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Drug Treatment

Drugs Today (Barc). 2012 May;48(5):317-29.

Aflibercept for the treatment of neovascular age-related macular degeneration.

Verner-Cole EA, Davis SJ, Lauer AK.

Casey Eye Institute, Oregon Health and Science University, Department of Ophthalmology, Portland, Oregon, USA. lauera@ohsu.edu.

Abstract

Age-related macular degeneration (AMD) can have devastating effects on vision, especially in its neovascular form. In the last decade, the use of intravitreal pharmacotherapy targeted to vascular endothelial growth factor (VEGF) has significantly improved the visual outcomes in patients with neovascular AMD. Although we have become accustomed to these unprecedented improvement outcomes, maintaining good visual results with anti-VEGF therapy requires tremendous effort, time and cost, typically involving monthly clinic visits and intravitreal injections. The introduction of aflibercept, an anti -VEGF drug that targets all isoforms of VEGF as well as placenta growth factor, has shown promise throughout recent clinical trials as an equally effective treatment for neovascular AMD that requires less frequent dosing than either ranibizumab or bevacizumab. Based on clinical trial results, the U.S. Food and Drug Administration approved aflibercept in November 2011 for use in neovascular AMD, giving patients the hope of alleviating some of the burden associated with treatment.

PMID: 22645720 [PubMed - in process]

Curr Eye Res. 2012 May 25. [Epub ahead of print]

Intravitreal Ranibizumab (Lucentis) for the Treatment of Diabetic Macular Edema: A Systematic Review and Meta-Analysis of Randomized Clinical Control Trials.

Wang H, Sun X, Liu K, Xu X.

Department of Ophthalmology, Shanghai First People's Hospital, Affiliate of Shanghai Jiaotong University , Shanghai , PR China.

Purpose: To evaluate the therapeutic effect and safety of intravitreal ranibizumab (RBZ) or RBZ combined with focal/grid laser in diabetic macular edema (DME).

Design: Systematic review of randomized clinical control trials (RCCTs) comparing RBZ or RBZ combined with focal/grid laser to non-drug control or focal/grid laser in DME was performed. Methods: The RCCTs in Cochrane Central Register of Controlled Trials, PUBMED, EMBASE, the metaRegister of Controlled Trials, and ClinicalTrials.gov were included. The means and standard deviations of change from baseline in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were extracted at 12 or 24 months. Data regarding complications were collected. The Review Manager 5.1.2 was used.

Results: Four trials with a total of 1313 DME patients were included. Our analysis showed that intravitreal RBZ appeared to be superior to non-drug therapy in reducing CMT (12 months, $p = 0.02$), and improving BCVA with statistical significance (12 months, $p = 0.0003$). RBZ combined with focal/grid laser experienced statistically significant reduction in CMT (12 months, $p = 0.01$), and improvement in BCVA (12 months, $p < 0.00001$; 24 months, $p = 0.007$) compared with focal/grid laser. The incidence of adverse events (AEs) had no statistical difference between RBZ monotherapy or RBZ combined with laser and the noninvasive interventions. The improvement in BCVA and CMT from the RBZ and RBZ plus laser arms both had no statistically significant difference. While the mean number of intravitreal injections needed was lower in RBZ plus laser arm than RBZ arm at the end of 24 months.

Conclusions: Our analysis shows that RBZ and RBZ combined with focal/grid laser is more advantageous than non-drug treatment or focal/grid laser in reducing CMT and improving BCVA in DME during 12 and 24 months follow-up period and can be well tolerated based on the safety assessment. Intravitreal RBZ may be equivalent to RBZ combined with focal/grid laser.

PMID: 22631452 [PubMed - as supplied by publisher]

Case Report Ophthalmol. 2012 Jan;3(1):136-41. Epub 2012 Apr 30.

Combination of intravitreal ranibizumab and laser photocoagulation for aggressive posterior retinopathy of prematurity.

