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Belzutifan as the Primary Treatment of Bilateral Juxtapapillary Retinal Hemangioblastoma in a Patient With Von Hippel-Lindau Disease

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Abstract

Purpose: To describe the efficacy of belzutifan as a treatment for juxtapapillary retinal hemangioblastomas in patients with von Hippel-Lindau disease. **Methods:** A case and its findings were analyzed, and a systematic literature review was conducted using PubMed and Ovid MEDLINE. **Results:** At a routine follow-up, a 63-year-old woman with a history of von Hippel-Lindau disease and slowly progressive bilateral juxtapapillary retinal hemangioblastomas presented with decreased visual acuity (VA) in the right eye resulting from significant lesion growth and an increase in central macular edema and exudate. Oral belzutifan therapy was initiated. A significant bilateral regression and decrease in tumor size, improved macular thickening and edema, and improved VA were seen over a 6-month period. **Conclusions:** The current literature on the therapeutic effects of oral belzutifan is limited; however, recent reports have been promising. This case shows the potential efficacy of belzutifan as a first-line treatment for vision-threatening juxtapapillary retinal hemangioblastomas in patients with von Hippel-Lindau disease.

Keywords

von Hippel-Lindau, hemangioblastoma, belzutifan

Introduction

Von Hippel-Lindau disease is a rare, autosomal-dominant condition characterized by the development of multiorgan tumors as a result of a mutation in the von Hippel-Lindau tumor suppressor gene.[1–3] The incidence is between 1 in 27 300 to 39 000 live births.[4,5] Lesions associated with von Hippel-Lindau disease can occur in the central nervous system (CNS), kidneys, adrenal glands, pancreas, and reproductive organs. Notably, ocular manifestations emerge early, with a median age at onset of 24.8 years, and serve as key diagnostic indicators in approximately 50% of cases.[2,6]

Retinal hemangioblastomas in von Hippel-Lindau disease are often categorized into peripheral or juxtapapillary lesions.[3] Although peripheral lesions are far more common than optic nerve lesions, both may be complicated by hemorrhages, exudate, and edema and thus can be vision-threatening.[7] In addition, fibrosis resulting from angiogenesis renders eyes susceptible to tractional retinal detachments. The emergence of new juxtapapillary retinal capillary hemangioblastomas is the most significant risk for vision loss over time in eyes with von Hippel-Lindau disease.[8]

The current treatment for retinal hemangioblastoma varies depending on the tumor size and location, degree of exudation, and epiretinal fibrosis, among other factors.[9,10] For peripheral lesions measuring less than 1.5 mm, laser photocoagulation may be the best treatment choice.[9] For tumors larger than 1.5 mm, cryotherapy, plaque radiotherapy, transpupillary thermotherapy, and vitreoretinal surgery are treatment options.[3,9] In contrast to peripheral retinal hemangioblastomas, the options for juxtapapillary lesions are limited because ablative treatments carry the risk for irreversible vision loss.[9] Regardless of the mode of treatment, up to 25% of cases result in permanent vision degradation, with a visual acuity (VA) worse than 20/40 in the involved eye.[11]

The discovery of the role of hypoxia-inducing factor in von Hippel-Lindau tumors led to the development of a small-molecule inhibitor for targeted therapy.[12,13] Von Hippel-Lindau tumor suppressor, or pVHL, is a protein encoded by the von Hippel-Lindau

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gene that regulates the ubiquitination and breakdown of hypoxia-inducing factor.[14,15] A mutation or deletion of pVHL disrupts this regulatory mechanism, resulting in an increase in the hypoxia-inducing factor and subsequent vascular growth, which drives the development of retinal hemangioblastomas.[8]

In August 2021, the US Food and Drug Administration approved belzutifan, a small-molecule inhibitor of HIF-2α, for renal cell carcinoma, CNS hemangioblastomas, and pancreatic neuroendocrine tumors in patients with von Hippel-Lindau disease.[16,17] This targeted oral treatment, which has been used successfully to treat other von Hippel-Lindau tumors, is a promising nonablative approach to treat vision-threatening retinal hemangioblastomas.[17–20]

We present a unique case of bilateral juxtapapillary hemangioblastoma successfully treated with belzutifan, which led to rapid tumor regression and an improvement in vision. In addition, we performed a systematic literature review using PubMed, Ovid MEDLINE, and Google Scholar using the search terms "von Hippel-Lindau", "belzutifan", "retina", "retinal", and "ocular".

