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Pharmacological treatment of neoplasms associated with Von Hippel-Lindau disease. A literature review

Tratamiento farmacológico de las neoplasias asociadas con la enfermedad de von Hippel-Lindau. Revisión bibliográfica

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ABSTRACT

Background: Von Hippel-Lindau disease is an autosomal dominant syndrome characterized by the development of benign and malignant tumors throughout life. For many years, neoplasms associated with this disease were treated by surgical resection or ablation with the aim of reducing the risk of metastatic disease and controlling local or systemic sequelae. An effective systemic alternative could reduce the surgical burden and represents a new approach to oncological treatment. **Objective:** To evaluate the efficacy and safety of different drugs used in the treatment of neoplasms associated with Von Hippel-Lindau disease. **Search methods:** An electronic search was carried out without language restriction, until July 31, 2024, in the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and SCIELO databases. **Selection criteria:** Clinical trials with patients with malignancies associated with Von Hippel-Lindau disease, and any targeted drug therapy as intervention were included. **Data collection and analysis:** Data from each clinical study were entered into a data table for qualitative analysis. **Results:** Five articles were selected, four of them are prospective studies and one is a retrospective study that evaluates the efficacy of treatment with Sunitinib, Dovitinib, Pazopanib, and Belzutifan. **Conclusions:** The inhibition of HIF-2α with Belzutifan presents a safer and more effective profile than the antiangiogenic agents Sunitinib and Pazopanib.

Keywords: Von Hippel-Lindau Disease; Drug Therapy; Belzutifan; Carcinoma, renal cell; Hemangioblastoma; VHL protein, Sunitinib.

RESUMEN

Antecedentes: La enfermedad de von Hippel-Lindau es un síndrome autosómico dominante que se caracteriza por el desarrollo de tumores benignos y malignos a lo largo de la vida. Durante muchos años, las neoplasias asociadas a la enfermedad fueron tratadas mediante resección quirúrgica o ablación, con el objetivo de reducir el riesgo de enfermedad metastásica y controlar las secuelas locales o sistémicas. Una alternativa sistémica eficaz podría reducir la carga quirúrgica y representar un nuevo enfoque para el tratamiento oncológico. **Objetivo:** Evaluar la eficacia y la seguridad de los diferentes fármacos utilizados en el tratamiento de las neoplasias asociadas con la enfermedad de von Hippel-Lindau. **Métodos de búsqueda:** Se realizó una búsqueda electrónica sin restricción de idioma hasta el 31 de julio del 2024 en las bases de datos del Registro Cochrane Central de Ensayos Controlados (Central), en PubMed y en SciELO. **Criterios de selección:** Se incluyeron los ensayos clínicos que reclutaron pacientes con neoplasias asociadas con la enfermedad de von Hippel-

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Lindau. En cuanto a la intervención, se incluyó cualquier tratamiento farmacológico dirigido. **Obtención y análisis de datos:** Los datos de cada estudio clínico se ingresaron en una tabla para su análisis cualitativo. **Resultados:** La revisión muestra que las terapias dirigidas (sunitinib, dovitinib, pazopanib y belzutifan) en pacientes con enfermedad de von Hippel-Lindau fueron efectivas, logrando respuestas parciales en carcinoma de células renales (≈50%) y estabilización en otras lesiones. Los estudios de fase II incluyeron entre 6 y 61 pacientes. Los efectos adversos fueron principalmente leves a moderados, incluyendo fatiga, anemia y síndrome mano-pie. El tratamiento prolongado permitió reducir las intervenciones quirúrgicas. **Conclusiones:** La inhibición de la hipoxia alfa con el belzutifan ofrece un mejor perfil de seguridad y eficacia que los agentes antiangiogénicos sunitinib y pazopanib

Palabras Clave: MESCH: enfermedad de von Hippel-Lindau; tratamiento farmacológico; belzutifan; carcinoma, células renales; hemangioblastoma; VHL proteína, sunitinib..

