American Journal of Ophthalmology Case Reports 37 (2025) 102266

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Resolution of subretinal fluid in intractable central serous chorioretinopathy with high-dose intravitreal aflibercept

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ARTICLE INFO

Keywords:
Central serous chorioretinopathy
Eylea® HD
VEGF
CSCR

ABSTRACT

Purpose: To report an unusual case of a patient with intractable central serous chorioretinopathy with a dramatic treatment response to high-dose intravitreal aflibercept.
Methods: Retrospective case report.
Results: A 40-year-old female patient presented with decreased vision after use of intranasal fluticasone and recent life stressors and was diagnosed with central serous chorioretinopathy. Over a three-year period, she underwent numerous therapies, including seven sessions of photodynamic therapy, intravitreal bevacizumab, standard-dose intravitreal aflibercept, intravitreal faricimab, oral eplerenone, oral acetazolamide, and topical ketorolac, with minimal to no treatment response. After a single treatment with high-dose intravitreal aflibercept, 8 mg, she achieved resolution of subretinal fluid.
Conclusion: High-dose intravitreal aflibercept may have a role in management of treatment-resistant central serous chorioretinopathy; further studies are needed.

1. Introduction

Central serous chorioretinopathy (CSCR) is a common cause of unilateral vision loss among patients in middle age.[1] CSCR is often idiopathic but has been found to be associated with glucocorticoid exposure, obstructive sleep apnea, psychological stress, and Type A personality.[2–5] Though the exact pathophysiology of CSCR remains unknown, choroidal vascular hyperpermeability and retinal pigment epithelium dysfunction are thought to contribute.[6,7] For most patients, CSCR is self-limited with spontaneous resolution of subretinal fluid without treatment.[8,9] However, for patients with persistent subretinal fluid, intervention is warranted; options include oral mineralocorticoid receptor antagonists, intravitreal agents against vascular endothelial growth factor (VEGF), focal laser photocoagulation, or photodynamic therapy (PDT), among others, but there is no clear consensus regarding the optimal approach.[10,11] Here, we present an unusual case of a monocular patient with CSCR who had fluctuating subretinal fluid that never resolved despite treatment with numerous interventions; after receiving one off-label treatment with high-dose intravitreal aflibercept, 8 mg (Eylea® HD), the subretinal fluid resolved completely and has not recurred over three-month follow up.

2. Case report

A 40-year-old woman presented with decreased vision in her right eye for 1 month. The vision symptoms had begun approximately 1 month after she had started intranasal fluticasone for the first time to her knowledge, and on further questioning, she reported multiple stressful life events around this time. Notably, the patient denied the use of any other steroid-containing products, including anabolic steroids, inhaled steroids, topical steroids, excessive caffeine intake, or use of phosphodiesterase type 5 (PDE5) inhibitors. She had an ocular history of bilateral congenital cataracts and had previously undergone cataract extraction with subsequent secondary intraocular lens placement in the left eye during childhood. She was monocular with no light perception in her left eye for the prior two decades due to a history of congenital corneal dystrophy with failed penetrating keratoplasty graft and secondary glaucoma. On presentation, the visual acuity was 20/40 in the right eye and no light perception in her left eye. Slit lamp examination of the right eye revealed chronic/stable findings of stromal opacities in the cornea and a congenital cataract with anterior capsular plaque. Dilated fundus examination of the right eye revealed pigmentary changes in the macula and a blunted foveal light reflex (Fig. 1A). Fundus autofluorescence revealed hyper- and hypo-autofluorescence changes in the

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https://doi.org/10.1016/j.ajoc.2025.102266
Received 29 October 2024; Received in revised form 29 December 2024; Accepted 17 January 2025
Available online 19 January 2025

fovea and in an area inferotemporal to the optic nerve just beyond the inferior arcade (Fig. 1B). Optical coherence tomography (OCT) of the right eye revealed fovea-involving subretinal fluid (Fig. 1C). At this point, she was diagnosed with presumed CSCR and advised to discontinue fluticasone with lifestyle modifications to control stress.