Case Report

A 63-year-old woman with a history that included longstanding von Hippel-Lindau disease, partial nephrectomy, and adrenal involvement was followed biannually in our retina clinic from 2015 through 2022 with relatively stable bilateral optic nerve capillary hemangioblastomas. During this time, the best-corrected VA (BCVA) in the right eye remained stable at 20/50. The tumor in the right eye, which encompassed the inferior half of the optic nerve, was growing at a very slow rate with the gradual development of an epiretinal membrane and secondary macular thickening. The lesion in the patient's left eye encompassed approximately 25% of the nasal optic nerve, and the BCVA was stable at 20/20.

By November 2022, the patient's best spectacle-corrected VA had decreased to 20/150 OD and remained stable at 20/25 OS. A fundus examination and optical coherence tomography (OCT) imaging showed a corresponding increase in central macular exudate and edema in the right eye.

The patient was referred to ocular oncology for a second opinion regarding treatment options for the right eye. Off-label use of intravitreal (IVT) steroid, bevacizumab, and a trial of oral belzutifan were discussed. The patient deferred IVT therapy and started on daily 120 mg belzutifan in March 2023. The drug was obtained with previous authorization through the patient's commercial private insurance using a diagnosis code for CNS hemangioblastoma.

By May 2023, the BCVA had improved to 20/100 OD and 20/20 OS with corresponding improvement in macular edema and exudate in the right eye. In November 2023, 6 months after the patient started on belzutifan, the BCVA had improved further to 20/60 OD and 20/20 OS, with significant regression of both optic nerve hemangioblastomas and a corresponding decrease in macular exudates and thickening in the right eye, as seen on OCT. In addition, fluorescein angiography showed decreased leakage (Figures 1 and 2).

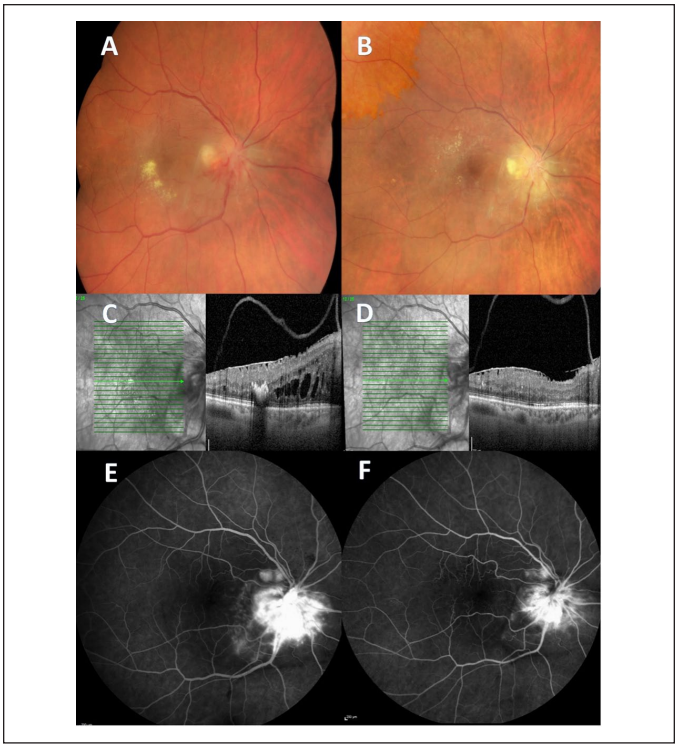

Figure 1. Improvement of a juxtapapillary retinal capillary hemangioblastoma in the right eye is seen after the use of oral belzutifan, as indicated by decreased lesion size, improvement in juxtapapillary vessel engorgement, decreased macular thickening and intraretinal fluid, and decreased leakage on fluorescein angiography (FA). (A) Fundus photograph, (C) macular optical coherence tomography (C), and (E) late-stage FA before treatment with belzutifan. Results of 6 months of belzutifan treatment are shown in corresponding images B, D, and F.