1. Introduction

Von Hippel-Lindau disease (VHL) is an autosomal dominant syndrome caused by mutations in the VHL gene. This a tumor suppressor gene located on chromosome 3p25-26; it was sequenced in 1988 and cloned in 1993, and it encodes the VHL protein (pVHL) [1,2]. About 20% of patients have no family history and present de novo mutations [3]. The incidence is 1/35,000 to 1/45,500 people [4,5]. The clinical manifestations of the disease are hemangioblastomas of the central nervous system (CNS), 60-80% [6]; retinal hemangioblastomas, 49-62% [7]; endolymphatic sac tumors, 6-15% [8,9]; renal cell carcinoma or renal cysts, 30-70% [7]; Pheochromocytomas (PCC), 10-20% [7]; pancreatic neuroendocrine tumors (pNET) or pancreatic cysts, 35-70% [8]; and epididymal cystadenomas, 25-60% [7].

In 1894, Treacher Collins, a British ophthalmologist, was the first to observe several lesions in the form of a plexus of blood vessels in the retina of two brothers. He concluded that it was a new, hereditary disease and called it capillary nevus [10]. Later in 1904, Von Hippel reported retinal events in two patients, with progression to multiple lesions in one of them, and named the disease angiomatosis retinae [11,12]. In 1926, the pathologist Arvid Lindau described in his monograph the retinal, cerebral, and visceral components of this disease; to do so, he compiled information from 40 cases, which Cushing called Lindau disease [10,13].

The diagnosis is made when the patient is a carrier of the genetic variant and has one or more clinical manifestations of the disease, at least one clinical manifestation, a first-degree relative who is a carrier of the mutation; genetic confirmation is suggested in patients without a family history, who have a minimum of two types of tumors associated with the disease, one of them being a hemangioblastoma (HB) [14] .

Although most tumors appear in adulthood, some can develop earlier, e.g., retinal angioma, pheochromocytoma, and renal cell carcinoma. Therefore, annual clinical/neurological and retinal surveillance is recommended from birth and for life and imaging studies of the abdomen and CNS every 2 years, from age 15, with an initial magnetic resonance imaging (MRI) of the CNS at 10 years of age [14,15]. It is estimated that VHL disease is present in one third of patients with CNS hemangioblastoma, in more than 50% of retinal angiomas, in 1% of renal cell cancer (RCC), in 50% of familial pheochromocytoma, and in 11% of apparently sporadic pheochromocytoma [3,16,17].

Renal cell carcinoma occurs in up to 70% of patients with VHL disease. In these cases, nephron-sparing surgery is recommended when the tumor diameter is ≥3.0 cm due to the risk of metastasis, and when accelerated tumor growth is evident [18,19]. It results in a recurrence-free survival rate of 76% at 5 years and 20% at 8 years [20]. In a retrospective study, 181 patients with renal tumors associated with VHL disease were divided into two groups: Group 1 (108 patients) presented tumors smaller than 3 cm, the mean follow-up was 58 months, and surgery was recommended when the tumor reached 3 cm, in this group, no metastatic disease was developed; Group 2 (73 patients) presented a tumor diameter greater than 3 cm, the mean follow-up was 72.9 months and metastasis occurred in 27.4% of patients. It was concluded that the larger the tumor size, the greater the risk of metastasis [18].

Regarding tumor growth rate, 41 patients with clear cell renal cell carcinoma (ccRCC) were evaluated retrospectively. Tumor growth kinetics ranged from 0.24-2.74 cm/year, with a mean of 0.287 cm/year, patients showed great variation in growth rates: 27.5% had slow-growing tumors, 44.1% moderate-growing tumors, and 28.4% fast-growing tumors [21] .

For many years, neoplasms associated with VHL disease were treated by surgical resection or ablation with the aim of reducing the risk of metastatic disease and controlling local or systemic sequelae [20,22–27]. An effective systemic alternative could reduce the surgical burden and represents a new approach to oncologic treatment.

2. Genetics and molecular biology of VHL disease

The VHL protein plays a key role in cellular oxygen sensing. Under normoxic conditions, it targets hypoxia-inducible factor alpha (HIF-α) for proteasomal degradation. In hypoxia, HIF-α accumulates, and leads to overproduction of vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), platelet-derived growth factor (PDGF), glucose transporter 1 (GLUT-1) and erythropoietin (EPO), and promoting angiogenesis, differentiation, migration and cell proliferation. The HIF-α pathway presents two isoforms: HIF-1α and HIF-2α that play distinct roles in response to hypoxia [28,29].

