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FEATURED ARTICLE

Choroidal Microvascular Alterations in COVID-19 Patients.

Ocular Immunology and Inflammation 2022 Apr 12

Shrivastav A, Zhou WS, Ng S, Ding J, Gilada T, Chua CH, Dutt S, Natarajan S, Agrawal R.

Objective: To evaluate alterations in the choroidal angioarchitecture of COVID-19 patients using optical Coherence Tomography (OCT) based surrogate markers.
Methods: This prospective case-control study recruited 56 COVID-19 patients (111 eyes) and 61 healthy individuals (120 eyes). Choroidal thickness (CT) and Choroidal vascularity index (CVI) were derived from OCT images using a purpose-built automated software for choroidal image segmentation. A linear mixed model with age and gender as covariates was employed to compare CVI and CT between groups.
Results: COVID-19 patients had significantly higher subfoveal (81.3um vs 86.8um, p = .02), temporal (78.8um vs 84.3um, p = .005), nasal (87.5um vs 95.1um, p = .001) and average CT (82.5um vs 88.7um, p = .001). COVID-19 patients had significantly lower subfoveal (64.0 vs 63.5, p = .02) and average CVI (63.5 vs 63.1, p = .02).
Conclusion: COVID-19 results in significantly thicker choroid with reduced relative vascularity. This may be attributable to increased vascular permeability secondary to inflammation, resulting in choroidal stromal edema.

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GENETICS

Identifying Genetic Biomarkers Predicting Response to Anti-Vascular Endothelial Growth Factor Injections in Diabetic Macular Edema.

International Journal of Molecular Science. 2022 Apr 6

Gurung RL, FitzGerald LM, Liu E, McComish BJ, Kaidonis G, Ridge B, Hewitt AW, Vote BJ, Verma N, Craig JE, Burdon KP.

Intraocular anti-vascular endothelial growth factor (VEGF) therapies are the front-line treatment for diabetic macular edema (DME); however, treatment response varies widely. This study aimed to identify genetic determinants associated with anti-VEGF treatment response in DME. We performed a genome-wide association study on 220 Australian patients with DME treated with anti-VEGF therapy, genotyped on the Illumina Global Screening Array, and imputed to the Haplotype Reference Consortium panel. The primary outcome measures were changes in central macular thickness (CMT in microns) and best-corrected visual acuity (BCVA in ETDRS letters) after 12 months. Association between single nucleotide polymorphism (SNP) genotypes and DME outcomes were evaluated by linear regression, adjusting for the first three principal components, age, baseline CMT/BCVA, duration of diabetic retinopathy, and HbA1c. Two loci reached genome-wide significance ($p < 5 \times 10\text{-}8$) for association with increased CMT: a single SNP on chromosome 6 near CASC15 (rs78466540, $p = 1.16 \times 10\text{-}9$) and a locus on chromosome 12 near RP11-116D17.1 (top SNP rs11614480, $p = 2.69 \times 10\text{-}8$). Four loci were significantly associated with reduction in BCVA: two loci on chromosome 11, downstream of NTM (top SNP rs148980760, $p = 5.30 \times 10\text{-}9$) and intronic in RP11-744N12.3 (top SNP rs57801753, $p = 1.71 \times 10\text{-}8$); one near PGAM1P1 on chromosome 5 (rs187876551, $p = 1.52 \times 10\text{-}8$); and one near TBC1D32 on chromosome 6 (rs118074968, $p = 4.94 \times 10\text{-}8$). In silico investigations of each locus identified multiple expression quantitative trait loci and potentially relevant candidate genes warranting further analysis. Thus, we identified multiple genetic loci predicting treatment outcomes for anti-VEGF therapies in DME. This work may potentially lead to managing DME using personalized treatment approaches.

DOI: 10.3390/ijms23074042

Rare and common variants in ROM1 and PRPH2 genes trans-modify Stargardt/ABCA4 disease.

PLoS Genetics. 2022 Mar 30

Zernant J, Lee W, Wang J, Goetz K, Ullah E, Nagasaki T, Su PY, Fishman GA, Tsang SH, Tumminia SJ, Brooks BP, Hufnagel RB, Chen R, Allikmets R.

