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MD Research News

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Drug treatment

Ophthalmology. 2011 Jun;118(6):1098-106.

The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing.

Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, Yancopoulos G, Stahl N, Ingerman A, Vitti R, Berliner AJ, Yang K, Brown DM; CLEAR-IT 2 Investigators.

Ophthalmic Consultants of Boston, Boston, Massachusetts.

OBJECTIVE: To evaluate anatomic outcomes and vision, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with vascular endothelial growth factor (VEGF) Trap-Eye for neovascular (wet) age-related macular degeneration (AMD).

DESIGN: Multicenter, randomized, double-masked trial.

PARTICIPANTS: We included 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD.

METHODS: Patients were randomly assigned to 1 of 5 intravitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1-12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their assigned dose (0.5, 2, or 4 mg).

MAIN OUTCOME MEASURES: Change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in best-corrected visual acuity (BCVA), proportion of patients with 15-letter loss or gain, time to first PRN injection, reinjection frequency, and safety at week 52.

RESULTS: The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (-130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm(2) at 48 weeks. After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; P<0.0001). The most robust improvements and consistent maintenance of visual acuity generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first reinjection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well tolerated, with few ocular or systemic adverse events.

CONCLUSIONS: PRN dosing with VEGF Trap-Eye at weeks 16-52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of reinjections. Repeated dosing with VEGF Trap-Eye was well tolerated over 52 weeks of treatment.

PMID: 21640258 [PubMed - in process]

Ophthalmology. 2011 Jun;118(6):1089-97.

Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration.

Brown DM, Heier JS, Ciulla T, Benz M, Abraham P, Yancopoulos G, Stahl N, Ingerman A, Vitti R, Berliner AJ, Yang K, Nguyen QD; CLEAR-IT 2 Investigators.

Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

OBJECTIVE: To evaluate the biologic effects and safety of vascular endothelial growth factor (VEGF) Trap-Eye during a 12-week fixed-dosing period in patients with neovascular (wet) age-related macular degeneration (AMD).

DESIGN: Multicenter, prospective, randomized, double-masked clinical trial with initial 12-week fixed dosing period. Data were analyzed to week 16.

PARTICIPANTS: We included 159 patients with subfoveal choroidal neovascularization secondary to wet AMD.

METHODS: Patients were randomized 1:1:1:1:1 to VEGF Trap-Eye during the fixed-dosing phase (day 1 to week 12): 0.5 or 2 mg every 4 weeks (0.5 mg q4wk, 2 mg q4wk) on day 1 and at weeks 4, 8, and 12; or 0.5, 2, or 4 mg every 12 weeks (0.5 mg q12wk, 2 mg q12wk, or 4 mg q12wk) on day 1 and at week 12.

MAIN OUTCOME MEASURES: The primary endpoint was change from baseline in central retinal/lesion thickness (CR/LT) at week 12; secondary outcomes included change in best-corrected visual acuity (BCVA), proportion of patients with a gain of ≥15 letters, proportion of patients with a loss of >15 letters, and safety.

RESULTS: At week 12, treatment with VEGF Trap-Eye resulted in a significant mean decrease in CR/LT of 119 μm from baseline in all groups combined (P<0.0001). The reduction in CR/LT with the 2 mg q4wk and 0.5mg q4wk regimens was significantly greater than each of the quarterly dosing regimens. The BCVA increased significantly by a mean of 5.7 letters at 12 weeks in the combined group (P<0.0001), with the greatest mean gain of >8 letters in the monthly dosing groups. At 8 weeks, BCVA improvements were similar with 2 mg q4wk and 2 mg q12wk dosing. After the last required dose at week 12, CR/LT and visual acuity were maintained or further improved at week 16 in all treatment groups. Ocular adverse events were mild and consistent with safety profiles reported for other intraocular anti-VEGF treatments.

CONCLUSIONS: Repeated monthly intravitreal dosing of VEGF Trap-Eye over 12 weeks demonstrated significant reductions in retinal thickness and improvements in visual acuity, and was well-tolerated in patients with neovascular AMD.

