von Hippel- Lindau syndrome-related congenital polycythemia and response to belzutifan

by Paulo Siqueira do Amaral, Sanjay R. Mohan, and Kathryn E. Beckermann

Received: April 30, 2024.
Accepted: August 1, 2024.


Publisher’s Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors’ final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
von Hippel–Lindau syndrome-related congenital polycythemia and response to belzutifan

Paulo Siqueira do Amaral¹, Sanjay R. Mohan¹, Kathryn E. Beckermann¹*

¹Vanderbilt University Medical Center, Nashville, TN, United States of America

Kathryn E. Beckermann⁵
Division of Hematology/Oncology
Department of Internal Medicine
Vanderbilt University Medical Center
2220 Pierce Avenue
Nashville, TN 37212
615-936-5000
Katy.beckermann@vumc.org

Author contributions: PA, SM, and KEB contributed to the review of data, creation of the manuscript, and editing for revisions.

Conflicts of interest: PA and SM do not have related conflicts to declare. KEB receives funding to the institution for research from Aravive, Pionyr, and BMS-LCFA-IASLC. KEB has served as a consultant for Alpine Bioscience, Aravive, Aveo, Adicept, Arcus, BMS, Exelixis, Nimbus, Eisai, Merck, Seagen, and Xencor. KEB given speaker led talks for VHL education funded by Merck.

Data Sharing: All data are presented in the text and figure of this case report.
**Von Hippel-Lindau (VHL) syndrome** is an inherited, autosomal dominant disease with an estimated incidence of 1 in 36,000 live births. It is characterized by a wide spectrum of benign and malignant tumors such as craniospinal hemangioblastomas, retinal capillary hemangioblastomas, clear cell renal carcinoma (RCC), pancreatic neuroendocrine tumors (pNET), pheochromocytomas, middle ear endolymphatic sac tumors and epididymal cystadenomas. An atypical clinical manifestation of VHL is the Chuvash erythrocytosis (CE), a congenital polycythemia, provoked by a homozygotic 598C>T (R200W) mutation in the *VHL* gene located on chromosome 3p25. This syndrome can present with plethora, fatigue, and headache. Cohort studies suggest an associated trend towards a higher mortality in CE patients due to an elevated incidence of peripheral and central nervous and vascular system thromboses including stroke, myocardial infarction, pulmonary embolism. The VHL protein normally interacts with the E3 ubiquitin complex, disrupting proteolysis of hypoxia-inducible factor α (HIFα). Therefore, the pathogenesis of CE occurs with the loss-of-function of *VHL* leading to a pseudohypoxic state and accumulation of HIF-1α and 2α causing further activation of genes responsible for angiogenesis, cycle-cell progression and erythropoiesis. In this context, belzutifan emerges as a novel class of anti-HIF2α agents, inhibiting the transcription of HIF2α-sensitive genes. The efficacy of belzutifan on VHL-associated neoplasm was reported by Jonasch and colleagues showing an objective response of 59%, 90%, 38% in RCC, pNET and central nervous system (CNS) hemangioblastomas, respectively. Consequently, it exhibits antitumor activity and concurrently reduces plasma erythropoietin levels, which potentially elucidates the mechanism leading to a decline in hemoglobin levels. Herein, we report a patient with congenital polycythemia (CP) who was treated with belzutifan, the response and tolerance to treatment. Research conducted under IRB approved protocol 160979. Case report. A 30-year-old female was referred to our clinic due to polycythemia. Her elevated hematocrit was known since birth, and she underwent therapeutic phlebotomies for chronic headaches and fatigue since puberty, which had recently failed to relieve her symptoms or to reduce her hematocrit. Genetic analysis found two heterozygous germline mutations on the *VHL* gene: the Chuvash documented R200W (c598C>T) as well as second L118V (c562C>G). At presentation, her complete blood count (CBC) revealed a red blood cell (RBC) count of 7.83 \( \times 10^6 \) (4.04 - 5.48), hemoglobin (Hb) of 11.8 mmol/L (7.5 - 9.4), hematocrit (HCT) of 63.8% (37.7 - 47.9) and erythropoietin (EPO) levels of 138 mIU/mL (3 – 19) (Table 1). Her VHL related screening included abdominal, CNS and spine MRI, audiometry and ophthalmological evaluation, and metanephrine levels, all of which were unrevealing. Her family history was not known. In March 2022, belzutifan 120 mg daily was started with a decrease in her Hb at four weeks to 10.5 mmol/L and at eight weeks her Hb normalized at 8.0. After 16 weeks of treatment, her Hb reduced to 5.8 resulting in grade 2 anemia and the belzutifan dose was reduced to 80 mg which she remains with normalization of Hb and EPO levels (Figure 1). Chuvash erythrocytosis, a rare manifestation of *VHL* disease, is caused by homozygous R200W. However, *VHL* heterozygous biallelic mutations have also been implicated in congenital polycythemia. Pastore et al documented a case series involving seven patients with VHL mutations and polycythemia: three with homozygous *VHL* R200W mutations, three heterozygous *VHL* R200W mutations (including two with *VHL* R200W and *VHL* L118V mutations similar to our patient), and one with homozygous *VHL* L118V mutation. Our patient’s baseline Hb and EPO levels were above the median values typically reported in patients with CE. However, it is important to note that there is a wide range of measurements in these cases. Specifically, in two patients with the same *VHL* R200W/L118V genotype as our patient, Hb levels ranged from 10.1 mmol/L to 13.0 mmol/L. This variability highlights the challenge of making comparisons among patients with rare and heterogeneous conditions. Historically, the data on management is limited and has included the controversial use of phlebotomies. A study by Gourda et al did not find a clear
association between high hematocrit levels and an increased incidence of thrombotic events. Instead, patients with history of therapeutic phlebotomy appeared to be at higher risk for thrombosis due to the impact on iron storage, which can culminate in a cyclical elevation of HIF and EPO levels. The use of aspirin has shown risk-reduction in acute myocardial infarction, nonfatal strokes, or death from cardiovascular disease in patients with polycythemia vera (PV), but it has not been prospectively tested in CE patients. A Janus kinase (JAK) 1 and 2 inhibitor, ruxolitinib, is a drug often used in the management of patients with PV. Unlike CE, PV is characterized by mutations in the JAK2 gene. Nonetheless, the use of JAK-2 inhibitors decreased hematocrit levels in mouse models carrying VHL$^{R200W}$ mutation. Building on this rationale, Zhou et al. evaluated the use of ruxolitinib in three patients with CE, reporting symptom improvement and a reduction in the frequency of phlebotomies.

