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MD Research News

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Drug treatment

Br J Ophthalmol. 2012 Mar 7. [Epub ahead of print]

Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial.

Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, Knudsen M, Onwordi H.

Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia.

BACKGROUND/AIMS:

To evaluate the cost-effectiveness of ranibizumab as either monotherapy or combined with laser therapy, compared with laser monotherapy, in the treatment of diabetic macular oedema (DME) causing visual impairment from a UK healthcare payer perspective.

METHODS:

A Markov model simulated long-term outcomes and costs of treating DME in one eye (BCVA ≤75 letters) based on data from the RESTORE Phase III trial. Outcomes measured in quality-adjusted life-years (QALYs) were simulated for a 15-year time horizon based on 12-month follow-up from RESTORE and published long-term data. Costs included treatment, disease monitoring, visual impairment and blindness (at 2010 price levels).

RESULTS:

Ranibizumab monotherapy resulted in a 0.17 QALY gain at an incremental cost of £4191 relative to laser monotherapy, yielding an incremental cost-effectiveness ratio (ICER) of £24 028. Probabilistic sensitivity analysis showed a 64% probability of being cost-effective at a threshold of £30 000 per QALY. Combined ranibizumab and laser therapy resulted in a 0.13 QALY gain at an incremental cost of £4695 relative to laser monotherapy (ICER £36 106; 42% probability of ICER <£30 000).

CONCLUSIONS:

Based on RESTORE 1-year follow-up data, ranibizumab monotherapy appears to be cost-effective relative to laser monotherapy, the current standard of care. Cost-effectiveness of combination therapy is less certain. Ongoing studies will further inform on disease progression and the need for additional ranibizumab treatment.

PMID: 22399690 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Int Ophthalmol Clin. 2012 Spring;52(2):73-80.

Cataract Surgery and Intraocular Lens Selection in Patients With Age-related Macular Degeneration: Pearls for Success.

Banta JT, Rosenfeld PJ.

PMID: 22395630 [PubMed - in process]

Bratisl Lek Listy. 2012;113(2):114-6.

Fundus autofluorescence in age-related macular disease imaged with a laser scanning ophthalmoscope.

Struharova K, Cernak M.

Abstract

Age-related macular degeneration (ARMD) as the most common cause of legal blindness in industrialized countries remains an incompletely understood, complex retinal disease. Prophylactic and therapeutic options are still limited. Sensitive diagnostic tools and prognostic markers to evaluate disease stage and progression in the individual patient are needed. The retinal pigment epithelium (RPE) plays a key role in the disease process both in early and late variants of AMD. An excessive accumulation of lipofuscin granules in the lysosomal compartment of RPE cells represents a common downstream pathogenetic pathway in various retinal diseases including AMD. Fundus autofluorescence (FAF) imaging allows the visualization of the topographic distribution of lipofuscin over large retinal areas (Fig. 3, Ref. 13). Key words: fundus autofluorescence, lipofuscin, retinal pigment epithelium (RPE), age-related macular degeneration (ARMD), geographic atrophy, confocal laser scan ophthalmoscopy (cSLO). Keywords: fundus autofluorescence, lipofuscin, retinal pigment epithelium (RPE), age-related macular degeneration (ARMD), geographic atrophy, confocal laser scan ophthalmoscopy (cSLO).

PMID: 22394043 [PubMed - in process]

Future Med Chem. 2012 Mar;4(3):277-87.

miRNAs as potential therapeutic targets for age-related macular degeneration.

Wang S, Koster KM, He Y, Zhou Q.

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Abstract

Since their recent discovery, miRNAs have been shown to play critical roles in a variety of pathophysiological processes. Such processes include pathological angiogenesis, the oxidative stress response, immune response and inflammation, all of which have been shown to have important and interdependent roles in the pathogenesis and progression of age-related macular degeneration (AMD). Here we present a brief review of the pathological processes involved in AMD and review miRNAs and other noncoding RNAs involved in regulating these processes. Specifically, we discuss several candidate miRNAs that show promise as AMD therapeutic targets due to their direct involvement in choroidal neovascularization or retinal pigment epithelium atrophy. We discuss potential miRNA-based therapeutics and delivery methods for AMD and provide future directions for the field of miRNA research with respect to

AMD. We believe the future of miRNAs in AMD therapy is promising.