In VHL disease, one allele of the VHL gene is mutated in the germline and the second allele may be lost somatically (usually through loss of chromosome 3p). Subsequent loss of pVHL causes HIF-α to accumulate in the absence of hypoxia (referred to as "pseudohypoxia"), thus resulting in activation of downstream HIF targets and tumorigenesis of affected tissues [30].

Previous investigation showed that binding small molecules to an internal pocket in HIF-2α could allosterically inhibit the protein-protein interaction between HIF-2α and transcriptional ribonucleic acid (TRNA), which would lead to the inhibition of transcriptional activity by stopping the processes of tumorigenesis [31-33].

3. Materials and methods

3.1 Main goal

This study aims at establishing the level of efficacy of the different study drugs in neoplasms associated with Von Hippel-Lindau disease.

3.2 Secundary goal

Determine the type of drug toxicity that led to discontinuation of treatment, and describe which tumors were most sensitive to the study drugs.

3.3 Study Design

We conducted a descriptive, observational systematic review with a qualitative approach.

3.4 Databases and Terminology Search

We conducted an electronic search for systemic treatment in neoplasms associated with von Hippel-Lindau disease until July 31, 2024. The search was made in Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and SCIELO databases using MeSH terms and free text, in addition to the Boolean operators AND, OR and NOT. In PUBMED the search equation was **(((clinical trial) OR (pilot study)) OR (drug therapy)) AND ("von Hippel-Lindau" [Title])**, 148 medical articles were found, out of which 5 met the selection criteria to be part of the study. In COCHRANE, the search equation was **"von Hippel Lindau Disease":ti,ab,kw AND Therapy**, 14 articles were found and 4 were selected. In addition, a search was performed in the SCIELO database using the equation **((ab:("von hippel Lindau"))) AND (therapy)**, 3 articles were found, but none met the selection criteria. A search was attempted in SCOPUS, but medical articles were not open access.

3.5 Inclusion Criteria

- Clinical studies in which the patient sample presented a diagnosis of Von Hippel-Lindau disease with genetic confirmation, or with clinical characteristics of the disease but with a family history.
- Human clinical trials.
- Study participants over 18 years of age.
- Studies published by July 31, 2024.
- Open access articles.

3.6 Exclusion Criteria

- Research reviews, single case studies, books or manuals.
- Studies in pediatric patients.
- Animal studies.
- Studies with symptomatic brain metastases.
- Clinical trials with solid tumors not associated with VHL disease.
- Research whose patients received surgical treatments, radiotherapy, radiosurgery or radiofrequency ablation.
- Studies aimed solely at the treatment of hemangioblastomas, or retinal hemangiomas associated with VHL disease.

3.7 Selection of articles

We selected clinical studies evaluating the effectiveness and toxicity of a drug in a sample of patients with tumors associated with Von Hippel Lindau disease. The information was selected by title and abstract in electronic databases. Then, full-text articles were downloaded, read, and those that included clinical trials with systemic treatment for neoplasias associated with VHL disease were selected. Data were extracted in a table and the methodological quality was analyzed. The heterogeneity of these studies was assessed. There were no restrictions on language or publication status (Figura 1).

4. Results and Discussion

Table 1 shows the characteristics of the four prospective studies and the retrospective article, with a small sample in each study.

Currently, the majority of patients with neoplasias associated with VHL disease undergo repetitive surgical procedures, leading to neurological sequelae, renal or pancreatic failure, and a decline in their quality of life. As a result, targeted therapy studies have been done on VGFR, FGFR, and HIF-2α, and the results have been positive in terms of how well it works and how safe it is.

