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MD Research News

Issue 314

Wednesday 8 February, 2017

Drug treatment

Adv Ther. 2017 Jan 31. [Epub ahead of print]

A Retrospective Study of Ranibizumab Treatment Regimens for Neovascular Age-Related Macular Degeneration (nAMD) in Australia and the United Kingdom.

Johnston RL, Carius HJ, Skelly A, Ferreira A, Milnes F, Mitchell P.

INTRODUCTION: Neovascular age-related macular degeneration (nAMD) is the leading cause of vision loss among persons aged 65 years and older. Anti-vascular endothelial growth factor (anti-VEGF) treatment is the recommended standard of care. The current study compares the effectiveness of ranibizumab in routine clinical practice in two countries that generally apply two different treatment regimens, treat-and-extend (T&E) in Australia or pro re nata (PRN) in the UK.

METHODS: This retrospective, comparative, non-randomised cohort study is based on patients' data from electronic medical record (EMR) databases in Australia and the UK. Treatment regimens were defined based on location, with Australia as a proxy for analysing T&E and UK as a proxy for analysing PRN. The study included patients with a diagnosis of nAMD who started treatment with ranibizumab between January 2009 and July 2014. A total of 647 eyes of 570 patients in Australia and 3187 eyes of 2755 patients in the UK with complete 12-months follow-up were analysed.

RESULTS: Baseline patient characteristics were comparable between the two cohorts. After 1 year of treatment, T&E-treated eyes achieved higher mean (±SE) visual acuity (VA) gains (5.00 ± 0.54 letters [95% confidence interval (CI) 3.93-6.06]) than PRN-treated eyes [3.04 ± 0.24 letters (95% CI 2.57-3.51); difference in means 2.07 ± 0.69 (95% CI 0.73-3.41), $p < 0.001$]. Non-inferiority of T&E compared to PRN was concluded based on the change in mean visual acuity gains at 12 months. Over the 12-month follow-up, T&E-treated eyes received a higher mean [±standard deviation (SD)] number of injections (9.29 ± 2.43) than PRN-treated eyes (6.04 ± 2.19) ($p < 0.0001$). Australian patients had a lower mean (±SD) number of total clinic visits (10.29 ± 2.90) than UK patients (11.47 ± 2.93) ($p < 0.0001$).

CONCLUSION: The higher injection frequency in the T&E cohort may account for the trend toward improved vision.

PMID: 28144918

Retina. 2017 Jan 31. [Epub ahead of print]

TWO YEAR OUTCOMES OF "TREAT AND EXTEND" INTRAVITREAL THERAPY USING AFLIBERCEPT PREFERENTIALLY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Barthelmes D, Nguyen V, Daien V, Campain A, Walton R, Guymer R, Morlet N, Hunyor AP, Essex RW, Arnold JJ, Gillies MC; Fight Retinal Blindness Study Group.

PURPOSE: To report 24-month outcomes of a treat and extend (T&E) regimen using aflibercept in eyes with neovascular age-related macular degeneration.

METHODS: This was a database observational study that included treatment-naive eyes with neovascular age-related macular degeneration tracked by the Fight Retinal Blindness! outcome registry completing 24 months of sole monotherapy with aflibercept treatment under a T&E regimen between November 1, 2012 and January 31, 2014. Locally weighted scatterplot smoothing curves were used to display visual acuity outcomes. Main outcome measures were change in visual acuity at 24 months and number of injections and visits during the study period.

RESULTS: The study population, identified by reviewing the database, consisted of 136 eyes from 123 patients completing 24 months of follow-up on aflibercept. Mean (SD) age was 77.2 (7.0) years, 59% were female. Mean visual acuity increased from 61.4 (~20/60; SD 17.4) letters at baseline to 67.4 (~20/45; SD 17.7) letters at 24 months (+6.0 letters [95% confidence interval: 3.3-8.5]; P < 0.001). From baseline to 24 months, the proportion of eyes with visual acuity ≥70 letters (20/40) increased (40%-58%, P < 0.001) and the proportion of eyes with visual acuity ≤35 letters (20/200) remained the same (10%; P = 0.547). Ninety-eight per cent of eyes starting with visual acuity ≥70 letters (20/40) were able to maintain this up to 24 months. From the first to the second year of treatment, the mean number of injections (7.8 [2.1] vs. 5.7 [2.6]; P < 0.001) and visits (8.7 [1.7] vs. 6.5 [2.4]; P < 0.001) decreased for eyes completing 24 months of treatment. When data from 60 eligible eyes that did not complete 2 years follow-up, along with 14 eyes that switched to ranibizumab, were included using last observation carried forward, the mean change in visual acuity from baseline was +5.6 letters (95% confidence interval: 3.3-7.7).

CONCLUSION:

These data indicate that eyes treated with aflibercept, as a sole therapy, in routine clinical practice with a T&E regimen can achieve good visual outcomes while decreasing the burden of treatments and clinic visits.

PMID: 28145976

Acta Ophthalmol. 2017 Jan 31. [Epub ahead of print]

Switching from pro re nata to treat-and-extend regimen improves visual acuity in patients with neovascular age-related macular degeneration.