PMID: 21640257 [PubMed - in process]

Korean J Ophthalmol. 2011 Jun;25(3):161-5. Epub 2011 May 24.

Multifocal electroretinogram findings after intravitreal bevacizumab injection in choroidal neovascularization of age-related macular degeneration.

Park JY, Kim SH, Park TK, Ohn YH.

Department of Ophthalmology, Soonchunhyang University College of Medicine, Bucheon, Korea.

PURPOSE: To evaluate the changes in multifocal electroretinogram (mfERG) and optical coherence tomography (OCT) after intravitreal bevacizumab injection in the treatment of age-related macular degeneration (AMD).

METHODS: Twenty-one eyes with choroidal neovascularization secondary to AMD were studied before and after intravitreal bevacizumab injection for best corrected visual acuity (BCVA), OCT, and mfERG.

RESULTS: The BCVA improved, while central macular thickness and total macular volume in OCT decreased after intravitreal bevacizumab injection ($p = 0.03$, 0.01, and 0.01, respectively). In mfERG, the amplitude of P1, and implicit time of P1 and N1 indicated a statistically significant improvement of retinal response after intravitreal bevacizumab injection.

CONCLUSIONS: There is a potential role for mfERG in evaluating the effect on retinal function of intravitreal bevacizumab injection.

PMID: 21655040 [PubMed - in process]

Retina. 2011 Jun 4. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY WITH RECURRENT OR RESIDUAL EXUDATION.

Saito M, Iida T, Kano M.

From the Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Japan.

PURPOSE: To clarify the efficiency of ranibizumab for polypoidal choroidal vasculopathy in patients with regressed polypoidal lesions after previous photodynamic therapy (PDT) applications but recurrent or residual exudation from branching vascular network vessels.

METHODS: We retrospectively reviewed 59 eyes of 59 Japanese patients (47 men and 12 women) with polypoidal choroidal vasculopathy. Treatments were chosen according to the period. Thirty-four patients were treated with PDT (PDT group) and 25 patients were treated with intravitreal injections of ranibizumab (ranibizumab group).

RESULTS: In the ranibizumab group, the mean best-corrected visual acuity levels at baseline and 6 months were 0.27 and 0.41, respectively, showing a significant ($P < 1\times 10$) improvement from baseline. In the PDT group, the mean best-corrected visual acuity levels at baseline and 6 months were 0.29 and 0.24, respectively, showing a significant ($P < 0.01$) decline from baseline. The mean numbers of treatments at 6 months in the ranibizumab and the PDT groups were 3.6 and 1.4, respectively. A subretinal hemorrhage (>1 disk diameter) developed in 5 eyes in the PDT group.

CONCLUSION: Intravitreal ranibizumab is an effective treatment for maintaining or improving visual acuity and the anatomical changes in patients with polypoidal choroidal vasculopathy with recurrent or residual exudation from branching vascular network vessels.

PMID: 21654347 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2011 Jun 7. [Epub ahead of print]

[New treatments in vascular diseases other than age related macular degeneration.]

[Article in French]

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Abstract

Recent multicenter randomized studies about persistent macular edema in venous occlusions provided us with interesting results. Until now, the standard of care treatment of macular edema due to branch vein occlusion remained grid laser in contrast with central vein occlusion where the absence of treatment was still recommended. Score, Geneva, Bravo and Cruise studies recently provided us with the following results. Score study found triamcinolone to be interesting to treat macular edema due to central vein occlusion but not from branch occlusion. Geneva study assessed the effect of a delivery system of dexamethasone to treat macular edema due to venous occlusion whatever the clinical form with an improvement of visual acuity. Cruise and Bravo studies assessed the effect of ranubizumab, which was found to improve the visual acuity of macular edema due to either central or branch vein occlusions. At this stage we need comparative studies to precise the indication of these different approaches that remain perhaps complementary of laser treatment.

