Efficient Control of Hemolysis and Thrombophilia by Iptacopan in a Patient with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Factor V Leiden Mutation

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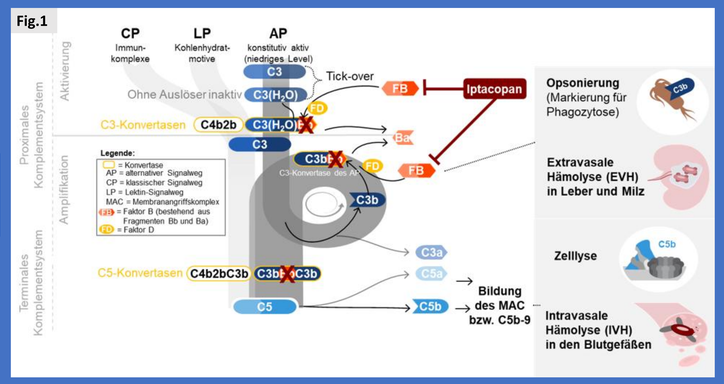
Introduction

Iptacopan, a first-in-class oral factor B inhibitor, has shown significant inhibition of complement-mediated intra- and extravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) leading to approval in treatment-naïve and C5-complement- inhibitor pre-treated patients. There is few data reported on iptacopan‘s activity in high risk thrombophilic conditions. The present case refers a high risk thrombophilic PNH patient due to concomitant factor V Leiden mutation and non severe aplastic anemia (nSAA).

Fig. 1: Mechanism of action of iptacopan[2-5].



Patient and methods

52-year-old female
Relevant comorbidities:
- Factor V Leiden mutation, deep vein thrombosis of V. fibularis dex., 2016 + 2018 ➔ therapeutic anticoagulation with apixaban
- arterial hypertension

08/2017	nSAA: CSA + eltrombopag (EMAA trial) → **CR**
08/2020	PNH with hemolytic anemia, DNMT3A mut. → start C5-complement-inhibition with **ravulizumab 09/20** → **PR**[1]
11/2021	detection of GPI deficiency in 85,1% of granulocytes, 86,3% of monocytes + 60% of erythrocytes → switch to **crovalimab** (C5-complement-inhibitor, COMMODORE trial) → **SAE 12/21:** especially dermal vasculitis of right lower leg, myalgia, rash → corticosteroid pulse therapy
02/2022	study termination
03/2022	incomplete central occlusion of A. ophthalmica dextra
05/2022	switch back to **ravulizumab** → **PR**[1] (extravasal hemolysis, anemia (Hb: 8-10 g/dl), occasional transfusions, breakthrough hemolysis episodes (BTH), reticulocytosis, fatigue (FACIT-Fatigue Score[6]: 29 points, Fig. 7)
04/2025	tripple vaccination against pneumococci + Haemophilus influenzae type b (Hib) + meningococci) → switch to oral factor B inhibitor **iptacopan → quick CR**[1] (Fig. 4 + 5); dyspnea + fatigue (Fig. 7) dissolved

Response category	Red blood cell transfusions	Haemoglobin level	Residual haemolysis and breakthrough episodes
Complete response	None	≥130 g/l (males) or ≥120 g/l (females)	LDH ≤1.5 × ULN and ARC ≤150 000/µl,§ no breakthrough episodes
Major response	None	≥130 g/l (males) or ≥120 g/l (females)	LDH >1.5 × ULN and/or ARC >150 000/µl,§ only subclinical breakthrough episodes
Good response	None	≥10 and <130 g/l (males) or ≥10 and <120 g/l (females)	Any LDH and ARC value, only subclinical breakthrough episodes (rule out bone marrow failure)†
Partial response	None or occasional (≤2 every 6 months)	≥8 and <100 g/l	
Minor response#	None or occasional (≤2 every 6 months)	<80 g/l	
	Regular (3–6 every 6 months)	<100 g/l	
	Reduction by ≥50%^	<100 g/l	
No response#	Regular (>6 every 6 months)	<100 g/l	

ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; ULN, upper limit of the normal.

Table 1: Hematological response to complement inhibitors in PNH was defined according to **Risitano criteria**[1].

Results: Disease Course on Iptacopan

Shortly after switch to iptacopan, her Hb and LDH values normalized. Unfortunately, 10 days after switch a cholecystitis required laparoscopic cholecystectomy and was subsequently complicated by a cholangitis (Fig. 2 + 3) with severe abdominal pain and jaundice (bilirubin: 10 mg/dl). Re-hospitalization for i.v. antibiotics and interventional ERCP due to multiple concrements and sludge was necessary. Following papillotomy and stent implantation the patient‘s symptoms improved significantly.

Throughout the entire inflammation period iptacopan was administered regularly together with low molecular weight heparin. Remarkably, no BTH or thrombotic events occured, stable Hb values and hemolysis could be maintained.