Mota A, Carneiro A, Breda J, Rosas V, Magalhães A, Silva R, Falcão-Reis F.

Department of Ophthalmology, Hospital S. João, University of Porto, Porto, Portugal.

PURPOSE: To report on 2 cases of aggressive posterior retinopathy of prematurity (ROP) treated with intravitreal ranibizumab (Lucentis(®)) and laser photocoagulation.

METHODS: Two premature females, born at 25 and 26 weeks' gestation with a birth weight of 530 and 550 g, respectively, with aggressive posterior ROP received combined treatment with laser photocoagulation and intravitreal ranibizumab (0.3 mg [30 µl]) to each eye. Structural outcomes were evaluated by indirect ophthalmoscopy and documented by retinography.

RESULTS: An intravitreal injection was made at 34 weeks of postmenstrual age in the first case, followed by laser photocoagulation 1 week later. There was a partial regression of ROP with treatment. Five weeks later, neovascularization regrowth with bleeding in both eyes (intraretinal and subhyaloid) occurred and retreatment with combined therapy was performed. In the second case, single therapy with laser photocoagulation was made at 34 weeks of postmenstrual age. In spite of the confluent photocoagulation in the avascular area, progression to 4A ROP stage occurred 1 week later. Both eyes were retreated 1 week later with intravitreal ranibizumab and laser photocoagulation. Treatment resulted in ROP regression in both cases. There were no signs of systemic or ocular adverse side effects.

CONCLUSION: The cases presented show that combination therapy of indirect laser photocoagulation and intravitreal ranibizumab can be effective in the management of aggressive posterior ROP. Further investigation on anti-VEGF safety in premature infants is necessary. Additional studies are needed to define the role of anti-VEGF in ROP treatment.

PMID: 22649347 [PubMed - in process]

Med Sci Monit. 2012 Jun 1;18(6):CR374-380.

A prospective study on different methods for the treatment of choroidal neovascularization. The efficacy of verteporfin photodynamic therapy, intravitreal bevacizumab and transpupillary thermotherapy in patients with neovascular age-related macular degeneration.

Nowak MS, Jurowski P, Grzybowski A, Goś R, Pastuszka M, Kapica A, Smigielski J.

Department of Ophthalmology and Visual Rehabilitation, Medical University of Lodz, Lodz, Poland.

Background: The aim of this study was to compare the efficacy of verteporfin photodynamic therapy (PDT), intravitreal injections of bevacizumab (IVB) and transpupillary thermotherapy (TTT) in patients with neovascular age-related macular degeneration (AMD).

Material/Methods: The study design was a prospective, interventional, comparative case series. Between December 2006 and March 2009, 426 eyes of 426 consecutive patients presenting with neovascular AMD were included into the study. Patients presented with subfoveal CNV predominantly classic, minimally classic, and occult with no classic component; lesion size less than 5000 µm in the greatest linear dimension, and the area of hemorrhages ≤1/3 were randomized to receive either PDT (group I) or IVB (group II) in a 1:1 ratio. Other patients with CNV were included into the group III and received TTT.

Results: One hundred eyes were treated with PDT. Mean baseline logMAR BCVA was 0.62 and final visual acuity decreased to 0.74 ($p<0.05$, Wilcoxon test); 104 eyes were treated with IVB. Mean baseline BCVA was 0.82 and final visual acuity increased to 0.79 ($p>0.05$, Wilcoxon test); 222 patients were treated with TTT. Mean baseline BCVA was 1.10 and final visual acuity decreased to 1.15 ($p>0.05$, Wilcoxon test). Among all eyes the average number of treatment sessions was 2.34 (SD 1.17).

Conclusions: Our study shows that IVB injections had the best efficacy in the improvement of final BCVA. However, both IVB and TTT demonstrated good stabilization of vision. Although after PDT final BCVA was significantly worse from baseline, it may also be beneficial for some patients with neovascular age-related macular degeneration.