Kvannli L, Krohn J.

PURPOSE: To evaluate the visual outcome after transitioning from a pro re nata (PRN) intravitreal injection regimen to a treat-and-extend (TAE) regimen for patients with neovascular age-related macular degeneration (AMD).

METHODS: A retrospective review of patients who were switched from a PRN regimen with intravitreal injections of bevacizumab, ranibizumab or aflibercept to a TAE regimen. The best corrected visual acuity (BCVA), central retinal thickness (CRT) and type of medication used at baseline, at the time of changing treatment regimen and at the end of the study were analysed.

RESULTS: Twenty-one eyes of 21 patients met the inclusion criteria. Prior to the switch, the patients received a mean of 13.8 injections (median, 10; range, 3-39 injections) with the PRN regimen for 44 months (range, 3-100 months), which improved the visual acuity in five patients (24%). After a mean of 6.1 injections (median, 5; range, 3-14 injections) with the TAE regimen over 8 months (range, 2-16 months), the visual acuity improved in 12 patients (57%). The improvement in visual acuity during treatment with the TAE regimen was statistically significant (p = 0.005). The proportion of patients with a visual acuity of 0.2 or better was significantly higher after treatment with the TAE regimen than after treatment with the PRN regimen (p = 0.048). No significant differences in CRT were found between the two treatment regimens.

CONCLUSION: Even after prolonged treatment and a high number of intravitreal injections, switching AMD patients from a PRN regimen to a strict TAE regimen significantly improves visual acuity.

PMID: 28139082

Retina. 2017 Jan 30. [Epub ahead of print]

RISK FOR LOW VISUAL ACUITY AFTER 1 AND 2 YEARS OF TREATMENT WITH RANIBIZUMAB OR BEVACIZUMAB FOR PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Westborg I, Albrecht S, Rosso A.

PURPOSE: To investigate how patients with neovascular age-related macular degeneration treated with ranibizumab or bevacizumab respond to treatment in daily clinical practice.

METHODS: Data from the Swedish Macula Register on the treatment received by 3,912 patients during 2011 to 2014 is reported. Patients' characteristics at the first visit, visual acuity, number of injections, and reason for terminating the treatment if applicable are discussed. Furthermore, the risk of having poor vision (visual acuity under 60 Early Treatment Diabetes Retinopathy Study letters or approximately 20/60 Snellen) is calculated for the treated eye after 1 year and 2 years.

RESULTS: The treatment outcome depends on the visual acuity at the first visit. For patients with visual acuity more than 60 letters, the risk of having a visual acuity lower than 60 letters after 1 year or 2 years of treatment is approximately 20%. However, for patients with low visual acuity at diagnosis (fewer than 60 letters), the risk is approximately 60%. The risk of having a visual acuity lower than 60 letters does not depend on the choice of treatment drug.

CONCLUSION: Treatment with anti-vascular endothelial growth factor intravitreal injections mainly maintains the visual acuity level, and only approximately 20% and 40% of the patients required vision rehabilitation after 1 year and 2 years, respectively.

PMID: 28141748

J Curr Glaucoma Pract. 2017 Jan-Apr;11(1):3-7. Epub 2017 Jan 18.

Incidence of Intraocular Pressure Elevation following Intravitreal Ranibizumab (Lucentis) for Age-related Macular Degeneration.

Reis GM, Grigg J, Chua B, Lee A, Lim R, Higgins R, Martins A, Goldberg I, Clement CI.

AIM: The aim of this article is to evaluate the rate of patients developing sustained elevated intraocular pressure (IOP) after ranibizumab (Lucentis) intravitreal (IVT) injections.

DESIGN: This is a retrospective study.

PARTICIPANTS: Charts of 192 consecutive patients receiving Lucentis for age-related macular degeneration (AMD) were retrospectively reviewed.

MATERIALS AND METHODS: We enrolled patients with at least two IOP measurements between injections. Elevated IOP was defined as >21 mm Hg with an increase of at least 20% from baseline. Noninjected contralateral eyes of the same patient cohort were used as control.

MAIN OUTCOME MEASURES: Primary outcome was defined as elevated IOP. Secondary outcomes were presence and type of glaucoma, number of injections, and time to IOP elevation.

RESULTS: Elevated IOP occurred at a significantly higher rate in eyes receiving IVT ranibizumab (7.47%; n = 9) compared with control (0.93%; n = 1). Patients with preexisting glaucoma or ocular hypertension (OHT) were more likely to develop elevated IOP after IVT ranibizumab injection.

CONCLUSION: Intravitreal ranibizumab injections are associated with sustained IOP elevation in some eyes.

PMID: 28138211 PMCID: PMC5263879

Int J Ophthalmol. 2017 Jan 18;10(1):91-97. eCollection 2017.

Efficacy and safety of ranibizumab for wet age-related macular degeneration in Chinese patients.

Qi HJ, Li XX, Zhang JY, Zhao MW.

AIM: To evaluate the clinical efficacy and safety of ranibizumab for wet age-related macular degeneration (wAMD) in Chinese patients and to determine the mean number of injections administered over one year of follow-up.