In 2021, Jonasch et al. reported in a phase 2 trial the significant efficacy and safety of belzutifan in patients with VHL disease and renal cell carcinoma with notable objective responses in RCC, CNS hemangioblastomas and pancreatic tumors. Notably, anemia was the most common adverse event, affecting 90% of patients, which reinforces the impact of belzutifan on erythropoiesis. Also, prior research in VHL$^{R200W}$ homozygous murine models demonstrated elevated EPO levels that diminished upon the initiation of oral belzutifan, leading to the reversal of polycythemia and reduction of pulmonary hypertension. In our case, the patient achieved normal hemoglobin and hematocrit levels following belzutifan treatment, with a rapid and well-tolerated response, even at a reduced dose of belzutifan. While a standard treatment for CE remains elusive, belzutifan appears to be a promising, efficient, and safe tool for the management of that condition. Prospective studies with extended follow-up are needed to evaluate clinical outcomes such as symptom improvement, reduction of cardiovascular events, need of phlebotomies and the development of treatment resistance. Furthermore, it is important to address other risk factors, such as tobacco smoking, hypertension, and maintain regular follow-up and genetic counselling due to potential association with other conditions related to VHL syndrome. In conclusion, this case report is the first to highlight the activity and safety of belzutifan in a patient with VHL-related polycythemia, suggesting a path for future prospective trials and discussion with global regulatory agencies.

All available data is provided in the case report. Additional requests for information can be made to the corresponding author.
REFERENCES:


<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 40</th>
<th>Week 98</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPO (mIU/ml)</strong></td>
<td>138</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td><strong>Hb (mmol/L)</strong></td>
<td>11.8</td>
<td>10.5</td>
<td>8.0</td>
<td>5.8</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>HCT (%)</strong></td>
<td>63.8</td>
<td>54.0</td>
<td>41.0</td>
<td>28.0</td>
<td>39.0</td>
<td>43.0</td>
</tr>
</tbody>
</table>

Table 1 – Baseline levels of erythropoietin (EPO), hemoglobin (Hb) and hematocrit (HCT) and its variation during treatment
Figure 1. Patient with VHL-related congenital polycythemia laboratory evaluation and response to belzutifan. This figure represents the dosing and response over time in weeks for decreased red blood cells measured by hematocrit (HCT) and hemoglobin (Hb) as well as initial and final erythropoietin (EPO) levels.