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Drug treatment

J Ophthalmol. 2012;2012:483034. Epub 2011 Dec 18.

Development of Anti-VEGF Therapies for Intraocular Use: A Guide for Clinicians.

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Abstract

Angiogenesis is the process by which new blood vessels form from existing vessel networks. In the past three decades, significant progress has been made in our understanding of angiogenesis; progress driven in large part by the increasing realization that blood vessel growth can promote or facilitate disease. By the early 1990s, it had become clear that the recently discovered "vascular endothelial growth factor" (VEGF) was a powerful mediator of angiogenesis. As a result, several groups targeted this molecule as a potential mediator of retinal ischemia-induced neovascularization in disorders such as diabetic retinopathy and retinal vein occlusion. Around this time, it also became clear that increased intraocular VEGF production was not limited to ischemic retinal diseases but was also a feature of choroidal vascular diseases such as neovascular age-related macular degeneration (AMD). Thus, a new therapeutic era emerged, utilizing VEGF blockade for the management of chorioretinal diseases characterized by vascular hyperpermeability and/or neovascularization. In this review, we provide a guide for clinicians on the development of anti-VEGF therapies for intraocular use.

PMID: 22220269 [PubMed - in process]

Retina. 2012 Jan 3. [Epub ahead of print]

COMBINED REDUCED FLUENCE PHOTODYNAMIC THERAPY AND INTRAVITREAL RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY.

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PURPOSE: We performed a prospective noncomparative study to report the results of reduced fluence

photodynamic therapy (PDT) combined with intravitreal ranibizumab in patients with polypoidal choroidal vasculopathy with active exudation and hemorrhage.

METHODS: Seventeen polypoidal choroidal vasculopathy eyes were treated, and follow-up for all patients was 12 months. Photodynamic therapy was administered with reduced fluence (exposure time of 70") and followed (48 hours later) by intravitreal ranibizumab (0.5 mg in 50 µL). Intravitreal ranibizumab, with or without reduced fluence PDT, was repeated as indicated by clinical and angiographic findings.

RESULTS: During the follow-up, the mean best-corrected visual acuity significantly improved from 0.45 ± 0.29 logarithm of the minimum angle of resolution at baseline to 0.29 ± 0.28 logarithm of the minimum angle of resolution at 12 months. The mean total macular volume (documented by optical coherence tomography retinal map examination) decreased from 7.5 ± 1.18 mm to 6.7 ± 0.8 mm. In 95% of the cases, best-corrected visual acuity remained stable or improved.

CONCLUSION: Reduced fluence PDT limits laser exposure, minimizing the risks of PDT-induced adverse effects. Intravitreal injections of ranibizumab 0.5 mg reduced bleeding and leakage in polypoidal choroidal vasculopathy eyes and interfere with rebound upregulation of vascular endothelial growth factor because of PDT-induced choroidal hypoperfusion. Combined treatment may improve treatment outcomes in polypoidal choroidal vasculopathy while minimizing ocular and systemic complications of treatment.

PMID: 22218148 [PubMed - as supplied by publisher]

Mayo Clin Proc. 2012 Jan;87(1):77-88.

The expanding role of vascular endothelial growth factor inhibitors in ophthalmology.

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Abstract

Vascular endothelial growth factor (VEGF) plays an important role in both physiologic and pathologic angiogenesis and contributes to increased permeability across both the blood-retinal and blood-brain barriers. After 2 decades of extensive research into the VEGF families and receptors, specific molecules have been targeted for drug development, and several medications have received US Food and Drug Administration approval. Bevacizumab, a full-length antibody against VEGF approved for the intravenous treatment of advanced carcinomas, has been used extensively in ophthalmology for exudative age-related macular degeneration, diabetic retinopathy, retinal vein occlusions, retinopathy of prematurity, and other chorioretinal vascular disorders. Pegaptanib and ranibizumab have been developed specifically for intraocular use, whereas the soon-to-be-introduced aflibercept (VEGF Trap-Eye) is moving through clinical trials for both intraocular and systemic use. Although these drugs exhibit excellent safety profiles, ocular and systemic complications, particularly thromboembolic events, remain a concern in patients receiving therapy. Patients experiencing adverse events that may be related to VEGF suppression should be carefully evaluated by both the ophthalmologist and the medical physician to reassess the need for intraocular therapy and explore the feasibility of changing medications. For this review a search of PubMed from January 1, 1985 through April 15, 2011, was performed using the following terms (or combination of terms): vascular endothelial growth factors, VEGF, age-related macular degeneration, diabetic retinopathy, retina vein occlusions, retinopathy of prematurity, intravitreal injections, bevacizumab, ranibizumab, and VEGF Trap. Studies were limited to those published in English. Other articles were identified from bibliographies of retrieved articles and archives of the author.

