Author Affiliations: Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark (Bjerager, Rothenbuehler); Department of Ophthalmology, University Hospital Basel, Basel, Switzerland (Hasler, Maloca, Rothenbuehler); Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland (Maloca).

Corresponding Author: Jakob Bjerager, MD, Department of Ophthalmology, Rigshospitalet, Valdemar Hansens Vej 1-23, 2600 Glostrup, Denmark (jakob.kondras.bjerager.02@regionh.dk).

Published Online: September 28, 2023. doi:10.1001/jamaophthalmol.2023.4215

Conflict of Interest Disclosures: Dr Hasler has received personal fees from Roche and Biogen. Dr Maloca has received personal fees from Roche and Zeiss Forum and holds intellectual property for machine learning at MIMO AG and VisionAI. No other disclosures were reported.

Additional Contributions: We thank the patient for granting permission to publish this information.

1. Yasunari T, Shiraki K, Hattori H, Miki T. Frequency of choroidal abnormalities in neurofibromatosis type 1. *Lancet*. 2000;356(9234):988-992. doi:10.1016/S0140-6736(00)02716-1

2. Parrozzani R, Frizziero L, Trainiti S, et al. Retinal vascular abnormalities related to neurofibromatosis type 1: natural history and classification by optical coherence tomography angiography in 473 patients. *Retina*. 2021;41(5):979-986. doi:10.1097/IAE.0000000000002962

3. Touzé R, Abitbol MM, Bremond-Gignac D, Robert MP. Retinal vascular abnormalities in children with neurofibromatosis type 1. *Retina*. 2021;41(12):2589-2595. doi:10.1097/IAE.0000000000003234

4. Umunakwe OC, Zhang W, Chen X, Grewal DS, Gospe SM III. Neurofibromatosis type 1 vasculopathy presenting as impending central retinal artery occlusion. *J Neuroophthalmol*. 2019;39(2):234-236. doi:10.1097/WNO.0000000000000739

5. McAllister IL. Chorioretinal anastomosis for central retinal vein occlusion: a review of its development, technique, complications, and role in management. *Asia Pac J Ophthalmol (Phila)*. 2020;9(3):239-249. doi:10.1097/APO.0000000000000286

6. Kwok AKH, Lee VYW, Lai TYY, Hon C. Laser induced chorioretinal venous anastomosis in ischaemic central retinal vein occlusion. *Br J Ophthalmol*. 2003;87(8):1043-1044. doi:10.1136/bjo.87.8.1043

Bruton Tyrosine Kinase Inhibitor in 2 Patients With Vitreoretinal Lymphoma

Tirabrutinib is an orally administered, small-molecule, second-generation Bruton tyrosine kinase inhibitor, approved in Japan for treating recurrent or refractory central nervous system (CNS) lymphoma.[1] Approximately 15% to 25% of patients with CNS lymphoma present with or ultimately develop vitreoretinal lymphoma (VRL).[2] Ibrutinib, the first selective Bruton tyrosine kinase inhibitor, showed clinical activity in the intraocular compartment in CNS lymphoma.[3] However, it is unclear whether tirabrutinib is also effective for VRL. We present 2 patients with VRL whose retinal appearances appeared to improve after the administration of tirabrutinib for treating concurrent CNS lymphoma, highlighting its potential as a new therapeutic agent for this disease.

Report of Cases | *Case 1*. An 80-year-old female patient previously treated with chemotherapy and radiotherapy for primary CNS lymphoma presented with decreased vision in the right eye (**Figure 1**A). She was diagnosed with secondary VRL. After treatment with repeated doses of intravitreal methotrexate, she achieved remission. However, the VRL recurred 1 year later (Figure 1B) and was refractory to intravitreal methotrexate. Eight days after the 11th dose of intravitreal methotrexate (Figure 1C), CNS recurrence was evident. After discontinuing intravitreal methotrexate, tirabrutinib was administered for refractory CNS lymphoma. The CNS and VRL lesions appeared less evident within 2 weeks (Figure 1D), and she remained in remission for 3 months. However, 4 months after the start of tirabrutinib, it was discontinued due to recurrent CNS lymphoma.