PMID: 22393936 [PubMed - in process]

Vojnosanit Pregl. 2012 Jan;69(1):85-9.

Idiopathic polypoidal choroidal vasculopathy.

Cekić S, Risimić D, Jovanović I, Jocić JD.

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BACKGROUND:

Idiopathic polypoidal choroidal vasculopathy (IPCV) is uncommon condition. It is considered to be a variant of neovascular age-related macular degeneration, but it can be also found in younger patients.

CASE REPORT:

We presented a case of otherwise healthy, 36-year-old women, with sudden unilateral visual impairment in the left eye and metamorphosia. Slit lamp biomicroscopy examination of the eye anterior segment was normal. Intraocular pressure determined by aplanation tonometry was 16 mmHg in both eyes. Indirect slit lamp biomicroscopy examination showed signs of serosanquinous detachments of the retinal pigment epithelium. Fluorescein angiography showed a subretinal vessel network through the pigment epithelial atrophy with hyperfluorescence in superior part of serohemorrhagic pigment epithelial detachment and the inferior hypofluorescence, caused by hemorrhage. Optical coherence tomography proved detachment of the retinal pigment epithelium.

CONCLUSION:

In patients with IPCV a mild, natural course with spontaneous resorption of exudations and hemorrhage and improvement in visual acuity can be observed. There is no approved treatment at present.

PMID: 22397302 [PubMed - in process]

Biomed Microdevices. 2012 Mar 4. [Epub ahead of print]

Mesh-supported submicron parylene-C membranes for culturing retinal pigment epithelial cells.

Lu B, Zhu D, Hinton D, Humayun MS, Tai YC.

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Abstract

In this work, a mesh-supported submicron parylene-C membrane (MSPM) is proposed as an artificial Bruch's membrane for the therapy of age-related macular degeneration (AMD). Any artificial Bruch's membrane must first satisfy two important requirements. First, it should be as permeable as healthy human Bruch's membrane to support nutrients transportation. Secondly, it should be able to support the adherence and proliferation of retinal pigment epithelial (RPE) cells with in vivo-like morphologies and functions. Although parylene-C is widely used as a barrier layer in many biomedical applications, it is found that parylene-C membranes with submicron thickness are semipermeable to macromolecules. We first measure the permeability of submicron parylene-C and find that 0.15-0.30 μm parylene-C has similar permeability to healthy human Bruch's membranes. Blind-well perfusion cell viability experiments further demonstrate that nutrients and macromolecules can diffuse across 0.30 μm parylene-C to nourish the cells. A mesh-

supported submicron parylene-C membrane (MSPM) structure is design to enhance the mechanical strength of the substrate. In vitro cells culture on the MSPM (with 0.30 μm ultrathin parylene-C) shows that H9-RPE cells are able to adhere, proliferate, form epithelial monolayer with tight intracellular junctions, and become well-polarized with microvilli, which exhibit similar characteristics to RPE cells in vivo. These studies have demonstrated the potential of the MSPM as an artificial Bruch's membrane for RPE cell transplantation.

PMID: 22391881 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2012 Mar 2. [Epub ahead of print]

Photodynamic Therapy in the Treatment of Persistent Central Serous Chorioretinopathy: a Two-Year Follow-Up.

Valmaggia C, Haueter I, Niederberger H.

Background: The aim of this study was to assess during a follow-up period of two years the efficacy and safety of photodynamic therapy (PDT) in central serous chorioretinopathy (CSC) showing no spontaneous resolution four months after the onset of the symptoms.

Patients and Methods: We present a prospective interventional non-comparative case series. The diagnosis of CSC was confirmed by fluorescein angiography (FA), and optical coherence tomography (OCT) in 46 eyes of 42 consecutive patients. PDT was performed according to the protocol used for treating choroidal neovascularization in age-related macular degeneration. The primary end point was to assess the anatomic re-attachment of the retina. The secondary end point was to record the visual function. A paired t-test and a linear regression and correlation test were used for the statistics.