PMID: 22212972 [PubMed - in process]

Ophthalmologica. 2011 Dec 29. [Epub ahead of print]

Intravitreal Ranibizumab for Macular Edema Secondary to Retinal Vein Occlusion.

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Background/Aims: To investigate the effects of intravitreal ranibizumab treatment for macular edema (ME) secondary to retinal vein occlusion (RVO) and the relationship between spectral-domain optical coherence tomography (SD-OCT) findings and visual outcome after successful resolution of ME.

Methods: Forty consecutive eyes with ME secondary to branch RVO (BRVO; 29 eyes of 29 patients) or central RVO (CRVO; 11 eyes of 11 patients) were included in a prospective study and treated with 3 initial intravitreal injections of 0.5 mg ranibizumab at monthly intervals. Retreatment was based on visual acuity changes and OCT findings. Patients with complete resolution of ME were classified into two groups according to final best-corrected visual acuity (BCVA) of better than 0.30 logMAR (group 1) or poorer than 0.30 logMAR (group 2), and SD-OCT findings were analyzed at baseline and at 12 months.

Results: In patients with BRVO, mean BCVA at 12 months (0.19 ± 0.18) was significantly better than that at baseline (0.76 ± 0.37; p = 0.000). The mean number of injections was 4.4 ± 1.2. In patients with CRVO, the mean BCVA at 12 months (0.39 ± 0.23) was slightly improved from that at baseline (0.84 ± 0.68), but the difference was not significant (p = 0.063). Patients with CRVO received a mean number of 6.1 ± 1.4 injections of ranibizumab. Baseline SD-OCT more frequently detected the foveal inner/outer segment (IS/OS) line and external limiting membrane (ELM) in group 1 (p = 0.003) than in group 2 (p = 0.012). Preservation of the foveal IS/OS line (odds ratio = 5.400; p = 0.036) and ELM (odds ratio = 7.312; p = 0.016) at baseline correlated with good final visual outcome.

Conclusion: Intravitreal ranibizumab injections effectively treat ME secondary to RVO. Good visual outcome was associated with preservation of the foveal IS/OS line and ELM at baseline.

PMID: 22212151 [PubMed - as supplied by publisher]

Theranostics. 2011;1:395-402. Epub 2011 Dec 12.

Lasting controversy on ranibizumab and bevacizumab.

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Source

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Abstract

Vascular endothelial growth factor (VEGF), an important angiogenic factor that is able to stimulate the proliferation and migration of endothelial cells, is the best-studied hallmark of angiogenesis. Neovascularization is a major cause of age-related macular degeneration (AMD) which is a leading cause of blindness in the elderly population. Specific molecular inhibitors of VEGF have been proved to be useful in the treatment of AMD. Ranibizumab and Bevacizumab are structurally similar to anti-VEGF drugs in the treatment of AMD. Many studies have indicated that Ranibizumab and Bevacizumab are of roughly equal short-term efficacy and safety, Bevacizumab is an attractive alternative to Ranibizumab due to its lower cost. However, only Ranibizumab has received Food and Drug Administration (FDA) approval for the treatment of macular degeneration. More multicenter clinical trials are required to compare the relative efficacy and safety of these two drugs and some progress has been achieved. This review discusses the clinical effectiveness, safety, cost and other practical implications of Ranibizumab and Bevacizumab.

PMID: 22211145 [PubMed - in process] PMCID: PMC3248643

Other treatment & diagnostics

Retina. 2012 Jan 3. [Epub ahead of print]

ACQUIRED VITELLIFORM LESION ASSOCIATED WITH LARGE DRUSEN.

Lima LH, Laud K, Freund KB, Yannuzzi LA, Spaide RF.

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PURPOSE: The purpose of this study was to describe the association of acquired vitelliform lesion (AVL) and large drusen in patients with non-neovascular age-related macular degeneration.