She was monitored for five months after initial presentation with no subjective improvement in vision. OCT over this period showed interval improvement but persistent subretinal fluid at two months (not shown) and five months (Fig. 1D). Fluorescein angiography showed very minimal leakage in the inferotemporal macula without evidence of neovascularization suggestive of an alternative etiology (Fig. 2A). Indocyanine green angiography did not show any lesions suggestive of polypoidal choroidal vasculopathy (Fig. 2B). Given the patient's persistent symptoms, a discussion of risks, benefits, and alternatives was performed, and the decision was made to proceed with half-fluence PDT.

Paradoxically, subretinal fluid worsened after the patient underwent one session of half-fluence PDT (Fig. 3A). Review of high-resolution OCT from a few years prior to initial presentation to the retina service demonstrated choroidal thickness of approximately 400 μm and large hyporeflective spaces within the choroid consistent with pachyvessels, supporting the diagnosis of pachychoroid disease (Fig. 3B). Over the next three years, the patient underwent numerous treatments, including topical ketorolac, oral eplerenone, oral acetazolamide, intravitreal bevacizumab, standard-dose intravitreal aflibercept, intravitreal faricimab, and a total of seven sessions of PDT. Fluorescein angiography was performed prior to each session of PDT, and there was no evidence of secondary choroidal neovascularization at any point. Fig. 4 exhibits the central subfield thickness as measured on OCT in relation to the various treatments and interventions that the patient underwent. For over three years, the patient had fluctuation of subretinal fluid, with occasional improvement, but the subretinal fluid remained persistent without apparent relationship to treatment timing or modality. Notably, during this period, the patient did take a short course of oral prednisone to rule out an underlying inflammatory process, and the patient exhibited significant worsening of subretinal fluid during this time. After cessation of oral prednisone, the subretinal fluid improved but did not resolve.

The patient underwent her seventh session of half-fluence PDT nearly three years after initial presentation. Fluorescein angiography performed just prior to the seventh planned session of PDT revealed small areas of possible pinpoint leakage but no obvious secondary choroidal neovascular membrane (Fig. 5A and B). After the seventh session of PDT, the patient, again, had incomplete resolution of subretinal fluid (Fig. 5C). Because she had failed so many other therapies and with no other alternatives available, off-label use of high-dose aflibercept was discussed with the patient. Just over three years after initial presentation, the patient received her first injection of high-dose intravitreal aflibercept, 8 mg. Six weeks after this injection, the patient returned for follow up with complete resolution of subretinal fluid (Fig. 5D). She received a second injection of high-dose intravitreal aflibercept thirty-eight months after initial presentation and continues to have resolved subretinal fluid at forty months after initial