Case 2. A 73-year-old female patient experienced blurred vision in the right eye (**Figure 2**A and B). Three weeks later, she developed dysarthria, and a brain magnetic resonance imaging scan showed a lesion near the thalamus. A chorioretinal biopsy was performed, and a diagnosis of CNS lymphoma and VRL was confirmed by cytological examination (class V). The patient was administered tirabrutinib in suspension through a nasogastric tube due to her low Karnofsky performance status.[4] The VRL lesions rapidly became less apparent (Figure 2C and D), and she was in remission for the next 3 months. The brain lesions slowly improved, and after a month, the patient was able to take tablets. However, 3 months later she experienced a hemorrhagic stroke and the tirabrutinib was discontinued. She died 1 month later.

Discussion | The experiences of these 2 patients with coexisting VRL and CNS lymphoma and short-term remission of VRL associated with tirabrutinib suggest this Bruton tyrosine kinase inhibitor may be an effective treatment for VRL. The pivotal clinical trial for tirabrutinib approval in Japan for relapsed or refractory CNS lymphoma included 3 patients with VRL who showed a partial CNS lymphoma response. The details of the ocular lesions were not described.[1] Tirabrutinib was detected intrathecally in the trial; however, it is not clear whether it was also detected in the ocular fluid. The measurement of intraocular levels of tirabrutinib after oral administration may be associated with the changes in the VRL lesions noted after initiating this therapy.

The recommended therapy for patients with coexisting VRL and CNS lymphoma includes high-dose methotrexate-based chemotherapy, radiation therapy, and local ocular chemotherapy.[5] However, a second course of radiotherapy is not indicated for recurrence, and intensive systemic and ocular chemotherapy are difficult for older patients or those with severe cognitive impairment due to the CNS malignancy. Thus, there is an urgent need to develop new treatment strategies. Tirabrutinib may be a new option for patients who are unable to tolerate current standard treatment options.

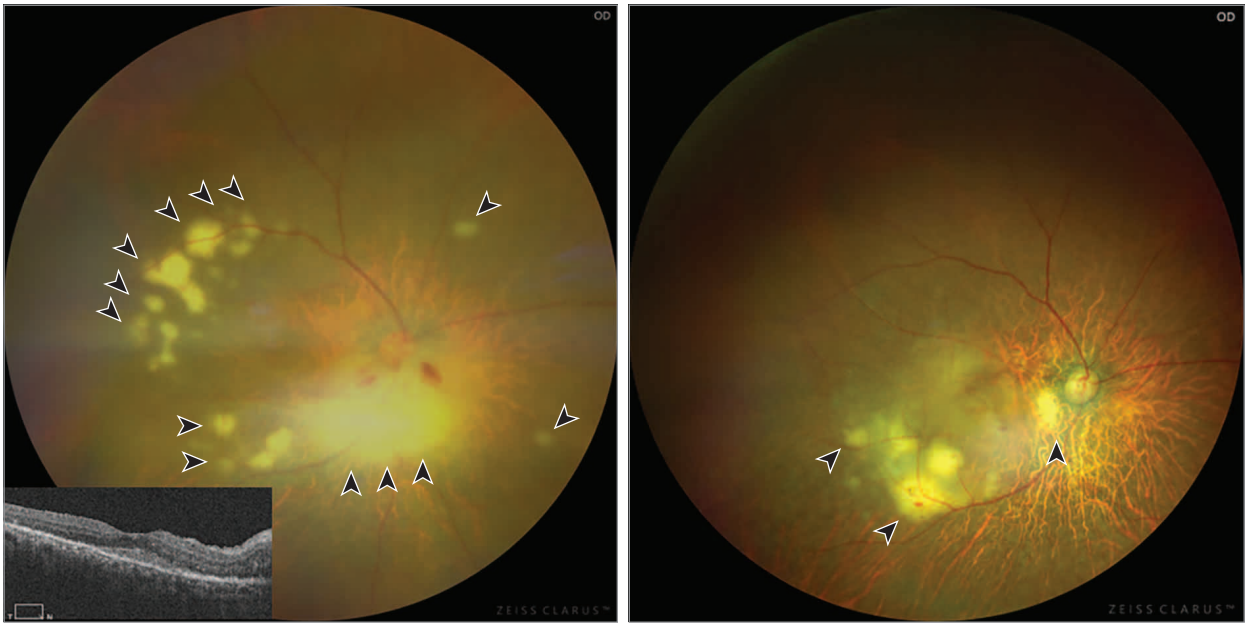
In conclusion, we report on 2 patients who achieved remission of VRL associated with tirabrutinib treatment. A possible combination of tirabrutinib and intravitreal methotrexate injections or tirabrutinib for eyes refractory to intravitreal methotrexate may lead to better management and reduced morbidity in cases of VRL.

