Drug treatment

*Biosimilars in ophthalmology: "Is there a big change on the horizon?"


**Abstract**: Retinal disease management has witnessed remarkable advances in posterior segment pharmacotherapy with the development of anti-VEGF molecules such as Lucentis® (ranibizumab), Eylea® (aflibercept), and off-label bevacizumab (Avastin). The US patents for ranibizumab and aflibercept will expire in 2020 (though Regeneron has indicated that it might attempt to extend its US patent to June 2023 with additional patent claims), and their European patents will expire in 2022 and 2025. Aflibercept comes off patent in 2022 in People's Republic of China and Japan. As soon as each patent expires, biosimilar molecules could potentially come in the mainstream clinical practice as a more cost-efficient choice in the form of generic biosimilars. It is difficult to predict how significant this shift would be in terms of more cost-effective clinical management and how it will impact the care in developed and developing world. It is important for clinicians to have a clear understanding about ophthalmic biosimilars before the industry brings these molecules to the mainstream clinical use globally.

PMID: 30498330 PMCID: PMC6207386 DOI: 10.2147/OPTH.S180393


**Strategies for modifying drug residence time and ocular bioavailability to decrease treatment frequency for back of the eye diseases.**


**ABSTRACT**: Treating posterior eye diseases has become a major area of focus for pharmaceutical and biotechnology companies. Current standard of care for treating posterior eye diseases relies on administration via intravitreal injection. Although effective, this is not without complications and there is great incentive to develop longer-acting therapeutics and/or sustained release delivery systems. Here, we present an overview of emerging technologies for delivery of biologics to the back of the eye. Areas covered: Posterior eye diseases, intravitreal injection, age-related macular degeneration, anti-VEGF, ocular pharmacokinetics, novel technologies to extend half-life, in vivo models, translation to the clinic, hurdles to
Effective patient care. Expert opinion: Posterior eye diseases are a worldwide public health issue. Although anti-VEGF molecules represent a major advance for treating diseases involving choroidal neovascularization, frequent injection can be burdensome for patients and clinicians. There is a need for effective and patient-friendly treatments for posterior eye diseases. Many technologies that enable long-acting delivery to the back of the eye are being evaluated. However, successful development of novel therapies and delivery technologies is hampered by a multitude of factors, including patient education, translatability of in vitro/in vivo preclinical data to the clinic, and regulatory challenges associated with novel technologies.

PMID: 30488721 DOI: 10.1080/17425247.2019.1553953

Int Ophthalmol. 2018 Nov 23. [Epub ahead of print]

Dexamethasone implant as an adjuvant therapy to ranibizumab loading dose in persistent diabetic macular edema.


PURPOSE: This study evaluates the effectiveness of a single-dose dexamethasone implant (DI) as an auxiliary therapy to continued intravitreal ranibizumab (IVR) treatment in patients with persistent diabetic macular edema (DME).

METHODS: Twenty-five pseudophakic eyes of 25 patients with DME who underwent a single injection of DI as an adjuvant therapy following an IVR loading dose were examined retrospectively. All patients were treatment naive and had a poor response to a loading dose of three consecutive monthly IVR injections. IVR treatments were continued pro re nata after the DI. The main outcome measures were changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) at 1, 3, 6 and 8 months post-DI treatment.

RESULTS: After the IVR loading dose, the mean BCVA and CMT were 0.9 ± 0.6 LogMAR and 478.2 ± 107.8 µm, respectively. One month after the DI, the mean BCVA and CMT had improved to 0.6 ± 0.4 LogMAR (p = 0.005) and 313.8 ± 62.7 µm (p < 0.001), respectively. This improvement was maintained with mean 0.8 ± 0.8 IVR injections throughout the follow-up period. The final mean BCVA and CMT were 0.5 ± 0.5 LogMAR and 298.4 ± 71.5 µm. Subgroup analyses revealed that different DME types did not have any effect on CMT or BCVA improvement (p = 0.188, p = 0.136; respectively).

CONCLUSION: Adding DI results in rapid anatomical and visual improvement in patients who respond poorly to an IVR loading dose. Improvements may be maintained with additional IVR in follow-up.