METHODS: A retrospective review of clinical examination and multimodal imaging data of patients with AVL and large drusen seen over a 12-month period was performed. Acquired vitelliform lesion was defined as subretinal accretion of hyperautofluorescent yellowish material within the macular region not due to vitelliform macular dystrophy. Large drusen were diagnosed by the presence of mounded deposits in the subretinal pigment epithelial space between the retinal pigment epithelium and the Bruch membrane using multimodal imaging analysis (color photography, autofluorescence, and spectral domain optical coherence tomography).

RESULTS: Thirteen eyes of 9 white patients with a mean age of 74 years were observed to have AVL associated with large drusen. The median visual acuity was 20/60. All AVLs were hyperautofluorescent and were located in the subretinal space between the retinal pigment epithelium and the photoreceptor inner segment/outer segment junction. The AVL in this series had similar color, autofluorescence, and optical coherence tomographic findings as the AVL seen in association with cuticular drusen and subretinal drusenoid deposits.

CONCLUSION: Acquired vitelliform lesions, which have previously been related to cuticular drusen and subretinal drusenoid deposits, can occur in association with large drusen. Abnormalities leading to drusen formation or processes that function in parallel to these may be causative in AVL formation.

PMID: 22218150 [PubMed - as supplied by publisher]

Pathogenesis

Exp Diabetes Res. 2012;2012:589589. Epub 2011 Dec 14.

ER Stress and Apoptosis: A New Mechanism for Retinal Cell Death.

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Abstract

The endoplasmic reticulum (ER) is the primary subcellular organelle where proteins are synthesized and folded. When the homeostasis of the ER is disturbed, unfolded or misfolded proteins accumulate in the ER lumen, resulting in ER stress. In response to ER stress, cells activate a set of tightly controlled regulatory programs, known as the unfolded protein response (UPR), to restore the normal function of the ER. However, if ER stress is sustained and the adaptive UPR fails to eliminate unfolded/misfolded proteins, apoptosis will occur to remove the stressed cells. In recent years, a large body of studies has shown that ER stress-induced apoptosis is implicated in numerous human diseases, such as diabetes and

neurogenerative diseases. Moreover, emerging evidence supports a role of ER stress in retinal apoptosis and cell death in blinding disorders such as age-related macular degeneration and diabetic retinopathy. In the present review, we summarize recent progress on ER stress and apoptosis in retinal diseases, focusing on various proapoptotic and antiapoptotic pathways that are activated by the UPR, and discuss how these pathways contribute to ER stress-induced apoptosis in retinal cells.

PMID: 22216020 [PubMed - in process] PMCID: PMC3246718

Prog Retin Eye Res. 2011 Dec 22. [Epub ahead of print]

The bisretinoids of retinal pigment epithelium.

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Abstract

The retina exhibits an inherent autofluorescence that is imaged ophthalmoscopically as fundus autofluorescence. In clinical settings, fundus autofluorescence examination aids in the diagnosis and follow-up of many retinal disorders. Fundus autofluorescence originates from the complex mixture of bisretinoid fluorophores that are amassed by retinal pigment epithelial (RPE) cells as lipofuscin. Unlike the lipofuscin found in other cell-types, this material does not form as a result of oxidative stress. Rather, the formation is attributable to non-enzymatic reactions of vitamin A aldehyde in photoreceptor cells; transfer to RPE occurs upon phagocytosis of photoreceptor outer segments. These fluorescent pigments accumulate even in healthy photoreceptor cells and are generated as a consequence of the light capturing function of the cells. Nevertheless, the formation of this material is accelerated in some retinal disorders including recessive Stargardt disease and ELOVL4-related retinal degeneration. As such, these bisretinoid side-products are implicated in the disease processes that threaten vision. In this article, we review our current understanding of the composition of RPE lipofuscin, the structural characteristics of the various bisretinoids, their related spectroscopic features and the biosynthetic pathways by which they form. We will revisit factors known to influence the extent of the accumulation and therapeutic strategies being used to limit bisretinoid formation. Given their origin from vitamin A aldehyde, an isomer of the visual pigment chromophore, it is not surprising that the bisretinoids of retina are light sensitive molecules. Accordingly, we will discuss recent findings that implicate the photodegradation of bisretinoid in the etiology of age-related macular degeneration.

PMID: 22209824 [PubMed - as supplied by publisher]

Mol Vis. 2011;17:3512-22. Epub 2011 Dec 29.

Protective effect of paeoniflorin against oxidative stress in human retinal pigment epithelium in vitro.

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PURPOSE: This study was conducted to determine whether paeoniflorin (PF) could prevent H(2)O(2)-induced oxidative stress in ARPE-19 cells and to elucidate the molecular pathways involved in this protection.