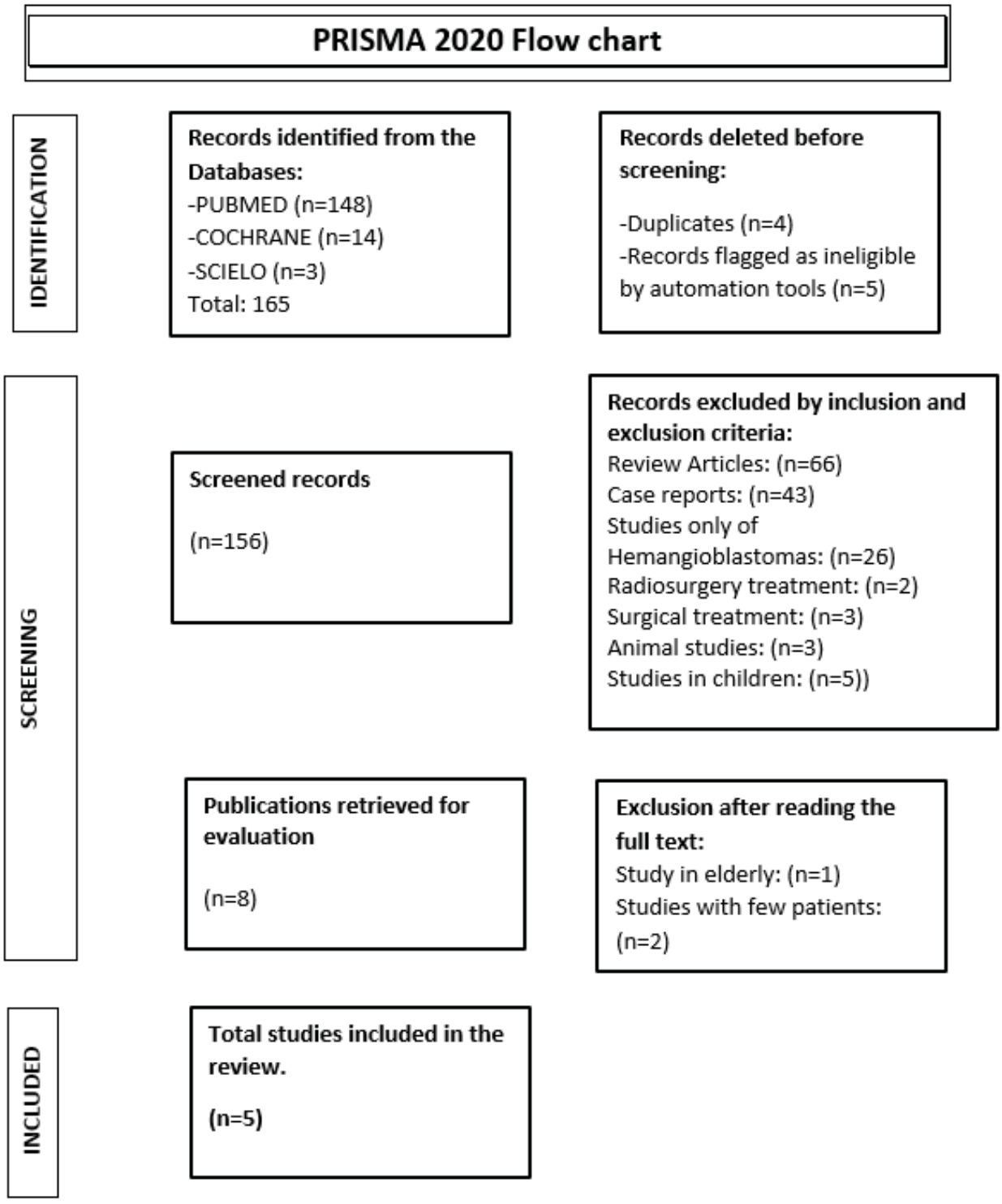

Figure 1. PRISMA 2020 Flowchart
Source: Own elaboration based on PRISMA 2020 flow chart

