Clinical effectiveness of ranibizumab and conbercept for neovascular age-related macular degeneration: a meta-analysis.

Wang L, Zhang C, Hua R.

INTRODUCTION: To assess the ocular efficacy of intravitreal ranibizumab and conbercept injection in patients with neovascular age-related macular degeneration.

MATERIALS & METHODS: We searched PubMed, Web of Science, Cochrane Library, EMBASE, Google Scholar, Medline, China National Knowledge Infrastructure, and WANFANG DATA databases, up to June 20, 2018. We also searched abstracts and clinical study presentations at meetings as well as trial registries; we contacted authors of included studies if questions arose. Eligibility criteria for selection of studies were randomized controlled trials and retrospective trials that compared ranibizumab with conbercept for treatment of neovascular age-related macular degeneration.

RESULTS: Eight randomized controlled trials and four retrospective studies were included with a total of 853 patients. Best-corrected visual acuity after loading dosage was improved in the conbercept group, compared with the ranibizumab group (weighted mean difference: -0.04; 95% CI: -0.07 to 0.00; P=0.04). There was a significant difference between conbercept and ranibizumab therapy with respect to unchanged or recurrent leakage of choroidal neovascularization (OR: 0.46; 95% CI: 0.24-0.88; P=0.02). No significant differences were observed in central macular thickness (weighted mean difference: -2.92; 95% CI: -9.00 to 3.17; P=0.35), complete and partial closure of leakage of choroidal neovascularization (complete closure, P=0.70; partial closure, P=0.35), or number of injections (weighted mean difference: 0.42; 95% CI: -0.46 to 1.29; P=0.35) between the conbercept and ranibizumab groups at the end of the follow-up periods.

CONCLUSION: Pooled evidence confirmed that conbercept was superior to ranibizumab with respect to visual gain after treatment. Additional studies with long-term follow-up are needed to support our conclusion.

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Eichenbaum DA, Duerr E, Patel HR, Pollack SM.

**BACKGROUND & OBJECTIVE:** Compare fixed monthly dosing of ranibizumab to treat-and-extend (T&E) ranibizumab during a period of 24 months for diabetic macular edema (DME) treatment.

**PATIENTS & METHODS:** Single-center, randomized, prospective pilot study that included 20 eyes of 20 subjects. Patients' best-corrected visual acuity (BCVA) was less than or equal to 20/40 and central foveal thickness on spectral-domain optical coherence tomography was greater than 325 µm. Intravitreal ranibizumab was dosed monthly or by protocol-specified treat-and-extend. Primary outcome was mean change in mean BCVA. Institutional review board approval was obtained.

**RESULTS:** At month 24 (M24), there was a mean 8.3-letter gain in the monthly treatment group and an 8.5-letter gain in the T&E group (P = .082; 90% confidence interval). The average change from baseline BCVA was not statistically significantly different at any timepoint. At M24, the median number of injections in the monthly and T&E groups were 22.5 and 18.5, respectively (P = .287).

**CONCLUSIONS:** Visual acuity with monthly dosing appears equivalent to T&E dosing during the course of 24 months. There was a trend toward a lower injection burden in the T&E arm.

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Ranibizumab versus dexamethasone implant in macular edema secondary to branch retinal vein occlusion: two-year outcomes.

Ozkaya A, Tarakcioglu HN, Tanir I.

**SIGNIFICANCE:** We compared the 24-month outcomes of ranibizumab and dexamethasone implants in treatment-naive branch retinal vein occlusion patients. Ranibizumab was effective in improving visual outcomes, whereas the dexamethasone implant was not.

**PURPOSE:** The aim of this study was to compare the 2-year real-world outcomes of intravitreal ranibizumab with dexamethasone implants in patients with macular edema secondary to branch retinal vein occlusion.

**METHODS:** The treatment-naive branch retinal vein occlusion patients with macular edema who were treated with intravitreal ranibizumab or dexamethasone implant were included retrospectively. Primary outcome measures were the change in best-corrected visual acuity and central retinal thickness.

