Drug treatment

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**Efficacy comparison of intravitreal anti-VEGF therapy for three subtypes of neovascular age-related macular degeneration: a systematic review and meta-analysis.**

Li J, Xu J, Chen Y, et al.

**PURPOSE:** Intravitreal antivascular endothelial growth factor (anti-VEGF) therapy has been widely used for the treatment of neovascularization (NV) secondary to age-related macular degeneration (AMD). This study aimed to compare the efficacy among different subtypes of neovascular age-related macular degeneration (nAMD).

**METHODS:** PubMed, Embase, and the Cochrane Library were searched for eligible studies. We performed meta-analysis using Review Manager 5.3 and Stata/SE 12.0.

**RESULTS:** A total of 24 studies met our inclusion criteria and were included in the systematic review. At 3 months, the mean logarithm of the minimum angle of resolution (logMAR) improvements were -0.09, -0.18, and -0.23 for type 1, 2, and 3, respectively, while the mean macular thickness (MT) changes were -104.83, -130.76, and -196.29 μm. At 12 months, the mean changes in Early Treatment of Diabetic Retinopathy Study (ETDRS) letters were 6.38, 8.12, and 9.37, while the MT decrease was 126.51, 126.52, and 139.85 μm, respectively. However, statistically significant difference was only found between type 1 and 3 in vision improvement, both in the short term (p=0.0002) and long term (p=0.01).

**CONCLUSIONS:** The reactivity to VEGF inhibitors varied among different subtypes of nAMD. The efficacy of intravitreal anti-VEGF therapy in type 3 nAMD was statistically better than type 1 when considering vision improvement at 3 and 12 months. Thus, the lesion subtype is a predictor for the treatment outcome which can help guide prognosis.

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The effect of ranibizumab and aflibercept treatment on the prevalence of outer retinal tubulation and its influence on retreatment in neovascular age-related macular degeneration.

Kovacs A, Kiss T, Rarosi F, et al.

**Background:** We aimed to analyze the differences in the prevalence of outer retinal tubulation (ORT) in neovascular age-related macular degeneration (AMD) treated with anti-vascular endothelial growth factor (anti-VEGF) agents, either aflibercept or ranibizumab. Our further aim was to examine the changes in the frequency of injections of ranibizumab before and after ORT appearance.

**Methods:** Two hundred thirty six eyes of 230 patients were included in the study (184 eyes treated with ranibizumab by pro re nata regimen (PRN), 52 eyes with aflibercept bimonthly) and followed for 6-24 months. Using optical coherence tomography (OCT), the first appearance of ORT was documented, and fixed time point evaluations were also made every six months to determine the existence of ORT. The number of injections, the presence or absence of subretinal hyperreflective material (SHRM) at treatment initiation and visual acuity were also noted.

**Results:** The survival analysis with Cox proportional hazard model showed no significant difference between the ranibizumab and aflibercept groups in relation to the development of ORT (p = 0.79, hazard ratio 0.92). In the PRN treated ranibizumab group the number of injections showed significant decrease after ORT development (p = 0.004). When SHRM was present at treatment initiation the chance of developing ORT was 2.75 and 11.14 times higher in the ranibizumab and aflibercept groups, respectively.

**Conclusions:** The prevalence of ORT increased over time independently from the chosen anti-VEGF drug. Our results suggest that upon the appearance of ORT a decrease in retreatments can be expected.

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**Durability of diabetic retinopathy improvement with as-needed ranibizumab: open-label extension of RIDE and RISE Studies.**

Sun JK, Wang PW, Taylor S, Haskova Z.

**Objective:** To evaluate durability of diabetic retinopathy (DR) improvements after a change in ranibizumab dosing from monthly to individualized pro re nata (PRN) therapy.

**Design:** Pooled analysis of the open-label extension (OLE) of RIDE/RISE (NCT00473382/NCT00473330) patients with DR and diabetic macular edema (DME).

