Ocular Oncology and Pathology

Research Article

Ocul Oncol Pathol 2024;10:154–161
DOI: 10.1159/000539434

Received: March 30, 2024
Accepted: May 17, 2024
Published online: May 24, 2024

Belzutifan in Individuals with von Hippel-Lindau Retinal Hemangioblastomas: Institutional Experience and Review of the Literature

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Keywords
Retinal hemangioblastoma · Belzutifan · von Hippel-Lindau

Abstract
Introduction: The systemic HIF-2 alpha inhibitor, belzutifan, has been approved for use in patients with von Hippel-Lindau disease (VHL)-associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, and pancreatic neuroendocrine tumors. This drug has also shown promise in controlling VHL retinal hemangioblastomas (RHs), but little work has been published on the use of the drug in this setting. ***Methods:*** We conducted a retrospective review of patients with VHL-associated RHs followed by the retina service at our institution who were treated with systemic belzutifan. Patient age, gender, genotype, presence of systemic tumors, indication for the drug, initial dose, adjusted dose, side effects, and tumor response were recorded. We also conducted a literature search for all manuscripts describing the effect of belzutifan on VHL-associated ocular tumors. ***Results:*** We identified 12 eyes of 7 patients with VHL-associated ocular tumors who were treated with belzutifan at our institution. Of these, 5 eyes of 3 patients had progressing ocular tumors when belzutifan was started. Of the 7 total patients, 2 were treated for renal cell carcinoma, 2 for CNS hemangioblastomas, 2 for RHs, and one for pancreatic neuroendocrine tumors. Initial dose was 120 mg PO daily in 6 patients and 80 mg PO daily in 1 patient. The dose was reduced in all but 1 patient due to side effects. The ocular tumors were controlled in all patients with an average follow-up of 13 months (range 4–24 months). Literature review identified 7 manuscripts that described belzutifan-mediated control of ocular tumors in patients with VHL-associated RHs in 21 patients. ***Conclusion:*** The drug belzutifan shows great promise for controlling RHs and preventing vision loss in patients with VHL. Further work needs to address the optimal dose, role of the drug as a neoadjuvant therapy, and long-term efficacy and tolerability of the drug in a larger cohort of patients with ocular tumors.

Introduction

Von Hippel-Lindau disease (VHL) is an autosomal-dominantly inherited tumor predisposition syndrome caused by mutations in the *VHL* gene located on chromosome 3 [1]. The causative gene was mapped in 1993, and mutations result in constitutive overproduction of

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pro-angiogenic factors such as hypoxia-inducible factors 1 and 2 alpha (HIF-1α and HIF-2α) [1–3]. Individuals with this syndrome manifest tumors in multiple organs including the adrenal gland, brain, endolymphatic sac, eye, kidney, pancreas, and spinal cord [1]. These tumors lead to significant morbidity and increased mortality [4].

In the eye, retinal hemangioblastomas (RHs) can result in significant vision loss and ocular morbidity, particularly for tumors presenting at an advanced stage or involving the optic nerve or the macula [1, 5]. Treatment of RHs has traditionally incorporated locally destructive techniques including laser, cryotherapy, photodynamic therapy, radiotherapy, pars plana vitrectomy with local resection, and adjuvant anti-VEGF and/or steroid injections [5]. These treatments often result in visual morbidity, particularly in the setting of posteriorly located tumors [1, 5].

In 2021, the FDA approved the HIF-2α antagonist belzutifan (Welireg) for use in treating renal cell carcinoma in individuals with VHL [6]. Indications were subsequently expanded to include VHL-associated central nervous system (CNS) hemangioblastomas and pancreatic neuroendocrine tumors as well as non-VHL-associated advanced renal cell carcinoma [7, 8]. This drug has shown promise as a targeted therapy in individuals with these tumors. The phase 2 study for use in renal cell carcinoma reported 16 eyes of patients with concomitant ocular tumors showing improvement in 100% of cases during the study period; however, the drug remains off-label for use in individuals with isolated ocular tumors and the optimal dosing for ocular lesions is not known [6]. We aimed to describe our institutional experience with belzutifan in patients with VHL followed in our retina clinic and review the literature on the use of this drug in individuals with VHL-associated RHs. Of note, we report 2 cases where the primary indication of treatment was off-label use for vision-threatening ocular disease which led to excellent outcomes, further highlighting the benefit of this medication in challenging cases of RHs.