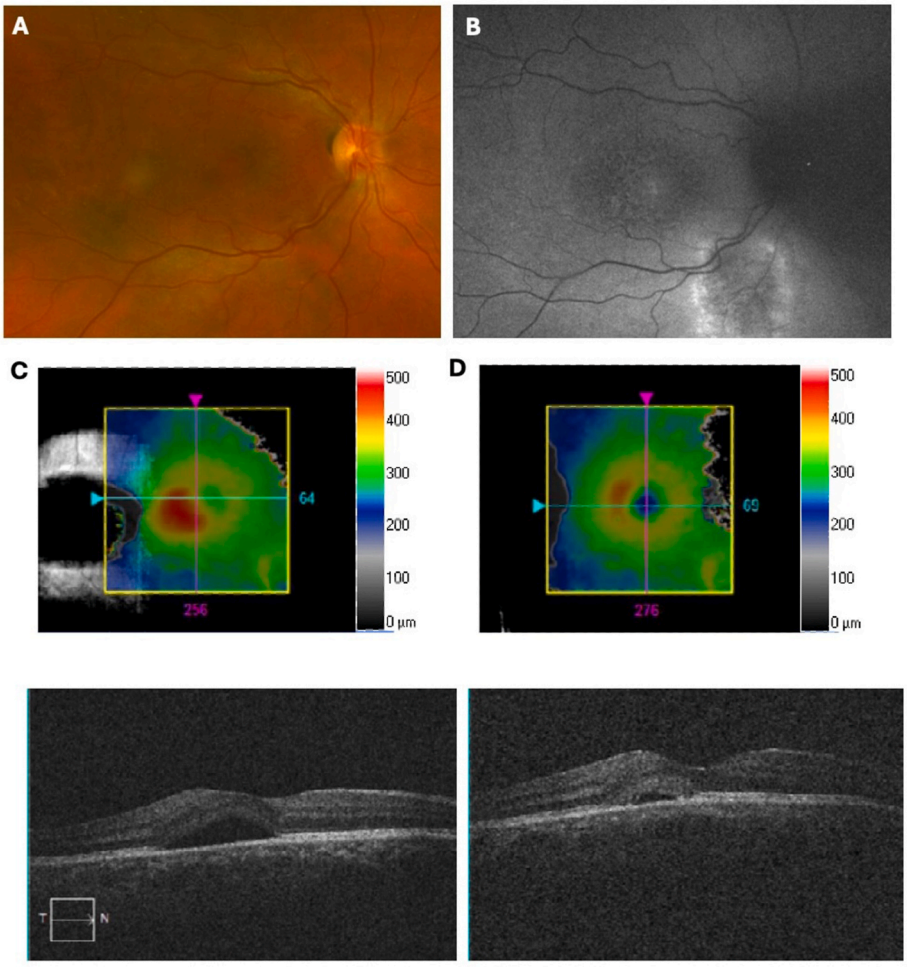

Fig. 1. Color fundus photograph of right eye from patient with central serous chorioretinopathy (A). Fundus autofluorescence of right eye from patient with central serous chorioretinopathy (B). Optical coherence tomography of the right eye showed subretinal fluid in the inferotemporal macula at initial presentation (C), which remained persistent at five months (D).

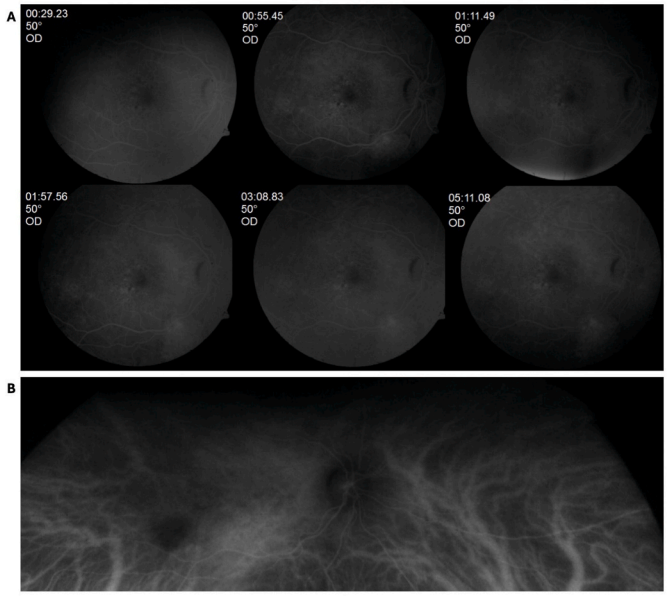

Fig. 2. Fluorescein angiography of the right eye showing very minimal leakage in the inferotemporal macula corresponding with the area of subretinal fluid and no evident choroidal neovascularization (A). Indocyanine green angiography showed no lesions suggestive of polypoidal choroidal vasculopathy (B).

presentation (Fig. 5E).

3. Discussion

We present a case of chronic CSCR in a female patient who had persistent subretinal fluid for over three years despite numerous treatments, including seven sessions of PDT, intravitreal bevacizumab, standard-dose intravitreal aflibercept (2 mg), intravitreal faricimab, oral prednisone, oral eplerenone, oral acetazolamide, and topical ketorolac. For over three years, the patient had a fluctuating course with occasional interval improvement after some treatments followed by subsequent recurrence; during this period, she never had complete resolution of subretinal fluid. After one off-label treatment with high-dose intravitreal aflibercept, 8 mg, she had complete resolution of her subretinal fluid. For the first time in over three years, she has remained free of subretinal fluid for three months.