**Participants:** Patients who completed 36-month participation in RIDE/RISE and entered the OLE.

**Methods:** In the RIDE/RISE studies, patients (N = 759) were randomized 1:1:1 to ranibizumab 0.3 mg monthly, 0.5 mg monthly, or monthly sham injections with rescue macular laser available after 6 months, per protocol-specified criteria. After 24 months, sham patients crossed over to ranibizumab 0.5 mg monthly. After 36 months in the core studies, patients in the OLE (n = 500) could receive ranibizumab 0.5 mg through an individualized PRN dosing regimen based on predefined DME re-treatment criteria. DR severity was evaluated photographically using the Early Treatment Diabetic Retinopathy Study DR severity scale.

**Main Outcome Measure:** Change in DR severity from months 36 to 48 by re-treatment status.

**Results:** Among patients who entered the OLE, 121/500 (24%) did not require additional ranibizumab injections. In total, 442 patients had evaluable DR outcomes during the OLE; 367 had evaluable DR at months 36 and 48. Among patients not requiring ranibizumab re-treatment from months 36 to 48 (88/367), 57% to 78%, 0% to 7%, and 22% to 36% experienced DR severity stability, ≥2-step improvement, and ≥2-step worsening, respectively. Among patients requiring ranibizumab re-treatment (279/367), 84% to 94%,
2%, and 3% to 14% experienced DR severity stability, ≥2-step improvement, and ≥2-step worsening, respectively. On average, vision improvements were maintained during the OLE regardless of change in DR severity.

CONCLUSIONS: DR severity improvements with ranibizumab were maintained in the majority of patients in the OLE after switching from ranibizumab monthly to an individualized best-corrected visual acuity- and optical coherence tomography-based ranibizumab 0.5 mg PRN dosing regimen. Because nearly one-third of OLE patients not requiring further therapy for DME experienced DR worsening, once DME resolves, patients should be watched carefully for worsening of DR and possible need for more frequent follow-up and/or treatment of vision-threatening disease with anti-VEGF or other modalities.

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Facile synthetic Photoluminescent Graphene Quantum dots encapsulated β-cyclodextrin drug carrier system for the management of macular degeneration: Detailed analytical and biological investigations.

Qian C, Yan P, Wan G, et al.

ABSTRACT: Drug administration by effective nano-carriers is an emerging and growing technology in the field of bio-medicine and particularly Age-related macular degeneration (AMD). This developed nanomaterials based methods with drug administration maximizes the biocompatibility and systemically increases drug delivery profile for the drugs. Herein, we described the effective drug molecules delivery profiles by the hydrothermally synthesized graphene quantum dots (GQDs) encapsulated with supramolecular β-cyclodextrin (β-CD) as a drug delivery system for AMD. The drug release profiles were analysed and plotted by two different types of drugs ((Bevacizumab (Bev) and Ranibizumab (Ran)) and compounds displayed an initial burst delivery percentage of 55.7 ± 1.6% and 52.2 ± 2.6, respectively, within 15 min. After 1 h, 94.2% (Ran) and 93.1% (Bev) of loaded drug molecules were released from the β-CD encapsulated GQDs in sustained manner. The biocompatibility of the synthesized carriers was investigated quantitatively and qualitatively with the mouse Fibroblast L929 cell line. The biological cell analysis observed by calculated cell count and green fluorescence visualization has been clearly confirmed the samples are non-toxic and highly compatible to the cells with more than 90% cell viability after 5 days cell culture. The observed material properties and biological results demonstrated that the suitability of the developed nano-carriers for the drug delivery system in the AMD.

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Other treatment

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Initial clinical results with a novel monofocal-type intraocular lens for extended macular vision in patients with macular degeneration.

Robbie SJ, Tabernero J, Artal P, Qureshi MA.

PURPOSE: To determine the feasibility of a novel intraocular lens (IOL) designed to improve retinal image quality at up to 10° of retinal eccentricity and optionally provide retinal magnification in patients with macular disease.

