RETINA ROUNDUP

December 2024

RETINA ROUND UP ARTICLES – DECEMBER 2024

1. **COMPLEX MACULAR HOLE CLOSURE BY TEMPORAL INTERNAL LIMITING MEMBRANE FLAP WITHOUT ENDOTAMPONADE**

Szeto SKH, Yu AHY, Tsang CW, Mohamed S, Chen LJ, Lai TYY. Complex macular hole closure by temporal internal limiting membrane flap without endotamponade. Retina. 2024 Nov 1;44(11):1915-1922. doi: 10.1097/IAE.0000000000004201. PMID: 39436300.

Purpose:

To evaluate the safety, efficacy, and imaging features of a novel surgical technique without endotamponade in repairing complex macular hole (MH).

Methods:

Retrospective review of consecutive cases with complex MH underwent pars plana vitrectomy with temporal internal limiting membrane flap, which was stabilized using perfluorocarbon liquid and viscoelastics. At the conclusion of surgery, perfluorocarbon liquid was removed, and no endotamponade agent would be used. Complex MH was defined as a basal linear diameter of ≥400 μ m and/or associated with high myopia. Visual acuity, pattern of MH closure on optical coherence tomography, formation of epiretinal membrane, and operative complications were reported.

Results:

Twenty-four eyes were included, and the mean basal linear diameter was 988.3 μ m. MH closure was achieved in 24 (100%), of which, 8 (33%) achieved type 1A closure. The mean postoperative logarithm of the minimum angle of resolution visual acuity improved from 0.93 at baseline to 0.74, 0.51, 0.55, and 0.52 at 1-month, 3-month, 6-month, and last follow-up, respectively. Foveal gliosis was observed in 3 eyes (12.5%), and 10 (41.7%) developed nasal epiretinal membrane. One eye developed vitreous hemorrhage, which resolved spontaneously.

Conclusion:

This novel surgical technique that requires no endotamponade is effective in achieving complex MH closure. A substantial proportion of patients developed epiretinal membrane, and its clinical significance requires further investigation.

2. **LEVODOPA IS ASSOCIATED WITH REDUCED DEVELOPMENT OF NEW-ONSET GEOGRAPHIC ATROPHY IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION**

Background:

Geographic atrophy (GA) is a significant cause of vision loss in patients with age-related macular degeneration (AMD). Current treatments are limited to anti-complement drugs, which have limited efficacy to delay progression with significant risk of complications. Levodopa (L-DOPA) is a byproduct of melanin synthesis that is associated with reduced development of neovascular AMD. In this study, we determined if L-DOPA was associated with a reduced likelihood of new-onset GA.

Methods:

We performed a retrospective analysis in the Vestrum Health Retina Database. We included eyes with non-neovascular AMD without GA and 1-5 years of follow-up. Eyes were divided into two groups. Exposed to L-DOPA before or on the date of non-neovascular AMD without GA diagnosis, and eyes not exposed to L-DOPA. We extracted age, sex, AREDS2 status, dry AMD stage, smoking history, and conversion rate to GA at years 1 through 5. Propensity score matching was used to match L-DOPA and control groups. Cox proportional hazard regression, adjusting for age, sex, AMD severity, AREDS2 use, smoking status, and L-DOPA use was employed to calculate hazard ratios for new-onset GA detection.

Results:

We identified 112,089 control and 844 L-DOPA exposed eyes with non-neovascular AMD without GA. After propensity score matching, 2532 control and 844 L-DOPA exposed eyes remained that were well-matched for age, sex, AMD severity, AREDS2 use, and smoking status. We found that L-DOPA exposure was associated with a significantly reduced likelihood (HR = 0.68, 95% CI: 0.48-0.95, P = 0.025) of new-onset GA detection.

Conclusion:

L-DOPA use was associated with reduced detection of new-onset GA.

3. **P SCORE: A REFERENCE IMAGE-BASED CLINICAL GRADING SCALE FOR VASCULAR CHANGE IN RETINOPATHY OF PREMATURITY**

Binenbaum G, Stahl A, Coyner AS, He J, Ying GS, Ostmo S, Chan RVP, Toth C, Vinekar A, Campbell JP; International Classification of Retinopathy of Prematurity Committee. P Score: A Reference Image-Based Clinical Grading Scale for Vascular Change in Retinopathy of Prematurity. Ophthalmology. 2024 Nov;131(11):1297-1303. doi: 10.1016/j.ophtha.2024.05.019. Epub 2024 May 23. PMID: 38795976; PMCID: PMC11499040.

Purpose:

The International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), acknowledged that plus-like retinopathy of prematurity (ROP) vascular changes occurs along a spectrum. Historically, clinician-experts demonstrate variable agreement for plus diagnosis. We developed a 9-photograph reference image set for grading plus-like changes and compared intergrader agreement of the set with standard grading with no plus, preplus, and plus disease.