Results: The leakage in FA and the detachment of the neurosensory retina in OCT were no longer present in 42 eyes six weeks after PDT and in the remaining four eyes three months after PDT. At the end of the follow-up, the best-corrected visual acuity measured with an ETDRS chart improved in 36 eyes, and remained stable in 10 eyes (mean improvement, 10.2 letters; $p < 0.001$). Two cases of recurrence were diagnosed. No treatment-related complications were noticed.

Conclusions: PDT could be an effective and durable option for treating patients with persistent CSC.

PMID: 22389262 [PubMed - as supplied by publisher]

Gene Ther. 2012 Mar 8. doi: 10.1038/gt.2012.20. [Epub ahead of print]

Directed evolution of novel adeno-associated viruses for therapeutic gene delivery.

Bartel MA, Weinstein JR, Schaffer DV.

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Abstract

Gene therapy vectors based on adeno-associated virus (AAV) are currently in clinical trials for numerous disease targets, such as muscular dystrophy, hemophilia, Parkinson's disease, Leber's congenital amaurosis and macular degeneration. Despite its considerable promise and emerging clinical success, several challenges impede the broader implementation of AAV gene therapy, including the prevalence of neutralizing antibodies in the human population, low transduction of a number of therapeutically relevant cell and tissue types, an inability to overcome physical and cellular barriers in vivo and a relatively limited carrying capacity. These challenges arise as the demands we place on AAV vectors are often different from or even at odds with the properties nature bestowed on their parent viruses. Viral-directed evolution-the

iterative generation of large, diverse libraries of viral mutants and selection for variants with specific properties of interest-offers an approach to address these problems. Here we outline progress in creating novel classes of AAV variant libraries and highlight the successful isolation of variants with novel and advantageous in vitro and in vivo gene delivery properties.Gene Therapy advance online publication, 8 March 2012; doi:10.1038/gt.2012.20.

PMID: 22402323 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Mar 6. [Epub ahead of print]

Preferred Retinal Locus - Hand Coordination in a Maze Tracing Task.

Timberlake GT, Omoscharka E, Grose SA, Bothwell R.

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Purpose: Fine manual tasks require coordination of vision, eye movements, and motor control. Macular scotomas from Age-related Macular Degeneration (AMD) may adversely affect this coordination. The purpose of this research was to find whether the Preferred Retina Locus for fixation (fPRL) also guided the hand in performing fine manual tasks and how the fingers, fPRL and scotomas interacted in task performance.

Methods: Subjects with bilateral macular scotomas from AMD and normally-sighted controls traced an irregular "maze" line pattern with the index finger while viewing their hand and the maze in a Scanning Laser Ophthalmoscope (SLO). Video images from the SLO showing the fingers and maze on the retina during the task were analyzed to produce retinal maps showing the scotoma and bivariate ellipses of fPRL and fingertip retinal positions.

Results: Fingertip retinal ellipses surrounded and were approximately centered on the fPRL ellipses. Fingertip retinal bivariate area was positively correlated with fPRL bivariate area, fPRL eccentricity and the percent time the fPRL was on the maze was correlated with visual acuity. Maze tracing accuracy was positively correlated with saccade rate for scotoma subjects. Conclusions: Concentric overlap of fPRL and fingertip retinal ellipses indicates that it is the fPRL that guides the hand in the maze tracing visuomotor task just as the fovea guides the fingertip for visually normal subjects. It is likely that factors other than fPRL and scotoma characteristics contribute to poorer maze tracing performance by scotoma subjects in comparison to controls.

PMID: 22395879 [PubMed - as supplied by publisher]

Ophthalmic Res. 2012 Mar 6;48(1):43-49. [Epub ahead of print]

Road to Fulfilment: Taming the Immune Response to Restore Vision.