Chiharu Iwahashi, MD
Masuo Sakamoto, MD
Nobuyuki Ohguro, MD
Shunji Kusaka, MD

Figure 1. Color Fundus Images of the Right Eye of Patient 1

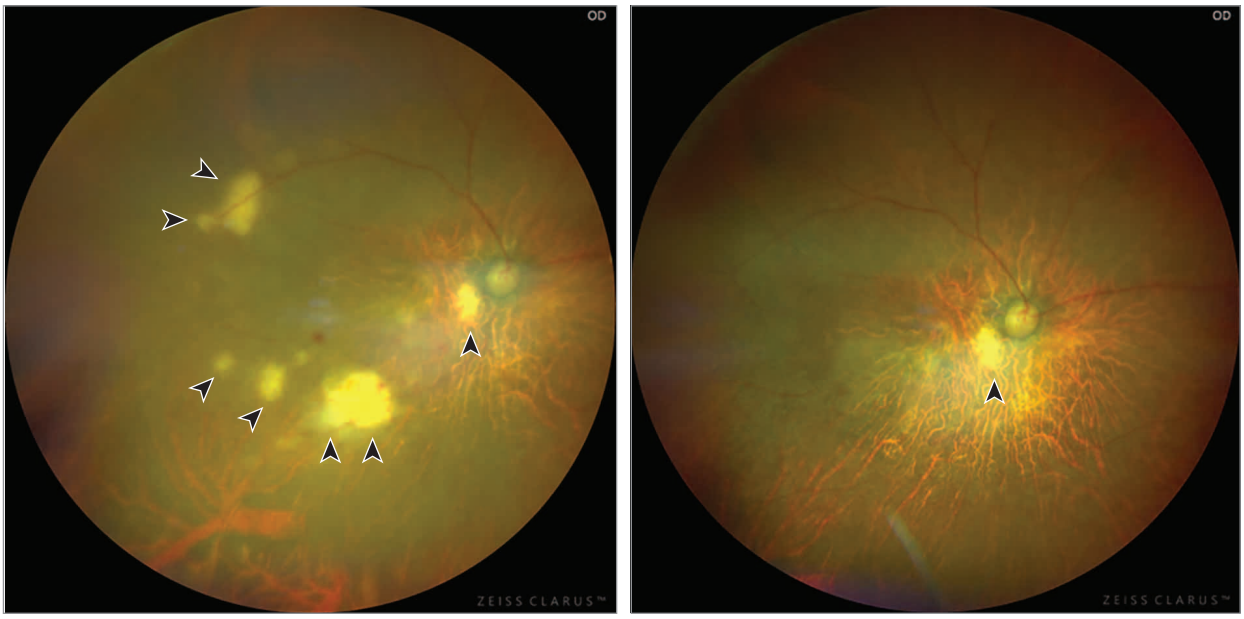
A VRL lesions

B VRL lesions recurrent 1 y after intravitreal methotrexate therapy



C VRL lesions refractory following additional methotrexate therapy

D VRL lesions resolved 2 wk after starting oral tirabrutinib administration



A, Prior to treatment, color fundus image demonstrates confluent subretinal yellowish lesions in the posterior pole (arrowheads). Horizontal cross-sectional optical coherence tomography image (lower left) shows subretinal infiltrates. B, Vitreoretinal lymphoma recurred 1 year after maintenance therapy. C, Vitreoretinal lymphoma persisted despite 11 additional intravitreal injections of methotrexate. D, Overall improvement was observed 2 weeks after starting oral tirabrutinib administration.