METHODS: This single centre, retrospective observational case series study included data from 121 patients with wAMD (121 eyes) who were diagnosed by indirect ophthalmoscopy, fluorescence fundus angiography (FFA), indocyanine green angiography, and optical coherence tomography. Ranibizumab was injected into the vitreous cavities once per month for 3mo and as needed afterwards. Changes in visual acuity and central foveal thickness (CFT) during the follow-up period were compared, and the mean number of injections over the year was calculated. Patients with one or more adverse events related to the drugs and injections were recorded for further adverse events analysis.

RESULTS: The study population included 70 males and 51 females aged between 50 and 87y (mean: 71.32±9.41y). The mean number of injections over the first year was 5±1 (range: 3-9). The mean best-corrected visual acuity by Early Treatment Diabetic Retinopathy Study increased from 43.2±19.3 (95%CI: 39.8-46.7) at baseline to 51.7±20.1 (95%CI: 48.1-55.3), and central foveal thickness (CFT) decreased from 526.5±277.0 μm (95%CI: 476.6-576.4) to 258.2±161.6 μm (95%CI: 229.2-287.3) at 12mo. The differences were statistically significant (P<0.001). Visual acuity significantly improved in 34.1% of the patients (38 eyes), stabilized in 66.1% of the patients (80 eyes), and significantly decreased in 2.5% of the patients (3 eyes). CFT at baseline was an independent risk factor of decreased CFT and increased visual acuity. None of the patients had severe adverse events during the follow-up period.

CONCLUSION: Ranibizumab can effectively control disease progression and improve visual acuity in patients with wAMD. The disease conditions of most patients stabilized after a one-year treatment with an average of 5 injections.

PMID: 28149783 PMCID: PMC5225355

Int J Ophthalmol. 2017 Jan 18;10(1):81-90. eCollection 2017.

Six-year outcomes in neovascular age-related macular degeneration with ranibizumab.

Jacob J, Brié H, Leys A, Levecq L, Mergaerts F, Denhaerynck K, Vancayzeele S, Van Craeyveld E, Abraham I, MacDonald K.

AIM: To evaluate the outcomes of ≥6y ranibizumab therapy in neovascular age-related macular degeneration (AMD).

METHODS: HELIX was a retrospective, observational effectiveness study using medical records of patients treated in three clinics in Belgium. Patients had neovascular AMD and were initially treated with intravitreal ranibizumab (0.5 mg) between November 1, 2007 and October 31, 2008, had ≥6y of data available, and were treated on an ongoing, as-needed basis. Outcomes included best-corrected visual acuity (BCVA) and central retinal thickness (CRT).

RESULTS: The sample consisted of 88 eyes from 69 patients. Mean age was 76.4±6.5y, most patients were female (62.3%). Most eyes (62.5%) were treatment-naive, 33 previously treated eyes had received predominantly other anti-vascular endothelial growth factor agents and verteporfin. Mean baseline BCVA was 57.4±12.7 ETDRS letters and CRT was 291.5±86.1 μm. On average, patients received 20.6±11.9 ranibizumab injections over the ≥6y. Intervals between injections were on average 12.7±16.1wk. Mean change in BCVA from baseline to last observation for the sample was less than one letter (-0.9±17.3 letters), with an average loss of -3.2±15.6 letters in previously treated eyes versus a gain of 0.6±18.4 letters in treatment-naïve eyes. When considering a loss of <15 letters over 6y as stabilization of disease, 75.9%

of all eyes showed a positive (improvement or stabilization) outcome. Mean change in CRT from baseline to last observation for the sample was -26.9±148.4 µm with the greatest reduction observed in treatment-naive eyes.

CONCLUSION: This retrospective study of 69 neovascular AMD patients treated for ≥6y with ranibizumab demonstrates long-term visual stabilization. In light of the natural evolution of the disease, these data confirm that ranibizumab is effective long-term under real-world conditions of heterogeneity of patients, clinicians, and centers.

PMID: 28149782 PMCID: PMC5225354

Invest Ophthalmol Vis Sci. 2017 Feb 1;58(2):797-800.

Functional and Anatomical Outcomes in Patients With Serous Retinal Detachment in Diabetic Macular Edema Treated With Ranibizumab.

Giocanti-Aurégan A, Hrarat L, Qu LM, Sarda V, Boubaya M, Levy V, Chaine G, Fajnkuchen F.

PURPOSE: To assess the effect of serous retinal detachment (SRD) on functional and anatomical outcomes in ranibizumab-treated patients with diabetic macular edema (DME).

METHODS: All consecutive ranibizumab-treated patients with SRD were included in this retrospective study. For each patient with SRD, a patient without SRD with the same baseline best-corrected visual acuity (BCVA) was randomly included for adjustment on their baseline BCVA. All patients with SRD were included in group 1 (G1) and those without SRD in G2. The primary endpoint was the mean change in BCVA between baseline and month 12 (M12). Secondary endpoints were the mean change in central retinal thickness (CRT) between baseline and M12, injection number, and proportion of patients who gained/lost ≥15 letters.