Over 1,500 variants in the ABCA4 locus cause phenotypes ranging from severe, early-onset retinal degeneration to very late-onset maculopathies. The resulting ABCA4/Stargardt disease is the most prevalent Mendelian eye disorder, although its underlying clinical heterogeneity, including penetrance of many alleles, are not well-understood. We hypothesized that a share of this complexity is explained by trans-modifiers, i.e., variants in unlinked loci, which are currently unknown. We sought to identify these by performing exome sequencing in a large cohort for a rare disease of 622 cases and compared variation in seven genes known to clinically phenocopy ABCA4 disease to cohorts of ethnically matched controls. We identified a significant enrichment of variants in 2 out of the 7 genes. Moderately rare, likely functional, variants, at the minor allele frequency (MAF) <0.005 and CADD>25, were enriched in ROM1, where 1.3% of 622 patients harbored a ROM1 variant compared to 0.3% of 10,865 controls ($p = 2.41E04$; OR 3.81 95% CI [1.77; 8.22]). More importantly,

analysis of common variants (MAF>0.1) identified a frequent haplotype in PRPH2, tagged by the p.Asp338 variant with MAF = 0.21 in the matched general population that was significantly increased in the patient cohort, MAF 0.25, p = 0.0014. Significant differences were also observed between ABCA4 disease subgroups. In the late-onset subgroup, defined by the hypomorphic p.Asn1868Ile variant and including c.4253+43G>A, the allele frequency for the PRPH2 p.Asp338 variant was 0.15 vs 0.27 in the remaining cohort, p = 0.00057. Known functional data allowed suggesting a mechanism by which the PRPH2 haplotype influences the ABCA4 disease penetrance. These associations were replicated in an independent cohort of 408 patients. The association was highly statistically significant in the combined cohorts of 1,030 cases, p = 4.00E-05 for all patients and p = 0.00014 for the hypomorph subgroup, suggesting a substantial trans-modifying role in ABCA4 disease for both rare and common variants in two unlinked loci.

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EPIDEMIOLOGY

Menopause and the Risk of Developing Age-Related Macular Degeneration in Korean Women.

Journal of Clinical Medicine. 2022 Mar 29

Yuk JS, Hwang JH.

Previous studies have shown that menopausal hormone therapy in postmenopausal women results in a higher prevalence of age-related macular degeneration. This study aimed to evaluate the effects of menopause and patient factors on the development of age-related macular degeneration in Korean women. Data between 2011 and 2014 were collected from the Korean National Health Insurance database. In this retrospective cohort study, 97,651 participants were premenopausal and 33,598 were menopausal. Participants were divided into menopausal and premenopausal groups to analyze the risk factors associated with the development of age-related macular degeneration. The prevalence of age-related macular degeneration was compared between the two groups. Other patient factors were also analyzed. Using a 1:1 propensity score matching method and adjusting for variables, the incidence of age-related macular degeneration was not significantly different between the two groups. Age and diabetes mellitus were associated with an increased risk of developing age-related macular degeneration, regardless of menopause. Menopause was not a risk factor for age-related macular degeneration. These findings may help physicians identify women with diabetes who are at a greater risk of developing age-related macular degeneration.

DOI: 10.3390/jcm11071899

NUTRITION

Curcumin in Retinal Diseases: A Comprehensive Review from Bench to Bedside.

International Journal of Molecular Science. 2022 Mar 24

Allegrini D, Raimondi R, Borgia A, Sorrentino T, Montesano G, Tsoutsanis P, Cancian G, Verma Y, De Rosa FP, Romano MR.

Recent evidence in basic science is leading to a growing interest in the possible role of curcumin in treating retinal diseases. Curcumin has been demonstrated to be able to modulate gene transcription and reduce ganglion cell apoptosis, downgrade VEGF, modulate glucose levels and decrease vascular dysfunction. So far, the use of curcumin has been limited by poor bioavailability; to overcome this issue, different types of carriers have been used. Multiple recent studies disclosed the efficacy of using curcumin in treating different retinal conditions. The aim of this review is to comprehensively review and discuss the role of curcumin in retinal diseases from bench to bedside.