PMID: 22648253 [PubMed - in process]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2012 May 26. [Epub ahead of print]

Six-month visual prognosis in eyes with submacular hemorrhage secondary to age-related macular degeneration or polypoidal choroidal vasculopathy.

Cheung CM, Bhargava M, Xiang L, Mathur R, Mun CC, Wong D, Wong TY.

Singapore National Eye Centre, Singapore, Singapore, gemmy.cheung.c.m@snec.com.sg.

BACKGROUND: To determine clinical or imaging prognostic features for visual outcome in eyes with submacular hemorrhage secondary to age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV).

METHODS: A prospective case series of 11 eyes from 11 patients with submacular hemorrhage secondary to AMD or PCV. All participants had measurement of clinical characteristics, fundus angiogram, and indocyanine green angiography, spectral domain optical coherence tomography (OCT, Cirrus, Zeiss) at baseline and 6 months.

RESULTS: Median visual acuity improved from 20/132 to 20/63 at month 6. The median improvement in vision was 0.20 LogMAR units. Proportion of eyes with best-corrected visual acuity (BCVA) ≥1.0 increased from 6/11 (54.5 %) at baseline to 8/11 (72.7 %) at month 6. Eyes with BCVA > 1.0 were more likely to have

larger area of hemorrhage and thinner subfoveal neurosensory retinal thickness at baseline and at month 6.

CONCLUSIONS: Thinner neurosensory retina demonstrated on OCT at baseline may be a useful prognostic sign for limited visual recovery.

PMID: 22638617 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Jun 1. doi: 10.1038/eye.2012.101. [Epub ahead of print]

Tomographic fundus features in pseudoxanthoma elasticum: comparison with neovascular age-related macular degeneration in Japanese patients.

Ellabban AA, Hangai M, Yamashiro K, Nakagawa S, Tsujikawa A, Yoshimura N.

1] Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan [2] Department of Ophthalmology, Suez Canal University, Ismailia, Egypt.

Purpose: To determine the retinal and subretinal features characteristic to pseudoxanthoma elasticum (PXE) compared with age-related macular degeneration by using spectral-domain optical coherence tomography (SD-OCT) in Japanese patients.

Methods: We reviewed colour fundus photographs, fluorescein angiograms, and SD-OCT images of 52 eyes (27 Japanese patients) with angioid streaks (AS) due to PXE. Then we compared the incidence of tomographic features between 24 eyes (24 patient) with choroidal neovascularization (CNV) secondary to AS and 44 eyes (44 patients) with CNV secondary to age-related macular degeneration (AMD).

Results: Secondary CNV was found in 44 eyes (84.6%) of 52 patients with PXE during follow-up. We found characteristic round or ovoid tubular structures with highly reflective annular lines (termed 'outer retinal tubulation' (ORT)) in 31 (70.5%) of 44 eyes with CNV, but none were found in eyes without CNV. We also found characteristic undulations of Bruch's membrane in 38 (73.1%) eyes with AS. The incidence of ORT was significantly greater in eyes with CNV secondary to AS (70.8%; P=0.005) compared with eyes with CNV secondary to AMD (34.1%). The incidence of Bruch's membrane undulation was significantly greater in eyes with CNV secondary to AS (70.8%; P<0.0001) than in eyes with CNV secondary to AMD (11.4%).

Conclusion: SD-OCT imaging clearly revealed a greater incidence of unique lesions, including ORT and Bruch's membrane undulation, in eyes in PXE patients with CNV secondary to AS than in eyes with CNV secondary to AMD.Eye advance online publication, 1 June 2012; doi:10.1038/eye.2012.101.

PMID: 22653517 [PubMed - as supplied by publisher]

Pathogenesis

Biochem Biophys Res Commun. 2012 May 22. [Epub ahead of print]

Elevated amyloid β production in senescent retinal pigment epithelium, a possible mechanism of subretinal deposition of amyloid β in age-related macular degeneration.

