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TO THE EDITOR:

Experience of compassionate-use pegcetacoplan for paroxysmal nocturnal hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired condition characterized by intravascular hemolysis (IVH) and thrombosis. Patients classically have elevated levels of lactate dehydrogenase (LDH) and anemia.[1,2] Eculizumab has significantly improved life expectancy.[3] Eculizumab and ravulizumab bind at complement protein C5 in the complement cascade, inhibiting terminal complement activation, preventing IVH, and reducing thrombosis risk.[4,5]

Two-thirds of the patients on C5 inhibition are anemic due to C3 red cell opsonization, leading to extravascular hemolysis (EVH), and one-third require blood transfusions.[6-8] EVH is often represented by a disproportionally low percentage of PNH erythrocytes compared with PNH white cells and high PNH red cell C3 loading.

Pegcetacoplan, which targets proximal complement protein C3, prevents IVH and EVH. The PEGASUS clinical trial for patients with PNH on eculizumab with hemoglobin (Hb) of <105 g/L showed marked improvement with an adjusted mean Hb difference with an increase of 38.4 g/L while on pegcetacoplan compared with eculizumab and significantly improved Functional Assessment of Chronic Illness Therapy–Fatigue scores.[9]

Breakthrough IVH is a recognized, potentially life-threatening event in patients with complement-inhibited PNH. The presentation includes PNH symptom recurrence, sudden Hb drop, and LDH rise.[10,11] Breakthrough events can occur toward the end of the eculizumab dosing interval (pharmacokinetic [PK] breakthrough) or during complement-amplifying events; for example, infection (pharmacodynamic [PD] breakthrough).[11] Approximately 20% of the patients on eculizumab require higher than standard dosing,[12] thereby resolving PK issues. PD breakthrough can be managed by treating the underlying causes and considering an early/extra C5 inhibitor dose.

Breakthrough events while on proximal complement inhibitors differ; PNH red cells are not selectively removed because of EVH and are similar to PNH white cell levels. Breakthrough events can be more severe in patients with C5 inhibition owing to rapid hemolysis. Patient education is essential, along with prompt contact with treating clinicians if symptoms occur.

Management of these events is currently difficult, with no clear pathway.

Our center is participating in the PEGASUS 307 extension study (#NCT03531255) and a pegcetacoplan compassionate-use program. We present cases of patients treated within the compassionate-use program with pegcetacoplan 1080 mg twice a week, and breakthrough event management. Five patients were identified, all of whom experienced transfusion-dependent EVH with eculizumab.

The definition of breakthrough hemolysis was an increase in LDH >2 times the upper limit of normal (ULN) and an Hb drop.

Breakthrough management per investigator choice includes (1) daily subcutaneous pegcetacoplan for 3 days (1080 mg per dose), (2) 1 IV pegcetacoplan dose (1080 mg), or (3) single eculizumab dose (900 mg) as per #NCT03531255.

Patients experiencing clinical breakthrough symptoms were assessed, and samples were collected for complete blood counts, biochemistry, and LDH levels.

Four of the 5 patients were male, with a median age of 52.5 years. The mean PNH red cell population once established on pegcetacoplan was 96.25% from 42.25% (mean increase 54%) (1 result not available) (Table 1). Patients were treated with eculizumab before pegcetacoplan for 8 to 206 months. The mean duration of treatment with pegcetacoplan was 13.8 months per patient. The total number of years of pegcetacoplan was 5.75, resulting in a mean breakthrough event per patient every 8 months.

Seven breakthrough events were experienced by 3 patients (Table 2). The mean LDH increase for 6 out of 7 events was 4.61× ULN. LDH was not available in 1 event (1c) owing to 2 previous acute BTH events, hemolyzed LDH, and Hb drop, and the clinical decision was to treat. The mean Hb drop was 29.1 g/L; the mean time for Hb drop was 1.1 days from the start of symptoms.

One patient experienced 2 unprecipitated events. Three patients had 5 precipitated events (vaccination [1/5] and infection [4/5]). All the infections were treated with antibiotics.

Three of 6 breakthrough events were treated with single eculizumab doses (Table 2) followed by an increased pegcetacoplan dosing frequency for 1 out of 3 events; 1 event (patient 4), unprecipitated day 19 after eculizumab cessation (eculizumab before pegcetacoplan, 1800 mg biweekly), was managed with eculizumab reintroduction; the same patient at the second unprecipitated event had eculizumab increased to 1200 mg biweekly and increased pegcetacoplan dose every 3 days: third precipitated event for this patient, daily subcutaneous pegcetacoplan for 3 days, and eculizumab increased to 1500 mg biweekly. One event required no intervention (physician's decision).

The mean time required for breakthrough resolution (LDH normalization to baseline) was 16.6 days. There were no thrombotic breakthrough events.

Here, we present a patient cohort on the compassionate use of pegcetacoplan. Four were clinical trial ineligible,

Table 1. Patient baseline data and demographics

Patient	Indication for C5 inhibition	Time on eculizumab before treatment with pegcetacoplan (mo)	BTH on eculizumab before treatment with single agent (n)	Eculizumab dose (mg) before treatment with pegcetacoplan*	Granulocyte PNH population at commencement of C5 inhibition (%)	PNH red cell population on C5 inhibition (%)	PNH red cell population once established on pegcetacoplan (%)	Long-term eculizumab and pegcetacoplan†
1	Transfusion-dependent classic PNH	206	3	1200	99	54	99	No
2	Transfusion-dependent classic PNH	40	1	1200	65	35	90	Yes
3	Classic PNH with thrombosis	84	4	900	89	28	97	Yes
4	Transfusion-dependent classic PNH	8	0	1800	99	52	99	No
5‡	Transfusion-dependent classic PNH	146	4	1200	68	25	NA	Yes

BTH, breakthrough hemolysis; NA, not available.