Table 1. Characteristics of the studies

Author	Study design	Number of patients. Manifestations of VHL disease	Assessment criteria	Median age in years	Methodology (Intervention – dose)	Median follow-up	Responses according to RECIST	Median time to RECIST response	Adverse events	Observations
Jonasch E et al., 2011 [34]	Prospective, open-label, single-arm phase II study	N = 15 6 discontinued treatment 12: CCR. 11: Renal cysts. 11: CNS HB. 9: Retinal hemangiomas. 7: Pancreatic cysts. 7: Neuroendocrine tumors of the pancreas. 3: Adrenal lesions. 2:Endolymphatic sac tumor. 1: Cystadenoma of epididymis.	Main objective: security. Secondary objective: Efficacy of complete responses (CR) + partial responses (PR).	36 (22–57)	Sunitinib 50 mg/ day for 28 days, followed by 14 days of rest , for 4 cycles, with the possibility of dose reduction to 37.5 or 25 mg due to toxicity.	48 weeks	33% of RCC responded partially to none of the HBs (P = 0.014) . HB: 91% stable disease. The rest of the injuries were stable.		Fatigue, hand-foot syndrome, nausea, grade 3 neutropenia.	At 48 weeks, RCC and neuroendocrine tumors had grown again, reaching measurements close to the initial ones, but not larger.
Roma A et al., 2015 [35]	Retrospective Study	N = 14 No. of injuries in the study 11: Hemangioblastomas of the cerebellum. 11: Pancreatic cysts. 9: Renal cysts. 8: Spinal hemangioblastomas 7: Retinal angiomas. 3: Neuroendocrine tumors of the pancreas. 3: Epididymal cysts. 2: Pheochromocytoma. 1: Supratentorial hemangioblastoma. 1: Adrenal adenoma	Primary objective: progression-free survival (PFS). Secondary objectives: radiological response, toxicity and overall survival (OS)	48 (27-71)	Sunitinib 50 mg/ day for 28 days, followed by 14 days of rest , with the possibility of dose reduction to 37.5 or 25 mg due to toxicity.	39.4 months	RP: 64.3% of patients. Stable disease: 35.7% SLP: 85.7% the first year. 71.4% in the second year. With the exception of HB, there was a response in all lesions.		Mucositis, hand-foot syndrome, asthenia, hypertension, hypothyroidism.	Patients received a median of 19.5 cycles, treatment was continued until maximum response, progression, unacceptable toxicity, or patient refusal.

Continuation. Table 1. Characteristics of the studies

Pilié P et al., 2018 [36]	Prospective, single-center, open-label, single-arm, phase 2 study.	N = 6 3 discontinued treatment 5: HB in cerebellum. 4: HB of the brain stem. 3: Retinal HB 2: RCC 2: Pancreatic cysts.	Main objective: security. Secondary objectives: Effectiveness	44 (18-61)	Dovitinib 500 mg/day in a 4-week cycle with a 5-day on, 2-day off schedule, for 6 cycles.		No RECIST response was evident. The HBs showed stability.		Rash, diarrhea, fatigue.	The study was discontinued due to toxicity.
Jonasch E et al., 2018 [37]	Prospective, single-arm, phase 2 study.	N = 31 7 discontinued treatment 23: CNS lesions. 22: Kidney injuries. 9: Lesions in the pancreas. 3: Eye injuries. 1:Lesions in Adrenal.	Objective response rate (ORR) and safety.	38 (32-42).	Pazopanib 800 mg/day, with dose reduction in 200 mg increments permitted if patients experienced grade 3 or higher toxicity for 24 weeks.	12 months	RP: 42 %. Stable disease: 58%. **TRO by organ:** RCC: 52%. Pancreatic lesions: 53%. CNS HB: 4%.	RCC: 3 months. HB: 6 months. Pancreatic lesions: 6 months	Fatigue, diarrhea or transaminitis.	Most patients decided to continue treatment after 24 weeks.

Continuation. Table 1. Characteristics of the studies

Jonasch E et al., 2021 [38]	Prospective, open-label, single-arm phase 2 study.	N = 61 7 discontinued treatment. All patients had RCC and pancreatic lesions. 22:Neuroendocrine tumors of the pancreas. 50: CNS HB. 12: Retinal HB: 12.	Main objective: objective response. Secondary objectives: duration of response, time to response and progression-free survival in RCC, other criteria were efficacy in non-renal carcinomas associated with VHL disease and safety of Belzutifan.	41 (19-66),	Belzutifan 120 mg/day.	21.8 months	**TRO by organ:** RCC: 49%. Neuroendocrine tumors of the pancreas: 91%. CNS HB: 30% The median duration of response was not reached.	RCC: 8.2 months. Pancreatic neuroendocrine tumors: 5.5 months. CNS HB: 3.2 months.	Anemia grade 1 and 2 (90%), Fatigue grade 1 and 2 (66%).	54 Patients (89%) were still receiving treatment with Belzutifan at the data cut-off date. Prior to the initiation of Belzutifan, patients had undergone 327 procedures (surgery, radiofrequency ablation), out of which 64 occurred in the 2.5 years prior to the start of the study, and only three surgeries were required during the 22 months of Belzutifan.