Wang J, Ohno-Matsui K, Morita I.

Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.

Abstract

Age-related macular degeneration (AMD) is the most common cause of legal blindness in the elderly individuals in developed countries. Subretinally-deposited amyloid β (A β) is a main contributor of

developing AMD. However, the mechanism causing A β deposition in AMD eyes is unknown. Aging is the most significant risk of AMD, thus, we examined the effect of aging on subretinal A β deposition. mRNAs and cell lysates were isolated from retinal pigment epithelial (RPE) cells derived from 24-month-old (24M RPE) and 2-month-old (2M RPE) C57BL/6 mice. A β concentration in culture supernatants was measured by ELISA. Activity and expression of proteins that regulate A β level were examined by activity assay and real time PCR. Effect of β -secretase (BACE) on A β production was examined by siRNA silencing. A β amounts in supernatants of 24M RPE were significantly higher than 2M RPE. Activity and mRNA levels of neprilysin, an A β degrading enzyme, were significantly decreased in 24M RPE compared to 2M RPE. PCR analysis found that BACE2 was significantly more abundantly expressed than BACE1 in RPE cells, however, inactivation of BACE2 gene did not affect A β production. BACE1 protein amounts did not differ between 24M and 2M RPE, however, BACE1 activity was significantly higher in 24M RPE compared to 2M RPE. There were no significant changes in the activities of α- or γ-secretase between 2M and 24M RPE. In conclusion, RPE cells produce more amounts of A β when they are senescent, and this is probably caused by a decrease in A β degradation due to a reduction in the expression and activity of neprilysin and an increase in A β synthesis due to increased activity of BACE1.

PMID: 22634014 [PubMed - as supplied by publisher]

Biochim Biophys Acta. 2012 May 23. [Epub ahead of print]

Inhibitory role of adiponectin peptide I on rat choroidal neovascularization.

Lyzogubov VV, Tytarenko RG, Bora NS, Bora PS.

Abstract

Age-related macular degeneration (AMD) is a leading cause of central blindness in the elderly population. The wet type of AMD is characterized by extensive growth of new vessels. One of the effective strategies to treat wet AMD is to limit the choroidal neovascularization (CNV). We studied the effects of adiponectin peptide I (APNpI) on new vessel growth in laser-induced rat model of wet AMD and on rat choroidal endothelial cell (CEC) culture. CNV size and vessel density were investigated by microscopy. Immunohistochemical staining (IHC) for von Willebrand Factor (vWF), APN, APN receptors 1 (AdipoR1), 2 (AdipoR2), VEGF, VEGF receptor 2 (VEGF-R2), proliferating cell nuclear antigen (PCNA) was performed in CNV area. The mRNA expression of VEGF and VEGF-R2 in RPE-choroid was investigated by RT-PCR and real-time PCR. APNpI inhibited area of CNV by 4 fold, number of vWF positive vessels by 99% and area of subretinal tissue by 40%. The expression of VEGF and VEGF-R2 at mRNA and protein levels decreased after APNpI treatment in vivo. Proliferative index (PCNA) was 5 folds less in laser spots of APNpI treated rats compared to controls. In conclusion, APNpI inhibited formation of new vessels in rat model of CNV by decreasing VEGF, VEGF-R2 expression and cell proliferation. Thus, APNpI may have potential therapeutic use for AMD treatment since it significantly inhibited CNV.

PMID: 22633972 [PubMed - as supplied by publisher]

Front Biosci (Schol Ed). 2012 Jun 1;4:1449-60.

Receptor-associated prorenin system in the pathogenesis of retinal diseases.

Satofuka S, Kanda A, Ishida S.

Department of Ophthalmology, Teikyo University School of Medicine, Tokyo 173-8605, Japan Laboratory of Retinal Cell Biology, Department of Ophthalmology, Keio University School of Medicine, Tokyo 160-8582, Japan.