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BIOMARKERS

Macular Choroidal Thickness and the Risk of Referable Diabetic Retinopathy in Type 2 Diabetes: A 2-Year Longitudinal Study.

Investigative Ophthalmology and Visual Science. 2022 Apr 1

Wang W, Li L, Wang J, Chen Y, Kun X, Gong X, Wei D, Wang D, Liang X, Liu H, Huang W.

Purpose: The purpose of this study was to evaluate the associations between choroidal thickness (CT) and the 2-year incidence of referable diabetic retinopathy (RDR).
Methods: This was a prospective cohort study. Patients with type 2 diabetes in Guangzhou, China, aged 30 to 80 years underwent comprehensive examinations, including standard 7-field fundus photography. Macular CT was measured using a commercial swept-source optical coherence tomography (SS-OCT) device (DRI OCT Triton; Topcon, Tokyo, Japan). The relative risk (RR) with 95% confidence intervals (CIs) was used to quantify the association between CT and new-onset RDR. The prognostic value of CT was assessed using the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI).
Results: A total of 1345 patients with diabetes were included in the study, and 120 (8.92%) of them had newly developed RDR at the 2-year follow-up. After adjusting for other factors, the increased RDR risk was associated with greater HbA1c (RR = 1.35, 95% CI = 1.17-1.55, P < 0.001), higher systolic blood pressure (SBP; RR = 1.02, 95% CI = 1.01-1.03, P = 0.005), lower triglyceride (TG) level (RR = 0.81, 95% CI = 0.69-0.96, P = 0.015), presence of diabetic retinopathy (DR; RR = 8.16, 95% CI = 4.47-14.89, P < 0.001), and thinner average CT (RR = 0.903, 95% CI = 0.871-0.935, P < 0.001). The addition of average CT improved NRI (0.464 ± 0.096, P < 0.001) and IDI (0.0321 ± 0.0068, P < 0.001) for risk of RDR, and it also improved the AUC from 0.708 (95% CI = 0.659-0.757) to 0.761 (95% CI = 0.719-0.804).
Conclusions: CT thinning measured by SS-OCT is an early imaging biomarker for the development of RDR, suggesting that alterations in CT play an essential role in DR occurrence.

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PATHOGENESIS

Choroidal vascularity index change in macular telangiectasia type 2.

PLoS One. 2022 Apr 7

Chun H, Suh H, Kim JY, Kwak JH, Kim RY, Kim M, Park YG, Park YH.

Purpose: To analyze choroidal structure using subfoveal choroidal thickness (SFCT) and choroidal vascularity index (CVI) in Macular Telangiectasia (MacTel) type 2.
Methods: Medical records of 43 eyes with MacTel type 2 and 30 sex and age-matched healthy eyes were retrospectively reviewed. Their SFCT and CVI were measured using the SS-OCT scan passing through the central fovea and image binarization. The difference in baseline SFCT and CVI from each group and their yearly changes up to second year of follow up were analyzed. The baseline characteristics of the groups were also compared.
Results: The baseline characteristics, including CVI and SFCT, of the MacTel group and the control group were not significantly different, except for BCVA. The mean CVI of MacTel group were 64.59 ± 2.92%, 63.76 ± 2.67%, and 62.97 ± 2.74% ($p < 0.001$) whereas that of control group were 63.33 ± 2.45%, 63.04 ± 2.46%, and 63.43 ± 2.25% ($p = 0.636$) at baseline, 1 and 2 years, respectively. The mean SFCT of MacTel group were 324.65 ± 89.65μm, 326.14 ± 93.11μm, and 322.65 ± 91.77μm ($p = 0.436$), whereas that of control group were 304.30 ± 51.86 μm, 300.86 ± 52.64μm, and 298.55 ± 53.71μm ($p = 0.275$) at baseline, 1 and 2 years, respectively.

Conclusion: CVI decreases at a faster rate in MacTel type 2 in comparison with healthy subjects. This may suggest possible choroidal involvement in the progression of MacTel type 2.

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REVIEW

Efficacy, safety, and treatment burden of treat-and-extend versus alternative anti-VEGF regimens for nAMD: a systematic review and meta-analysis.