PMID: 30470985 DOI: 10.1007/s10792-018-1053-5

Artificial Intelligence and Machine Learning


A novel machine learning algorithm to automatically predict visual outcomes in intravitreal ranibizumab-treated patients with diabetic macular edema.

Chen SC, Chiu HW, Chen CC, et al.

PURPOSE: Artificial neural networks (ANNs) are one type of artificial intelligence. Here, we use an ANN-based machine learning algorithm to automatically predict visual outcomes after ranibizumab treatment in diabetic macular edema.

METHODS: Patient data were used to optimize ANNs for regression calculation. The target was established as the final visual acuity at 52, 78, or 104 weeks. The input baseline variables were sex, age, diabetes type or condition, systemic diseases, eye status and treatment time tables. Three groups were randomly devised
to build, test and demonstrate the accuracy of the algorithms.

**RESULTS:** At 52, 78 and 104 weeks, 512, 483 and 464 eyes were included, respectively. For the training group, testing group and validation group, the respective correlation coefficients were 0.75, 0.77 and 0.70 (52 weeks); 0.79, 0.80 and 0.55 (78 weeks); and 0.83, 0.47 and 0.81 (104 weeks), while the mean standard errors of final visual acuity were 6.50, 6.11 and 6.40 (52 weeks); 5.91, 5.83 and 7.59; (78 weeks); and 5.39, 8.70 and 6.81 (104 weeks).

**CONCLUSIONS:** Machine learning had good correlation coefficients for predicating prognosis with ranibizumab with just baseline characteristics. These models could be the useful clinical tools for prediction of success of the treatments.

PMID: 30477203 DOI: 10.3390/jcm7120475


**DeepSeeNet: A deep learning model for automated classification of patient-based age-related macular degeneration severity from color fundus photographs.**


**PURPOSE:** In assessing the severity of age-related macular degeneration (AMD), the Age-Related Eye Disease Study (AREDS) Simplified Severity Scale predicts the risk of progression to late AMD. However, its manual use requires the time-consuming participation of expert practitioners. While several automated deep learning (DL) systems have been developed for classifying color fundus photographs of individual eyes by AREDS severity score, none to date has utilized a patient-based scoring system that employs images from both eyes to assign a severity score.

**DESIGN:** DeepSeeNet, a DL model, was developed to classify patients automatically by the AREDS Simplified Severity Scale (score 0-5) using bilateral color fundus images.

**PARTICIPANTS:** DeepSeeNet was trained on 58,402 and tested on 900 images from the longitudinal follow up of 4,549 participants from AREDS. Gold standard labels were obtained using reading center grades.

**METHODS:** DeepSeeNet (composed of three sub-networks) simulates the human grading process by first detecting individual AMD risk factors (drusen size; pigmentary abnormalities) for each eye and then calculating a patient-based AMD severity score using the AREDS Simplified Severity Scale.

**MAIN OUTCOME MEASURES:** Overall accuracy, specificity, sensitivity, Cohen's kappa, area under the curve (AUC). The performance of DeepSeeNet was compared to that of retinal specialists.

**RESULTS:** DeepSeeNet performed better on patient-based, multi-class classification (accuracy=0.671; kappa=0.558) than retinal specialists (accuracy=0.599; kappa=0.467) with high AUCs in the detection of large drusen (0.94), pigmentary abnormalities (0.93) and late AMD (0.97), respectively. DeepSeeNet also outperformed retinal specialists in the detection of large drusen (accuracy 0.742 vs 0.696; kappa 0.601 vs 0.517) and pigmentary abnormalities (accuracy 0.890 vs 0.813; kappa 0.723 vs 0.535) but showed lower performance in the detection of late AMD (accuracy 0.967 vs 0.973; kappa 0.663 vs 0.754).

**CONCLUSIONS:** By simulating the human grading process, DeepSeeNet demonstrated high accuracy with increased transparency in the automated assignment of individual patients to AMD risk categories based on the AREDS Simplified Severity Scale. These results highlight the potential of deep learning systems to assist and enhance clinical decision-making processes in AMD patients such as early AMD detection and risk prediction for developing late AMD. DeepSeeNet is publicly available on https://github.com/ncbi-nlp/DeepSeeNet.

