Retina Roundup

April 2023

1) Retina March 8, 2023

doi: 10.1097/IAE.0000000000003771

Outcomes of switching from proactive to reactive treatment after developing advanced central neovascular age-related macular degeneration

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Purpose: We assessed outcomes of eyes with neovascular age-related macular degeneration (nAMD) that switched from proactive (treat-and-extend) to reactive (*pro re nata*) treatment regimen after developing macular atrophy (MA) or submacular fibrosis (SMFi).

Methods: Data were collected from a retrospective analysis of a prospectively designed, multinational registry of "real-world" nAMD treatment outcomes. Eyes without MA or SMFi when starting treatment with a vascular endothelial growth factor inhibitor regimen that subsequently developed MA or SMFi were included.

Results: Macular atrophy developed in 821 and SMFi in 1166 eyes. Seven percent of eyes that developed MA, and 9% of those that developed SMFi, were switched to reactive treatment. Vision was stable at 12 months for all eyes with MA and inactive SMFi eyes. Active SMFi eyes that switched to reactive treatment had significant vision loss. No eyes that continued proactive treatment developed ≥15 letter loss, but 8% of all eyes that switched to a reactive regimen, and 15% of active SMFi eyes did.

Conclusion: Eyes that switch from proactive to reactive treatment after developing MA and inactive SMFi, can have stable visual outcomes. Physicians should be aware of the risk of a significant loss of vision in eyes with active SMFi that switch to reactive treatment.

PMID: 36893432

DOI: 10.1097/IAE.0000000000003771

2) Retina March 8, 2023

doi: 10.1097/IAE.0000000000003769

Retinal Vasculitis or Vascular Occlusion after Brolucizumab for Neovascular Age-Related Macular Degeneration: A Systematic Review of Real-World Evidence

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Purpose: Retinal vasculitis or vascular occlusion (RV/RO) have been reported following brolucizumab for neovascular age-related macular degeneration. This systematic literature review evaluated RV/RO events after brolucizumab in real-world practice.

Methods: Systematic literature searches identified 89 publications; 19 were included.

Results: Publications described 63 patients (70 eyes) with an RV/RO event following brolucizumab. Mean age was 77.6 years and 77.8% of patients were women; 32 eyes (45.7%) received one brolucizumab injection before RV/RO. Mean (range) time to event from last brolucizumab injection was 19.4 (0-63) days, with 87.5% of events occurring within 30 days. Among eyes with both pre- and post-event visual acuity (VA) assessments, 22/42 eyes (52.4%) showed unchanged (±0.08 logMAR) or improved vision from last recorded pre-event assessment at latest follow-up, while 15/42 eyes (35.7%) showed ≥0.30 logMAR (≥15 letters) VA reduction. Patients with no VA loss were on average slightly younger and had a higher proportion of non-occlusive events.

Conclusion: Most RV/RO events reported after brolucizumab in early real-world practice occurred in women. Among eyes with VA measurements, approximately half experienced VA loss; overall, about one third had VA reduction of ≥0.30 logMAR at latest follow-up, with indications of regional variations.

PMID: 36893438

DOI: 10.1097/IAE.0000000000003769

3) Int J Pharm 2023(Mar); : 122809.

doi: 10.1097/IAE.0000000000003536.

Nanofiber-coated implants: Development and safety after intravitreal application in rabbits

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Abstract :

Intravitreal injections are the preferred choice for drug administration to the posterior segment of the eye. However, the required frequent injections may cause complications to the patient and low adherence to the treatment. Intravitreal implants are able to maintain therapeutic levels for a long period. Biodegradable nanofibers can modulate drug release and allow the incorporation of fragile bioactive drugs. Age-related macular degeneration is one of the world major causes of blindness and irreversible vision loss. It involves the interaction between VEGF and inflammatory cells. In this work we developed nanofiber-coated intravitreal implants containing dexamethasone and bevacizumab for simultaneously delivery of these drugs. The implant was successfully prepared and the efficiency of the coating process was confirmed by scanning electron microscopy. Around 68% of dexamethasone was released in 35 days and 88% of bevacizumab in 48hs. The formulation presented activity in the reduction of vessels and was safe to the retina. It was not observed any clinical or histopathological change, neither alteration in retina function or thickness by electroretinogram and optical coherence tomography during 28 days. The nanofiber-coated implants of dexamethasone and bevacizumab may be considered as a new delivery system that can be effective for the treatment of AMD.