RESULTS: Seventy-eight eyes were included, 39 in each group. Baseline BCVA was similar in both groups (45.2 and 45.3 letters). Mean change in BCVA between baseline and M12 was not statistically different: 11 ± 12 letters in G1 and 12 ± 13 letters in G2 (P = 0.78). Baseline CRT was 650 ± 130 µm in G1 and 480 ± 79 µm in G2. Mean change in CRT was -235 ± 170 µm in G1 and -130 ± 96 µm in G2 (P = 0.013). Patients received 5.2 and 5.5 injections in G1 and G2 (P = 0.46). In group 1, 38.5% and 2.6% of patients respectively gained and lost ≥15 letters versus 41% (P = 0.1) and 5.1% (P = 0.1) in G2.

CONCLUSIONS: Similar BCVA gains were observed regardless of the presence of SRD. The higher visual gain usually observed in DME with SRD could be associated with a lower baseline BCVA.

PMID: 28152140

Other treatment & diagnosis

Retina. 2017 Jan 30. [Epub ahead of print]

THICKNESS OF THE MACULA, RETINAL NERVE FIBER LAYER, AND GANGLION CELL-INNER PLEXIFORM LAYER IN THE AGE-RELATED MACULAR DEGENERATION: The Repeatability Study of Spectral Domain Optical Coherence Tomography.

Shin IH, Lee WH, Lee JJ, Jo YJ, Kim JY.

PURPOSE: To determine the repeatability of measuring the thickness of the central macula, retinal nerve fiber layer, and ganglion cell-inner plexiform layer (GC-IPL) using spectral domain optical coherence tomography (Cirrus HD-OCT) in eyes with age-related macular degeneration.

METHODS: One hundred and thirty-four eyes were included. The measurement repeatability was assessed

by an experienced examiner who performed two consecutive measurements using a 512 × 128 macular cube scan and a 200 × 200 optic disk cube scan. To assess changes in macular morphology in patients with age-related macular degeneration, the patients were divided into the following three groups according to the central macular thickness (CMT): A group, CMT < 200 μm; B group, 200 μm ≤ CMT < 300 μm; and C group, CMT > 300 μm.

RESULTS: Measurement repeatability was assessed using test-retest variability, a coefficient of variation, and an intraclass correlation coefficient. The mean measurement repeatability for the central macular, retinal nerve fiber layer, and GC-IPL thickness was high in the B group. The mean measurement repeatability for both the central macula and retinal nerve fiber layer thickness was high in the A and C groups, but was lower for the GC-IPL thickness. The measurement repeatability for GC-IPL thickness was high in the B group, but low in the A group and in the C group.

CONCLUSION: The automated measurement repeatability for GC-IPL thickness was significantly lower in patients with age-related macular degeneration with out of normal CMT range. The effect of changes in macular morphology should be considered when analyzing GC-IPL thicknesses in a variety of ocular diseases.

PMID: 28141749

Retina. 2017 Feb 1. [Epub ahead of print]

ANGIOPOIETIN-LIKE 4 CORRELATES WITH RESPONSE TO INTRAVITREAL RANIBIZUMAB INJECTIONS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Kim JH, Shin JP, Kim IT, Park DH.

PURPOSE: To investigate whether the aqueous angiopoietin-like 4 (ANGPTL4) level correlates with clinical features in neovascular age-related macular degeneration (AMD).

METHODS: The control and study groups consisted of all consecutive patients who received senile cataract surgery or intravitreal ranibizumab injection for treatment-naïve neovascular AMD, respectively. The AMD group received 3 monthly ranibizumab injections followed by monthly pro re nata for at least 12 months. Aqueous ANGPTL4 and vascular endothelial growth factor (VEGF) were measured at baseline and 4 weeks after the first injection. In the AMD group, best-corrected visual acuity, lesion area by fluorescein angiography, and central subfield thickness were measured at baseline and at 12 months.

RESULTS: The AMD group (30 eyes) had higher baseline aqueous ANGPTL4 and VEGF levels than those of the control group (32 eyes) (both P < 0.001). Four weeks after the first injection, VEGF in the patients with AMD had dropped significantly (P < 0.001). Baseline ANGPTL4 correlated with the lesion area at baseline and at 12 months (P < 0.05, respectively), and also correlated with the frequency of anti-VEGF injections during 12 months (P = 0.008).

CONCLUSION: Aqueous ANGPTL4 levels correlated with the lesion area and anti-VEGF treatment frequency. Angiopoietin-like 4 may be a potential diagnostic and/or therapeutic biomarker in the neovascular AMD.

PMID: 28151839

Retina. 2017 Jan 31. [Epub ahead of print]

DETAILED CHARACTERIZATION OF CHOROIDAL MORPHOLOGIC AND VASCULAR FEATURES IN AGE-RELATED MACULAR DEGENERATION AND POLYPOIDAL CHOROIDAL VASCULOPATHY.

Gupta P, Ting DS, Thakku SG, Wong TY, Cheng CY, Wong E, Mathur R, Wong D, Yeo I, Gemmy Cheung CM.