Methods

This work was reviewed by the Institutional Review Board at the University of Iowa and was granted an IRB exemption. A waiver of informed consent was granted by the IRB at the University of Iowa for both adult and pediatric patients. Records of individuals with VHL who are actively followed by the ophthalmology department at the University of Iowa were reviewed. The age, gender, genotype, ocular disease burden, presence of systemic tumors, prior ophthalmic treatments, indication for treatment, initial and adjusted belzutifan dosing, side effects, duration of therapy, and ocular response were recorded for included patients. Ophthalmic imaging including color fundus photography, optical coherence tomography, and fluorescein angiography where available were reviewed for each patient.

A literature search for the use of belzutifan for ocular tumors was conducted. A search using the terms "belzutifan and retina," "belzutifan and eye," and "belzutifan and retinal hemangioblastoma" was performed in PubMed and Google on February 16, 2024. Published manuscripts reporting the response of ocular tumors to belzutifan in individuals with VHL were identified and reviewed.

Results

Seven individuals (12 eyes) with VHL who were followed by the retina service at the University of Iowa and treated with belzutifan were identified. Average age was 37 years (range 14–58 years). Five patients were female and 2 patients were male. One patient had over 80 RHs, 1 had over 20 RHs, 3 had fewer than 10 RHs, 1 had RHs involving both optic nerves and fewer than 10 peripheral RHs, and one had a solitary RH involving the optic nerve in one eye. Five patients had concomitant CNS tumors, 3 had pancreatic neuroendocrine tumors, 2 had pheochromocytoma, and 1 had renal cell carcinoma. VHL gene mutations included Gln73fs, Tyr98His, Arg167Gln, Leu63del, Asn78Ser, and Val130Leu (Table 1).

Ocular treatments prior to starting belzutifan included laser ablation, cryotherapy, enucleation, external beam radiation, and intravitreal injections of anti-VEGF and steroid medications. Indications for belzutifan use included CNS hemangioblastomas (2 patients), renal cell carcinoma (2 patients), RHs (2 patients), and pancreatic neuroendocrine tumors (1 patient). In patients in which the drug was used for RHs, off-label insurance approval was obtained as all other treatment options to prevent progressive vision loss had been exhausted. Six patients were started on a dose of 120 mg PO daily, and 1 pediatric patient was started on a dose of 80 mg PO daily. Side effects included anemia in 5 patients, fatigue in 2 patients, nausea in 1 patient, lightheadedness in 1 patient, and tinnitus, headache, and lower extremity edema in 1 patient. The dose remained at 120 mg PO daily for 1 patient, was reduced to 80 mg PO daily in 4 patients, was reduced to 40 mg PO daily in 1 patient, and was reduced to 40 mg PO five times weekly in 1 patient. The average duration of belzutifan therapy was 13 months (range 4–24 months). In the 3 patients (5 eyes, 1 patient having unilateral disease) with active ocular tumors, the RHs were noted to involute after starting therapy. In the 4 patients (7 eyes, 1 patient being monocular) followed with inactive tumors, ocular disease remained quiescent without new ocular tumors while on treatment (Table 1). Of the 3

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Table 1. Patient characteristics, indication for belzutifan initiation, dose adjustments, belzutifan treatment duration, and ocular response

