Annals of Hematology (2022) 101:2537–2539
https://doi.org/10.1007/s00277-022-04933-5

LETTER TO THE EDITOR

# The first successful expanded compassionate use of Iptacopan in a patient with paroxysmal nocturnal hemoglobinuria

**Bing Han[1] · Jiang Ji[1] · Bo Zhang[1] · Hua Bai[1] · Daobin Zhou[1] · Feng Feng[1] · Yan Huang[1] · Huijuan Zhu[1] · Limeng Chen[1] · Zhihong Wu[1] · Xiuchun Jiang[1] · Xuemei Li[1] · Qing Jia[1] · Qing Chang[1] · Hui Pan[1] · Hua Peng[1] · Wenting Zheng[1] · Hui Huang[1] · Zheng Chen[1] · Chen Yang[1] · Miao Chen[1] · Bin Du[1] · Shuyang Zhang[1]**

Received: 18 April 2022 / Accepted: 23 July 2022 / Published online: 15 August 2022


Dear Editors,

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultrarare disease characterized by bone marrow failure and deficiency of complement regulators which leads to hemolysis and thrombophilia [1]. The regular therapy for classic PNH are C5 inhibitors like eculizumab or ravulizumab [2]. Novel oral anti-complement inhibitors targeting C3 or alternative pathway (AP) are emerging to show benefits on untreated patients or those failing or only partially responding to established C5 inhibitors [3]. Among them, Iptacopan is designed to block AP while selectively inhibiting complement factor B (CFB) [4] and shows promising results on Phase 2 clinical trials [5, 6]. However, Iptacopan has not been approved by any Health Authority and not launched globally so far. Therefore, there is no data on the real-world setting published.

Here, we reported a Chinese patient with efficient treatment by Iptacopan who has been switched from previous eculizumab treatment. In an 8-month follow-up after start of Iptacopan, this patient showed normal hemolysis parameters and stable thrombophilia status. To our knowledge, she was the first case of compassionate use (CU) and expanded access (EA) to unapproved drug in China and also the first attempt of Iptacopan in the real world.

A 41-year-old woman came to our clinic reporting pancytopenia for 17 years, continuous hematuria for 14 years, and intermittent seizures for 3 years. She was previously diagnosed with aplastic anemia in 2004 according to standard criteria [7], and her diagnosis was clarified as PNH in 2007 (detailed history was in supplementary material). Afterwards, she was treated with glucocorticoids plus cyclosporine A, androgen, erythropoietin, and RBC transfusions. The patient suffered from recurrent abdominal deep vein thrombosis and upper limb superficial vein thrombosis even under anticoagulation treatment. From 2007 to 2017, HGB was kept between 60 and 80 g/L, and lactate dehydrogenase (LDH) fluctuated between 1611 and 2046 U/L. She stopped cyclosporine A and androgen in 2017.

In February 2018, the patient had an acute hemiplegia, speech difficulty and loss of consciousness, and MRI detected thrombosis in the superior sagittal sinus. HGB at 65 g/L, WBC count at $5.03\times10^9$/L, PLT count at $40\times10^9$/L, and reticulocyte percentage at 3.7% were found. Direct/indirect bilirubin levels were 10.9/4.8μM, LDH was 1092 U/L, and PNH clone size (FLAER negative neutrophil) was 97%. Though anticoagulation and anti-epilepsy therapies were applied, the patient had seizures and severe headache afterwards, and she was once admitted into ICU for supportive care as symptoms aggravated. In April 2018, the patient started eculizumab 900 mg qw for 4 weeks, then 900 mg q2w for 34 months. Blood routine parameters were normal after 6 months of eculizumab administration; LDH levels became normal after 1.5 months of eculizumab treatment and were maintained around 200 U/L. Bilirubin was kept normal, while PNH clone size was 97%. Her reticulocyte percentage was normal after 16 months of treatment. The patient did not report recurrent symptoms until April 2021, when the interval of eculizumab treatment was extended to 16–17 days due to limited access to eculizumab; then, she suffered from minor seizures. MRI suggested thrombosis recurrence in the superior sagittal sinus, and reticulocyte percentage increased to 2.4%. Since eculizumab is not available in China, and her stock from abroad was running out due to the COVID-19 pandemic, she could not continue treatment after June 2021. In April 2021, the patient's PNH clone size was 100% in granulocytes, so it was very likely for her to experience hemolysis outbreak and seizure after eculizumab discontinuation.

