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MD Research News

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Drug treatment

Retina. 2011 Sep 16. [Epub ahead of print]

Effectiveness at 1 Year of Monthly versus Variable-Dosing Intravitreal Ranibizumab in the Treatment of Choroidal Neovascularization Secondary to Age-related Macular Degeneration.

Katz G, Giavedoni L, Muni R, Evans T, Pezda M, Wong D, Moffat A, Altomare F, Boyd S, Berger A.

From the Ophthalmology Department, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

PURPOSE: To evaluate the visual acuity results of monthly ranibizumab injections compared with a variable-dosing schedule for the treatment of neovascular age-related macular degeneration.

METHODS: A retrospective study that compared two cohorts of consecutive patients. All patients were treatment naive, with baseline visual acuity of 20/400 or better, and completed 12 months of therapy. In the first group all patients received monthly injections. In the other group, after 3 monthly loading doses, a variable-dosing schedule was used, based on a monthly clinical assessment and optical coherence tomography.

RESULTS: Fifty-six consecutive patients (60 eyes) were included. At 12 months the median number of injections were 12 and 8, respectively, and the mean change in Snellen visual acuity was an improvement of 0.27 logarithm of the minimum angle of resolution in the monthly treated group versus 0.21 logarithm of the minimum angle of resolution improvement in the variable-dosing group (P = 0.53). In the monthly treated group 96.8% of eyes lost <0.3 logarithm of the minimum angle of resolution versus 96.6% of eyes in the variable-dosing group (P = 1.0).

CONCLUSION: We were able to show that in our clinical setting patients achieved similar visual acuity results with either monthly injections or with a variable-dosing protocol. There was a trend toward better results with monthly treatment.

PMID:21926941 [PubMed - as supplied by publisher]

Exp Eye Res. 2011 Sep 14. [Epub ahead of print]

Pharmacokinetics of a long-lasting anti-VEGF fusion protein in rabbit.

Li H, Lei N, Zhang M, Li Y, Xiao H, Hao X.

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Abstract

Conbercept(KH902), a recombinant fusion protein in clinical trial II/III, shows good potential to treat the ne-

ovascular age-related macular degeneration (AMD). This investigation evaluated its ocular pharmacokinetics and pharmacodynamic profile in rabbits following intravitreal administration (IVT). Rabbits (n = 120) received single bilateral conbercept IVT administration or single IV administration. Conbercept concentrations in ocular tissues and serum were measured after dosing. VEGF concentration was also measured simultaneously. The results showed that conbercept rapidly distributed from vitreous into targeted tissues and lasted over 81 days. Clearance in ocular tissues was parallel and exhibited a terminal half of 2.5-4.2 days. The drug exposure in the retina was 1/4 to 1/5 of that in vitreous. Serum conbercept concentrations after IVT dosing were low and bioavailability was approximately 44%. And single intravitreal injection induced that ocular VEGF concentration declined over 60 days and serum VEGF concentration decreased for a short time but rebounded to higher level than baseline later. All these indicated conbercept good pharmacokinetic profile in rabbits, with good ocular tropism and systemic tolerance. Combined with the efficacy data from our earlier in vitro and in vivo studies, it should have a promising clinical application for AMD treatment.

PMID:21933673 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2011 Jul 25. pii: 222F7EA3-2753-4AE6-9729-75DD0B5AF381. doi: 10.5301/ejo.5000032. [Epub ahead of print]

Cyclooxygenase inhibitor improved an exudative lesion of choroidal neovascularization in age-related macular degeneration.

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Purpose: To report a case in which a nonselective cyclooxygenase (COX) inhibitor improved an exudative lesion in age-related macular degeneration.