Methods:

The development set included 34 international ICROP3 committee members. The validation set included 30 ophthalmologists with ROP expertise (15 ICROP3 committee members and 15 non-ICROP3 members). Retinal photographic grading and expert consensus opinion where in study participants graded 150 fundus photographs 2 ways, separated by a 1-week washout period: (1) no plus, preplus, or plus disease and (2) choosing the closest P score image. Main Outcome Measure was Intergrader agreement measured by intraclass correlation coefficient.

Results:

Intergrader agreement was higher using the P score (intraclass correlation coefficient, 0.75; 95% confidence interval, 0.71–0.79) than no plus, preplus, or plus disease (intraclass correlation coefficient, 0.67; 95% confidence interval, 0.62–0.72). Mean ± standard deviation P scores for images with mode gradings of no plus, preplus, and plus disease were 2.5 ± 0.7, 4.8 ± 0.8, and 7.4 ± 0.8, respectively.

Conclusions:

Intergrader agreement of plus-like vascular change in ROP using the P score is high. We now incorporate this 9-image reference set into ICROP3 for use in clinician daily practice alongside zone, stage, and plus assessment. P score is not yet meant to replace plus diagnosis for treatment decisions, but its use at our institutions has permitted better comparison between examinations for progression and regression, communication between examiners, and documentation of vascular change without fundus imaging. P score also could provide more detailed ROP classification for clinical trials, consistent with the spectrum of plus-like change that is now formally part of the International Classification of Retinopathy of Prematurity.

4. **PARACENTRAL ACUTE MIDDLE MACULOPATHY AND RISK OF CARDIOVASCULAR DISEASE, STROKE, AND DEATH: A LONGITUDINAL STUDY**

Limoli C, Raja LD, Wagner SK, Patel PJ, Nicholson L, Bolz M, Vujosevic S, Nucci P, Keane PA, Khalid H, Huemer J. Paracentral Acute Middle Maculopathy and Risk of Cardiovascular Disease, Stroke, and Death: A Longitudinal Study. Am J Ophthalmol. 2024 Nov;267:286-292. doi: 10.1016/j.ajo.2024.08.005. Epub 2024 Aug 21. PMID: 39154925.

Purpose:

To evaluate the risk of acute cardiovascular events (CVE), including cardiovascular diseases, cerebrovascular diseases, and all-cause mortality in patients with paracentral acute middle maculopathy (PAMM).

Methods:

In a retrospective cohort study, we studied 43 individuals with optical coherence tomography-documented PAMM attending Moorfields Eye Hospital between January 2014 and June 2021. We excluded patients with preceding (<2 years) major adverse cardiac events. We stratified patients by age (<50 and ≥50 years) and whether associated with retinal vascular diseases (RVD) or isolated (iPAMM). We assessed risk factors, clinical characteristics, and visual prognosis of the patients. CVE risk was estimated using Kaplan-Meier curves, the log-rank test, and Cox proportional hazards regression.

Results:

In young patients with iPAMM patients (n = 12), underlying predisposing factors included six (50%) sickle cell disease and five (41.6%) others, including breakthrough bleeding in pregnancy, migraine, genetic cardiomyopathy, amphetamine use; among those with PAMM + RVD (n = 12) one (9%) had a vascular disorder, and four (44.4%) oral contraceptive use. In the older group of 20 patients, 15 (75%) had at least one coronary risk factor. During a median follow-up of 14 months (range 12-54), older subjects with iPAMM had a higher risk of developing CVE than those with PAMM + RVD (P < .001). Notably, iPAMM displayed a significantly earlier peak in peri-PAMM CVE risk compared to PAMM + RVD (median: one month, range 1-40 months vs 36 months, range 12-54 months). Relative to those with PAMM + RVD, risk of CVE was significantly higher in patients with iPAMM, adjusted for age and sex (hazard ratio: 6.37, 95% confidence interval 1.68-24.14, P = .017). No young patients experienced adverse CVE. At baseline, older iPAMM patients mean best corrected visual acuity of 0.7 (0-1.8) logarithm of the minimum angle resolution, which improved significantly to 0.2 (0-1.30) logarithm of the minimum angle resolution at the latest visit (P = .033).

Conclusions:

Young individuals with iPAMM have a higher prevalence of predisposing factors compared to those presenting with combined PAMM + RVD. Older patients with iPAMM had a higher risk of CVE than those with PAMM + RVD, especially in the peri-onset timeframe. This suggests the need for a prompt cardiovascular assessment to rule out systemic etiologies and optimize cardiovascular risk factors, in addition to ongoing ophthalmology input.