METHODS: Cultured ARPE-19 cells were subjected to oxidative stress with H(2)O(2) in the presence and

absence of PF. The preventive effective of PF on reactive oxygen species (ROS) production and retinal pigment epithelium (RPE) cell death induced by H(2)O(2) was determined by 2',7'-dichlorodihydrofluorescein diacetate (H(2)DCFDA) fluorescence and 3-(4, 5-dimethylthiazol-2-yl)-2, 5 diphenyl tetrazolium bromide (MTT) assay. The ability of PF to protect RPE cells against ROS-mediated apoptosis was assessed by caspase-3 activity and 4', 6-diamidino-2-phenylindole (DAPI) staining. Furthermore, the protective effect of PF via the mitogen-activated protein kinase (MAPK) pathway was determined by western blot analysis.

RESULTS: PF protected ARPE-19 cells from H(2)O(2)-induced cell death with low toxicity. H(2)O(2)-induced oxidative stress increased ROS production and caspase-3 activity, which was significantly inhibited by PF in a dose-dependent manner. Pretreatment with PF attenuated H(2)O(2)-induced p38MAPK and extracellular signal regulated kinase (ERK) phosphorylation in human RPE cells, which contributed to cell viability in ARPE-19 cells.

CONCLUSIONS: This is the first report to show that PF can protect ARPE-19 cells from the cellular apoptosis induced by oxidative stress. The results of this study open new avenues for the use of PF in treatment of ocular diseases, such as age-related macular degeneration (AMD), where oxidative stress plays a major role in disease pathogenesis.

PMID: 22219646 [PubMed - in process]

Curr Pharm Des. 2011 Oct 27. [Epub ahead of print]

From Small to Big Molecules: How Do We Prevent and Delay the Progression of Age- Related Neurodegeneration?

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Abstract

Age-related neurodegeneration in the brain and retina is complicated. It comprises a series of events encompassing different modes of degeneration in neurons, as well as inflammation mediated by glial cells. Systemic inflammation and risk factors can contribute to disease progression. Age-related conditions such as Alzheimer's disease (AD), Parkinson's disease (PD) and Age-related Macular Degeneration (AMD) affect patients for 5 to 20 years and are highly associated with risk factors such as hyperhomocysteinæmia, hypercholesterolæmia, hypertension, and symptoms of mood disorder. The long duration of the degeneration and the wide array of systemic factors provide the opportunity for nutraceutical intervention to prevent or delay disease progression. Small molecules such as phenolic compounds are candidates for neuroprotection because they have anti-oxidant activities and can modulate intracellular signaling pathways. Bigger entities such as oligosaccharides and polysaccharides have often been neglected because of their complex structure. However, certain big molecules can provide neuroprotective effects. They may also have a wide spectrum of action against risk factors. In this review we use an integrative approach to the potential uses of nutraceutical products to prevent age-related neurodegeneration. These include direct effects of phenolic compounds and polysaccharides on neurons to antagonize various neurodegenerative mechanisms in AD, PD and AMD, and indirect effects of these compounds on peripheral disease-related risk factors.

PMID: 22211681 [PubMed - as supplied by publisher]

Genetics

Mol Vis. 2011;17:3574-82. Epub 2011 Dec 31.

Difference between age-related macular degeneration and polypoidal choroidal vasculopathy in the hereditary contribution of the A69S variant of the age-related maculopathy susceptibility 2 gene (ARMS2).

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PURPOSE: To investigate whether the A69S variant of the age-related maculopathy susceptibility 2 gene (ARMS2) has a different hereditary contribution in neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: We initially conducted a comparative genetic analysis of neovascular AMD and PCV, genotyping the ARMS2 A69S variant in 181 subjects with neovascular AMD, 198 subjects with PCV, and 203 controls in a Japanese population. Genotyping was conducted using TaqMan technology. Results were then integrated into a meta-analysis of previous studies representing an assessment of the association between the ARMS2 A69S variant and neovascular AMD and/or PCV, comprising a total of 3,828 subjects of Asian descent. The Q-statistic test was used to assess between-study heterogeneity. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a fixed effects model.