Methods/Results: A 64-year-old man had a complaint of metamorphopsia in the left eye. Visual acuity was 0.5 in the left eye. Fluorescein angiography and indocyanine angiography showed juxtafoveal occult choroidal neovascularization (CNV) in the left eye, and pegaptanib sodium 0.3 mg was administered once every 6 weeks. After 4 months, visual acuity improved to 0.8. After 8 months follow-up, optical coherence tomography (OCT) showed subretinal fluid (SRF) and retinal pigment epithelium (RPE) irregularity. Visual acuity was 0.4. We recommended further pegaptanib sodium injections, but the patient did not consent to the treatment. Onset of cellulitis of the left toe occurred 1 week before the scheduled visit after 9 months. The patient was treated with loxoprofen sodium (nonselective COX inhibitor) and cefdinir for 7 days. At 2 weeks after onset of cellulitis, SRF had disappeared and OCT showed improvement of RPE irregularity.

Conclusions: A COX inhibitor had an effect on vascular permeability in CNV and may have improved exudative changes.

PMID:21928264 [PubMed - as supplied by publisher]

Retina. 2011 Sep 16. [Epub ahead of print]

LONGITUDINAL ANATOMICAL RESPONSE OF RETINAL-CHOROIDAL ANASTOMOSIS TO ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY.

Querques G, Rousseau A, Forte R, Scemama C, Caillaux V, Querques L, Souied EH.

From the Department of Ophthalmology, University of Paris XII, Centre Hospitalier Intercommunal de Creteil, Creteil, France.

PURPOSE: To evaluate the longitudinal anatomical response of retinal-choroidal anastomosis (RCA) to intravitreal ranibizumab injection using spectral-domain optical coherence tomography (SD-OCT).

METHODS: We reviewed the medical records of 21 consecutive patients with RCA who underwent intravitreal ranibizumab injections at the University Eye Clinic of Creteil between January 2009 and June 2010. The SD-OCT features at baseline, at 3 months, and at 12 months were retrospectively analyzed.

Based on SD-OCT, RCAs were classified as showing a focal retinal pigment epithelium (RPE) erosion ("erosion sign") over a small, localized RPE elevation; a focal RPE break leaving two free RPE flaps ("flap sign") at the level of a small, localized RPE elevation; or a large convex RPE prominence and a focal funnel-shaped RPE kissing an inverted focal funnel-shaped inner neuroepithelium ("kissing sign").

RESULTS: Twenty-one eyes of 21 patients (3 men and 18 women, aged 81.6 ± 6.8 years) diagnosed with RCA naive to any treatment were included for analysis. Spearman ρ correlation between best-corrected visual acuity and lesion classification was 0.54 (P = 0.01) at Month 3 and 0.85 (P < 0.001) at Month 12. Eyes showing the flap sign at baseline underwent significantly less ranibizumab injections after the loading phase (2.14 ± 0.89 vs. 3.40 ± 0.96, P = 0.007) and showed a greater improvement in best-corrected visual acuity at Month 12 (from 0.52 ± 0.14 to 0.38 ± 0.15, P = 0.03) compared with eyes showing the kissing sign. At 12 months, 3 of 10 eyes with flap sign at baseline showed RCA activity, whereas 7 of 10 regressed to erosion sign phase. Of the 10 eyes with kissing sign at baseline, 6 progressed to a fibroglial scar.

CONCLUSION: A flap sign of RCA at baseline seems a favorable prognostic factor as concerns best-corrected visual acuity improvement and the need for retreatment.

PMID:21926939 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eur J Ophthalmol. 2011 Jul 29. pii: 79854744-6584-4524-A1B6-957D60443F9C. doi: 10.5301/ejo.5000031. [Epub ahead of print]

Multifocal electroretinograms in age-related macular degeneration before and after photodynamic therapy.

Kojima M, Yukawa E, Shimoyama K, Nochioka K, Tsujinaka H, Matsuura T.

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Purpose: To evaluate multifocal electroretinograms (mfERG) and macular retinal thickness before and after photodynamic therapy (PDT) for predominantly classic choroidal neovascularization (CNV) (classic type) and occult with no classic CNV (occult type).

Methods: Recording of mfERG and measurement of macular retinal thickness were performed before and after PDT in 19 patients (19 eyes) with the classic type and 24 (26 eyes) with the occult type. The evaluation items were the amplitude of the first negative wave (N1), the amplitude from the peak of the negative wave to that of the following positive wave (P1), and the peak latencies of the negative and positive waves.