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Abstract

While traditionally considered to be an immune privileged site, the eye, and in particular the retina, is nonetheless endowed with immune-competent cells capable of engaging powerful immune regulatory networks. By understanding the mechanisms that promote immune well-being in the eye, we are able to generate therapies which combat undue immune-mediated damage not only by revealing mechanisms that promote tissue damage, but also by an ability to restore tissue immune homeostasis by harnessing intrinsic immune-regulatory mechanisms. The result is to maintain or restore immune health as well as combat

tissue damage evoked during, for example, intra-ocular inflammatory disease (uveitis), angiogenesis (age-related macular degeneration) and retinal degenerative disorders. Immune activation and regulation is a balance that is dictated by cognate and soluble factors at both a tissue and cellular level. These continuously respond to and eradicate danger and pathogenic signals whilst maintaining tissue function by controlling, and not exclusively, vascular barriers, complement activation, macrophage activation and keeping in check local T cell proliferation. Loss of the balance between activation and inhibitory signals leads to uncontrolled tissue damage. Understanding the mechanisms has gained potential therapeutic opportunities not only to suppress on-going inflammation, but also to restore homeostasis and prevent recrudescence.

PMID: 22398563 [PubMed - as supplied by publisher]

Pathogenesis

Biochem Med (Zagreb). 2012;22(1):39-48.

The role of CRP and inflammation in the pathogenesis of age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD) is a complex, degenerative and progressive disease involving the multiple genetic and environmental factors that can result in severe visual loss. The etiology of AMD is not well understood. Many theories exist and feature mechanisms of oxidative stress, atherosclerotic-like changes, genetic predisposition and inflammation. The most recent clinical studies appointed to a great role of inflammation and C-reactive protein (CRP) in the pathogenesis of AMD. There is a large body of evidence indicating the association of CRP with endothelial dysfunction, oxidative stress and production of reactive oxygen species (ROS), as well as with lipid status disorder in AMD patients. According to recent studies, CRP is definitely not only the inflammatory marker but also a mediator of development of the vascular disorders in the retinal circulation. The results obtained from the present studies may help our understanding the pathogenesis of the retinal vascular disease associated with high levels of CRP.

PMID: 22384518 [PubMed - in process]

Genetics

Neurosci Lett. 2012 Feb 25. [Epub ahead of print]

Adiponectin receptor 1 gene (ADIPOR1) variant is associated with advanced age-related macular degeneration in Finnish population.

Kaarniranta K, Paananen J, Nevalainen T, Sorri I, Seitsonen S, Immonen I, Salminen A, Pulkkinen L, Uusitupa M.

Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland; Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland.

Abstract

Adiponectin is an adipocyte-expressed protein that regulates the glucose, lipid, and energy metabolism via adiponectin receptors 1 and 2. Obesity is a known risk factor for age-related macular degeneration (AMD).

We, therefore, examined associations of single nucleotide polymorphisms in Adiponectin (ADIPOQ) and Adiponectin receptors 1 and 2 (ADIPOR1 and ADIPOR2) genes with the prevalence of advanced AMD in Finnish population. Thirty-seven markers for ADIPOQ, ADIPOR1 and ADIPOR2 were genotyped in a sample collection of 91 men and 177 women having exudative AMD and 18 men and 26 women having severe atrophic AMD. Patients were diagnosed by fundus photographs and fluorescein angiography. The control group (no signs of AMD in fundus photographs) consisted of 55 men and 111 women. Inclusion criteria age was over 65 years old without diabetes diagnosis. Out of the tested SNPs, rs10753929 located in intron of ADIPOR1 gene was significantly associated (p=0.0471) with AMD status when using a permutation procedure that controlled for the number of tested genotypes and genetic models. Odds ratio (OR) for the association was 1.699 (95% CI 1.192-2.423). The SNP consists of C/T alleles and the risk allele T had a minor allele frequency (MAF) of 20.4%. Distribution of proportion of cases/controls between alleles revealed an additive genetic model. Our findings reveal that rs10753929 ADIPOR1 variant is a novel candidate for AMD genetic risk factor in Finnish population.

PMID: 22387454 [PubMed - as supplied by publisher]

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