5. **ANALYZING FORMATION AND ABSORPTION OF AVASCULAR SUBRETINAL HYPERREFLECTIVE MATERIAL IN NAMD FROM OCTA-BASED INSIGHTS**

Pu J, Zhuang X, Li M, Zhang X, Su Y, He G, Hao X, Wen F. Analyzing Formation and Absorption of Avascular Subretinal Hyperreflective Material in nAMD From OCTA-Based Insights. Am J Ophthalmol. 2024 Nov;267:192-203. doi: 10.1016/j.ajo.2024.06.019. Epub 2024 Jun 23. PMID: 38914153.

Purpose:

To investigate the formation and absorption of avascular subretinal hyperreflective material (avSHRM) in neovascular age-related macular degeneration (nAMD) based on optical coherence tomography angiography (OCTA) characteristics. • DESIGN: Prospective cohort study.

Methods:

This study included patients with treatment-naive nAMD who were followed up for 3 months. Subjects were classified into an avSHRM group and a non-avSHRM group based on the presence of avSHRM at baseline. Quantitative OCTA characteristics including explant area, perimeter, vessel area, density, length, junctions, endpoints, lacunarity, maximum vessel caliber, vessel dispersion, and fractal dimension were assessed, and 3-dimensional volume and optical density ratio (ODR) of avSHRM were measured. Comparison analyses, correlation coefficients, and regression models were applied to explore factors associated with avSHRM formation and absorption.

Results:

A total of 88 eyes from 88 patients (39 female) were enrolled. Compared to the non-avSHRM group, the avSHRM group exhibited a more intricate vasculature, characterized by higher values of macular neovascularization (MNV) perimeter, vessel area, total vessel length, total number of junctions, and total number of endpoints (all $P < .05$), as well as the maximum vessel caliber ($P < .001$). In the multivariate model, which was adjusted for age, sex, and types of medications, avSHRM absorption was correlated with baseline average vessel length, maximum vessel caliber, and avSHRM ODR (standardized $\beta = 0.274$, -0.367, and -0.334; $P = .049$, .010, and .018, respectively), with an adjusted R^2 of 0.453.

Conclusions:

Quantitative OCTA measurements can be used for assessing the dynamics of avSHRM in nAMD. Patients with more complex vasculature are at higher risk for avSHRM formation. Average vessel length, maximum vessel diameter, and avSHRM ODR play a role in its absorption.

6. **AFLIBERCEPT BIOSIMILAR MYL-1701P VS REFERENCE AFLIBERCEPT IN DIABETIC MACULAR EDEMATHE INSIGHT RANDOMIZED CLINICAL TRIAL**

Bressler SB, Barve A, Ganapathi PC, Beckmann K, Apte RS, Marcus DM, Baumane K, Agarwal S, Oleksy P, Reichstein DA, Patel SS, Ernest J, Dégi R, Gupta V, Kishino G, Kamei M, Loganathan S; INSIGHT Study Group. Aflibercept Biosimilar MYL-1701P vs Reference Aflibercept in Diabetic Macular Edema: The INSIGHT Randomized Clinical Trial. JAMA Ophthalmol. 2024 Oct 1;142(10):952-960. doi: 10.1001/jamaophthalmol.2024.3458. PMID: 39264599; PMCID: PMC11393752.

Purpose:

To compare efficacy and safety of MYL-1701P, an aflibercept biosimilar, with reference aflibercept (Eylea [Regeneron]) in DME.

Methods:

This was a double-masked, randomized clinical trial that included participants at 77 centers across the US, Europe, Japan, and India. Included in the analysis were individuals 18 years and older with type 1 or type 2 diabetes with central DME and best-corrected visual acuity (BCVA) letter score of 73 to 38 in the study eye using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Study data were analyzed from October to December 2021. Formulations of MYL-1701P (0.5-mg vial) or reference aflibercept every 4 weeks for 5 consecutive intravitreal injections, followed by every 8 weeks through week 52. The primary outcome was the adjusted difference in least squares mean (SE) change from baseline BCVA letter score at week 8 with an equivalence margin of −3 to +3 letters. Secondary outcomes included change in central subfield thickness (CST), BCVA, number of injections over 52 weeks, incidence of adverse events (AEs), and antidrug antibodies (ADAs).