PURPOSE: To characterize and compare morphologic and vascular features of the choroid in patients with typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) and to determine if PCV subtypes can be identified based on these choroidal features.

METHODS: Choroidal features of patients with AMD and PCV recruited from the prospectively planned Asian AMD Phenotyping Study were analyzed. Patients underwent choroidal imaging using spectral-domain optical coherence tomography with enhanced depth imaging. Raw optical coherence tomographic images were loaded on a custom-written application on MATLAB that enabled delineation for detailed morphologic and vascular analyses, including the curvature of the choroid-sclera interface, number of inflection points, choroidal thickness and choroidal vascular area within the macular (6 mm centered on fovea) and foveal (1.5 mm centered on fovea) regions. An inflection point represents the contour of the choroid-sclera interface, with >1 point signaling irregular shape.

RESULTS: A total of 156 eyes of 156 patients (78 affected eyes of 78 patients with typical AMD and 78 affected eyes of 78 patients with PCV) were analyzed. Eyes with PCV had thicker baseline choroidal thickness and greater choroidal vascular area compared with those with typical AMD ($P < 0.05$); these differences were no longer significant after adjusting for age and hypertension ($P > 0.05$). Typical PCV subtype with choroidal thickness of ≥257 μm had significantly greater choroidal vascular area at macular (mean difference = 0.054 mm; $P < 0.001$) and foveal (mean difference = 0.199 mm; $P < 0.001$) regions compared with eyes with typical AMD. However, eyes with PCV without thick choroid had similar choroidal vascular area as eyes with typical AMD.

CONCLUSION: Based on the choroidal vascular features, two subtypes of PCV can be classified: typical PCV with increased choroid vascularity and polypoidal choroidal neovascularization with low choroidal vascularity. These data provide further understanding of different AMD and PCV subtypes.

PMID: 28145972

JAAPA. 2017 Feb 1. [Epub ahead of print]

Recognizing age-related macular degeneration in primary care.

Cunningham J.

Abstract: Age-related macular degeneration (AMD) is a disabling condition that results in central vision loss and significantly affects the quality of life for the growing population of older adults. Primary care providers play a vital role in early recognition of disease. This article reviews the risk factors, symptoms, physical examination findings, and management of AMD. Although there is no cure at this time, early referral and treatment may prevent some patients from progressing to complete.

PMID: 28151737

Graefes Arch Clin Exp Ophthalmol. 2017 Feb 1. [Epub ahead of print]

Choroidal structures in polypoidal choroidal vasculopathy, neovascular age-related maculopathy, and healthy eyes determined by binarization of swept source optical coherence tomographic images.

Bakthavatsalam M, Ng DS, Lai FH, Tang FY, Brelén ME, Tsang CW, Lai TY, Cheung CY.

PURPOSE: To evaluate quantitatively the choroidal vascularity in polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (AMD) patients compared to healthy controls.

METHODS: All eyes underwent swept source optical coherence tomography (OCT), and choroidal images were binarized into blood vessels lumen and stroma. The choroidal vascular index (CVI) was defined as the ratio of luminal area (LA) over total choroidal area of the subfoveal region with a width of 1500 μm.

RESULTS: The study included 73 patients with neovascular AMD or PCV with mean ± standard deviation (SD) age of 71.8 ± 9.3 years, which was older than the mean age of 65.1 ± 10.8 years of 72 healthy eyes from control group ($p < 0.01$). The 44 PCV eyes had significantly higher mean SFCT of 214.23 ± 95.21 μm than neovascular AMD eyes (172.74 ± 96.48 μm, $p = 0.03$) and greater luminal area (0.23 ± 0.09 mm2 vs. 0.19 ± 0.08 mm2, $p = 0.05$). After adjusting for age, axial length, and gender in multivariate regression analysis, the SFCT of PCV and neovascular AMD eyes were not significantly different from healthy eyes (195.55 ± 93.11 μm), but the CVI of both PCV (64.94 ± 5.43%, $p = 0.01$) and neovascular AMD (62.54 ± 5.57%, $p = <0.01$) were significantly lower than control (68.53 ± 5.91%).

CONCLUSION: Despite physiological changes of choroidal vasculature due to aging, the choroidal morphology is different in PCV, neovascular AMD and healthy eyes, which has implication on disease pathogenesis.

PMID: 28150038

Ophthalmologica. 2017 Feb 3. [Epub ahead of print]

The Blood-Retinal Barrier in the Management of Retinal Disease: EURETINA Award Lecture.

Cunha-Vaz J.