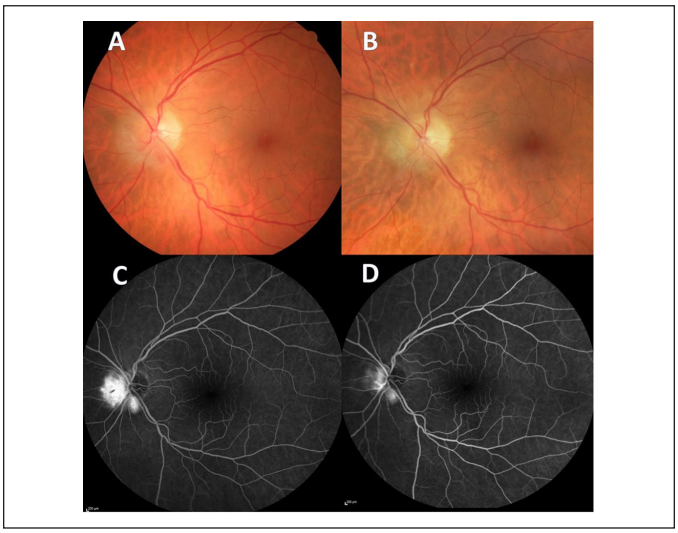

Figure 2. Improvement of a small juxtapapillary retinal capillary hemangioblastoma in the left eye is seen after the use of oral belzutifan, as indicated by a decrease in lesion size, reduced vessel engorgement with fibrosis, and decreased leakage on fluorescein angiography (FA). (A) Fundus photograph and (C) late-stage FA before treatment with belzutifan. Results of 6 months of belzutifan treatment are shown in corresponding images B and D.

Table 1. Reported Cases of Successful Belzutifan Treatment of von Hippel-Lindau–Associated Retinal Hemangioblastomas.

Author (Year)[a]	Age (y)	Visual Acuity		Previous Treatment	Treatment Effect of Belzutifan
		Before Belzutifan	After Belzutifan		
Grimes[21] (2024)					
Case 1	40	20/25 OS 20/25 OD	NR	Observation	Resolving SRF; decrease in intrinsic vascularity; decrease in tortuosity of feeder vessels
Case 2	66	20/40 OD	NR	Laser photocoagulation, cryotherapy	Fibrosis of lesion; reduction in retinal edema, SRF, and lesion size and thickness
Mustafi[22] (2024)	11	20/400 OS	20/400 OS	None	Engorgement and tortuosity of feeding arterioles and draining veins improved; decreased exudative RD; decreased lesion elevation with fibrosis
Cotton[23] (2023)	71	NLP	NLP	Prednisolone acetate, atropine	80% reduction in pain; tumor regression of nearly 50%; 31% decrease in intraocular mass thickness; 60% reduction in transscleral component; decreased IOP (48 mm Hg to 21 mm Hg)
Jones[24] (2024)	15	20/30 OS	20/30 OS	Focal laser therapy, PDT, bevacizumab injection, vitrectomy/ membrane peel/ endolaser ablation, cryotherapy	Significant improvement in feeder vessel engorgement and tortuosity and less vascularization of tumor
Fairbanks[25] (2023)	24	NR	NR	NR	Improvement in engorgement and tortuosity of the feeding arterioles and draining veins; reduction in number and size of the retinal capillary and CNS hemangioblastomas
Ercanbrack[26] (2024)					
Case 1	23	20/20 OD $20/25^{-1}$ OS	OD NR $20/25^{-2}$ OS	Laser OD None OS	OS reduction in tumor size from 2.1 mm^2 to 1.4 mm^2; received subsequent laser treatments
Case 2	32	$20/20^{-1}$ OD 20/20 OS	$20/20^{-1}$ OD $20/20^{-1}$ OS	None	OD reduction in tumor size from 2.7 mm^2 to 1.9 mm^2 OS reduction in tumor sizes from 5.4 mm^2 to 4.3 mm^2 and 12.3 mm^2 to 11.4 mm^2
Case 3	44	NLP OD 20/20 OS	NLP OD 20/20 OS	None	OD reduction in tumor size from 10.3 mm^2 to 5.5 mm^2; resolution of serous RD

Abbreviations: CNS, central nervous system; IOP, intraocular pressure; NLP, no light perception, NR, not reported; PDT, photodynamic therapy; RD, retinal detachment; SRF, subretinal fluid.
[a]First author.