**RESULTS:** Eighty-seven eyes of 87 patients were included. Mean ± SD best-corrected visual acuity in the intravitreal ranibizumab group at baseline and 24 months was 0.64 ± 0.48 and 0.49 ± 0.44 logMAR (P < .05). Mean ± SD best-corrected visual acuity in the intravitreal dexamethasone implant group at baseline and 24 months was 0.98 ± 0.56 and 0.92 ± 0.61 logMAR (P > .05). Mean ± SD central retinal thickness in the intravitreal ranibizumab group at baseline and 24 months was 530 ± 150 and 337 ± 103 µm (P < .05). Mean ± SD central retinal thickness in the intravitreal dexamethasone implant group at baseline and 24 months was 591 ± 113 and 335 ± 99 µm (P < .05). Mean ± SD number of injections at 24 months was 5.6 ± 1.8 in the intravitreal ranibizumab group and 2.7 ± 1.1 in the dexamethasone implant group (P < .0001). Progression in lens opacity was detected in 5.7% of the phakic patients in the intravitreal ranibizumab group and 46.1% of them in the dexamethasone implant group (P < .0001). None of the patients in the intravitreal ranibizumab group and 9 (22.0%) of 41 patients in the dexamethasone implant group showed an increase of more than 10 mmHg in intraocular pressure.

**CONCLUSIONS:** Ranibizumab was effective in the treatment of macular edema secondary to branch retinal vein occlusion in both visual and anatomical outcomes; however, dexamethasone implant was effective only in anatomical outcomes.
Polypoidal choroidal vasculopathy (PCV): the 4-year review of the real-life treatment experiences.

Ratanasukon M, Bhurayanontachai P, Jirarattanasopa P.

PURPOSE: The purpose of this article was to study the real-life treatment results of polypoidal choroidal vasculopathy (PCV).

DESIGN: This was a retrospective study.

METHODS: Patients with presumed age-related macular degeneration were reviewed, and PCV diagnosis was made using the EVEREST study criteria. Outcomes were changes in visual acuity (VA) and central retinal thickness, time between treatments, follow-up time, and number of treatments.

RESULTS: The prevalence of PCV was 30.8%. At the beginning, 195 eyes received monotherapy of anti-vascular endothelial growth factor (anti-VEGF) injections, either bevacizumab or ranibizumab, and only six eyes received the combination of anti-VEGF injection and photodynamic therapy (PDT) at the time of the first treatment. During the follow-up, some patients received "rescue or add-on" PDT when they had a poor response after anti-VEGF injections. After 4 years, the average number of injections was 8.25 and 9.15 for the anti-VEGF monotherapy and the combination groups, respectively. The average time between the first anti-VEGF injections and the first PDT was 21.4 months. The average VA in the anti-VEGF monotherapy group increased by 1.5 letters, whereas it decreased by 0.95 letters in the combination group (P=0.48).

CONCLUSION: The review demonstrated the same visual outcomes between the combination therapy of anti-VEGF injections and rescue or add-on PDT vs monotherapy anti-VEGF injections in PCV treatment. When compared with EVEREST II and Planet studies, the "initial" or "rescue or add-on PDT" might have different effects on the final visual outcomes.
**CONCLUSIONS:** Ranibizumab treatment influences various inflammatory cytokine concentrations in addition to reducing aqueous VEGF concentrations in patients with DME. This may contribute to its therapeutic effect in patients with DME.

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**Current management strategy of polypoidal choroidal vasculopathy.**

Ho CPS, Lai TYY.

**ABSTRACT:** Polypoidal choroidal vasculopathy (PCV) is a retinal disorder commonly found in Asians presenting as neovascular age-related macular degeneration and is characterized by serous macular detachment, serous or hemorrhagic pigment epithelial detachment, subretinal hemorrhage, and occasionally visible orange-red subretinal nodular lesions. PCV is diagnosed using indocyanine green angiography (ICGA), and the lesions appear as polypoidal aneurysmal vascular lesions with or without abnormal branching vascular network. Although ICGA remains the gold standard for the diagnosis of PCV, various imaging modalities have also facilitated the diagnosis and monitoring of PCV. Recent advances in imaging technology including the use of high resolution spectral domain optical coherence tomography (OCT) and OCT angiography have provided new insights on the pathogenesis of PCV, suggesting a link between PCV and pachychoroid spectrum of macular disorders. With the evolving understanding on the pathogenesis and clinical characteristics of PCV, different therapeutic options have been proposed. These include intravitreal anti-vascular endothelial growth factor (anti-VEGF) monotherapy, combination therapy with anti-VEGF and verteporfin photodynamic therapy, and thermal laser photocoagulation. In recent years, major multi-center randomized clinical trials such as EVEREST, EVEREST II, and PLANET studies have been conducted to compare the efficacy and safety of various treatment options for PCV. This review aims to summarize the results of recent literature, clinical trials and studies to provide an update on the management options of PCV. An overall management strategy for PCV will also be proposed.