Abstract: Retinal diseases are the main causes of blindness in the Western world. Diabetic retinopathy and age-related macular degeneration continue to increase in prevalence and as main causes of vision loss. Intravitreal anti-VEGF and steroid injections have raised new expectations for their successful treatment. These agents act by stabilizing the blood-retinal barrier (BRB). Our group defined the BRB by identifying for the first time the tight junctions that unite retinal endothelial cells and are the basis for the inner BRB, an observation later confirmed in retinal pigment epithelial cells and in brain vessels. A major role of active transport processes was also identified. Today, the BRB is understood to play a fundamental role in retinal function in both health and disease. Retinal edema, an ubiquitous manifestation of retinal disease, is directly associated with breakdown of the BRB and with vision loss. In its most common form (i.e., vasogenic edema), due to breakdown of the BRB, Starling's law of capillary filtration may be used to interpret the mechanisms of fluid accumulation in the retina. The main factors involved in the development of retinal edema are BRB permeability, capillary hydrostatic pressure, tissue hydrostatic pressure, tissue osmotic pressure, and plasma osmotic pressure. In the clinical environment, breakdown of the BRB has been identified by fluorescein angiography and vitreous fluorometry, requiring the intravenous administration of fluorescein. An OCT-based method, OCT-Leakage, recently introduced by our group is capable of noninvasively identifying and quantifying sites of alteration of the BRB by mapping areas of lower-than-normal optical reflectivity, thus reflecting changes in the retinal extracellular fluid. We found good correspondence between the location of increased areas of low optical reflectivity identified by OCT-Leakage and the main sites of leakage on fluorescein angiography. Furthermore, with OCT-Leakage the areas of abnormal fluid accumulation can be identified in specific retinal layers, clearly offering more information than previously obtained with fluorescein angiography. OCT angiography has become available, replacing much of the information yielded by fluorescein angiography in a noninvasive manner. However, OCT angiography cannot visualize the leakage, i.e., the alteration of the BRB. OCT-Leakage is able to identify the locations of increases in extracellular fluid in the different layers of the retina. The complementarity of these 2 methods is of potential great interest for the diagnosis and management of several retinal diseases in which the presence and amount of fluid, as a marker of severity and activity, is paramount to treatment and management decisions in clinical practice.

PMID: 28152535

J Clin Nurs. 2017 Feb 2. [Epub ahead of print]

Nursing actions that create a sense of good nursing care in patients with Wet Age-related Macular Degeneration.

Emsfors Å, Christensson L, Elgán C.

BACKGROUND: People who suffer from wet age-related macular degeneration (AMD) risk central vision loss. Treatment with anti-VEGF is the only available option at present that preserves vision and no definitive cure currently exists. Patients feel that they are compelled to accept this treatment because they might otherwise become blind.

AIM: To identify and describe nursing actions performed by nurses that create a sense of good nursing care in patients with wet (AMD).

DESIGN AND METHODS: An explorative and descriptive qualitative design based on the critical incident technique was implemented to interview 16 Swedish patients who all suffered from wet AMD and who had received intravitreal treatment.

RESULTS: Two main areas of good nursing care were identified: "Being perceived as anindividual" and "Being empowered". The first area was divided into two categories: being respectful and being engaged. Being respectful was observed when nurses had a benevolent attitude towards their patients and answered questions kindly and politely. Patients saw themselves as individuals when nurses were available for conversation and focused on them. The second area was divided into two categories: encouraging participation and creating confidence. Encouraging participation refers to when nurses provided information continuously. Nurses instilled confidence and trust in their patients by keeping promises and by being honest.

CONCLUSIONS: A respectful interaction between patients and caregivers is necessary for patients to obtain beneficial healthcare. This article is protected by copyright. All rights reserved.

PMID: 28152206

Pathogenesis

Indian J Clin Biochem. 2017 Mar;32(1):3-8. Epub 2016 Mar 8.

Role of Lipids in Retinal Vascular and Macular Disorders.

Prakash G, Agrawal R, Natung T.

Abstract: Retinal diseases are significant by increasing problem in every part of the world. While excellent treatment has emerged for various retinal diseases, treatment for early disease is lacking due to an incomplete understanding of all molecular events. With aging, there is a striking accumulation of neutral lipids in Bruch's membrane. These neutral lipids leads to the creation of a lipid wall at the same locations where drusen and basal linear deposit, pathognomonic lesions of Age-related macular degeneration, subsequently form. High lipid levels are also known to cause endothelial dysfunction, an important factor in the pathogenesis of Diabetic Retinopathy. Various studies suggest that 20 % of Retinal Vascular Occlusion is connected to hyperlipidemia. Biochemical studies have implicated mutation in gene encoding ABCA4, a lipid transporter in pathogenesis of Stargardt disease. This article reviews how systemic and local production of lipids might contribute to the pathogenesis of above retinal disorders.

PMID: 28149006 PMCID: PMC5247360

Discov Med. 2016 Dec;22(123):337-349.

An emerging role of Alu RNA in geographic atrophy pathogenesis: the implication for novel therapeutic strategies.

Mao X, Fang W, Liu Q.