PMID: 21658790 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2011 Jun 7. [Epub ahead of print]

[AMD: Future therapies.]

[Article in French]

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Centre ophtalmologique d'imagerie et de laser, 11, rue Antoine-Bourdelle, 75015 Paris, France.

Abstract

Many drugs are presently tested in the different types of age-related macular degeneration (AMD), i.e. geographic atrophy or exudative AMD. In atrophic AMD, drugs attempt to spare the photoreceptors and the retinal pigment epithelium to prevent the oxidative damages or to suppress the inflammation process. In exudative AMD, some drugs try to challenge the available anti-VEGF drugs but others try to improve the visual prognosis in targeting other mechanisms or cells involved in angiogenesis, such as pericytes. The present article aims to summarize the available data, given in scientific meetings or given by the companies.

PMID: 21658792 [PubMed - as supplied by publisher]

Med J Aust. 2011 Jun 6;194(11):567-8.

Saving money on the PBS: ranibizumab or bevacizumab for neovascular macular degeneration?

Harvey KJ, Day RO, Campbell WG, Lipworth W.

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PMID: 21644867 [PubMed - in process]

Other treatment & diagnosis

Dan Med Bull. 2011 Jun;58(6):A4290.

Danish version of Visual Function Questionnaire-25 and its use in age-related macular degeneration.

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Department of Ophthalmology, Roskilde Hospital, 4000 Roskilde, Denmark. torbenls@dadlnet.dk.

INTRODUCTION: Assessment of visual function can be a complex task and objective means of measurement of visual function do not always correlate with patients' self-perceived visual abilities. The purpose of this study was to translate the visual function questionnaire (VFQ)-25 into Danish with particular focus on its use in patients with late age-related macular degeneration (AMD).

MATERIAL AND METHODS: The translation was done in accordance with standard internationally adopted methods. This includes forward translation, back translation, examination of translation quality, and adjudication by bilingual speakers. We presented the questionnaire to 120 consecutive patients with exudative AMD referred to our department and to 25 healthy individuals. We tested the reliability of the Danish version by measuring test-retest reliability, estimated the internal consistency of the questionnaire (Cronbach's α-value) and analysed the discriminatory power (validity) of the questionnaire by comparing scores of patients with scores from control individuals without known eye disease.

RESULTS: The translated questionnaire produced high test-retest correlations (range 0.8-0.9), had a relatively high-level of internal consistency (range 0.4-0.9) and a high discriminatory power.

CONCLUSION: The Danish version of VFQ-25 produces acceptable values of validity and reliability in patients with AMD.

PMID: 21651879 [PubMed - in process]

Acta Ophthalmol. 2011 Jun 8. doi: 10.1111/j.1755-3768.2011.02117.x. [Epub ahead of print]

Beta blocker use and age-related macular degeneration.

Davis A, Cohen SM, Pautler SE, Billiris-Findlay K, Eichenbaum DA.

University of Florida School of Medicine, Gainesville, Florida, USA Retina-Vitreous Associates of Florida and University of South Florida Department of Ophthalmology, Tampa, Florida, USA.

PMID: 21649869 [PubMed - as supplied by publisher]

Epidemiology & pathogenesis

Eye Contact Lens. 2011 Jun 3. [Epub ahead of print]

A Review: Role of Ultraviolet Radiation in Age-Related Macular Degeneration.

Chalam K, Khetpal V, Rusovici R, Balaiya S.

From the Department of Ophthalmology (K.V.C., V.K., R.R., S.B.), University of Florida-College of Medicine, Jacksonville, FL.

Abstract

Age-related macular degeneration (AMD) is a leading cause of blindness in the western world. The retina is

highly susceptible to photochemical damage from continuous exposure of light and oxygen. The cornea and the lens block a major portion of the ultraviolet (UV) radiation from reaching the retina (<295 nm). The relationship between UV light exposure and AMD is unclear, although short wavelength radiation and the blue light induce significant oxidative stress to the retinal pigment epithelium. Epidemiologic evidence indicates a trend toward association between severity of light exposure and AMD. In this review, we discuss type 1 and type 2 photochemical damage that occurs in response to UV exposure. We examine the impact of different doses of exposure to UV radiation and the subsequent production of oxidative stress in AMD. Local and systemic protective mechanisms of the retina including antioxidant enzymes and macular pigments are reviewed. This article provides a review of possible cellular and molecular effects of UV radiation exposure in AMD and potential therapies that may prevent blindness resulting from this disease.