✉ Shuyang Zhang
shuyangzhang103@nrdrs.org

[1] Peking Union Medical College Hospital, Beijing, China

**Table 1** Laboratory test results during Iptacopan treatment

| | Week 0 on Iptacopan | Week 8 on Iptacopan | Week 14 on Iptacopan | Week 26 on Iptacopan | Week 34 on Iptacopan |
|---|---|---|---|---|---|
| WBC, $\times 10^9$/L | 2.46 | 2.9 | 2.64 | 2.82 | 2.79 |
| Neutrophil count, $\times 10^9$/L | 0.96 | 1.47 | 1.2 | 0.97 | 1.27 |
| HGB, g/L | 117 | 134 | 146 | 133 | 143 |
| PLT, $\times 10^9$/L | 81 | 98 | 93 | 90 | 84 |
| Reticulocyte percentage, % | 2.48 | 1.73 | 1.41 | 1.69 | 1.64 |
| ALT, U/L | 22 | 27 | 18 | 9 | 10 |
| Total bilirubin, μM | 8.1 | 5.7 | 7.4 | 11.0 | 9.9 |
| Creatinine, μM | 57 | 56 | 59 | 51 | 58 |
| LDH, U/L | 197 | 174 | 201 | 199 | 166 |
| D-Dimer, mg/L FEU | 1.55 | 1.82 | 1.49 | 0.73 | 0.38 |
| FLAER clone size (neutrophil) | 95% | 98% | 77% | 77% | 91% |

*ALT*, alanine aminotransferase; *HGB*, hemoglobin; *LDH*, lactate dehydrogenase; *PLT*, platelet; *WBC*, white blood cell

Since no effective treatment is available in China for this life-threatening condition, and our center was involved in a clinical trial of Iptacopan for complement inhibitor-naïve patients (registered at ClinicialTrials.gov, NCT04820530), we decided to apply a CU and EA to Iptacopan to the manufacturer of Iptacopan and National Medical Products Administration (NMPA) according to Pharmaceutical Administration Law of the People's Republic of China [8]. A multi-disciplinary team was organized to evaluate the benefits and risks of CU and EA of Iptacopan. Meanwhile, ethics committee approval and patient consent was obtained, and the application was approved by NMPA. The patient started Iptacopan treatment on June 14, 2021 at 200 mg bid. Rivaroxaban and Depakine were continued as supportive treatments.

Compared with baseline parameters before Iptacopan administration, the patient achieved improved HGB, PLT, and steady neutrophil count (Table 1). Her reticulocyte count was normal after 8 weeks of treatment. Meanwhile, biochemistry parameters remained normal. PNH clone size fluctuated from 95 to 77% after Iptacopan administration. The quality of life (QOL) was greatly improved with regular inpatient drug administration avoided. No Iptacopan-related side effects were documented.

Iptacopan is a newly discovered orally administered drug that inhibits the enzymatic activity of serine protease CFB [9]. Since CFB is an initiator in the AP and is integral to the formation of C3 and C5 convertases, Iptacopan is hypothesized to effectively control extravascular hemolysis in addition to managing intravascular hemolysis. The case reported here displayed real-world data for Iptacopan in PNH for the first time.

