the short term. The ERG could, therefore, be used to monitor the effect of cell-mediated regenerative therapies.

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Diet & lifestyle

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Depression in ophthalmological patients.

Pop-Jordanova N, Ristova J, Loleska S.

Abstract

(Full text is available at http://www.manu.edu.mk/prilozi).

INTRODUCTION: Vision is the most important sensorial part of the human information system. Visual loss leads to reduced ability to perform routine activities of daily living and can be a risk for stable mental health.

AIM: The aim of this cross-sectional study is to assess the incidence of depression in patients treated in an ophthalmological outpatient clinic. To our knowledge this is the first study of its kind in our country.

SUBJECTS AND METHOD: The number of evaluated patients was a hundred; mean age 41.6 ± 15.9 years, with different educational levels and common ophthalmological disorders. For the assessment of the level of depression the Beck Depression Inventory was used. Patients were divided into two groups: serious ophthalmological diagnoses where we expected psychological problems (N = 65) and the simplest ones (N = 35) as a control.

RESULTS: Obtained results show that the levels of depression correlate with the diagnoses. Patients in the first group (serious ophthalmological diagnoses) showed moderate depression in 12% and severe in 13% of patients. It was shown that the most depressed were the patients suffering from age-related macular degeneration and proliferative diabetic retinopathy, as well as glaucoma and cataract. The second group showed BDI scores of normal values. The level of depression is positively correlated with age and the level of education ($p < 0.05$).

CONCLUSION: Depression is an important mental problem in ophthalmological practice. It is usually unrecognized and untreated. Depression could be the risk factor for treatment and prognosis of eyes diseases. Some measures for mitigation of psychological problems are proposed.

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