Case	Age	Ocular disease	Systemic disease	VHL variation(s)	Prior ocular treatments	Indication	Initial dose	Side effects	Adjusted dose	Duration	Ocular response
1	Teens	>80 RHs	CNS	Gln73del2caGG	Laser, Cryo, EBR, PPV, and IVI	RH	80 mg daily	Fatigue and light-headedness	40 mg 5x/ weekly	12 months	Involution*
2	40s	RH optic nerve OU and <10 peripheral RHs	PCC	Tyr98His TAC>CAC	Laser, EBR, IVI, and PDT	RH	120 mg daily	Anemia	80 mg daily	9 months	Involution
3	20s	RH optic nerve	pNET	Arg167Gln CGG>CAG	None	pNET	120 mg daily	Fatigue, anemia, and nausea	40 mg daily	13 months	Involution
4	20s	<10 RHs	CNS and pNET	Leu63 del4ctGCGC	Laser and Cryo	CNS	120 mg daily	None	None	19 months	No new tumors
5	50s	<10 RHs	CNS, pNET, and PCC	Val130Leu GTT>CTT	Laser	CNS	120 mg daily	Tinnitus, HA, and LE edema	80 mg daily	13 months	No new tumors
6	30s	>20 RHs	CNS and RCC	Asn78Ser AAT>AGT	Enucleation OD and laser	RCC	120 mg daily	Anemia	80 mg daily	24 months	No new tumors
7	50s	<10 RHs	RCC and CNS	Val130Leu GTT>CTT	Laser	RCC	120 mg daily	Anemia	80 mg daily	4 months	No new tumors

CNS, central nervous system hemangioblastoma; PCC, pheochromocytoma; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; RH, retinal hemangioblastoma; Cryo, cryotherapy; EBR, external beam radiation; PPV, pars plana vitrectomy; IVI, intravitreal injections of anti-vascular endothelial growth factor and steroids; PDT, photodynamic therapy; HA, headache; LE, lower extremity. *In this case, the ocular tumors had involuted after the initial dose. The dose was reduced to 40 mg three times weekly on which recurrent disease activity was noted. Upon readjustment of dose to 40 mg five times weekly, involution was again noted. Note: Ocular and systemic diseases refer to the presence of these findings prior to the initiation of belzutifan.

Table 2. Literature review of studies describing belzutifan use in patients with VHL-associated RHs

Study	Patients	Age	Sex	Indication	Dose, mg	Adjusted dose, mg	Dose adjusted for side effects?	Ocular tumor response	Follow-up on drug, months
Cotton et al. [9] (2023)	1	71	F	RH	120	80	Anemia	Reduction in tumor size	12
Ercanbrack et al. [10] (2024)	3	23	M	CNS and pancreas	120	NR	Discontinued due to anemia	Tumor shrunk and then lasered when medication held	21
		32	M	CNS	120	80	Anemia and fatigue	Tumors decreased in size	5
		44	M	CNS	120	40	Shortness of breath and anemia	Tumor OD decreased to 50% size with a reduction in exudative detachment	7
Fairbanks et al. [11] (2023)	1	24	M	RH	NR	NR	NR	Reduction in size and number of tumors	6
Grimes et al. [12] (2023)	2	40	M	CNS	120	N/A	No	Decreased size and reduction in vascularity and exudation	1
		66	F	Renal	120	NR	NR	Decreased in size and fluid	30
Jonasch et al. [6] (2021)	12*	NR	NR	Renal	120	NR	NR	100% showed improvement	Median 21.8 (entire study)
Jones et al. [13] (2023)	1	15	M	RH	120	N/A	No	Regression in tumor size and vascularity	12
Mustafi et al. [14] (2023)	1	11	F	RH	120	80	Anemia	Decreased size and decreased feeding/ draining vessels and exudative detachment	6

NR, not reported; N/A, not applicable; RH, retinal hemangioblastoma. *Study for use in renal cell carcinoma, 12 patients with ocular tumors.

patients with active ocular tumors, two were started on belzutifan specifically for their ocular disease, while the third patient was started on this medication for pancreatic neuroendocrine tumors (Table 1).