Abstract

Receptor-associated prorenin system (RAPS) refers to the pathogenic mechanisms whereby prorenin binding to (pro)renin receptor [(P)RR] dually activates tissue renin-angiotensin system (RAS) and RAS-independent intracellular signaling through the receptor. Although we found significant involvement of angiotensin II type 1 receptor (AT1-R) in intraocular inflammation and neovascularization, central pathologies of age-related macular degeneration and diabetic retinopathy, the association of RAPS with these vision-threatening disorders has not been defined. (P)RR blockade to murine disease models led to significant suppression of laser-induced choroidal neovascularization and diabetes-induced retinal inflammation together with the upregulation of intercellular adhesion molecule (ICAM)-1, monocyte chemotactic protein (MCP)-1 and vascular endothelial growth factor (VEGF). Either the genetic ablation or the pharmacological blockade of AT1-R exhibited significant reduction of choroidal and retinal abnormalities, both of which were further suppressed by (P)RR blockade. (P)RR blockade inhibited ERK activation and the production of VEGF and MCP-1, but not ICAM-1, in AT1-R-deficient mice with retinal and choroidal disorders. These recent findings indicate significant contribution of RAPS to the pathogenesis of age-related macular degeneration and diabetic retinopathy.

PMID: 22652885 [PubMed - in process]

Front Biosci (Elite Ed). 2012 Jun 1;4:2546-57.

Gene therapy in age related and hereditary macular disorders.

Kinnunen K, Yla-Herttuala S.

Department of Ophthalmology, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland, Department of Ophthalmology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland, Department of Biotechnology and Molecular Medicine, A.I.Virtanen Institute, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland.

Abstract

In ophthalmology, administration of the therapeutic agent can be difficult due to the tight barriers in the eye. Multiple injections may be needed to allow the therapeutic agent to reach adequate levels in retina and choroidea which may increase the risk of complications including endophthalmitis, cataract and haemorrhages. Optimal methods for the delivery of therapeutic agents to the posterior segments of the eye have not yet been developed. Gene therapy offers an alternative where the therapeutic protein or proteins can be induced in the target tissue for a prolonged period of time after a single injection. The eye is a promising target for gene therapy due to its small size and tissue boundaries preventing leakage of the therapeutic material to other tissues or systemic circulation. However, most of the work in ocular gene therapy is still at the preclinical phase; only three vectors have reached phase 1/2 clinical trials. This review summarizes basic principles and current status of gene therapy in age related macular degeneration and hereditary macular disorders.

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Jpn J Ophthalmol. 2012 May 30. [Epub ahead of print]

Retinal remodeling.

Jones BW, Kondo M, Terasaki H, Lin Y, McCall M, Marc RE.

Department of Ophthalmology, Moran Eye Center, University of Utah, 65 Mario Capecchi Dr., Salt Lake City, UT, 84132, USA, bryan.jones@m.cc.utah.edu.

Abstract

Retinal photoreceptor degeneration takes many forms. Mutations in rhodopsin genes or disorders of the retinal pigment epithelium, defects in the adenosine triphosphate binding cassette transporter, ABCR gene defects, receptor tyrosine kinase defects, ciliopathies and transport defects, defects in both transducin and arrestin, defects in rod cyclic guanosine 3',5'-monophosphate phosphodiesterase, peripherin defects, defects in metabotropic glutamate receptors, synthetic enzymatic defects, defects in genes associated with signaling, and many more can all result in retinal degenerative disease like retinitis pigmentosa (RP) or RP-like disorders. Age-related macular degeneration (AMD) and AMD-like disorders are possibly due to a constellation of potential gene targets and gene/gene interactions, while other defects result in diabetic retinopathy or glaucoma. However, all of these insults as well as traumatic insults to the retina result in retinal remodeling. Retinal remodeling is a universal finding subsequent to retinal degenerative disease that results in deafferentation of the neural retina from photoreceptor input as downstream neuronal elements respond to loss of input with negative plasticity. This negative plasticity is not passive in the face of photoreceptor degeneration, with a phased revision of retinal structure and function found at the molecular, synaptic, cell, and tissue levels involving all cell classes in the retina, including neurons and glia. Retinal remodeling has direct implications for the rescue of vision loss through bionic or biological approaches, as circuit revision in the retina corrupts any potential surrogate photoreceptor input to a remnant neural retina. However, there are a number of potential opportunities for intervention that are revealed through the study of retinal remodeling, including therapies that are designed to slow down photoreceptor loss, interventions that are designed to limit or arrest remodeling events, and optogenetic approaches that target appropriate classes of neurons in the remnant neural retina.