VEGF inhibition has been explored as a possible treatment for CSCR with or without associated choroidal neovascularization. Some small retrospective studies have suggested a possible benefit of VEGF inhibition for patients with CSCR.[12,13] However, anti-VEGF therapies did not demonstrate a clear positive signal in a recent meta-analysis.[14] This lack of effect is consistent with small case-control studies showing that aqueous humor and plasma levels of VEGF were not different in patients with CSCR versus controls.[15,16]

Pitcher and colleagues previously conducted a prospective pilot study of intravitreal aflibercept for treatment of chronic CSCR and found that six of twelve patients in the study had complete resolution of subfoveal fluid within the six-month treatment period.[17] One challenge of interventional studies in patients with CSCR is its clinical heterogeneity; since the subretinal fluid commonly fluctuates and often resolves without intervention, it can be difficult to ascertain whether a positive signal represents true treatment response without careful study design with a well-matched comparator arm.

High-dose intravitreal aflibercept, 8 mg, is delivered as 0.07 ml of 114.3 mg/ml solution compared to the standard dose of 2 mg, delivered as 0.05 ml of 40 mg/ml solution. Intravitreal aflibercept, 8 mg, has been shown to be safe and non-inferior to standard, 2 mg, dosing with the ability to achieve extended dosing intervals for neovascular age-related macular degeneration and diabetic macular edema.[18,19] The intriguing finding of this case is that the patient had complete resolution of subretinal fluid after high-dose intravitreal aflibercept injection despite previous incomplete response to bevacizumab, standard-dose aflibercept, and faricimab, and despite lack of obvious secondary choroidal neovascular membrane as identified on fluorescein angiography, including one performed just a few months prior to initiation of treatment with high-dose aflibercept.

The exact mechanism by which treatment with high-dose aflibercept led to complete resolution of subretinal fluid in intractable CSCR is unclear and requires further investigation. Though the pathobiology underlying CSCR remain under active investigation, alterations in the choroid, such as choroidal thickening and choroidal vasculature hyperpermeability, are thought to play a pathologic role.[20] Prior anatomic studies have shown that in addition to its effect on neovascular lesions, PDT also leads to choroidal vascular remodeling and decreased choroidal permeability, which may possibly contribute to its therapeutic effect.[21] One hypothesis for our clinical observation is that high-dose aflibercept may yield a higher peak concentration in the choroid that may allow it to affect choroidal biology beyond its potential effect on neovascular lesions. Prior pharmacokinetic studies in a rabbit model showed that there is movement of aflibercept between the aqueous humor, the vitreous humor, and the retina/choroid after intravitreal injection with differing maximal concentrations and residence times.[22] This higher peak concentration in the retina/choroid may allow for stronger and more consistent inhibition of choroidal VEGF.

This hypothesis is supported by prior studies in other disease settings that demonstrated that anti-VEGF therapy may induce changes in choroidal vasculature in addition to its pharmacological effect on neovascularization. In patients with neovascular age-related macular degeneration, treatment with aflibercept led to decreased choroidal thickness and decreased choroidal vascularity index.[23,24] Though the pathobiology of AMD and CSCR drastically differ, we speculate that in our patient, the drastic effect seen after high-dose aflibercept may be related to a possible effect on choroidal function.

We cannot rule out the possibility that our patient developed secondary choroidal neovascularization between her last fluorescein

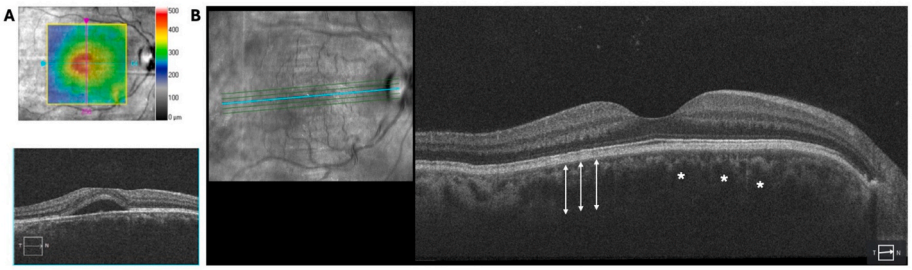

Fig. 3. Optical coherence tomography (OCT) of the right eye showed interval worsening of subretinal fluid after half-fluence photodynamic therapy (A). (B) High-resolution OCT from a few years prior to initial presentation showed thickened choroid of approximately 400 μm (see double-headed arrows) and pachyvessels (asterisks) supporting the diagnosis of pachychoroid disease.