The current patient was relieved by eculizumab from critical hemolysis and thrombotic complications 3 years ago. HGB further increased, reticulocyte returned to normal and all hemolysis- and thrombosis-related symptoms remained stable after switching to Iptacopan, providing convenience for regular treatments and improving the QOL. The capacity of maintaining hematological response by Iptacopan after anti-C5 treatment was also demonstrated in a clinical trial [5]. The findings in the current patient and published clinical trial verified that Iptacopan could not only block AP-driven extravascular hemolysis, but also control intravascular hemolysis [6]. More data from ongoing trials would further demonstrate the outcome of the direct switch from anti-C5 therapy to Iptacopan monotherapy or the effectiveness of Iptacopan as first-line therapy.

Iptacopan was well-tolerated in this case at least for the 34 weeks of follow-up, which was consistent with published studies [6, 10]. Longer follow-up is required to evaluate the safety of Iptacopan.

Another issue is the importance of CU and EA for globally unapproved medicine for this rare disease in China. With the efforts of physicians, hospital administrators, medicine manufacturer, and the NMPA of China, the patient was treated with Iptacopan right on time. This would be an example for managing the difficulties that other patients with rare diseases constantly face.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00277-022-04933-5.

**Acknowledgements** We thank Novartis Pharma AG for providing Iptacopan to the patient through Managed Access program.

**Author contribution** BH and JJ wrote the manuscript, which was revised and reviewed by all authors. BH, YH, BZ, HZ, LC, ZW, XJ, XL, QJ, HB, QC, HP, HP, WZ, HH, ZC, DZ, CY, MC, BD, and SZ were involved in patient diagnosis and management including CU and EA application. FF was responsible for patient cranial imaging. All authors approved for the final draft of manuscript.

**Funding** This work was funded by Chinese Academy of Medical Sciences (CAMS) innovation fund for medical sciences (CIFMS 2021–1-I2M-003) and National Natural Science Foundation of China (NSFC) (81970106).

## Declarations

**Ethics approval** An ethics approval was obtained from the hospital, and the patient signed a consent form to participate the CU and EA program.

**Consent for publication** The patient has signed a consent form to have her information published.

**Conflict of interest** The authors declare no competing interests.

## References


1. Brodsky RA (2014) Paroxysmal nocturnal hemoglobinuria. Blood 124(18):2804–2811
2. Parker C, Omine M, Richards S et al (2005) Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 106(12):3699–3709
3. Parker CJ (2016) Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program 2016(1):208–216
4. Schubart A, Anderson K, Mainolfi N et al (2019) Small-molecule factor B inhibitor for the treatment of complement-mediated diseases. Proc Natl Acad Sci USA 116(16):7926–7931
5. Risitano AM, Röth A, Soret J et al (2021) Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. The Lancet Haematology 8(5):e344–e354
6. Jang JH, Lee LWL, Ko B-S, et al (2022) Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2 cohort open-label proof-of-concept study. Blood Adv 2022006960
7. Killick SB, Bown N, Cavenagh J et al (2016) Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 172(2):187–207
8. Pharmaceutical Administration Law of the People's Republic of China. 2019; https://www.nmpa.gov.cn/xxgk/fgwj/flxzhfg/20190827083801685.html, 2019.
9. Mainolfi N, Ehara T, Karki RG et al (2020) Discovery of 4-((2S,4S)-4-ethoxy-1-((5-methoxy-7-methyl-1H-indol-4-yl) methyl)piperidin-2-yl)benzoic acid (LNP023), a factor b inhibitor specifically designed to be applicable to treating a diverse array of complement mediated diseases. J Med Chem 63(11):5697–5722
10. Risitano AM, Kulasekararaj A, Castro CMD, et al (2021) PH3 study of efficacy and safety of iptacopan (LNP023), an oral complement factor b inhibitor, in patients with paroxysmal nocturnal hemoglobinuria and residual anemia despite anti-C5 antibody treatment. Soc Hematol Oncol Annu Meet 2021; Texas, the United States