Results: Compared with mfERG before PDT, that after PDT showed a significant decrease in the P1 latency in the central area (31.1±1.9 ms before and 29.6±1.6 ms after PDT) for the classic type and significant decreases in both the central (32.0±2.0 ms before and 30.5±2.4 ms after PDT) and peripheral (30.2±2.0 ms before and 29.5±2.0 ms after PDT) areas for the occult type. Optical coherence tomography showed significant decreases in macular retinal thickness in both groups (464 and 314 μm before and after PDT, respectively, for the classic type and 516 and 340 μm for the occult type).

Conclusions: After PDT, retinal function evaluated by mfERG improved for both the classic and occult types, and the recovery of P1 latency may be due to improvement in retinal edema.

PMID:21928263 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2011;6(9):e24887. Epub 2011 Sep 13.

Analysis of VEGF-A Regulated Gene Expression in Endothelial Cells to Identify Genes Linked to Angiogenesis.

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Abstract

Angiogenesis is important for many physiological processes, diseases, and also regenerative medicine. Therapies that inhibit the vascular endothelial growth factor (VEGF) pathway have been used in the clinic for cancer and macular degeneration. In cancer applications, these treatments suffer from a "tumor escape phenomenon" where alternative pathways are upregulated and angiogenesis continues. The redundancy of angiogenesis regulation indicates the need for additional studies and new drug targets. We aimed to (i) identify novel and missing angiogenesis annotations and (ii) verify their significance to angiogenesis. To achieve these goals, we integrated the human interactome with known angiogenesis-annotated proteins to identify a set of 202 angiogenesis-associated proteins. Across endothelial cell lines, we found that a significant fraction of these proteins had highly perturbed gene expression during angiogenesis. After treatment with VEGF-A, we found increasing expression of HIF-1α, APP, HIV-1 tat interactive protein 2, and MEF2C, while endoglin, liprin β1 and HIF-2α had decreasing expression across three endothelial cell lines. The analysis showed differential regulation of HIF-1α and HIF-2α. The data also provided additional evidence for the role of endothelial cells in Alzheimer's disease.

PMID:21931866 [PubMed - in process] PMCID: PMC3172305

J Immunol. 2011 Sep 19. [Epub ahead of print]

Complement Regulation at Necrotic Cell Lesions Is Impaired by the Age-Related Macular Degeneration-Associated Factor-H His402 Risk Variant.

Lauer N, Mihlan M, Hartmann A, Schlötzer-Schrehardt U, Keilhauer C, Scholl HP, Charbel Issa P, Holz F, Weber BH, Skerka C, Zipfel PF.

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Abstract

Age-related macular degeneration is a leading form of blindness in Western countries and is associated with a common SNP (rs 1061170/Y402H) in the Factor H gene, which encodes the two complement inhibitors Factor H and FHL1. However, the functional consequences of this Tyr(402) His exchange in domain 7 are not precisely defined. In this study, we show that the Tyr(402) His sequence variation affects Factor H surface recruitment by monomeric C-reactive protein (mCRP) to specific patches on the surface of necrotic retinal pigment epithelial cells. Enhanced attachment of the protective Tyr(402) variants of both Factor H and FHL1 by mCRP results in more efficient complement control and further provides an anti-inflammatory environment. In addition, we demonstrate that mCRP is generated on the surface of necrotic retinal pigment epithelial cells and that this newly formed mCRP colocalizes with the cell damage marker annexin V. Bound to the cell surface, Factor H-mCRP complexes allow complement inactivation and reduce the release of the proinflammatory cytokine TNF-α. This mCRP-mediated complement inhibitory and anti-inflammatory activity at necrotic membrane lesions is affected by residue 402 of Factor H and defines a new role for mCRP, for Factor H, and also for the mCRP-Factor H complex. The increased protective capacity of the Tyr(402) Factor H variant allows better and more efficient clearance and removal of cellular debris and reduces inflammation and pathology.

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