The literature review identified seven manuscripts that reported the response of VHL-associated RHs to belzutifan [6, 9–14]. These described the ocular response in a total of 21 patients with VHL-associated RHs. Average age where available was 36 years (range 11–71 years). In studies where gender was recorded, 3 patients were female and 6 were male. Primary indications where recorded included renal cell carcinoma in 13 patients, RHs in 4 patients, CNS hemangioblastomas in 4 patients, and concomitant pancreatic neuroendocrine tumors in 1 patient. Starting dose was 120 mg PO daily in all patients. The dose was reduced to 80 mg in 3 patients and 40 mg in 1 patient. Five patients developed anemia. Ocular tumors decreased in size in all cases. Follow-up ranged from 1 to 30 months was recorded.

Discussion

Management of patients with VHL-associated RHs is often challenging, particularly in the setting of patients with a large tumor burden or with tumors located in the macula or optic nerve. These tumors often result in significant

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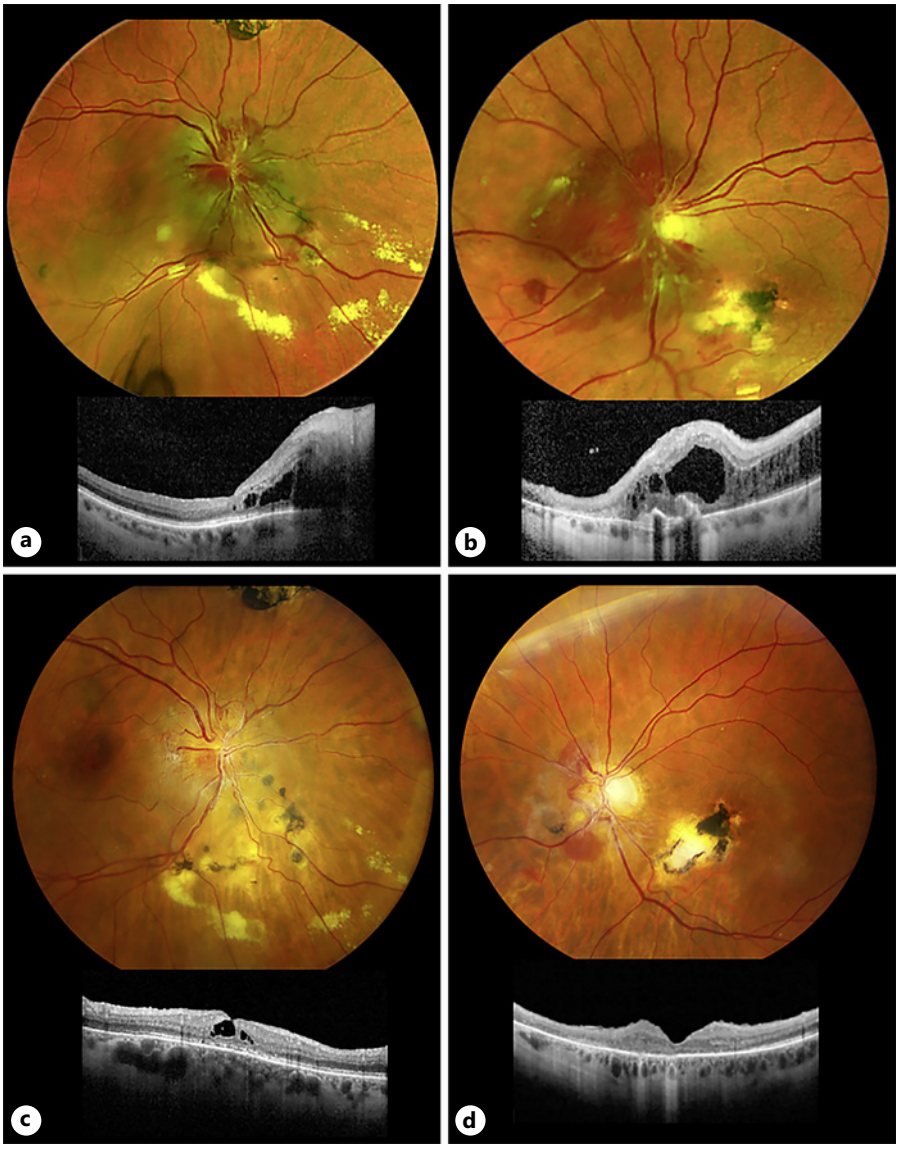