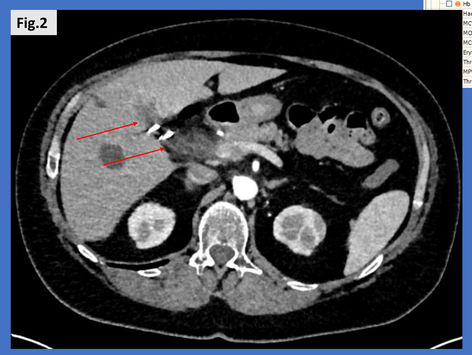
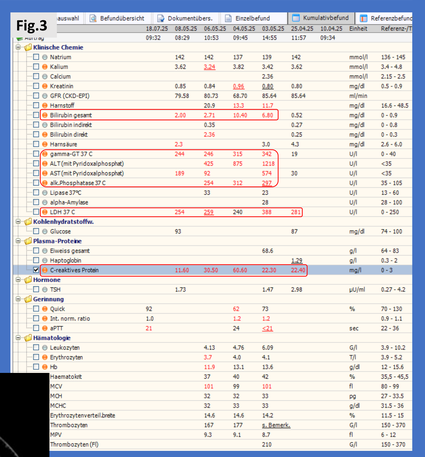
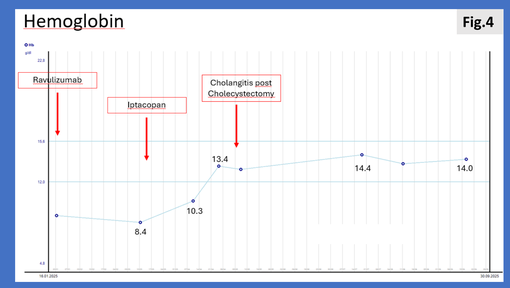


Fig. 2: CT scan revealing cholangitis with expanded DHC (11 mm) and fat tissue imbibition after cholecystectomy. **Fig. 3**: Laboratory values during cholangitis after cholecystectomy.





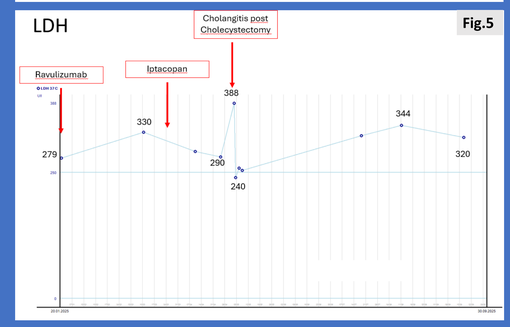
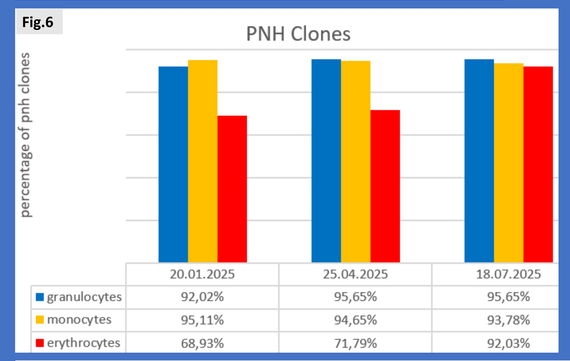


Fig. 4 + 5: Hemoglobin- and LDH-values in the course of treatment.



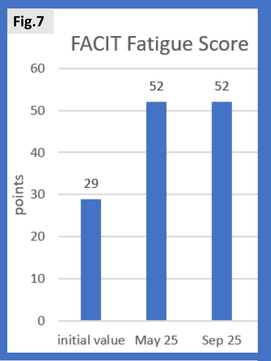


Fig. 6 + 7: PNH clone sizes and FACIT Fatigue Score[6] pre- and post-treatment-switch to iptacopan. The FACIT Fatigue scores range from 0-52. A score < 30 indicates severe fatigue. The higher the value the better the quality of life.

Conclusion

The present case demonstrates sufficient control of hemolysis and coagulation by iptacopan monotherapy in this very high risk thrombophilic constellation. Was the quick positive clinical outcome of the cholecystitis and cholangitis determined by the recent treatment switch to iptacopan especially rapidly leading to normalized Hb-values and fatigue condition? Given that iptacopan is recently availible in our daily practice, further real-world data will provide broader expertise in this context.

References
1. Risitano AM, Peffault de Latour R. How we('ll) treat paroxysmal nocturnal haemoglobinuria: diving into the future. Br J Haematol. 2022 Jan;196(2):288-303. 2. Specialist information of Iptacopan (with kind permission of Novartis). 3. Schubart A, et al. Proc Natl Acad Sci USA 2019;116:7926–31. 4. Schubart A, et al. Immunol Rev 2023;313:339–357. 5. Mainolfi N, et al. J Med Chem. 2020;63(11):5697–5722. 6. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Interessenskonflikte: 1. Anstellungsverhältnis oder Führungsposition: keine, 2. Beratungs- bzw. Gutachtertätigkeit: keine, 3. Besitz von Geschäftsanteilen, Aktien oder Fonds: keine, 4. Patent, Urheberrecht, Verkaufslizenz: keine; 5. Honorare: keine; 6. Finanzierung wissenschaftlicher Untersuchungen: keine, 7. Andere finanzielle Beziehungen: keine, 8. Immaterielle Interessenkonflikte: keine