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**Other treatment**


**Transplantation of photoreceptors into the degenerative retina: Current state and future perspectives.**

Gasparini SJ, Llonch S, Borsch O, Ader M.

**ABSTRACT:** The mammalian retina displays no intrinsic regenerative capacities, therefore retinal degenerative diseases such as age-related macular degeneration (AMD) or retinitis pigmentosa (RP) result in a permanent loss of the light-sensing photoreceptor cells. The degeneration of photoreceptors leads to vision impairment and, in later stages, complete blindness. Several therapeutic strategies have been developed to slow down or prevent further retinal degeneration, however a definitive cure i.e. replacement of the lost photoreceptors, has not yet been established. Cell-based treatment approaches, by means of photoreceptor transplantation, have been studied in pre-clinical animal models over the last three decades. The introduction of pluripotent stem cell-derived retinal organoids represents, in principle, an unlimited source for the generation of transplantable human photoreceptors. However, safety, immunological and reproducibility-related issues regarding the use of such cells still need to be solved. Moreover, the recent finding of cytoplasmic material transfer between donor and host photoreceptors demands reinterpretation of several former transplantation studies. At the same time, material transfer between healthy donor and dysfunctional patient photoreceptors also offers a potential alternative strategy for therapeutic intervention. In this review we discuss the history and current state of photoreceptor transplantation, the techniques used to assess rescue of visual function, the prerequisites for effective transplantation as well as the main roadblocks, including safety and immune response to the graft, that need to be overcome for successful
Screening & OCT


**Optical coherence tomography angiography (OCTA) flow speed mapping technology for retinal diseases.**


**ABSTRACT:** Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality for depth-resolved visualization of retinal vasculature. Angiographic data couples with structural data to generate a cube scan, from which en-face images of vasculature can be obtained at various axial positions. OCTA has expanded understanding of retinal vascular disorders and has primarily been used for qualitative analysis. Areas covered: Recent studies have explored the quantitative properties of OCTA, which would allow for objective assessment and follow-up of retinal pathologies. Various quantitative metrics have been developed, such as foveal avascular zone area and vessel density. However, quantitative assessment of the characteristics of retinal blood flow remains limited, as OCTA provides an image depicting either the presence or absence of flow at a particular region without information of relative velocities. The development of variable interscan time analysis (VISTA) overcomes this limitation. The VISTA algorithm generates a color-coded map of relative blood flow speeds. VISTA has already demonstrated utility in furthering our understanding of various retinal pathologies, such as geographic atrophy, choroidal neovascularization, aneurysmal type 1 neovascularization, and diabetic retinopathy. Expert commentary: VISTA, an OCTA flow speed mapping technique, may have a role in developing the utility of OCTA as a screening tool.

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Anatomic localization of Type 1 and Type 2 macular neovascularization using swept-source OCT Angiography.

Motulsky EH, Zheng F, Shi Y, Gregori G, Rosenfeld PJ.

**BACKGROUND & OBJECTIVE:** Swept-source optical coherence tomography angiography (SS-OCTA) and different boundary-specific segmentation strategies were used to distinguish type 1 macular neovascularization (MNV) from type 2 MNV in eyes with exudative age-related macular degeneration (AMD).

**PATIENTS & METHODS:** Eyes with exudative AMD were enrolled in a prospective study. Segmentation strategies included a slab from the outer retina (OR) to the choriocapillaris (CC) for the entire MNV, a slab from the retinal pigment epithelium (RPE) to the CC for the type 1 MNV, and a slab from the OR to the RPE for the type 2 MNV.

**RESULTS:** In 13 eyes, SS-OCTA B-scans and en face images using different segmentation strategies were able to identify type 1 and type 2 components of the MNV.