Results:

A total of 355 participants (mean [SD] age, 62.2 [9.2] years; 216 male [60.8%]) were randomized to MYL-1701P (179 participants [50.4%]) and aflibercept (176 participants [49.6%]). At week 8, mean (SE) change in BCVA was 6.60 (0.55) letters vs 6.56 (0.55) letters in the MYL-1701P vs aflibercept groups. The adjusted mean difference of 0.04 letters (90% CI, −1.16 to 1.24 letters) met the primary outcome. At week 8, mean (SE) change in CST was −112 (7) µm vs −124 (7) µm in the MYL-1701P vs aflibercept groups (adjusted mean difference, 12 µm; 90% CI, −3 to 26 µm). The incidence of treatment-emergent AEs in the MYL-1701P and aflibercept arms were ocular (30.9% [55 of 178] vs 29.5% [52 of 176]), serious ocular (0.6% [1 of 178] vs 1.1% [2 of 176]), nonocular (65.2% [116 of 178] vs 65.3% [115 of 176]), and serious nonocular (16.9% [30 of 178] vs 11.9% [21 of 176]). The mean (SD) total number of injections was 8.4 (2.1) vs 8.7 (1.8) in the MYL-1701P vs aflibercept groups. The incidence of treatment-induced or treatment-boosted ADAs was 2.8% (5 of 177) vs 5.7% (10 of 176) in the MYL-1701P vs aflibercept arms.

Conclusions:

Biosimilars may be lower-cost alternatives to originator biologic products, potentially offering expanded access or reduced economic burden, but have not been evaluated with aflibercept in diabetic macular edema (DME). MYL-1701P demonstrated clinical equivalence in regard to efficacy, with comparable safety and immunogenicity, to reference aflibercept. These findings support use of MLY-1701P as an alternative to reference aflibercept.

7. **LONG-TERM OUTCOMES OF ADDING LUTEIN/ZEAXANTHIN AND Ω-3 FATTY ACIDS TO THE AREDS SUPPLEMENTS ON AGE-RELATED MACULAR DEGENERATION PROGRESSION - AREDS2 REPORT 28**

Chew EY, Clemons TE, Agrón E, Domalpally A, Keenan TDL, Vitale S, Weber C, Smith DC, Christen W; AREDS2 Research Group. Long-term Outcomes of Adding Lutein/Zeaxanthin and ω-3 Fatty Acids to the AREDS Supplements on Age-Related Macular Degeneration Progression: AREDS2 Report 28. JAMA Ophthalmol. 2022 Jul 1;140(7):692-698. doi: 10.1001/jamaophthalmol.2022.1640. PMID: 35653117; PMCID: PMC9164119.

Purpose:

To assess 10-year risk of developing lung cancer and late age-related macular degeneration (AMD). Self-reported lung cancer and late AMD validated with medical records.

Methods:

This was a multicenter epidemiologic follow-up study of the AREDS2 clinical trial, conducted from December 1, 2012, to December 31, 2018. Included in the analysis were participants with bilateral or unilateral intermediate AMD for an additional 5 years after clinical trial. Eyes/participants were censored at the time of late AMD development, death, or loss to follow-up. Data were analyzed from November 2019 to March 2022. During the clinical trial, participants were randomly assigned primarily to lutein/zeaxanthin and/or ω-3 fatty acids or placebo and secondarily to no beta carotene vs beta carotene and low vs high doses of zinc. In the epidemiologic follow-up study, all participants received AREDS2 supplements with lutein/zeaxanthin, vitamins C and E, and zinc plus copper. Outcomes were assessed at 6-month telephone calls. Analyses of AMD progression and lung cancer development were conducted using proportional hazards regression and logistic regression, respectively.

Results:

This study included 3882 participants (mean [SD] baseline age, 72.0 [7.7] years; 2240 women [57.7%]) and 6351 eyes. At 10 years, the odds ratio (OR) of having lung cancer was 1.82 (95% CI, 1.06-3.12; P = .02) for those randomly assigned to beta carotene and 1.15 (95% CI, 0.79-1.66; P = .46) for lutein/zeaxanthin. The hazard ratio (HR) for progression to late AMD comparing lutein/zeaxanthin with no lutein/zeaxanthin was 0.91 (95% CI, 0.84-0.99; P = .02) and comparing ω-3 fatty acids with no ω-3 fatty acids was 1.01 (95% CI, 0.93-1.09; P = .91). When the lutein/zeaxanthin main effects analysis was restricted to those randomly assigned to beta carotene, the HR was 0.80 (95% CI, 0.68-0.92; P = .002). A direct analysis of lutein/zeaxanthin vs beta carotene showed the HR for late AMD was 0.85 (95% CI, 0.73-0.98; P = .02). The HR for low vs high zinc was 1.04 (95% CI, 0.94-1.14; P = .49), and the HR for no beta carotene vs beta carotene was 1.04 (95% CI, 0.94-1.15; P = .48).

Conclusions:

Results of this long-term epidemiologic follow-up study of the AREDS2 cohort suggest that lutein/zeaxanthin was an appropriate replacement for beta carotene in AREDS2 supplements. Beta carotene usage nearly doubled the risk of lung cancer, whereas there was no statistically significant increased risk with lutein/zeaxanthin. When compared with beta carotene, lutein/zeaxanthin had a potential beneficial association with late AMD progression.