Abstract: It is generally accepted that geographic atrophy (GA), a currently untreatable advanced form of age-related macular degeneration (AMD), is a multifactorial disease resulting in gradual and permanent blindness. Various risk factors are demonstrated to be responsible for its pathogenesis, such as aging, light exposure, and smoking. Molecular components associated with those risk factors form a complex and interwoven network at the confluence of inflammation, highlighting the significance of inflammasome activation in GA progression. Recently, a new type of modification in AMD microenvironment has been discovered, other than extensively-studied complement dysregulation, lipofuscin deposit, and oxidative by-products, to activate inflammasome. The accumulation of Alu RNA, resulting from DICER1 deficiency, is shown capable of triggering the activation of NLRP3 inflammasome and causing caspase-8-activated apoptosis in an IL-18/MyD88-dependent manner, which provides a new source of evidence for the interplay between cell death and inflammasome. In this review, we lay the emphasis on the mechanism by which Alu RNA activates NLRP3 inflammasome and downstream apoptotic proteins, and on its clinical relevance to GA and potential therapeutic approaches. We also point out several possible crosstalks among inflammasome and different acts of cell death which remain to be further investigated in Alu RNA-induced RPE degeneration.

PMID: 28147216

Mol Ther. 2017 Jan 28. [Epub ahead of print]

Cone Genesis Tracing by the Chrnb4-EGFP Mouse Line: Evidences of Cellular Material Fusion after Cone Precursor Transplantation.

Decembrini S, Martin C, Sennlaub F, Chemtob S, Biel M, Samardzija M, Moulin A, Behar-Cohen F, Arsenijevic Y.

Abstract: The cone function is essential to mediate high visual acuity, color vision, and daylight vision. Inherited cone dystrophies and age-related macular degeneration affect a substantial percentage of the world population. To identify and isolate the most competent cells for transplantation and integration into the retina, cone tracing during development would be an important added value. To that aim, the Chrnb4-EGFP mouse line was characterized throughout retinogenesis. It revealed a sub-population of early retinal progenitors expressing the reporter gene that is progressively restricted to mature cones during retina development. The presence of the native CHRNB4 protein was confirmed in EGFP-positive cells, and it presents a similar pattern in the human retina. Sub-retinal transplantations of distinct subpopulations of Chrnb4-EGFP-expressing cells revealed the embryonic day 15.5 high-EGFP population the most efficient cells to interact with host retinas to provoke the appearance of EGFP-positive cones in the photoreceptor layer. Importantly, transplantations into the DsRed retinas revealed material exchanges between donor and host retinas, as >80% of transplanted EGFP-positive cones also were DsRed positive. Whether this cell material fusion is of significant therapeutic advantage requires further thorough investigations. The Chrnb4-EGFP mouse line definitely opens new research perspectives in cone genesis and retina repair.

PMID: 28143742

Autoimmun Rev. 2017 Jan 27. [Epub ahead of print]

Can innate and autoimmune reactivity forecast early and advance stages of age-related macular degeneration?

Adamus G.

Abstract: Age-related macular degeneration (AMD) is a major cause of central vision loss in persons over 55years of age in developed countries. AMD is a complex disease in which genetic, environmental and inflammatory factors influence its onset and progression. Elevation in serum anti-retinal autoantibodies, plasma and local activation of complement proteins of the alternative pathway, and increase in secretion of proinflammatory cytokines have been seen over the course of disease. Genetic studies of AMD patients

confirmed that genetic variants affecting the alternative complement pathway have a major influence on AMD risk. Because the heterogeneity of this disease there is no sufficient strategy to identify the disease onset and progression sole based eye examination, thus identification of reliable serological biomarkers for diagnosis, prognosis and response to treatment by sampling patient's blood. This review provides an outline of the current knowledge on possible serological (autoantibodies, complement factors, cytokines, chemokines) and related genetic biomarkers relevant to the pathology of AMD, and discusses their application for prediction of disease activity and prognosis in AMD.

PMID: 28137479

Epidemiology

Int J Ophthalmol. 2017 Jan 18;10(1):140-147. eCollection 2017.

Population-based survey of prevalence, causes, and risk factors for blindness and visual impairment in an aging Chinese metropolitan population.

Hu JY, Yan L, Chen YD, Du XH, Li TT, Liu DA, Xu DH, Huang YM, Wu Q.

AIM: To assess the prevalence, causes, and risk factors for blindness and visual impairment among elderly (≥60 years of age) Chinese people in a metropolitan area of Shanghai, China.

METHODS: Random cluster sampling was conducted to identify participants among residents ≥60 years of age living in the Xietu Block, Xuhui District, Shanghai, China. Presenting visual acuity (PVA) and best-corrected visual acuity (BCVA) were checked by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual chart. All eligible participants underwent a comprehensive eye examination. Blindness and visual impairment were defined according to World Health Organization (WHO) criteria.

RESULTS: A total of 4190 persons (1688 men and 2502 women) participated in the study, and the response rate was 91.1%. Based on PVA, the prevalence of blindness was 1.1% and that of visual impairment was 7.6%. Based on BCVA, the prevalence of blindness and visual impairment decreased to 0.9% and 3.9%, respectively. Older (≥80 years of age) women, with low educational levels and smoking habits, exhibited a significantly greater chance for blindness and visual impairment than did those with high educational levels and no smoking habits ($P<0.05$). Based on PVA and BCVA, the main causes of blindness were cataract, myopic maculopathy, and age-related macular degeneration (AMD).

CONCLUSION: Our findings help to identify the population in need of intervention, to highlight the need for additional eye healthcare services in urban China.