**CONCLUSION:** In eyes with exudative AMD, SS-OCTA imaging and commercially available boundary-specific segmentation strategies were used to distinguish between type 1 and type 2 MNV.
**Correlation of optical coherence tomography angiography and microperimetry (MP3) features in wet age-related macular degeneration.**

Nagpal M, Khandelwal J, Juneja R, Mehrotra N.

**PURPOSE:** To evaluate and correlate the functional treatment response using microperimetry (MP3) with the morphological findings on optical coherence tomography angiography (OCTA) in wet AMD pre- and post-treatment with anti-vascular endothelial growth factor (VEGF). This was a single-centre prospective, interventional study.

**METHODS:** Patients with wet AMD were treated with 3 injections of intravitreal anti-VEGF at monthly intervals for 3 months and followed at 1, 2, 3, and 6 months postinjection. Using "overlay" features, morphologic characteristics of OCTA at the site of choroidal neovascular membrane (CNVM) lesion were analyzed and correlated functionally with MP3. Data were collected including visual acuity at presentation and follow-up with multimodal imaging features, treatment details, complications (if any), and treatment given for that complication. Descriptive observational analysis and paired t-test was used to compare the appearance of the neovascular network on OCTA imaging with retinal sensitivity on MP3.

**RESULTS:** OCTA in the pretreatment phase revealed CNVM as an abnormal vascular network arising from the choroid and invading the subretinal space. On MP3, decreased retinal sensitivity was observed corresponding to the area of CNVM. Post-treatment, OCTA revealed reduction in abnormal vascular network in 51 (91.07%) eyes that correlated with increased retinal sensitivity at the corresponding area on MP3. Statistical analysis showed baseline mean retinal sensitivity at the site of CNVM as 320.07 dB, which improved to 521.53 and 730.20 dB at 1 and 3 months postinjection follow-up, respectively.

**CONCLUSION:** Combining the findings of OCTA and MP3 using "overlay" features gives us precise information of structure-function correlation at presentation and also in response to treatment. It also helps to improve patient's compliance, confidence to treatment, and their understanding of the disease process as well.

PMD: 30451180 DOI: 10.4103/ijo.IJO_866_18

**A new and improved method for automated screening of age-related macular degeneration using ensemble deep neural networks.**

Govindaiah A, Smith RT, Bhuiyan A.

**ABSTRACT:** In this paper, we provide a new framework on deep learning based automated screening method for finding individuals at risk of developing Age-related Macular Degeneration (AMD). We studied the appropriateness of using the transfer learning to screen AMD by using color fundus images. We make use of the Age-Related Eye Disease Study (AREDS) dataset with nearly 150,000 images, which also provided qualitative grading information by expert graders and ophthalmologists. We use ensemble learning technique with two deep neural networks, namely, Inception-ResNet-V2 and Xception with a custom fine-tuning approach. For our study, we have identified two experiments that are most useful in the screening of AMD. First, we have categorized the images into two classes based on the clinical significance: None or early AMD and Intermediate or Advanced AMD. Second, we have categorized the images into four classes: No AMD, early AMD, Intermediate AMD and Advanced AMD. On AREDS dataset, we have achieved an accuracy of over 95.3% for two-class experiment with our ensemble method. With accuracies ranging from 86% (for four-class) to 95.3% (for two-class), we have demonstrated that the training of a deep neural network with the transfer of learned features with a sufficient number of images fares very well and is comparable to human grading.
Optical coherence tomography angiography in exudative age-related macular degeneration: a predictive model for treatment decisions.


AIMS: To evaluate on optical coherence tomography angiography (OCT-A), the predictive role of different qualitative findings of choroidal neovascularisations (CNV) in assessing the status of exudative age-related macular degeneration (eAMD) and to develop a potential model to predict the CNV activity.

METHODS: Retrospective review of the multimodal imaging records of patients with eAMD obtained during treatment for type 1 or type 2 CNV. The qualitative analysis of CNVs on OCT angiograms assessed the presence or absence of tiny branching vessels, loops, peripheral anastomotic arcades and choriocapillaris hypointense halo. These findings were then correlated with those of structural OCT scans. A score forecast was built and validated.