VHL: Von Hippel-Lindau; RCC: renal cell carcinoma; HB: Hemangioblastoma; CNS: Central nervous system; PFS: progression-free survival; PR: partial response; ORR: Objective response rate

The study conducted by Jonasch et al. in 2011 [34] revealed that the growth of RCC and pancreatic NETs recurred after 48 weeks, a maximum of four treatment cycles, despite prolonged administration of sunitinib, as reported by Rome. According to the response evaluation criteria for solid tumors (RECIST), most patients in a 2015 study maintained their responses, suggesting the need for additional research to determine the best doses for prolonged treatments, given the potential for adverse events that could result in treatment abandonment [34, 35].

The analysis of samples from the Tissue Bank of MD Anderson at the University of Texas revealed a null response of the HB to sunitinib, a VEGF receptor inhibitor, with low expression of the VEGF receptor 2 in the HB compared to the RCC ($p = 0.003$), and higher levels of the fibroblast growth factor receptor substrate 2 (FGF) in the HB ($p = 0.003$). This raises the hypothesis that treatment with FGF receptor blockers may benefit patients with HB [34].

It is unclear why VHL-derived malignancies respond differently to therapy. It looks like sunitinib is a better way to treat VHL-related RCC than other VHL-related lesions. However, its side effects have made it hard to use for long periods of time [34, 35].

By changing the molecular mechanism that affects clinical manifestations, the ultimate goal of systemic therapy is to lower the number of surgeries needed in people with VHL disease [30,32,33].

The review's analysis reveals that HIF-2 inhibition provides a superior safety and efficacy profile compared to the antiangiogenic agents sunitinib and pazopanib. On August 13, 2021, the Food and Drug Administration (FDA) approved belzutifan for patients with VHL who have developed clear-cell renal cell carcinoma, central nervous system HB, or pancreatic neuroendocrine tumors associated with the disease [39].

The belzutifan clinical trial results suggest that it could be used instead of or in addition to surgery to treat people with VHL disease. This is because it delays or eliminates the need for surgeries that are linked to serious problems like neurological sequelae or renal or pancreatic failure. It also lowers surgical morbidity and breaks the cycle of having to have surgeries over and over again [38, 40].

Reporting response in individual lesions is not a common way to share the results of a clinical study. However, for people with VHL disease, each clinical manifestation is a separate medical and surgical challenge, and a drug effect on any lesion may mean that surgery is not necessary. Limitations of the review for extrapolating the results to the general population include the limited number of studies, the heterogeneity of the samples, and the low number of patients per study. However, we should acknowledge that there remains a vast field to delve into. The studies that were looked at suggest that histopathological samples from people with VHL disease should be studied to find out the molecular differences in the affected tissues and then target therapies should be looked into.

Limitations of the review to extrapolate the results to the general population include the low number of studies, heterogeneity of the samples, and low number of patients per study. However, there is still a wide field to explore; the analyzed studies suggest the investigation of histopathological samples associated with VHL disease to determine the molecular differences of the affected tissues and subsequently investigate target therapies.

5. Conclusions

Mutations in patients with Von Hippel-Lindau disease (VHL) demand continuous surveillance and a multidisciplinary therapeutic approach. Repeated surgical interventions cause serious physical and psychological sequelae; thus, systemic management seeks to prevent invasive procedures and improve quality of life, especially in cases of associated neoplasia.

HIF-2α inhibition has shown a better safety and efficacy profile compared to traditional antiangiogenic agents, thus minimizing serious adverse events. Since its FDA approval in 2021, Belzutifan has revolutionized the treatment of renal carcinoma and other VHL-associated neoplasms by stopping or reversing tumor growth, reducing the need for surgery and the risk of metastasis.

6. Administrative information

6.1 Source of research support

The study was financed with each investigator's own resources.

6.2 Declaration of conflict of interest

The authors declare that they have no conflicts of interest.

6.3.2 Author contributions

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7. ABBREVIATIONS

VHL: Von Hippel-Lindau.

pVHL: Von Hippel-Lindau protein.

TKI: Tyrosine kinase inhibitor.

HB: Hemangioblastoma.

CNS: Central nervous system.

MRI: Magnetic resonance imaging.

RCC: Renal cell cancer.

ccRCC: Clear cell renal cell carcinoma.

FDA: Food and Drug Administration.

PCC: Pheochromocytoma.

pNET: Pancreatic neuroendocrine tumor.

HIF-α: Hypoxia-inducible factor alpha.

VEGF: Vascular endothelial growth factor.

TGFβ: Transforming growth factor beta.

PDGF: Platelet-derived growth factor.

FGF: Fibroblast-derived growth factor.

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