Fig. 1. Response to belzutifan in a patient with VHL-associated bilateral RHs. Right eye (**a**) and left eye (**b**) show color fundus photographs and optical coherence tomography (OCT) of a patient with bilateral optic disc angiomas with associated cystoid macular edema that had been treated with a combination of PDT laser, focal laser, intravitreal anti-VEGF, and intravitreal and subtenon's steroids to both eyes and external beam radiation to the right eye. Right eye (**c**) and left eye (**d**) show color fundus photographs and OCT images of the patient after 9 months of treatment with systemic belzutifan with regression of the tumors and marked improvement in the cystoid macular edema on OCT.

visual morbidity, and treatment options particularly for juxtapapillary tumors have been quite limited [5]. The development of the systemic drug belzutifan has the potential to revolutionize the management of these tumors by allowing for tumor control without locally destructive therapy. However, many patients experience side effects, most commonly anemia (90% of patients) and fatigue (66% of patients), which can lead to holding the medication or dose reductions [6]. Hence, the optimal dosing, duration of therapy, and its role as a neoadjuvant therapy in the setting of ocular tumors are still being defined.

Our data in conjunction with the work of others in published series show the remarkable efficacy of belzutifan for controlling severe ocular tumors in all cases described and also show a lack of ocular progression in patients being treated for other systemic tumors (Tables 1, 2; Fig. 1, 2) [6]. Though both our series and the other published cases include a relatively small number of patients, the results are nonetheless impressive. Given the relatively rare but vision-threatening presentation of exophytic optic disc angiomas, the excellent results demonstrated here are extremely important. If detected early, we may be able to preserve vision for patients who would have otherwise become legally blind from these tumors.

Most of the patients in our series, as well as those in the literature for use in ocular tumors (Table 2), used a starting dose of 120 mg PO daily of belzutifan. In most