RESULTS: One hundred and twenty-six eAMD eyes were enrolled in the study. Exudation was observed in 90 eyes (71%) on structural OCT. The qualitative OCT-A analysis revealed: tiny branching vessels in 82.5% of the cases, vascular loops in 81.7%, peripheral anastomotic arcades in 66.7% and choriocapillaris hypointense halo in 54.8%. In the univariate analysis, each OCT-A parameter showed a statistically significant correlation with exudation on structural OCT (p<0.001). The overall analysis demonstrated a sensitivity of 96.7% and a positive predictive value of 87.9%. In the multivariate analysis, a model with four criteria predicted an exudative lesion in 97.6% of cases and one with two criteria (tiny branching vessels and peripheral anastomotic arcades) in 71.2%.

CONCLUSIONS: The presence of tiny branching vessels and a peripheral anastomotic arcade appears to predict the lesion activity with a good accuracy and the model based on four criteria enables optimal decisions regarding retreatment in eAMD.

Pathogenesis

Outer retinal tubulation and neovascular age-related macular degeneration: a review of the pathogenesis and clinical implications.

Damasceno NA, Damasceno EF, Silva FQ, Singh RP.

ABSTRACT: Outer retinal tubulation (ORT) is a retinal finding that can mimic intraretinal fluid and has been identified with spectral-domain optical coherence tomography in patients with age-related macular degeneration (AMD). The purpose of this review is to summarize the findings related to the pathogenesis of ORT and its clinical implications. Studies reporting the pathogenesis and the clinical implications of ORT in patients with AMD were identified and summarized. A total of 18 studies were included in this review. The body of evidence to date regarding ORT in patients with AMD indicates that ORT is a structure associated with advanced macular diseases that does not require anti-vascular endothelial growth factor treatment.

PMID: 30457646 DOI: 10.3928/23258160-20181101-08
New insight into the role of the complement in the most common types of retinopathy- current literature review.

Chrzanowska M, Modrzejewska A, Modrzejewska M.

**ABSTRACT:** Pathological neovascularisation, which is a critical component of diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and retinopathy of prematurity (ROP), is a frequent cause of compromised vision or blindness. Researchers continuously investigate the role of the complement system in the pathogenesis of retinopathy. Studies have confirmed the role of factors H and I in the development of AMD, and factors H and B in the development of DR. Other components, such as C2, C3, and C5, have also been considered. However, findings on the involvement of the complement system in the pathogenesis of ROP are still inconclusive. This paper presents a review of the current literature data, pointing to the novel results and achievements from research into the role of complement components in the development of retinopathy. There is still a need to continue research in new directions, and to gather more detailed information about this problem which will be useful in the treatment of these diseases.

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**Epidemiology**

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**Ophthalmic conditions associated with inpatient falls among veterans.**


**SIGNIFICANCE:** Efforts to describe the relationship between pathological visual impairment and fall risk are typically confined to community dwellers. Among admitted patients, however, the associations are less understood. Fall risk assessment tools are used in some clinical settings, but most do not capture the suspected importance of ophthalmic pathologies in predicting the likelihood of an inpatient fall.

**PURPOSE:** The purpose of this study was to determine the association between ophthalmic conditions and inpatient falls at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC), where vision and ophthalmic conditions are not considered when assessing fall risk.

**METHODS:** This is a population-based, retrospective case-control study of 805 patients admitted to the MEDVAMC in January 2014 who had also visited the MEDVAMC Eye Clinic within 1 year of admission. The patients’ eye examinations, ophthalmic diagnoses, and other indicators of constitutive health were compared between 60 patients who experienced an inpatient fall (“cases”) and 749 patients who did not (“controls”). Significant differences between the cases and the controls were determined using logistic regression models.

**RESULTS:** Baseline demographics were similar among the two groups. Ophthalmic conditions associated with an increased incidence of inpatient falls included age-related macular degeneration (odds ratio, 3.9; 95% confidence interval, 1.5 to 9.9; P = .008) and a presenting visual acuity of worse than 20/40 in the better-seeing eye (odds ratio, 2.0; 95% confidence interval, 1.0 to 4.1; P = .04). Those without falls demonstrated a better mean presenting visual acuity in the better-seeing eye compared with those who fell (logMAR, 0.12 ± 0.23 vs. 0.28 ± 0.49, P < .001).