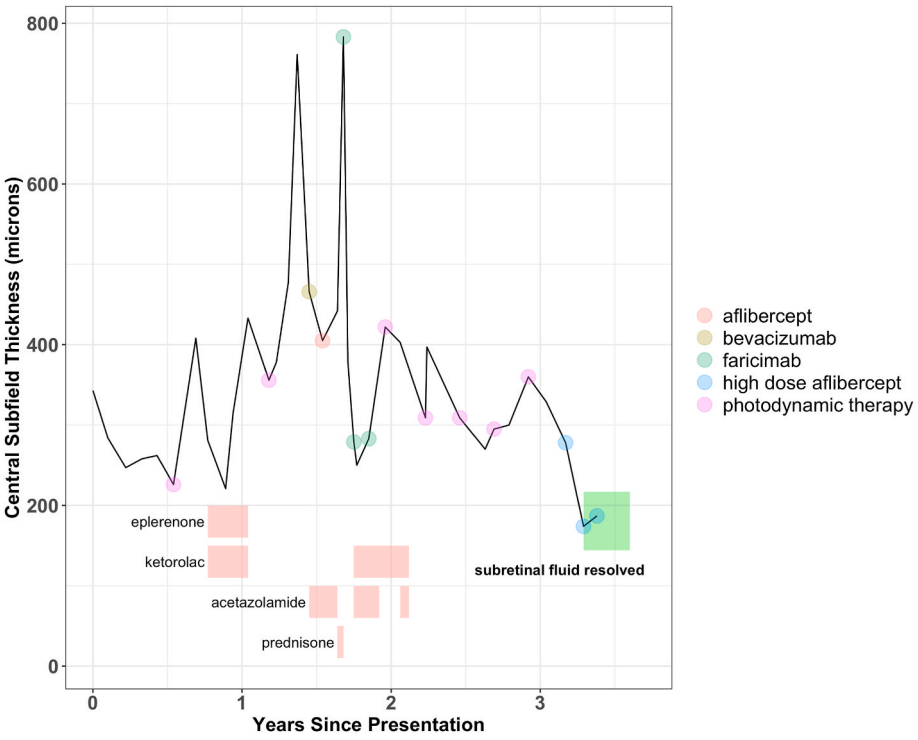

Fig. 4. Timeline showing central subfield thickness (microns) of the patient as measured by optical coherence tomography (OCT) in relation to various topical, systemic, and intravitreal treatments and seven sessions of photodynamic therapy. Until the patient received high-dose aflibercept, there was persistent subretinal fluid with fluctuation but no apparent relationship to treatment timing or modality.