DOI: https://doi.org/10.1016/j.ijpharm.2023.122809

4) PNAS Nexus. 2023 Mar; 2(3): pgad038

doi: 10.1093/pnasnexus/pgad038 eCollection 2023 Mar.

The function of lactate dehydrogenase A in retinal neurons: implications to retinal degenerative diseases

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The postmitotic retina is highly metabolic and the photoreceptors depend on aerobic glycolysis for an energy source and cellular anabolic activities. Lactate dehydrogenase A (LDHA) is a key enzyme in aerobic glycolysis, which converts pyruvate to lactate. Here we show that cell-type-specific actively translating mRNA purification by translating ribosome affinity purification shows a predominant expression of LDHA in rods and cones and LDHB in the retinal pigment epithelium and Müller cells. We show that genetic ablation of LDHA in the retina resulted in diminished visual function, loss of structure, and a loss of dorsal-ventral patterning of the cone-opsin gradient. Loss of LDHA in the retina resulted in increased glucose availability, promoted oxidative phosphorylation, and upregulated the expression of glutamine synthetase (GS), a neuron survival factor. However, lacking LDHA in Müller cells does not affect visual function in mice. Glucose shortage is associated with retinal diseases, such as age-related macular degeneration (AMD), and regulating the levels of LDHA may have therapeutic relevance. These data demonstrate the unique and unexplored roles of LDHA in the maintenance of a healthy retina.

PMID: 36896135

DOI: 10.1093/pnasnexus/pgad038

5) Current Opinion in Ophthalmology () March 02, 2023

doi: 10.1097/ICU.0000000000000942

Primary Retinal Detachment Outcomes Study: summary of reports number 1 to number 18

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Purpose: To highlight the recent work published from the Primary Retinal Detachment Outcomes (PRO) Study Group..

Findings: The PRO database was a large dataset made up of patients with primary rhegmatogenous retinal detachments (RRD) who had surgical repair during 2015. The database was constituted of nearly 3000 eyes from 6 centres across the United States and included 61 vitreoretinal surgeons. Nearly 250 metrics were collected for each patient, creating one of the richest datasets of patients with primary rhegmatogenous detachments and their outcomes. The importance of scleral buckling was demonstrated, particularly for phakic eyes, elderly patients, and those with inferior breaks. 360° laser may result in poorer outcomes. Cystoid macular edema was common, and risk factors were identified. We also found risk factors for vision loss in eyes presenting with good vision. A PRO Score was devised, to predict outcomes based on presenting clinical characteristics. We also identified characteristics of surgeons with the highest single surgery success rates. Overall, there were no major outcome differences between viewing systems, gauges, buckles sutured vs. scleral tunnels, drainage method, and techniques to address proliferative vitreoretinopathy. All incisional techniques were found to be very cost-effective treatment modalities.

Summary: **Numerous studies resulted from the PRO database that significantly added to the literature regarding the repair of primary RRDs in the current era of vitreoretinal surgery**

DOI: 10.1097/ICU.0000000000000942

6) BMC Ophthalmol 2023 Mar 3;23(1):83.

doi: 10.1186/s12886-023-02797-5.

Predictive value of pigment epithelial detachment markers for visual acuity outcomes in neovascular age-related macular degeneration

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Background: To determine the predictive value of quantitative morphological parameters for pigment epithelial detachment (PED) of neovascular age-related macular degeneration (nAMD) patients .

Methods: One eye from each of 159 patients with nAMD were studied. Polypoidal choroidal vasculopathy (PCV) group included 77 eyes, and non-PCV group 82. Patients received conbercept 0.05 ml (0.5 mg) in a 3 + ProReNata (PRN) treatment regimen. Correlations between retinal morphologic parameters at baseline and best-corrected visual acuity (BCVA) gain at 3 or 12 months after treatment (structure-function correlations) were assessed. Optical coherence tomography (OCT) scans were used to assess retinal morphologic features including intraretinal cystoid fluid (IRC), subretinal fluid (SRF), PED or PED type (PEDT), and vitreomacular adhesion (VMA). Greatest height (PEDH) and width of PED (PEDW), and volume of PED (PEDV) at baseline were also measured.

Results: For non-PCV group, BCVA gain from 3 or 12 months after treatment was negatively correlated with PEDV at baseline ($r = -0.329, -0.312$, $P = 0.027, 0.037$). BCVA gain at 12 months after treatment was negatively correlated with PEDW at baseline ($r = -0.305$, $P = 0.044$). For PCV group, there were no correlations with PEDV, PEDH, PEDW, and PEDT in BCVA gain between baseline and 3 or 12 months after treatment ($P > 0.05$). SRF, IRC, VMA at baseline did not correlate with short-term and long-term BCVA gain in patients with nAMD ($P > 0.05$).