**CONCLUSIONS:** In this population, age-related macular degeneration and poor presenting visual acuity in the better-seeing eye are associated with increased incidence of inpatient falls. An assessment of visual function and ophthalmic diagnoses may be warranted upon admission to the hospital for increased prevention of inpatient falls.

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Genetics


Epigenetics in Age-related Macular Degeneration (AMD).

Desmettre TJ.

ABSTRACT: Age-related Macular Degeneration (AMD) is a complex multifactorial condition involving multiple genetic, environmental and constitutional factors. Inflammation, oxidative stress and lipid metabolism seem to be the most important factors in the pathogenesis of the disease. The importance of genetic factors has mainly been revealed with the influence of histocompatibility complement factor H (CFH) variations and the ARSM2 susceptibility gene. Another component, epigenetics, could help to explain some of the relationships between environmental and genetic factors. Epigenetics is defined as the study of modulations of gene activity that can be transmitted over cell divisions without involving mutation of the DNA sequence. The molecules that are involved in these mechanisms are referred to as the epigenome. The mechanisms involve DNA methylation, histone modification, chromatin remodeling, and gene inhibition by non-coding RNA. Epigenetics could explain how the environment may induce relatively stable changes in traits or even diseases, possibly inheritable over several generations. Epigenetic traits established during development, and/or acquired under the influence of nutritional factors or other environmental factors, could influence the interactions between genes and the environment. Several authors have recently shown the influence of epigenetic factors in the pathogenesis of ocular diseases such as cataract, dry eye, glaucoma, diabetic retinopathy and more recently AMD. A better understanding of the involvement of genetic variants at risk, their relationship with epigenetics and environmental factors would certainly help to better assess the risk of developing AMD or better understand recent changes in the incidence of the disease.

PMID: 30458925 DOI: 10.1016/j.jfo.2018.09.001


Whole genome sequencing reveals novel mutations causing autosomal dominant inherited macular degeneration.

Borooah S, Stanton CM, Marsh J, et al.

BACKGROUND: Age-related macular degeneration (AMD) is a common sight threatening condition. However, there are a number of monogenic macular dystrophies that are clinically similar to AMD, which can potentially provide pathogenetic insights.

METHODS: Three siblings from a non-consanguineous Greek-Cypriot family reported central visual disturbance and nyctalopia. The patients had full ophthalmic examinations and color fundus photography, spectral-domain ocular coherence tomography and scanning laser ophthalmoscopy. Targeted polymerase chain reaction (PCR) was performed as a first step to attempt to identify suspected mutations in C1QTNF5 and TIMP3 followed by whole genome sequencing.

RESULTS: The three patients were noted to have symptoms of nyctalopia, early paracentral visual field loss and, in older patients, central vision loss. Imaging identified pseudodrusen, retinal atrophy and RPE-Bruch's membrane separation. Whole genome sequencing of the proband revealed two novel heterozygous variants in C1QTNF5, c.556C>T, and c.569C>G. The mutation segregated with disease in this family, occurred in cis, and resulted in missense amino acid changes P186S and S190W in C1QTNF5. In silico modeling of the variants revealed that the S190W mutations was likely to have the greatest pathologic effect and that the combination of the mutations was likely to have an additive effect.

CONCLUSIONS: The novel mutations in C1QTNF5 identified here expand the genotypic spectrum of mutations causing late-onset retinal dystrophy.

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Case reports


Sympathetic ophthalmia in fellow eye after vitrectomy for massive subretinal hemorrhage secondary to polypoidal choroidal vasculopathy.

Suetsugu T, Yasukawa T, Uemura A, et al.

**ABSTRACT:** We experienced a case of sympathetic ophthalmia in a fellow eye after vitrectomy for subretinal hemorrhage related to polypoidal choroidal vasculopathy. A 60-year-old male consulted us for polypoidal choroidal vasculopathy with subretinal hemorrhage in his left eye. The recurrence of massive subretinal hemorrhage refractory to repeated pars plana vitrectomies leads to phthisis bulbi. Two months later, multiple serous retinal detachments were observed in his right eye. Positive human leukocyte antigen-DR4 and the uveitis were helpful in distinguishing between sympathetic ophthalmia and age-related macular degeneration. High-dose pulse intravenous steroid contributed to recovery of visual acuity after resolution of serous retinal detachment.

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