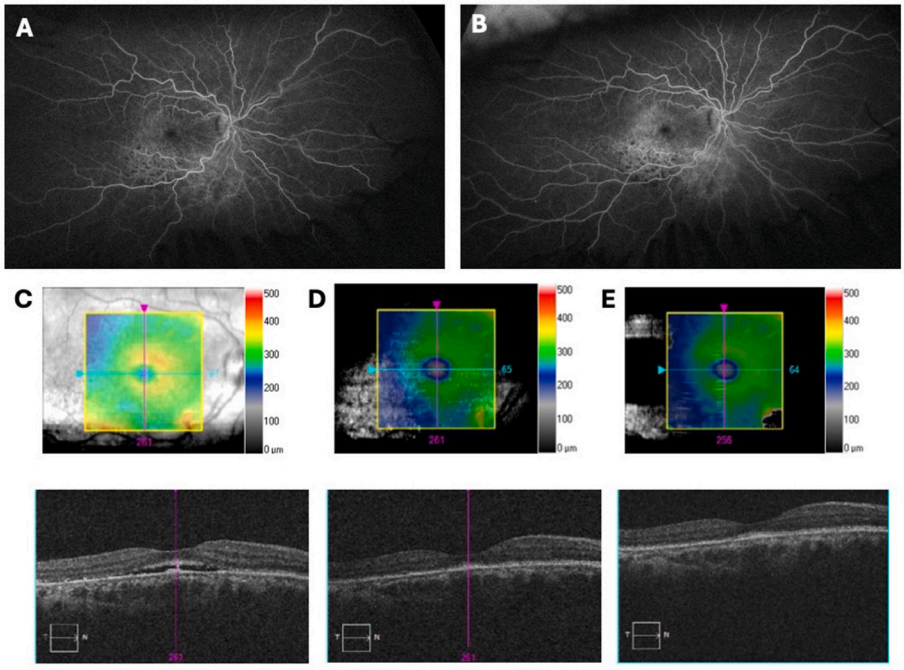

Fig. 5. Mid- (A) and late-phase (B) fluorescein angiography of the right eye performed just prior to the seventh and final session of photodynamic therapy revealed trace pinpoint leakage and granular staining without evidence of obvious secondary choroidal neovascular membrane, (C) Optical coherence tomography (OCT) of the right eye showed persistent subretinal fluid despite various treatments over three years. This OCT scan was obtained at the same visit during which the patient received her first dose of high-dose intravitreal aflibercept, 8 mg, which led to complete resolution of the subretinal fluid (D). She has been maintained on high-dose intravitreal aflibercept and exhibited no subretinal fluid at three months following initial treatment with high-dose aflibercept (E).

angiography and her first treatment with high-dose aflibercept, contributing to such a pronounced effect of anti-VEGF therapy, though we feel this is unlikely given the overall protracted course.

Since CSCR has a fluctuating clinical course, we cannot definitively conclude from our case report that resolution of subretinal fluid was caused by treatment with high-dose intravitreal aflibercept. However,

we believe this notable finding warrants further investigation and may serve as a foundation for future studies examining the use of high-dose intravitreal aflibercept for intractable CSCR.

CRediT authorship contribution statement

Jonathan B. Lin: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Loh-Shan B. Leung:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Claim of priority

After conducting a literature review on October 27, 2024 on PubMed and Google Scholar using the key words (high-dose aflibercept OR Eylea® HD AND central serous chorioretinopathy OR CSCR), we did not find any prior reports of patients with CSCR being treated with high-dose aflibercept.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Funding

No funding or grant support.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

J.B.L. was supported by the VitreoRetinal Surgery Foundation.