PMID: 30471319 DOI: 10.1016/j.ophtha.2018.11.015
Other treatment

Exp Eye Res. 2018 Nov 22. pii: S0014-4835(18)30522-0. [Epub ahead of print]

The potent small molecule integrin antagonist THR-687 is a promising next-generation therapy for retinal vascular disorders.


ABSTRACT: Integrins are associated with various eye diseases such as diabetic retinopathy (DR) and wet age-related macular degeneration (AMD) and implicated in main pathologic disease hallmarks like neovascularization, inflammation, fibrosis and vascular leakage. Targeting integrins has the potential to attenuate these vision-threatening processes, independent of anti-vascular endothelial growth factor (VEGF) responsiveness. The current investigation characterized THR-687 as a novel pan RGD (arginylglycylaspartic acid) integrin receptor antagonist able to compete for binding with the natural ligand with nanomolar potency (e.g. ανβ3 (IC50 of 4.4 ± 2.7 nM), ανβ5 (IC50 of 1.3 ± 0.5 nM) and α5β1 (IC50 of 6.8 ± 3.2 nM). THR-687 prevented the migration of human umbilical vein endothelial cells (HUVECs) into a cell-free area (IC50 of 258 ± 113 nM) as well as vessel sprouting in an ex vivo mouse choroidal explant model (IC50 of 236 ± 173 nM), and was able to induce the regression of pre-existing vascular sprouts. Moreover, combined intravitreal and intraperitoneal administration of THR-687 potently inhibited VEGF-induced leakage in the mouse retina. In addition, THR-687 injected intravitreally at 3 different dose levels (0.45 mg, 2.25 mg or 4.5 mg/eye) potently inhibited neovascularization-induced leakage in the cynomolgus laser-induced choroidal neovascularization (CNV) model. These data suggest that THR-687 is a promising drug candidate for the treatment of vision-threatening retinal vascular eye diseases such as DR and wet AMD.

PMID: 30472075 DOI: 10.1016/j.exer.2018.11.022

Screening & Diagnosis

Telemed J E Health. 2018 Nov 27. [Epub ahead of print]

Use of telehealth screening to detect diabetic retinopathy and other ocular findings in primary care settings.


PURPOSE: To determine the incidence of diabetic retinopathy (DR) and other ocular findings in previously diagnosed diabetes using telehealth retinal screening with nonmydriatic fundus photography (nFP) in primary care physicians' offices.

METHODS: A retrospective study based on electronic chart review was performed. All diabetic patients who participated in the Wills Eye Hospital (WEH) telehealth retinal screening program from July 1, 2012 to February 20, 2017 were included. In addition to evaluation of DR, other eye pathologies of the retina were detected using nFP.

RESULTS: Overall, 9,946 diabetics participated in the WEH telehealth screening system. After exclusion of missing or unreadable images, 15,180 eyes of 7,624 (76.7%) patients were eligible for final analysis. A total of 1,269 (16.6%) patients were noted to have DR changes in at least one eye. Of those, 475 (37.4%) had mild nonproliferative DR (NPDR) in the more severely affected eye, 712 (56.1%) had moderate NPDR, 33 (2.6%) had severe NPDR, 19 (1.5%) had proliferative DR, and 30 (2.4%) have received pan-retinal photocoagulation previously. In addition, there was evidence of diabetic macular edema detectable on nFP in 34 eyes of 29 patients. Other ocular findings included hypertensive retinopathy (709, 9.3%), increased or asymmetric cup-to-disc ratio (562, 7.4%), age-related cataract (379, 5.0%), cotton-wool spots (221, 2.9%), choroidal nevus (74, 1.0%), age-related macular degeneration (AMD) (66, 0.9%), and epiretinal membrane (48, 0.6%). Patients with hypertensive retinopathy, glaucomatous findings, cataract, or AMD were significantly older (p < 0.001) than those without these ocular pathologies.
**CONCLUSION:** The WEH Telehealth Screening Program identified DR in approximately one out of six patients and other ocular pathologies in over 25% of the diabetic population that received screenings in Philadelphia area primary care offices. Given the importance of early detection and routine eye care to prevent vision loss for DR patients, these findings have a significant impact.