PMID: 28149791 PMCID: PMC5225363

Ophthalmic Epidemiol. 2017 Jan 31:1-12. [Epub ahead of print]

Age-Related Macular Degeneration and Mortality: A Systematic Review and Meta-Analysis.

McGuinness MB, Karahalios A, Finger RP, Guymer RH, Simpson JA.

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision loss in older adults. Evidence for an association between AMD and mortality remains inconclusive despite evidence for an association with cardiovascular and inflammatory diseases. We aim to compare all-cause, cardiovascular and cancer mortality between those with early or late AMD and control study participants.

METHODS: A protocol was registered at PROSPERO (CRD42015020622). A systematic search of Medline (Ovid), PubMed, and Embase (Ovid) was conducted on 6 June 2015. Reference lists from identified studies and four clinical trial registries were searched for additional studies. Participants were required to be over the age of 40 years, and AMD status must have been objectively assessed. The Risk Of Bias In Non-

Randomized Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias. Random-effects meta-analyses were performed.

RESULTS: A total of 12 reports from 10 studies were included in the meta-analysis. Late AMD was associated with elevated rates of all-cause (nine studies, hazard ratio (HR) 1.20, 95% confidence interval, CI, 1.02-1.41) and cardiovascular mortality (six studies, HR 1.46, 95% CI 1.13-1.98), but early AMD was not (all-cause mortality, 10 studies, HR 1.06, 95% CI 0.98-1.14; cardiovascular mortality, five studies, HR 1.12, 95% CI 0.96-1.31). There was no evidence of an association between early or late AMD and cancer mortality (early AMD, three studies, HR 1.17, 95% CI 0.78-1.75; late AMD, three studies, HR 1.01, 95% CI 0.77-1.33).

CONCLUSION: Late AMD is associated with increased rates of all-cause and cardiovascular mortality, suggesting shared pathways between late AMD and systemic disease.

PMID: 28139151

Genetics

Sci Rep. 2017 Jan 31;7:41835.

Simple and complex retinal dystrophies are associated with profoundly different disease networks.

Kiel C, Lastrucci C, Luthert PJ, Serrano L.

Abstract: Retinopathies are a group of monogenetic or complex retinal diseases associated with high unmet medical need. Monogenic disorders are caused by rare genetic variation and usually arise early in life. Other diseases, such as age-related macular degeneration (AMD), develop late in life and are considered to be of complex origin as they develop from a combination of genetic, ageing, environmental and lifestyle risk factors. Here, we contrast the underlying disease networks and pathological mechanisms of monogenic as opposed to complex retinopathies, using AMD as an example of the latter. We show that, surprisingly, genes associated with the different forms of retinopathies in general do not overlap despite their overlapping retinal phenotypes. Further, AMD risk genes participate in multiple networks with interaction partners that link to different ubiquitous pathways affecting general tissue integrity and homeostasis. Thus AMD most likely represents an endophenotype with differing underlying pathogenesis in different subjects. Localising these pathomechanisms and processes within and across different retinal anatomical compartments provides a novel representation of AMD that may be extended to complex disease in general. This approach may generate improved treatment options that target multiple processes with the aim of restoring tissue homeostasis and maintaining vision.

PMID: 28139756 PMCID: PMC5282568

Diet, lifestyle and low vision

Transl Vis Sci Technol. 2017 Jan 20;6(1):4.eCollection 2017.

Feasibility of Use of a Mobile Application for Nutrition Assessment Pertinent to Age-Related Macular Degeneration (MANAGER2).

Ali ZC, Silvioli R, Rajai A, Aslam TM.

PURPOSE: This is a feasibility study assessing use of a mobile phone application (app.) to measure nutrient intake relevant to age-related macular degeneration (AMD).

METHODS: Inclusion criteria were age over 40 and ownership of a smartphone. Participants included healthy volunteers and those with ophthalmic conditions. They were asked to record daily food intake for a minimum of 3 days in a paper food diary and the app. A dietician analyzed the food diaries, and an

independent researcher analyzed data from the app. Average daily intake of nutrients relevant to AMD (docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], vitamins E and C, copper, zinc, and lutein + zeaxanthin) were calculated for both and then compared.

RESULTS: A total of 54 participants completed the app. and food diary. Male-to-female ratio was 7:20. Median (interquartile range [IQR]) age was 57 years (45.3-68.7 years). More than 90% of all values were within the limits of agreement for all micronutrients. Bland Altman agreement plots demonstrated clinically acceptable agreement between the two systems of analysis.

CONCLUSIONS: This study has demonstrated that the app. is a feasible alternative to the food diary for assessing nutrient intake relevant to AMD. Further studies are suggested to assess long-term adherence and effect of the app. on nutrient intake in AMD patients.

TRANSLATIONAL RELEVANCE:

After smoking, nutritional modification is the key modifiable factor to reduce incidence of AMD. Use of the app. could be an efficient, easy way to monitor and improve dietary intake of required nutrients pertinent to AMD.

PMID: 28138414 PMCID: PMC5270627