Author Affiliations: Department of Ophthalmology, Kindai University Faculty of Medicine, Osaka, Japan (Iwahashi, Sakamoto, Kusaka); Department of Ophthalmology, Japan Community Health and Care Osaka Hospital, Osaka, Japan (Ohguro).

Corresponding Author: Chiharu Iwahashi, MD, Department of Ophthalmology, Kindai University Faculty of Medicine, 377-2, Ohonohigashi, Osakasayama, Osaka 589-8511, Japan (s.chiharu@gmail.com).

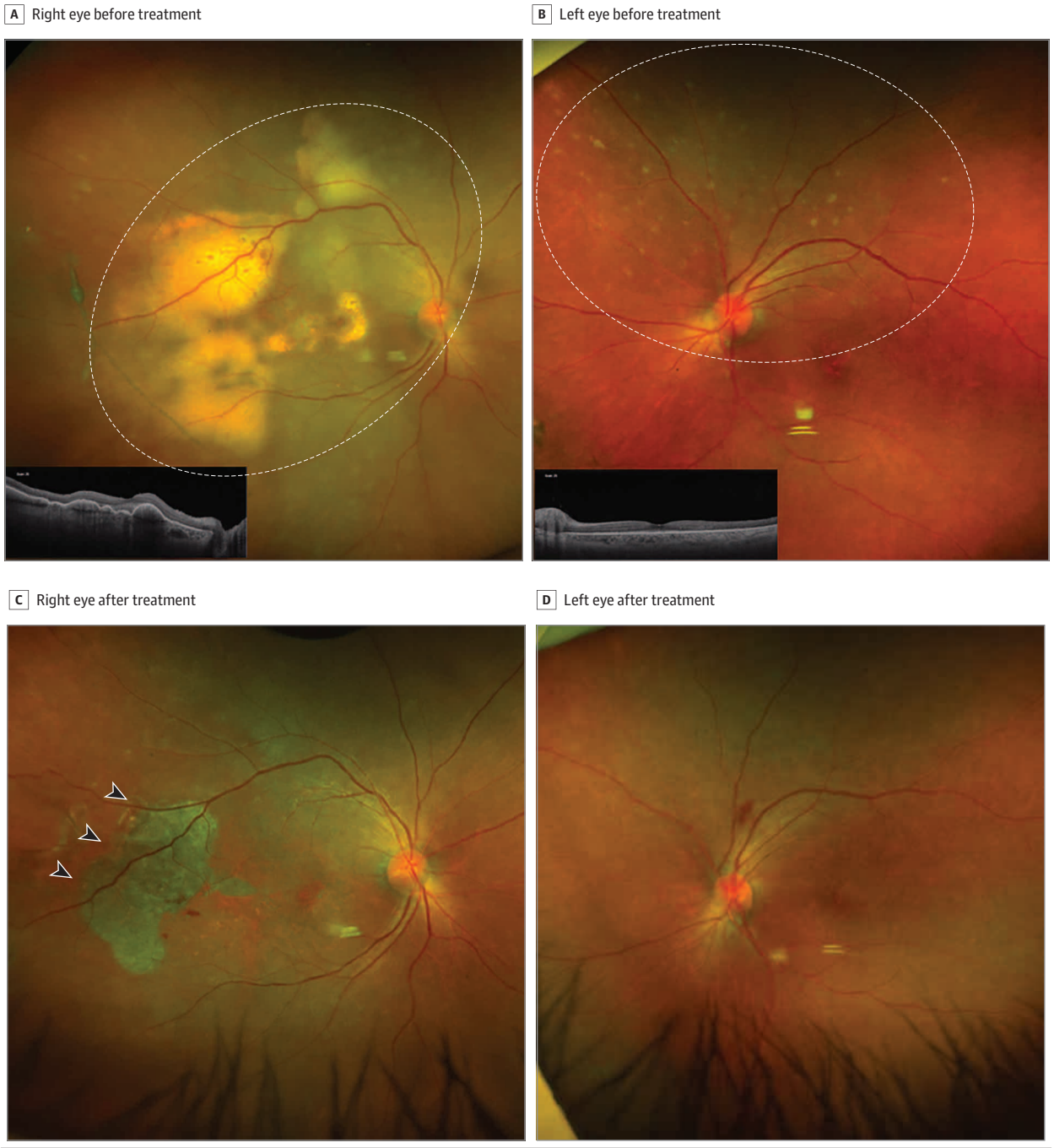
Published Online: October 19, 2023. doi:10.1001/jamaophthalmol.2023.4509

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the patients for granting permission to publish this information.