RESULTS: The genetic effect of the A69S variant was stronger in neovascular AMD (allelic summary OR=3.09 [95% CI, 2.71-3.51], fixed effects p<0.001) than in PCV (allelic summary OR=2.13 [95% CI, 1.91-2.38], fixed effects p<0.001). The pooled risk allele frequency was significantly higher in neovascular AMD (64.7%) than in PCV (55.6%). The population attributable risks for the variant allele were estimated to be 43.9% (95% CI, 39.0%-48.4%) and 29.7% (95% CI, 25.4%-34.0%) for neovascular AMD and PCV, respectively. No significant between-study heterogeneity was observed in any statistical analysis in this meta-analysis.

CONCLUSIONS: Our meta-analysis provides substantial evidence that the ARMS2 A69S variant confers a significantly higher risk of neovascular AMD than PCV. Furthermore, there is compelling evidence that the risk attributable to the A69S variant differs between geographic atrophy and neovascular AMD. Together with defining the molecular basis of susceptibility, understanding the relationships between this genomic region and disease subtypes will yield important insights, elucidating the biologic architecture of this phenotypically heterogeneous disorder.

PMID: 22219653 [PubMed - in process]

Diet

Neurobiol Aging. 2012 Jan 2. [Epub ahead of print]

Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function.

Lee V, Rekhi E, Kam JH, Jeffery G.

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Abstract

Vitamin D(3) plays a key role in immune regulation and may protect against the aging process. A focal point

for age-related changes is the outer retina of the eye where there is high metabolic demand resulting in a gradual increase in extracellular deposition, inflammation, and cell loss giving rise to visual decline. Here, we demonstrate that vitamin D(3) administration for only 6 weeks in aged mice significantly impacts on this aging process. Treated mice showed significant reductions in retinal inflammation and levels of amyloid beta (Aβ) accumulation, which is a hallmark of aging. They also had significant reductions in retinal macrophage numbers and marked shifts in their morphology. These changes were reflected in a significant improvement in visual function, revealing that vitamin D(3) is a route to avoiding the pace of age-related visual decline. Excess amyloid beta deposition and inflammation are risk factors leading to age-related macular degeneration (AMD), the largest cause of blindness in those older than 50 years in developed countries. Recently, vitamin D(3) has been linked epidemiologically to protection against age-related macular degeneration. Hence, vitamin D(3) enrichment is likely to represent a beneficial route for those at risk.

PMID: 22217419 [PubMed - as supplied by publisher]

PLoS One. 2011;6(12):e29245. Epub 2011 Dec 22.

Zinc deficiency leads to lipofuscin accumulation in the retinal pigment epithelium of pigmented rats.

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BACKGROUND: Age-related macular degeneration (AMD) is associated with lipofuscin accumulation whereas the content of melanosomes decreases. Melanosomes are the main storage of zinc in the pigmented tissues. Since the elderly population, as the most affected group for AMD, is prone to zinc deficit, we investigated the chemical and ultrastructural effects of zinc deficiency in pigmented rat eyes after a six-month zinc penury diet.

METHODOLOGY/PRINCIPAL FINDINGS: Adult Long Evans (LE) rats were investigated. The control animals were fed with a normal alimentation whereas the zinc-deficiency rats (ZD-LE) were fed with a zinc deficient diet for six months. Quantitative Energy Dispersive X-ray (EDX) microanalysis yielded the zinc mole fractions of melanosomes in the retinal pigment epithelium (RPE). The lateral resolution of the analysis was 100 nm. The zinc mole fractions of melanosomes were significantly smaller in the RPE of ZD-LE rats as compared to the LE control rats. Light, fluorescence and electron microscopy, as well as immunohistochemistry were performed. The numbers of lipofuscin granules in the RPE and of infiltrated cells (Ø>3 µm) found in the choroid were quantified. The number of lipofuscin granules significantly increased in ZD-LE as compared to control rats. Infiltrated cells bigger than 3 µm were only detected in the choroid of ZD-LE animals. Moreover, the thickness of the Bruch's membrane of ZD-LE rats varied between 0.4-3 µm and thin, rangy ED1 positive macrophages were found attached at these sites of Bruch's membrane or even inside it.

CONCLUSIONS/SIGNIFICANCE: In pigmented rats, zinc deficiency yielded an accumulation of lipofuscin in the RPE and of large pigmented macrophages in the choroids as well as the appearance of thin, rangy macrophages at Bruch's membrane. Moreover, we showed that a zinc diet reduced the zinc mole fraction of melanosomes in the RPE and modulated the thickness of the Bruch's membrane.

PMID: 22216222 [PubMed - in process] PMCID: PMC3245262