PMID: 22644448 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2012 May 23. [Epub ahead of print]

Disparities in Adult Vision Health in the United States.

Zambelli-Weiner A, Crews JE, Friedman DS.

Epidemiology International, Hunt Valley, Maryland.

PURPOSE: To review the existing knowledge on vision health disparities in major adult vision health outcomes (age-related macular degeneration, diabetic retinopathy, glaucoma, cataract, refractive errors) and visual impairment and to identify knowledge gaps as related to the development of enhanced vision health surveillance in the United States.

DESIGN: Literature review.

METHODS: Analysis of relevant publications in the peer-reviewed literature.

RESULTS: Prevalence data on vision health outcomes is limited to findings from a few key population-based studies. Study populations are not representative of all persons living in the United States. Vision loss and visual impairment are more common with age, and there is racial variation in the specific causes of vision loss (underlying health conditions). Women are at greater risk of vision loss than men (even after adjusting for age). Vision-related disability and disparities in visual outcomes are monitored poorly at present.

CONCLUSIONS: Data to assess and monitor trends in vision health disparities in the United States are not collected presently in a systematic fashion. This lack of data limits public health efforts to overcome barriers to eye care use and to improve vision outcomes.

PMID: 22633355 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 May 23. [Epub ahead of print]

Frequency, Genotype, and Clinical Spectrum of Best Vitelliform Macular Dystrophy: Data From a National Center in Denmark.

Bitner H, Schatz P, Mizrahi-Meissonnier L, Sharon D, Rosenberg T.

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

PURPOSE: To estimate the prevalence, genotype, and clinical spectrum of Best vitelliform macular dystrophy (Best disease).

DESIGN: Retrospective epidemiologic and clinical and molecular genetic observational study.

METHODS: setting: National referral center. participants: Forty-five individuals diagnosed with Best disease. observation procedures: Retrospective review of patients diagnosed according to clinical findings and sequencing of BEST1. Patients with recently established molecular genetic diagnosis were followed up including multifocal electroretinography (mfERG), spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) imaging. main outcome measures:BEST1 mutations, SD-OCT and FAF findings, mfERG amplitudes, prevalence estimate of Best disease.

RESULTS: BEST1 mutations described previously in Danish patients with Best disease are reviewed. In addition, we identified a further 8 families and 1 sporadic case, in whom 6 BEST1 missense mutations were found, 4 of which are novel. The mutation c.904G>T (p.Asp302Asn) was identified in members of 4 unrelated families. Structural alterations ranged from precipitate-like alterations at the level of the photoreceptor outer segments (OS) to choroidal neovascularization. The extent of the former correlated with the reduction of retinal function. A prevalence estimate of Best disease in Denmark based on the number of diagnosed cases was 1.5 per 100 000 individuals.

CONCLUSIONS: Our data expand the mutation spectrum of BEST1 in patients with Best disease. Alterations of the OS overlying lesions with subretinal fluid are similar to those seen in central serous retinopathy and may indicate impaired turnover of OS. Our frequency estimate confirms that Best disease is one of the most common causes of early macular degeneration.

PMID: 22633354 [PubMed - as supplied by publisher]