*All eculizumab dose increases were due to breakthrough events (because of PK events).

†Patients 2, 3, and 5 had pegcetacoplan added to the eculizumab regimen; planned withdrawal of eculizumab for patient 5 was not possible because of death.

‡Patient 5 died 2 months after starting pegcetacoplan because of noninfectious non–PNH-related causes.

Table 2. Breakthrough events (patients 3 and 5 had no events)

Patient	Time taken between initiation of pegcetacoplan and BTH (d)*	Precipitating event at BTH	LDH during stable pegcetacoplan treatment (× ULN)	LDH at time of breakthrough (× ULN)	Time taken for LDH return baseline (d)	Hb baseline (g/L)	Hb at BTH (g/L)	Time taken for Hb to fall (d)	Drop in Hb (g/L)	Management of BTH event
1a	262	Infection	Normal	4.9	9	97	86	0	11	Eculizumab single dose (900 mg)
1b	254	COVID-19 and flu vaccination	1.4	5.1	19	130	89	5	41	Eculizumab 2 doses (900 mg); increase pegcetacoplan dosing frequency to every 3 d
1c	315	Norovirus infection	1.4	Hemolyzed†	NA	145	117	1	28	Eculizumab single dose (900 mg)
2	174	Infection (site unclear)	Normal	2.1	13	103	78	0	25	No change
4a	19	No event	NA*	4.9	20	120	102	2	18	Eculizumab restarted (900 mg) every 2 wk
4b	60	No event	NA*	6.5	22	118	76	0	42	Eculizumab increased (1200 mg) every 2 wk; increase pegcetacoplan dosing frequency to every 3 d
4c	Already on combination treatment	Lower respiratory tract infection	Normal	4.2	Awaited	120	71	0	39	Eculizumab increased (1500 mg) every 2 wk; daily pegcetacoplan for 3 d

If more than 1 breakthrough event occurred per patient, this was indicated as a, event 1; b, event 2; and c, event 3.

*LDH was not obtained on single-agent pegcetacoplan because of limited time on single-agent treatment.

†Samples were hemolyzed. LDH before the event was normal and after the event was 1.1× ULN.

representing the most severe PNH and EVH spectrum. We recognized 2 breakthrough event types in treatment with pegcetacoplan. Patients experiencing breakthrough events soon after stopping eculizumab and commencing single-agent pegcetacoplan have insufficient disease control on C3 inhibition alone, similar to patients in the PEGASUS trial who returned to C5 inhibition.[9] Predicting patients this applies to is not currently possible. These patients may not have sufficient PNH control with any single-agent proximal complement inhibitor.

Patients experiencing breakthroughs due to complement-amplifying events have a different presentation and are likely to have repeated events, as our cohort has shown, with 5 of 7 events having precipitating causes. Although a missed dose cannot be categorically excluded, patients reported compliance and were considered reliable.

C3 is an acute phase reactant protein within the complement cascade; a complement-amplifying event, such as infection or surgery, causes increased levels, risking PD breakthroughs.

Patients on pegcetacoplan have large PNH red cell proportions (90%-99% in this series); thus, IVH breakthrough could lead to sudden profound anemia. This is a new experience for patients, and most had not experienced such high-erythrocyte PNH cell levels during C5 inhibition.

Patients experiencing increase in LDH levels and PNH symptoms or reduction in Hb levels should be considered as having a breakthrough event and require intervention to stop IVH, stabilize Hb, and reduce potential life-threatening thrombosis risk.

Our cohort had higher than expected eculizumab use to manage breakthroughs, partly due to the physician's experience at our center. Four of the 5 patients were on a combination of C5 and C3 inhibition. This is rare and represents a very small proportion of patients with complex conditions. For context, our center has 233 patients treated with C5 inhibitors and 37 patients within clinical trials, including 7 on single-agent pegcetacoplan. It has been proposed for many years that a small number of patients will likely benefit from combination treatment.[13] Current clinical trials are assessing combination treatments either with C5 inhibitors, for example, pozelimab and cemdisiran (#NCT04811716) or with C5 and factor D inhibitors (#NCT04469465).

Breakthrough events were higher than those reported in the PEGASUS trial, with 24% adverse events due to hemolysis, and 6 out of 77 patients discontinued treatment due to hemolysis after 48 weeks of treatment (3 discontinued in the first 16 weeks).[14] BY contrast, patients in the compassionate program demonstrated that precipitated breakthrough events can be managed effectively with patients remaining on pegcetacoplan.

The study's limitations include its retrospective nature, although the events were managed in real time. None of the patients were treated with IV pegcetacoplan. There are a small number of data points missing for the breakthrough events.

Many questions remain regarding the diagnosis and management of PNH breakthrough events associated with complement inhibitors. As proximal complement inhibitors become more widely available, the management of breakthrough events should become clearer, and the identification of patients who require combination treatment will hopefully become more evident.

We conclude that the management of these events requires patient and physician education, prompt assessment, and management. There exists a patient cohort in which patients have insufficient PNH control on single-agent pegcetacoplan. For most patients, breakthrough events are inevitable, and we propose that these can be managed with a single C5 inhibitor dose, with patients remaining on long-term pegcetacoplan. We await a clinical trial reporting the efficacy of managing events by increasing pegcetacoplan daily for 3 days or a single IV dose.

Authorship

Contribution: M.G. and R.K. devised the manuscript, reviewed the data, and wrote and edited the manuscript; T.M., P.M., S.N., and A.P. treated the patients and reviewed and edited the manuscript; and N.H., N.Y., C.B., B.F., and L.A. treated the patients and reviewed the manuscript.

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Footnotes

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