PMID: 30481134 DOI: 10.1089/tmj.2018.0016

**Pathogenesis**

*Acta Biochim Biophys Sin (Shanghai). 2018 Nov 29. [Epub ahead of print]*

**Emerging roles of transforming growth factor β signaling in wet age-related macular degeneration.**


**ABSTRACT:** Age-related macular degeneration (AMD) is one of the major causes of irreversible blindness among aging populations in developed countries and can be classified as dry or wet according to its progression. Wet AMD, which is characterized by angiogenesis on the choroidal membrane, is uncommonly seen but more severe. Controlling or completely inhibiting the factors that contribute to the progression of events that lead to angiogenesis may be an effective strategy for treating wet AMD. Emerging evidence has shown that transforming growth factor-β (TGF-β) signaling plays a significant role in the progression of wet AMD. In this review, we described the roles of and changes in TGF-β signaling in the development of AMD and discussed the mechanisms of the TGF-β superfamily in choroidal neovascularization (CNV) and wet AMD, including the modulation of angiogenesis-related factors, inflammation, vascular fibrosis, and immune responses, as well as cross-talk with other signaling pathways. These remarkable findings indicate that TGF-β signaling is a potential target for wet AMD treatment.

PMID: 30496406 DOI: 10.1093/abbs/gmy145


**Negative regulators of angiogenesis, ocular vascular homeostasis, and pathogenesis and treatment of exudative AMD.**

Farnoodian M, Sorenson CM, Sheibani N.

**ABSTRACT:** Angiogenesis, the formation of new blood vessels from pre-existing capillaries, is very tightly regulated and normally does not occur except during developmental and reparative processes. This tight regulation is maintained by a balanced production of positive and negative regulators, and alterations under pathological conditions such as retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration can lead to growth of new and abnormal blood vessels. Although the role of proangiogenic factors such as vascular endothelial growth factor has been extensively studied, little is known about the roles of negative regulators of angiogenesis in the pathogenesis of these diseases. Here, we will discuss the role of thrombospondin-1 (TSP1), one of the first known endogenous inhibitors of angiogenesis, in ocular vascular homeostasis, and how its alterations may contribute to the pathogenesis of age-related macular degeneration and choroidal neovascularization. We will also discuss its potential utility as a therapeutic target for treatment of ocular diseases with a neovascular component.

PMID: 30479719 PMCID: PMC6210860 DOI: 10.4103/jovr.jovr_67_18
Up-regulation of P-gp via NF-κB activation confers protection against oxidative damage in the retinal pigment epithelium cells.

Feng Q, Yang W, Gao Z, et al.

**ABSTRACT:** Dysfunction of retinal pigment epithelial (RPE) cells has been associated with the pathogenesis of age-related macular degeneration in relation to increased oxidative stress, subsequent mitochondrial dysfunction and cell death. Permeability-glycoprotein (P-gp), encoded by the multidrug resistance 1 gene (MDR1), is an active efflux pump involved in cell homeostasis and nuclear factor κB (NF-κB) shows potential involvement in P-gp regulation due to its binding to the promoter domains of MDR1 gene. This study sought to determine the role of P-gp expression regulated by NF-κB in RPE cells during oxidative stress. The human RPE D407 cells were exposed to increasing concentrations of hydrogen peroxide (H2O2) for 24 h. The small-interfering RNA (siRNA) transfection was used to down-regulate P-gp and NF-κB, and the expressions of P-gp and NF-κB p65 were determined by quantitative real-time PCR, western blot and immunofluorescence. The activity of NF-κB was detected by luciferase reporter assay. Mitochondrial membrane potential and cell death rate were detected by flow cytometry. We found that H2O2 exposure caused increasing rate of cell death and induced an elevated expression of P-gp as well as NF-κB activation and nucleus translocation in D407 cells. Inhibiting or silencing NF-κB led to a decrease in the oxidative-induced expression of P-gp. Down-regulation of P-gp by siRNA transfection further impaired the mitochondrial membrane potential and cell death rate in oxidative cells. Moreover, inhibition/knockdown of NF-κB decreased the high rate of cell death caused by H2O2. In conclusion, P-gp can provide moderate cytoprotection for the human RPE cells by ameliorating the mitochondrial dysfunction and NF-κB activation may be a potential regulator of P-gp expression response to oxidative stress.