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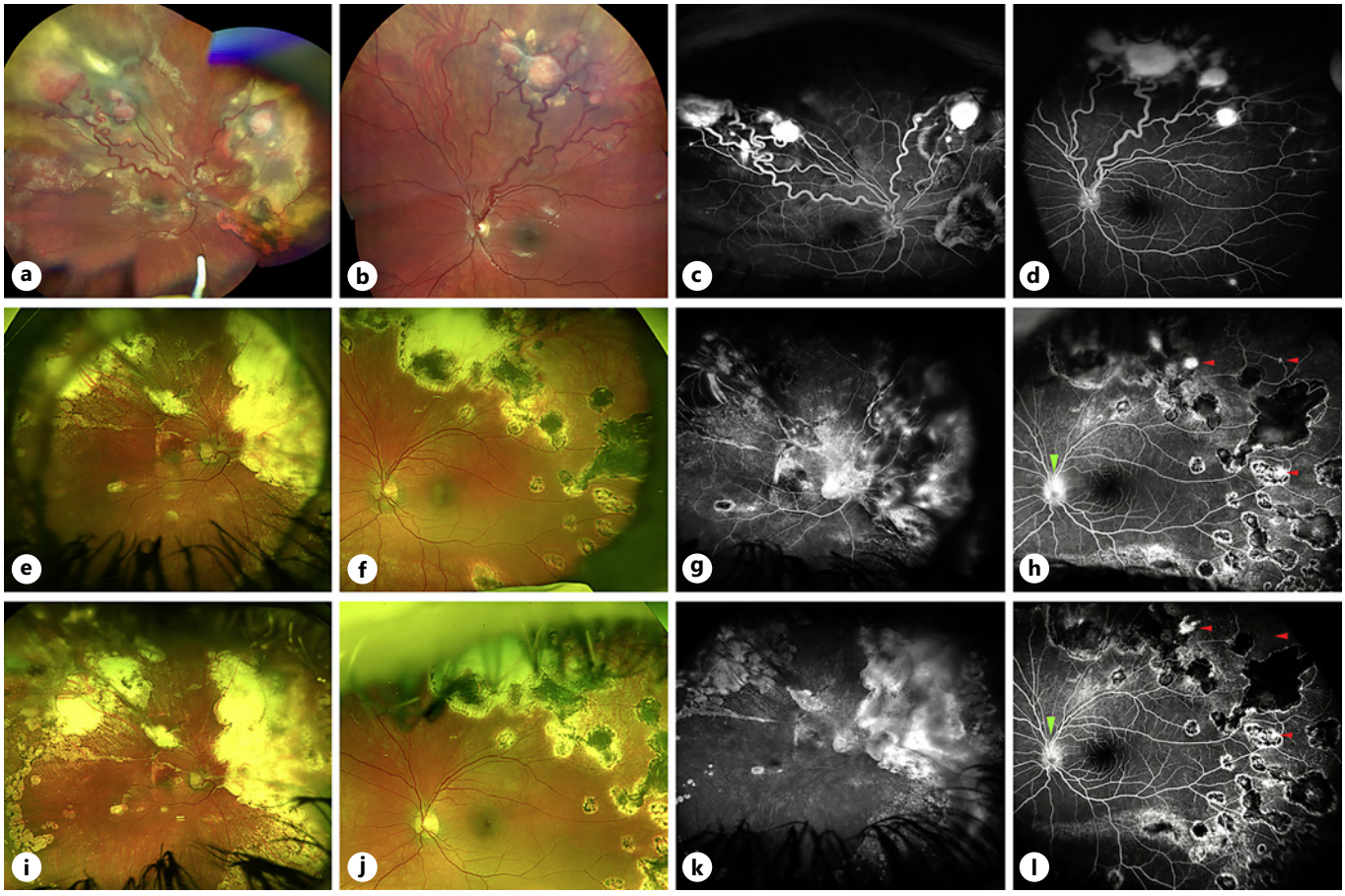

Fig. 2. Response to belzutifan in a patient with a high disease burden of RHs. Color fundus photographs of the right eye (**a**) and left eye (**b**) show multiple RHs in both eyes (dexamethasone implant visible in the vitreous cavity of the right eye) at presentation to our clinic (having previously been treated elsewhere). Late-frame fluorescein angiograms showed multiple active tumors (right eye (**c**) and left eye (**d**)). The patient underwent treatment with intravitreal anti-VEGF, intravitreal steroids, focal laser, and cryotherapy for both eyes as well as external beam radiation and pars plana vitrectomy for repair of traction retinal detachment in the right eye prior to initiation of systemic belzutifan. At this point, color fundus photographs (right eye (**e**) and left eye (**f**)) showed improvement in the tumors in both eyes. However, late-frame fluorescein angiograms showed peripheral leakage in ischemic areas of a previously treated tumor in the right eye and several small, active angiomas (red arrows) along with an early optic disc angioma (green arrow) in the left eye (right eye (**g**) and left eye (**h**)). Belzutifan was started at a dose of 80 mg PO daily with initial regression of the tumors in the left eye, followed by recurrence during a dose hold due to side effects. Two weeks after resuming the drug at a dose of 40 mg three times weekly, the right eye was stable without new tumors (**i**, **k**) and the small tumors (red arrows) and early optic disc angioma (green arrow) in the left eye had regressed both clinically and angiographically (**j**, **l**).

cases, side effects such as anemia required a dose reduction to 80 mg which was better tolerated by patients and still controlled their disease. One pediatric patient in our series had belzutifan held for anemia and then restarted on 40 mg PO three times weekly but developed small new RHs, which involuted following a dose increase to 40 mg five times weekly. Conversely, a 15-year-old male patient described by Jones et al. [13] developed control of the disease and was able to tolerate the 120 mg daily dose for 12 months. More work needs to be done to determine the optimal starting and maintenance dose for the use of belzutifan specifically to control RHs. Our data combined with the other published cases in Table 2 suggest that a dose of 80 mg is likely sufficient to control the ocular tumors in most cases and is better tolerated than the 120 mg dose. Defining dose guidelines in the pediatric setting is important as adolescence is a time in which many patients present with these tumors [15].