References

1. Fung AT, Yang Y, Kam AW. Central serous chorioretinopathy: a review. *Clin Exp Ophthalmol.* 2023;51(3):243–270. https://doi.org/10.1111/ceo.14201.
2. Mansour AM, Koaik M, Lima LH, et al. Physiologic and psychologic risk factors in central serous chorioretinopathy. *Ophthalmol Retina.* 2017;1(6):497–507. https://doi.org/10.1016/j.oret.2017.02.009.
3. Nicholson BP, Atchison E, Idris AA, Bakri SJ. Central serous chorioretinopathy and glucocorticoids: an update on evidence for association. *Surv Ophthalmol.* 2018;63(1):1–8. https://doi.org/10.1016/j.survophthal.2017.06.008.
4. Pan CK, Vail D, Bhattacharya J, Cao M, Mruthyunjaya P. The effect of obstructive sleep apnea on absolute risk of central serous chorioretinopathy. *Am J Ophthalmol.* 2020;218:148–155. https://doi.org/10.1016/j.ajo.2020.05.040.
5. Yannuzzi LA. Type-A behavior and central serous chorioretinopathy. *Retina.* 1987;7(2):111–131. https://doi.org/10.1097/00006982-198700720-00009.
6. Pauleikhoff LJB, Diederen RMH, Chang-Wolf JM, et al. Choroidal hyperpermeability patterns correlate with disease severity in central serous chorioretinopathy: CERTAIN study report 2. *Acta Ophthalmol.* 2024;102(6):e946–e955. https://doi.org/10.1111/aos.16679.
7. Fossataro F, Fossataro C, Abraham N, et al. Pathogenesis of central serous chorioretinopathy and the link between choroidal hyperpermeability and retinal pigment epithelium pump reversal. *Am J Ophthalmol.* 2024;266:206–217. https://doi.org/10.1016/j.ajo.2024.04.025.
8. Prakash G, Chauhan N, Jain S, Satsangi SK. Central serous chorioretinopathy: a review of the literature. *Asia Pac J Ophthalmol (Phila).* 2013;2(2):104–110. https://doi.org/10.1097/APO.0b013e31829069ee.
9. Burgett L, Aggarwal N, Latona J, Driban M, Chhablani J, Maturi RK. Retrospective large database study of central serous chorioretinopathy treatments and visual outcomes analysis in the United States. *J Vitreoretin Dis.* 2024;8(5):508–516. https://doi.org/10.1177/24741264241257021.
10. You EL, Hébert M, Jin TS, et al. Comparing interventions for chronic central serous chorioretinopathy: a network meta-analysis. *Surv Ophthalmol.* 2023;68(4):601–614. https://doi.org/10.1016/j.survophthal.2023.03.001.
11. Park JB, Kim K, Kang MS, Kim ES, Yu SY. Central serous chorioretinopathy: treatment. *Taiwan J Ophthalmol.* 2022;12(4):394–408. https://doi.org/10.4103/2211-5056.362040.
12. Lim JW, Kim MU. The efficacy of intravitreal bevacizumab for idiopathic central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2011;249(7):969–974. https://doi.org/10.1007/s00417-010-1581-9.
13. Kim M, Lee SC, Lee SJ. Intravitreal ranibizumab for acute central serous chorioretinopathy. *Ophthalmologica.* 2013;229(3):152–157. https://doi.org/10.1159/000345495.
14. Seraj H, Alhamoud M, Khoshhal MS, Alhashim H, Alsaif A, Abukhashabah A. The uses of photodynamic therapy versus anti-vascular endothelial growth factor in the management of acute central serous chorioretinopathy: a systematic review and meta-analysis. *Cureus.* 2023;15(9), e46100. https://doi.org/10.7759/cureus.46100.
15. Lim JW, Kim MU, Shin MC. Aqueous humor and plasma levels of vascular endothelial growth factor and interleukin-8 in patients with central serous chorioretinopathy. *Retina.* 2010;30(9):1465–1471. https://doi.org/10.1097/IAE.0b013e3181d8e7fe.
16. Shin MC, Lim JW. Concentration of cytokines in the aqueous humor of patients with central serous chorioretinopathy. *Retina.* 2011;31(9):1937–1943. https://doi.org/10.1097/IAE.0b013e31820a6a17.
17. Pitcher JD, Witkin AJ, DeCroos FC, Ho AC. A prospective pilot study of intravitreal aflibercept for the treatment of chronic central serous chorioretinopathy: the CONTAIN study. *Br J Ophthalmol.* 2015;99(6):848–852. https://doi.org/10.1136/bjophthalmol-2014-306018.
18. Lanzetta P, Korobelnik JF, Heier JS, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. *Lancet.* 2024;403(10432):1141–1152. https://doi.org/10.1016/S0140-6736(24)00063-1.
19. Brown DM, Boyer DS, Do DV, et al. Intravitreal aflibercept 8 mg in diabetic macular oedema (PHOTON): 48-week results from a randomised, double-masked, non-inferiority, phase 2/3 trial. *Lancet.* 2024;403(10432):1153–1163. https://doi.org/10.1016/S0140-6736(23)02577-1.
20. van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: towards an evidence-based treatment guideline. *Prog Retin Eye Res.* 2019;73, 100770. https://doi.org/10.1016/j.preteyeres.2019.07.003.
21. Chan WM, Lam DSC, Lai TYY, Tam BSM, Liu DTL, Chan CKM. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. *Br J Ophthalmol.* 2003;87(12):1453–1458. https://doi.org/10.1136/bjo.87.12.1453.
22. Park SJ, Choi Y, Na YM, et al. Intraocular pharmacokinetics of intravitreal aflibercept (Eylea) in a rabbit model. *Invest Ophthalmol Vis Sci.* 2016;57(6):2612–2617. https://doi.org/10.1167/iovs.16-19204.
23. Pellegrini M, Bernabei F, Mercanti A, et al. Short-term choroidal vascular changes after aflibercept therapy for neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol.* 2021;259(4):911–918. https://doi.org/10.1007/s00417-020-04957-5.
24. Shen M, Zhou H, Lu J, et al. Choroidal changes after anti-VEGF therapy in AMD eyes with different types of macular neovascularization using swept-source OCT angiography. *Invest Ophthalmol Vis Sci.* 2023;64(13):16. https://doi.org/10.1167/iovs.64.13.16.