METHODS: In this prospective, interventional pilot study, 8 eyes of 7 patients with bilateral dry age-related macular degeneration and 1+ or less cataract underwent phacoemulsification and capsular bag implantation of a single, injectable, hydrophobic acrylic IOL. Safety and efficacy were assessed by
monitoring logMAR corrected distance and near visual acuity, intraocular pressure, specular microscopy, 80-point visual field testing, and anterior segment and macular optical coherence tomography at baseline and 1 week, 1 month, and 2 months postoperatively. Microperimetry was undertaken at baseline and 1 and/or 2 months postoperatively. Reading performance was assessed at baseline and 1 month postoperatively using the Minnesota low vision reading chart (MNREAD; Precision Vision, LaSalle, IL).

**RESULTS:** Safety outcomes were equivalent to standard monofocal IOLs. Visual acuities improved in all patients. Mean corrected distance visual acuity improved from 0.93 ± 0.22 preoperatively to 0.59 ± 0.25 at 2 months postoperatively. Mean reading speed increased from 28 ± 19 to 44 ± 31 words per minute. Mean microperimetry threshold sensitivities increased from 8.2 ± 4.6 to 12 ± 5.6 dB. Mean percentage of fixation points within a 4° circle increased from 77% ± 17% to 91% ± 11% with evidence for progressive movement of preferred retinal loci away from areas of geographic atrophy.

**CONCLUSIONS:** Initial results indicate this novel IOL has a safety profile comparable with standard IOLs. Visual benefits may exceed those obtained with existing technologies in patients with macular disease. Further work is required to determine the full potential of extended macular vision technology.

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### Pathogenesis

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Absorption of blue light by cigarette smoke components is highly toxic for retinal pigmented epithelial cells.

Zinflou C, Rochette PJ.

**ABSTRACT:** Lesion to the retinal pigment epithelium (RPE) is a crucial event in the development of age-related macular degeneration (AMD), the leading cause of blindness in industrialized countries. Tobacco smoking and high-energy visible blue (HEV; 400-500 nm) light exposure are major environmental risk factors for AMD. Individually, they have been shown to cause damage to the RPE. Tobacco smoke contains toxic polycyclic aromatic hydrocarbons (PAH) that can accumulate in RPE and which absorb HEV light. It can thus be postulated that the interaction between both factors in RPE cells can have a synergic toxic effect to the RPE. To test this hypothesis, cultured human RPE cells (ARPE19) were treated with nanomolar concentrations of benzo[a]pyrene (BaP) or indeno[1,2,3-cd]pyrene (IcdP), then exposed to HEV light using an irradiation system that mimics the solar spectrum normally transmitted to the retina through the human ocular media. Using mitochondrial network morphology changes and key features of AMD-related RPE defects such as apoptotic cell death and oxidative stress, we demonstrate that a synergistic phototoxicity is generated when nanomolar concentrations (≤ 500 nM) of IcdP interact with sub-lethal amounts of HEV light. Indeed, we found IcdP to be at least 3000 times more toxic for RPE cells when irradiated with HEV light. This synergy translates into disruption of mitochondrial network, ROS enhanced accumulation and apoptosis of RPE cells. Our results underline an important interplay between two environmental risk factors involved in AMD progression and strongly indicate that IcdP, upon interaction with HEV light, may initiate the biological mechanisms underlying the association between cigarette smoking and AMD-related RPE degeneration.

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Glucose-regulated protein 78 in the aqueous humor in diabetic macular edema patients.

Kwon JW, Jung I, Jee D.

**ABSTRACT:** In this study, we explored the presence and elevation of glucose-regulated protein 78 (GRP78)
in aqueous humor of patients with diabetic macular edema (DME). After comparing DME patients with the controls, we analyzed GRP78 and vascular endothelial growth factor (VEGF) levels in DME patients. We examined factors associated with GRP78 levels in DME patients. GRP78 was detected in aqueous humor with elevated levels in DME patients. Stepwise backward regression analysis showed that GRP78 levels were associated with the VEGF levels and the duration of diabetes (P<.001 and P=.002, respectively). However, no statistical significance was observed between GRP78 levels and the decrease in CST following 3 monthly anti-VEGF treatments in univariate regression analysis (P=.695). We showed that GRP78 is elevated in DME patients. In addition, there is a correlation between GRP78 and VEGF levels in aqueous humor. However, GRP78 levels were not associated with the responsiveness of anti-VEGF in DME patients.