Another important question raised by the data in this manuscript both from our center and from those in other published cases is how to incorporate systemic belzutifan into the treatment paradigm for RHs and its role as a

neoadjuvant therapy. In one of the cases described by Ercanbrack et al. [10], RHs decreased in size after initiation of therapy but were then treated with laser after they had decreased in size and the medication was held due to side effects. Defining which tumors might be better controlled with this neoadjuvant approach as opposed to long-term belzutifan therapy should be addressed in the future. Likely, patients with a high disease burden or tumors in the macula/optic nerve will require long-term maintenance therapy, while larger peripheral tumors may be initially controlled with systemic therapy and then ablated to minimize the need for long-term systemic therapy which is not without cost and systemic side effects. Our understanding of which situations to maintain continuous therapy versus incorporating treatment breaks or ablative therapies/surgical resection is evolving for both ocular and systemic tumors [16]. There is likely a need for continuous therapy with belzutifan for ocular tumors that are not amenable to ablative treatment with laser or cryotherapy, but these cases must be carefully managed in conjunction with medical oncologists in the context of their other systemic tumors and ability to tolerate the drug.

With the addition of belzutifan as a novel therapy for the control of RHs, we may need to reassess ocular screening and monitoring protocols for patients who are being treated with this drug. CNS hemangioblastomas are biologically similar to RHs, and the literature on the role of long-term use of this drug and surveillance in this setting is also evolving without clearly established guidelines [17–19]. Zamarud et al. [17] have suggested a possible synergetic effect between stereotactic radiation and belzutifan in patients with VHL-associated CNS hemangioblastomas, and the combined effects of different treatment modalities also require further study for patients with RHs. Based upon the limited data for belzutifan use for RHs, we would recommend managing patient follow-up on a case-by-case basis at this time. For patients with vision-threatening or large RHs, closer follow-up at monthly intervals during dose reductions or dose holds may be necessary, while patients with only small, peripheral tumors may be followed at longer intervals. Data from the initial approval of the drug for renal cell carcinoma followed patients at 3-month intervals, and that is the interval that we have employed for our patients being treated with the drug for their ocular disease [6].

Patients with VHL require multiple subspecialty screenings and treatment visits due to the multisystem involvement of their disease. This results in a large financial and travel burden for patients and their families. Our series and others showed no new ocular tumors developing in patients treated with belzutifan while on therapeutic dosing. If future studies with larger cohorts and longer follow-up confirm the durability of tumor response, we may be able to increase ocular follow-up intervals for patients who are being maintained on belzutifan. Follow-up needs to be carefully tailored to each patient depending upon the size and location of their tumors, tumor burden, and presence of other VHL-associated tumors.

Conclusion

Belzutifan shows great promise for preventing vision-threatening complications in patients with VHL-associated RHs. Optimal dosing for treatment of ocular tumors requires further study, but it is likely that patients being treated for RHs could be maintained at an 80 mg daily dose. Further work needs to address the long-term efficacy of this drug and optimal strategy for incorporating its use into the treatment and surveillance protocols for patients with VHL-associated RHs.

Statement of Ethics

This work was reviewed by the Institutional Review Board at the University of Iowa and was granted an IRB exemption. A waiver of informed consent was granted by the IRB at the University of Iowa for both adult and pediatric patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Conception, design, data acquisition, analysis, and interpretation: E.B., F.J., H.C.B., and J.A. Drafting or reviewing for important intellectual content and final approval of the final version to be published: A.G., B.T., E.B., Elliott Sohn, Edwin Stone, F.J., H.C.B., J.A., L.L., and Y.Z.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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