Conclusion: For patients with non-PCV, PEDV at baseline was negatively correlated with short-term and long-term BCVA gain, and PEDW was negatively correlated with long-term BCVA gain. On the contrary, quantitative morphological parameters for PED at baseline had no correlation with BCVA gain in patients with PCV.

PMID: 36869310

DOI: 10.1186/s12886-023-02797-5

7) J Ocul Pharmacol Ther 2023(Mar); 39(2):148-158.

doi: 10.1089/jop.2022.0078

Pharmacological Therapy of Proliferative Vitreoretinopathy: Systematic *In Vitro* Comparison of 36 Pharmacological Agents

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Purpose: Proliferative vitreoretinopathy (PVR) is currently treated surgically. Reliable pharmaceutical options would be desirable, and numerous drugs have been proposed. This *in vitro* study is intended to systematically compare and determine the most promising candidates for the treatment of PVR.

Methods: A structured literature review was conducted in the "PubMed" database to identify previously published agents proposed for medical treatment of PVR -36 substances that met the inclusion criteria. Toxicity and antiproliferative effects were evaluated on primary human retinal pigment epithelial (hRPE) using colorimetric viability assays. The seven substances with the widest therapeutic range between toxicity and no longer detectable antiproliferative effect were then validated with a bromodeoxyuridine assay and a scratch wound healing assay using primary cells derived from surgically excised human PVR membranes (hPVR).

Results: Among 36 substances, 12 showed no effect on hRPE at all. Seventeen substances had a significant ($P < 0.05$) toxic effect of which nine did not have an antiproliferative effect. Fifteen substances significantly reduced hRPE proliferation ($P < 0.05$). The seven most promising drugs with the highest difference between toxicity and antiproliferative effects on hRPE were dasatinib, methotrexate, resveratrol, retinoic acid, simvastatin, tacrolimus, and tranilast. Whereof resveratrol, simvastatin, and tranilast additionally showed antiproliferative and dasatinib, resveratrol, and tranilast antimigratory effects on hPVR ($P < 0.05$).

Conclusions: This study presents a systematic comparison of drugs that have been proposed for PVR treatment in a human disease model. Dasatinib, resveratrol, simvastatin, and tranilast seem to be promising and are well-characterized in human use.

PMID: 36867160

DOI: 10.1089/jop.2022.0078

8) Ophthalmol Ther Mar 11 2023

doi: 10.1007/s40123-023-00695-z

Epiretinal Amniotic Membrane in Complicated Retinal Detachment: a Clinical and In Vitro Safety Assessment

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Introduction: Amniotic membrane (AM) is a popular treatment for external ocular diseases. First intraocular implantations in other diseases reported promising results. Here, we review three cases of intravitreal epiretinal human AM (iehAM) transplantation as an adjunct treatment for complicated retinal detachment and analyze clinical safety. Possible cellular rejection reactions against the explanted iehAM were evaluated and its influence was assessed on three retinal cell lines in vitro.

Methods: Three patients with complicated retinal detachment and implanted iehAM during pars plana vitrectomy are retrospectively presented. After removal of the iehAM at subsequent surgery, tissue-specific cellular responses were studied by light microscopy and immunohistochemical staining. We investigated the influence of AM in vitro on retinal pigment epithelial cells (ARPE-19), Muller cells (Mio-M1), and differentiated retinal neuroblasts (661W) . An anti-histone DNA ELISA for cell apoptosis, a BrdU ELISA for cell proliferation, a WST-1 assay for cell viability, and a live/dead assay for cell death were performed.

Results: Despite the severity of the retinal detachment, stable clinical outcomes were obtained in all three cases. Immunostaining of the explanted iehAM showed no evidence of cellular immunological rejection. In vitro, there was no statistical significant change in cell death or cell viability nor were proliferative effects detected on ARPE-19, MÃ¼ller cells, and retinal neuroblasts exposed to AM.

Conclusion: iehAM was a viable adjuvant with many potential benefits for treatment of complicated retinal detachment. Our investigations could not detect any signs of rejection reactions or toxicity. Further studies are needed to evaluate this potential in more detail.

PMID: 36905569

DOI: 10.1007/s40123-023-00695-z