Conclusions

Our case highlights the use of belzutifan for juxtapapillary retinal hemangioblastomas as a promising alternative to current ablative treatments, which pose a risk for irreversible vision loss. Previous data, albeit limited, corroborate the significant therapeutic potential of belzutifan in the treatment of von Hippel-Lindau–associated tumors.

A phase 2 trial of the efficacy of oral belzutifan for von Hippel-Lindau–associated renal cell carcinoma also found retinal hemangioblastomas on fundus imaging in 16 participants. In addition to a significant improvement in renal cell carcinoma with oral belzutifan therapy, 16 (55%) of 29 eyes showed improvement and 12 (41%) of 29 eyes showed stability of the retinal lesions.[20] Since then, case reports of oral belzutifan use for retinal hemangioblastomas have shown feeder vessels with reduced engorgement as well as decreased retinal tumor size. Our literature review identified 6 published case reports (Table 1).[21–26]

Grimes et al[21] reported an adult case of juxtapapillary retinal hemangioblastoma with a reduction in thickness and subretinal fluid as well as improved intraretinal fluid (IRF) and traction after 2.5 years of belzutifan treatment. Mustafi et al[22] reported an 11-year-old patient with severe vision loss resulting from a juxtapapillary lesion and macular exudative RD. Six months after the patient started on belzutifan, the feeding and draining vessels showed reduced prominence, the exudative RD had improved,

and the lesion had shrunk significantly in size. In our patient, we also noted juxtapapillary tumor regression with fibrosis and reduced IRF and exudate after treatment with belzutifan. In the previously mentioned cases, the patients' presenting vision was poor and remained unchanged with treatment. In contrast, our patient's BCVA improved after treatment with belzutifan, as shown by the structural and anatomic improvement seen on multimodal imaging.

Belzutifan has also been used to treat refractory retinal hemangioblastomas. Jones et al[24] reported a case of a 15-year-old boy with a peripheral retinal hemangioblastoma who was previously treated unsuccessfully with focal laser therapy, photodynamic therapy, cryotherapy, IVT bevacizumab, and vitrectomy with membrane stripping and endolaser ablation. After 11 months of treatment with systemic belzutifan, a dilated fundus examination showed significantly less vascularization of the tumor and distention of feeder vessels. Fairbanks et al[25] reported an adult patient with similar findings, with regression of multiple peripheral lesions after 6 months of systemic treatment with belzutifan. Of note, Ercanbrack et al[26] reported 3 cases of retinal hemangioblastoma that responded to belzutifan, albeit with dose-limiting anemia that led to 1 patient's discontinuation of the treatment. Our patient remained on the 120 mg dose of belzutifan for the entire duration, with no need for a transfusion because her hemoglobin levels remained higher than 9 g/dL. In addition, her fatigue was a manageable symptom.

The current literature on the therapeutic effects of oral belzutifan for ocular pathology is limited. Existing case reports describe significant improvement in von Hippel-Landau–associated retinal hemangioblastomas, including difficult-to-treat juxtapapillary lesions, giant retinal hemangioblastomas, and other refractory retinal hemangioblastomas. The response time to belzutifan varies widely, ranging between 4 weeks and 11 months.[21,24] Oral belzutifan may be a viable treatment option in a multimodal approach to management in bilateral cases, select cases in which tumor progression threatens vision and local ablative therapy poses a risk for vision loss, and as indicated for the treatment of associated systemic tumors. Further research involving larger samples and robust study designs is warranted.

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Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

Informed consent, including permission for publication of all photographs and images included herein, was obtained before data collection.

Declaration of Conflicting Interests

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