1. Narita Y, Nagane M, Mishima K, et al. Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory

Figure 2. Pseudocolor Fundus Images of Both Eyes of Patient 2



A, Fundus image of the right eye before chorioretinal biopsy shows confluent yellowish subretinal lesions and small white lesions distributed from the posterior pole to the midperipheral retina (dotted circle). A horizontal cross-sectional optical coherence tomography image (lower left) shows a mass between the retinal pigment epithelium and the Bruch membrane. B, Fundus image of the left eye before treatment, on the same day as A, shows granular white lesions (dotted circle) in the upper and nasal part of the retina. A horizontal cross-sectional OCT image (lower left) shows no abnormalities in the macula. C, Following chorioretinal biopsy and 1-month oral administration of tirabrutinib, imaging shows retinal degeneration at the biopsy site (arrowheads) and resolution of the vitreoretinal lymphoma. D, Imaging 1 month after starting oral administration of tirabrutinib shows resolution of the granular white lesions.

primary central nervous system lymphoma. *Neuro Oncol*. 2021;23(1):122-133. doi:10.1093/neuonc/noaa145

2. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. *Oncologist*. 2011;16(11):1589-1599. doi:10.1634/theoncologist.2011-0210

3. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma Study Association (LYSA) and the French Oculo-Cerebral Lymphoma (LOC) network. *Eur J Cancer*. 2019;117:121-130. doi:10.1016/j.ejca.2019.05.024

4. Yoshioka H, Okuda T, Nakao T, Fujita M, Takahashi JC. Experience with tirabrutinib in the treatment of primary central nervous system lymphoma that is difficult to treat with standard treatment. *Anticancer Res*. 2022;42(8):4173-4178. doi:10.21873/anticanres.15917

5. Habot-Wilner Z, Frenkel S, Pe'er J. Efficacy and safety of intravitreal methotrexate for vitreo-retinal lymphoma—20 years of experience. *Br J Haematol*. 2021;194(1):92-100. doi:10.1111/bjh.17451

COMMENT & RESPONSE

Advances in Artificial Intelligence Chatbot Technology in Ophthalmology

To the Editor We read with interest the timely article by Mihalache and colleagues.[1] Using the free GPT-3.5 version of ChatGPT released in November 2022, the authors show that this artificial intelligence (AI) chatbot correctly answered half of OphthoQuestions' practice questions. In this letter, we highlight the higher performance of the more recent GPT-4 version of ChatGPT (released in April 2023) compared with GPT-3.5, ophthalmologists, and ophthalmologists-in-training on practice material for the written examination of the American Board of Ophthalmology (ABO).[2]

Even before the advent of ChatGPT, AI demonstrated strong capabilities in ophthalmology. Since 2015, over 7 AI-enabled ophthalmic medical devices have been approved by the US Food and Drug Administration.[3] Performance of AI systems has been rated as comparable with or greater than that of experts for diabetic retinopathy grading, age-related macular degeneration grading, and disease diagnoses from optical coherence tomography imaging.[4] These AI systems were trained on ophthalmic clinical/imaging data, whereas ChatGPT was trained on online text data, including books and articles.

In our study,[2] GPT-3.5, GPT-4, and human users achieved overall scores (including nonimaging questions) of 63.1%, 76.9%, and 72.6%, respectively. Despite lacking image processing modalities at the time of our study, GPT-4 exceeded the ABO's passing threshold on American Academy of Ophthalmology practice material for the ABO written examination (65%). When imaging questions were excluded, GPT-4 significantly outperformed ophthalmologists and ophthalmologists-in-training. Technological advances, especially the integration of image processing, will improve AI's ability to support ophthalmic care.