PMID: 21646979 [PubMed - as supplied by publisher]

Am J Pathol. 2011 Jun;178(6):2665-81.

Angiotensin II-Induced MMP-2 Activity and MMP-14 and Basigin Protein Expression Are Mediated via the Angiotensin II Receptor Type 1-Mitogen-Activated Protein Kinase 1 Pathway in Retinal Pigment Epithelium Implications for Age-Related Macular Degeneration.

Pons M, Cousins SW, Alcazar O, Striker GE, Marin-Castaño ME.

Bascom Palmer Eye Institute, University of Miami, Miami, Florida.

Abstract

Accumulation of various lipid-rich extracellular matrix (ECM) deposits under the retinal pigment epithelium (RPE) has been observed in eyes with age-related macular degeneration (AMD). RPE-derived matrix metalloproteinase (MMP)-2, MMP-14, and basigin (BSG) are major enzymes involved in the maintenance of ECM turnover. Hypertension (HTN) is a systemic risk factor for AMD. It has previously been reported that angiotensin II (Ang II), one of the most important hormones associated with HTN, increases MMP-2 activity and its key regulator, MMP-14, in RPE, inducing breakdown of the RPE basement membrane, which may lead to progression of sub-RPE deposits. Ang II exerts most of its actions by activating the mitogen-activated protein kinase (MAPK) signaling pathway. Herein is explored the MAPK signaling pathway as a potential key intracellular modulator of Ang II-induced increase in MMP-2 activity and MMP-14 and BSG protein expression. It was observed that Ang II stimulates phosphorylation of extracellular signal-regulated kinase (ERK) and p38 MAPK in RPE cells and ERK/p38 and Jun N-terminal kinase (JNK) in mice. These effects were mediated by Ang II type 1 receptors. Blockade of ERK or p38 MAPK abrogated the increase in MMP-2 activity and MMP-14 and BSG proteins in ARPE-19 cells. A better understanding of the molecular events by which Ang II induces ECM dysregulation is of critical importance to further define its contribution to the progression of sub-RPE deposits in AMD patients with HTN.

PMID: 21641389 [PubMed - in process]

Clin Ophthalmol. 2011;5:593-601. Epub 2011 May 18.

Age-related macular degeneration.

Querques G, Avellis FO, Querques L, Bandello F, Souied EH.

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CLINICAL QUESTION: Is there any new knowledge about the pathogenesis and treatment of age-related macular degeneration (AMD)?

RESULTS: We now understand better the biochemical and pathological pathways involved in the genesis of AMD. Treatment of exudative AMD is based on intravitreal injection of new antivascular endothelial growth factor drugs for which there does not yet exist a unique recognized strategy of administration. No therapies are actually available for atrophic AMD, despite some experimental new pharmacological approaches.

IMPLEMENTATION: strategy of administration, safety of intravitreal injection.

PMID: 21654887 [PubMed - in process]

Genetics

Invest Ophthalmol Vis Sci. 2011 Jun 3. [Epub ahead of print]

Associations of Complement Factor H and smoking with early age-related macular degeneration: the ALIENOR study.

Delcourt C, Delyfer MN, Rougier MB, Amouyel P, Colin J, Le Goff M, Malet F, Dartigues JF, Lambert JC, Korobelnik JF.

Inserm, U897, Bordeaux, F-33076, France.

Purpose: To assess the associations of Complement Factor H (CFH) Y402H polymorphism and smoking with specific features of early AMD (type, location, area).