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**Purinergic Signal. 2018 Nov 10. [Epub ahead of print]**

Hypoxic expression of NLRP3 and VEGF in cultured retinal pigment epithelial cells: contribution of P2Y2 receptor signaling.

Doktor F, Prager P, Wiedemann P, et al.

**ABSTRACT:** Retinal hypoxia is a major condition of the chronic inflammatory disease age-related macular degeneration. Extracellular ATP is a danger signal which is known to activate the NLRP3 inflammasome in various cell systems. We investigated in cultured human retinal pigment epithelial (RPE) cells whether hypoxia alters the expression of inflammasome-associated genes and whether purinergic receptor signaling contributes to the hypoxic expression of key inflammatory (NLRP3) and angiogenic factor (VEGF) genes. Hypoxia and chemical hypoxia were induced by a 0.2%-O2 atmosphere and addition of CoCl2, respectively. Gene expression was determined with real-time RT-PCR. Cytosolic NLRP3 and (pro-) IL-1β levels, and the extracellular VEGF level, were evaluated with Western blot and ELISA analyses. Cell culture in 0.2% O2 induced expression of NLRP3 and pro-IL-1β genes but not of the pro-IL-18 gene. Hypoxia also increased the cytosolic levels of NLRP3 and (pro-) IL-1β proteins. Inflammasome activation by lysosomal destabilization decreased the cell viability under hypoxic, but not control conditions. In addition to activation of IL-1 receptors, purinergic receptor signaling mediated by a pannexin-dependent release of ATP and a release of adenosine, and activation of P2Y2 and adenosine A1 receptors, was required for the full hypoxic expression of the NLRP3 gene. P2Y2 (but not A1) receptor signaling also contributed to the hypoxic expression and secretion of VEGF. The data indicate that hypoxia induces priming and activation of the NLRP3 inflammasome in cultured RPE cells. The hypoxic NLRP3 and VEGF gene expression and the secretion of VEGF are in part mediated by P2Y2 receptor signaling.

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**Stem cells**

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Stemming retinal regeneration with pluripotent stem cells.

Jin ZB, Gao ML, Deng WL, et al.

**ABSTRACT:** Cell replacement therapy is a promising treatment for irreversible retinal cell death in diverse diseases, such as age-related macular degeneration (AMD), Stargardt's disease, retinitis pigmentosa (RP) and glaucoma. These diseases are all characterized by the degeneration of one or two retinal cell types that cannot regenerate spontaneously in humans. Aberrant retinal pigment epithelial (RPE) cells can be observed through optical coherence tomography (OCT) in AMD patients. In RP patients, the morphological and functional abnormalities of RPE and photoreceptor layers are caused by a genetic abnormality. Stargardt's disease or juvenile macular degeneration, which is characterized by the loss of the RPE and...
photoreceptors in the macular area, causes central vision loss at an early age. Loss of retinal ganglion cells (RGCs) can be observed in patients with glaucoma. Once the retinal cell degeneration is triggered, no treatments can reverse it. Transplantation-based approaches have been proposed as a universal therapy to target patients with various concomitant diseases. Both the replacement of dead cells and neuroprotection are strategies used to rescue visual function in animal models of retinal degeneration. Diverse retinal cell types derived from pluripotent stem cells, including RPE cells, photoreceptors, RGCs and even retinal organoids with a layered structure, provide unlimited cell sources for transplantation. In addition, mesenchymal stem cells (MSCs) are multifunctional and protect degenerating retinal cells. The aim of this review is to summarize current findings from preclinical and clinical studies. We begin with a brief introduction to retinal degenerative diseases and cell death in diverse diseases, followed by methods for retinal cell generation. Preclinical and clinical studies are discussed, and future concerns about efficacy, safety and immunorejection are also addressed.

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