It is also important to consider the ethical quandaries of using AI in ophthalmology.[5] Future models will inevitably make mistakes and the question of responsibility remains unclear: cyber ethicists have noted that computers cannot be held accountable.[5] Overreliance on AI systems poses the risk of ophthalmologists accepting erroneous results without deliberation. Moreover, the traditional training of AI models on relatively homogenous data sets endangers generalizability of its results and may perpetuate disparities in ophthalmic care for underserved populations.

The study by Mihalache and colleagues[1] is an important contribution to the scientific literature given the novelty and relevance of advanced chatbots. Our research indicates that GPT-4, which was released just 5 months after GPT-3.5, significantly outperformed GPT-3.5, and when imaging questions were excluded, outperformed human users on the American Academy of Ophthalmology practice written examination. Further research is needed to assess the utility, feasibility, and ethics of AI chatbot technology in ophthalmology.

John C. Lin, ScB
Sai S. Kurapati, MS
Ingrid U. Scott, MD, MPH

Author Affiliations: Perelman School of Medicine, University of Pennsylvania, Philadelphia (Lin); Department of Ophthalmology, Penn State College of Medicine, Hershey, Pennsylvania (Kurapati, Scott); Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania (Scott).

Corresponding Author: Ingrid U. Scott, MD, MPH, Penn State College of Medicine, 500 University Dr, HU19, Hershey, PA 17033-0850 (iscott@pennstatehealth.psu.edu).

Published Online: October 19, 2023. doi:10.1001/jamaophthalmol.2023.4619

Conflict of Interest Disclosures: None reported.

1. Mihalache A, Popovic MM, Muni RH. Performance of an artificial intelligence chatbot in Ophthalmic Knowledge Assessment. *JAMA Ophthalmol*. 2023;141(6):589-597. doi:10.1001/jamaophthalmol.2023.1144

2. Lin JC, Younessi DN, Kurapati SS, Tang OY, Scott IU. Comparison of GPT-3.5, GPT-4, and human user performance on a practice ophthalmology written examination. *Eye (Lond)*. 2023;1-2. doi:10.1038/s41433-023-02564-2

3. US Food and Drug Administration. Artificial intelligence and machine learning (AI/ML)-enabled medical devices. Accessed September 14, 2023. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

4. Benet D, Pellicer-Valero OJ. Artificial intelligence: the unstoppable revolution in ophthalmology. *Surv Ophthalmol*. 2022;67(1):252-270. doi:10.1016/j.survophthal.2021.03.003

5. Bressler NM. What artificial intelligence chatbots mean for editors, authors, and readers of peer-reviewed ophthalmic literature. *JAMA Ophthalmol*. 2023;141(6):514-515. doi:10.1001/jamaophthalmol.2023.1370

In Reply We sincerely thank Lin and colleagues for their comments on our article.[1] Using a free trial of OphthoQuestions, a popular question bank for ophthalmology board certification preparation, we found that ChatGPT-3.5 correctly answered 58 of 125 questions in January 2023 (46%) and 73 of 125 questions in February 2023 (58%).[1] Lin and colleagues[2] make the argument that since this time, the accuracy of ChatGPT has increased. We completely agree and note the findings of our recent investigation published in *JAMA Ophthalmology*.[3] Here, we found that ChatGPT-4 correctly answered 105 of 125 questions of the same question bank in March 2023 (84%), remarkably outperforming the previous model of this chatbot.[3]

Using practice material for the American Board of Ophthalmology written examination in April 2023, Lin and colleagues found that ChatGPT-4 outperformed both ChatGPT-3.5, as well as ophthalmologists and trainees.[2] Across 223 text-based American Board of Ophthalmology practice questions, ChatGPT-3.5, ChatGPT-4, and human users correctly answered 69.5%, 84.3%, and 72.9% of questions, respectively.[2] Hence, ChatGPT-4 appeared to have performed very similarly in our recent study compared with the work of Lin and colleagues, which used a different test bank with a larger sample of practice questions. Indeed, the findings of Lin and colleagues complement our previous work and represent an important contribution to the literature, helping to reinforce the notion that artificial intelligence (AI) chatbots may be ap-