Methods: The Alienor study is a population-based study on age-related eye diseases in 963 residents of Bordeaux (France), aged 73 years or more. AMD features were graded from non mydriatic color retinal photographs. CFH Y402H was genotyped using DNA extracted from blood. Statistical analyses included 796 subjects with complete data.

Results: CFH CC genotype was strongly associated with late neovascular AMD (OR=6.0, 95 % confidence interval (CI): 1.5-23.5) but not with late atrophic AMD (OR=0.9, 95% CI: 0.2-4.3). Among early characteristics, it was associated with central soft drusen (within 500 microns of the fovea), whether intermediate (63-125 microns) (OR=2.7, 95 % CI: 1.5-4.8) or large (>125 microns) (OR=5.9, 95 % CI: 2.2-15.7), but not with pericentral soft drusen (500-3000 microns from the fovea). It was also strongly associated with central large area of soft drusen (OR=5.7, 95 % CI: 1.7-19.2). Similarly, heavy smoking (> 20 pack-years) was strongly associated with central large drusen (OR=3.9, 95 % CI: 1.6-96) and central large area of drusen (OR=3.5, 95 % CI: 1.2-10.0), but not with pericentral soft drusen. By contrast, both CFH CC and smoking tended to be more strongly associated with pericentral pigmentary abnormalities.

Conclusions: Location of abnormalities, together with type and area, may prove useful for the identification of subjects at high risk for late AMD.

PMID: 21642625 [PubMed - as supplied by publisher]

Mol Biol Rep. 2011 Jun 7. [Epub ahead of print]

An association between polymorphism of the heme oxygenase-1 and -2 genes and age-related macular degeneration.

Synowiec E, Szaflik J, Chmielewska M, Wozniak K, Sklodowska A, Waszczyk M, Dorecka M, Blasiak J, Szaflik JP.

Department of Molecular Genetics, University of Lodz, Pomorska 141/143, 90-236, Lodz, Poland.

Abstract

Iron may be implicated in the generation of oxidative stress by the catalyzing the Haber-Weiss or Fenton reaction. On the other hand, oxidative stress has been implicated in the pathogenesis of age-related macular degeneration (AMD) and heme oxygenase-1 (HO-1), encoded by the HMOX1 gene and heme oxygenase-2 (HO-2), encoded by the HMOX2 gene are important markers of iron-related oxidative stress and its consequences. Therefore, variability of the HMOX1 and HMOX2 genes might be implicated in the pathogenesis of AMD through the modulation of the cellular reaction to oxidative stress. In the present work, we investigated the association between AMD and a G → C transversion at the 19 position in the HMOX1 gene (the 19G>C-HMOX1 polymorphism, rs2071747) and a A → G transition at the -42 + 1444 position in the HMOX2 gene (the -42 + 1444A>G-HMOX2 polymorphism, rs2270363) and its modulation by some environmental factors. 279 patients with AMD and 105 controls were recruited in this study and the polymorphisms were typed by restriction fragment length polymorphism and allele-specific polymerase chain reaction (PCR). We observed an association between the occurrence of dry AMD and the G/A genotype of the -42 + 1444A>G-HMOX2 polymorphism (odds ratio (OR) 2.72), whereas the G/G genotype reduced the risk of dry AMD (OR 0.41). The G/C genotype and the C allele of the 19 G>C-HMOX1 polymorphism and the G/G genotype and the G allele of the -42 + 1444A>G-HMOX2 polymorphism were associated with progression of AMD from dry to wet form (OR 4.83, 5.20, 2.55, 1.69, respectively). On the other hand, the G/G genotype and the G allele of the 19 G>C-HMOX1 polymorphism and the A/G genotype and the A allele of the -42 + 1444A>G-HMOX2 polymorphism protected against AMD progression (OR 0.19, 0.19, 0.34, 0.59, respectively). Therefore, the 19G>C-HMOX1 and the -42 + 1444A>G-HMOX2 polymorphisms may be associated with the occurrence and progression of AMD.

PMID: 21647550 [PubMed - as supplied by publisher]