PMID: 30496729 DOI: 10.1016/j.exer.2018.11.024

Myofibroblasts in macular fibrosis secondary to neovascular age-related macular degeneration - the potential sources and molecular cues for their recruitment and activation.

Little K, Ma JH, Yang N, et al.

**ABSTRACT:** Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in developed countries. Neovascular AMD (nAMD) accounts for 90% of AMD-related vision loss. Although intravitreal injection of VEGF inhibitors can improve vision in nAMD, approximately 1/3 of patients do not benefit from the therapy due to macular fibrosis. The molecular mechanism underlying the transition of the neovascular lesion to a fibrovascular phenotype remains unknown. Here we discussed the clinical features and risk factors of macular fibrosis secondary to nAMD. Myofibroblasts are key cells in fibrosis development. However, fibroblasts do not exist in the macula. Potential sources of myofibroblast precursors, the molecular cues in the macular microenvironment that recruit them and the pathways that control their differentiation and activation in macular fibrosis were also discussed. Furthermore, we highlighted the challenges in macular fibrosis research and the urgent need for better animal models for mechanistic and therapeutic studies.

PMID: 30473378 DOI: 10.1016/j.ebiom.2018.11.029

The question of a role for statins in age-related macular degeneration.

Roizenblatt M, Naranjit N, Maia M, Gehlbach PL.
ABSTRACT: Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss in patients over the age of 65 years in industrialized countries. Epidemiologic studies suggest that high dietary fat intake is a risk factor for the development and progression of both vascular and retinal disease. These, and other associations, suggest a hypothesis linking elevated cholesterol and AMD progression. It follows, therefore, that cholesterol-lowering medications, such as statins, may influence the onset and progression of AMD. However, the findings have been inconclusive as to whether statins play a role in AMD. Due to the significant public health implications of a potential inhibitory effect of statins on the onset and progression of AMD, it is important to continually evaluate emerging findings germane to this question.

PMID: 30469381 DOI: 10.3390/ijms19113688


Follow up at 5 Years of non-fibrotic scars in the Comparison of Age-related macular degeneration Treatments Trials (CATT).

Daniel E, Ying GS, Kim BJ, et al.

OBJECTIVE: To describe changes in visual acuity (VA) and macular morphology at 5 years in eyes with non-fibrotic scars (NFS) identified at 1 year in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: Participants in CATT.

METHODS: Participants assigned to ranibizumab or bevacizumab and to 1 of 3 dosing regimens were released from the clinical trial protocol after 2 years and recalled at 5 years. NFS was identified on color images at year 1 as flat, small, well-circumscribed areas of pigmentation with varying degrees of central hypopigmentation without exposure of underlying choroidal vessels, at the site of baseline choroidal neovascularization (CNV). Follow-up images were assessed for changes in and around the NFS.

MAIN OUTCOME MEASURES: Changes in pigmentation, VA, development of fibrotic scar (FS), non-geographic (NGA) and geographic atrophy (GA), retinal fluid on optical coherent tomography, and fluorescein leakage.

RESULTS: Among 474 eyes with images at 1, 2 and 5 years, 39 (8.2%) had NFS at 1 year with a mean VA of 80 letters (≈ 20/25). Among these eyes, FS developed in 5% at 2 and 28% at 5 years. NGA was observed in 34%, 47% and 65% of eyes at 1, 2 and 5 years, respectively. GA developed in 5% of eyes at 2 and 21% at 5 years. Among eyes with NFS, FS or no scar at 1 year, mean VA at 5 years was 73 letters (≈ 20/32), 48 (≈ 20/100) and 62 (≈ 20/63), respectively. At 5 years, NFS eyes had less GA, less intraretinal fluid, more subretinal fluid, and less sub-RPE fluid (all p<0.01). Among NFS eyes, mean thickness of the retina, subretinal tissue complex and total retina did not change across years 1 to 5 (p>0.50). The proportion of eyes with fluid on OCT also did not change (p=0.36). Subretinal hyperreflective material disappeared by 5 years in 40% of eyes with NFS.

CONCLUSION: These results indicate that, on average, eyes with NFS after anti-VEGF treatment have good visual acuity not only at 1 and 2 years, but also through 5 years.

PMID: 30476517 DOI: 10.1016/j.ophtha.2018.11.020

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