Eye (London). 2022 Apr 8

Rosenberg D, Deonarain DM, Gould J, Sothivannan A, Phillips MR, Sarohia GS, Sivaprasad S, Wykoff CC, Cheung CMG, Sarraf D, Bakri SJ, Chaudhary V.

This study aimed to compare efficacy and treatment burden of treat-and-extend (T&E) anti-VEGF against fixed and pro re nata (PRN) regimens for neovascular age-related macular degeneration (nAMD). MEDLINE, CENTRAL, and EMBASE were searched. Randomized-controlled trials and observational studies comparing T&E to PRN or fixed dosing for treatment-naïve AMD patients were included. Mean difference (MD) for visual acuity (VA) and number of injections are presented. Risk of bias was assessed according to Cochrane guidelines. Methodology was conducted

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). VA improvement was similar with T&E and fixed dosing at one (MD -0.08 letters, p = 0.95) and two years (MD 0.58 letters, p = 0.62). In contrast, VA improvements were significantly greater for T&E when compared against a PRN regimen at one (MD 3.95 letters, p < 0.0001) and two years (MD 4.08 letters, p < 0.001). Significantly fewer ranibizumab injections were administered in the T&E arm at one (MD -2.42 injections, p < 0.0001) and two years (MD -6.06 injections, p < 0.00001) relative to fixed dosing. Fewer aflibercept injections were likewise administered to patients on a T&E regimen versus fixed dosing at one year (MD -0.78 injections, p < 0.0001). Low-certainty evidence from the present synthesis implies that T&E preserves VA similar to fixed schedules with significantly fewer injections at one and two years. Also, patients with T&E dosing achieved better VA outcomes than those on PRN regimen but T&E dosing was associated with more injections.

DOI: 10.1038/s41433-022-02020-7

DRUG TREATMENT

Dosing Regimens of Intravitreal Aflibercept for Diabetic Macular Edema Beyond the First Year: VIOLET, a Prospective Randomized Trial.

Advanced Therapeutics. 2022 Apr 12

Garweg JG, Štefanickova J, Hoyng C, Niesen T, Schmelter T, Leal S, Sivaprasad S; VIOLET Investigators.

Introduction: The purpose was to compare two flexible regimens of intravitreal aflibercept (IVT-AFL) with fixed dosing every 8 weeks, beyond the first year of treatment, in patients with diabetic macular edema (DME). VIOLET was a 100-week, randomized, Phase IIIb, non-inferiority study in patients with center-involving DME previously treated with IVT-AFL for ≥ 1 year according to the European label.
Methods: Patients received an initial dose of IVT-AFL at study baseline and were randomly assigned (1:1:1) to treat-and-extend (T&E), pro re nata (PRN), or fixed regimens. The primary endpoint was mean change in best-corrected visual acuity (BCVA) from baseline (randomization) to Week 52.
Results: Full analysis set comprised 458 patients (baseline mean BCVA: 72.5, 71.0, and 72.7 letters in the T&E, PRN, and fixed-dose groups, respectively). Patients received a mean (min-max) of 10.0 (2-14; T&E), 11.5 (1-25; PRN), and 12.3 (3-13; fixed) injections over 100 weeks, with 13.3 (4-23), 25.0 (3-29), and 16.1 (5-25) clinic visits, respectively. At Week 52, mean (± standard deviation) BCVA changes from baseline were + 0.5 ± 6.7 (T&E), + 1.7 ± 6.8 (PRN), and + 0.4 ± 6.7 (fixed-dosing) letters (least squares mean difference [95% confidence interval]: T&E 0.01 [- 1.46, 1.47] and PRN 0.95 (- 0.52, 2.42) letters versus fixed dosing; p < 0.0001 for both non-inferiority tests [4-letter margin]). The IVT-AFL safety profile was consistent with previous studies.
Conclusion: The treatment burden associated with intravitreal injections for DME is lowest with T&E regimens, but there are a range of flexible IVT-AFL dosing regimens, allowing physicians to adopt an individualized treatment plan. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02818998.

DOI: 10.1007/s12325-022-02119-z