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Received: 11 October 2021 | Revised: 3 January 2022 | Accepted: 9 January 2022

DOI: 10.1002/ajh.26474

RESEARCH ARTICLE

Paroxysmal nocturnal hemoglobinuria and vascular liver disease: Eculizumab therapy decreases mortality and thrombotic complications

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Abbreviations: AA-PNH, aplastic anemia-PNH syndrome; BCS, Budd-Chiari syndrome; BMT, bone marrow transplantation; *JAK2*, *Janus kinase 2 gene*; MDS, myelodysplastic neoplasm; MPN, Myeloproliferative neoplasm; OLT, orthotopic liver transplantation; PNH, paroxysmal nocturnal hemoglobinuria; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; UGIB, upper gastrointestinal bleeding; VALDIG, European vascular liver disease network; VLD, vascular liver disease.

Presented in oral presentation, abstract #PS-018, and selected as "best of ILC" summary slide deck, at the ILC annual meeting April 2019, EASL, Vienna, Austria.

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Funding information
Centre de reference des maladies vasculaires du foie; Assistance Publique Hpitaux de Paris, Grant/Award Number: CRC 2017

Abstract

A total of 2%–10% of patients with vascular liver disease (VLD) have paroxysmal nocturnal hemoglobinuria (PNH). Eculizumab reduces complement-mediated haemolytic activity in PNH. This study was aimed at assessing the impact of eculizumab on VLD outcome. Retrospective cohort of PNH patients, in Valdig registry, who had VLD diagnosed between 1997 and 2019 is considered. Eculizumab was the exposure of interest. Studied outcomes were death, venous thrombosis, bleeding, arterial ischemic event, infection, and liver-related complications. We compared survival and new thrombotic events from PNH/VLD cohort to Envie2 non-PNH cohort. Sixty-two patients (33 women), median age 35 years (28–48) and median follow-up VLD diagnosis 4.7 years (1.2–9.5), were included. Clone size was 80% (70–90), median hemoglobin concentration was 10.0 g/dl (8–11), and lactate dehydrogenase (LDH) was 736 IU (482–1744). Forty-two patients (68%) had eculizumab; median exposure time was 40.1 [9.3–72.6] months. Mortality was significantly lower in exposed versus nonexposed period: 2.6 versus 8.7 per 100 (PY), incidence rate ratio (IRR) was 0.29, 95% CI (0.1–0.9), $p = .035$. Thrombosis recurrence occurred less frequently during the exposure to eculizumab: 0.5 versus 2.8 per 100 PY, IRR 0.22 (0.07–0.64). Other secondary end points (i.e., bleeding, arterial ischemic lesions, infection, and liver complications) were less common during the exposure to eculizumab, although not reaching statistical significance. Six-year thrombosis-free survival was 70%, 95% CI [0.60–0.83] for PNH cohort and 83%, 95% CI [0.70–1.00] for non-PNH Envie 2 patients, ($p < .001$). In conclusion, patients with PNH and VLD are at higher risk of recurrent thrombosis than non-PNH patients. Eculizumab is significantly associated with a lower mortality and less thrombotic recurrence in patients with PNH and VLD.

1 | BACKGROUND AND AIMS

Primary Budd-Chiari syndrome (BCS) is a rare disorder defined as a blocked hepatic venous outflow tract by thrombosis at various levels from small hepatic veins to the terminal portion of the inferior vena cava.[1] Nonmalignant noncirrhotic extrahepatic portal vein thrombosis (PVT) is characterized by a thrombus developed in the main portal vein and/or its right or left branches and/or splenic or mesenteric veins, or by the permanent obliteration that results from a prior thrombus.[2] The pathogenesis of these vascular liver diseases (VLD) is largely dependent on the presence of systemic prothrombotic conditions that promote thrombus formation in the respective splanchnic veins.[3,4]

Four to nineteen percent of patients with BCS have paroxysmal nocturnal hemoglobinuria (PNH), and small studies or case reports also described PNH in patients with portal and mesenteric vein thrombosis.[1,5,6] PNH is a rare acquired disorder of hematopoietic stem cells, related to a somatic mutation in the phosphatidyl-inositol Glycan class A (PIG-A), X-linked gene, responsible for a deficiency in glycosyl phosphatidilinositol-anchored proteins (GPI-AP). The lack of GPI-AP complement regulatory proteins leads to hemolysis. PNH often presents with hemolytic anemia, bone marrow failure, and episodes of venous thrombosis. Ten-year cumulative incidence of venous thrombosis varies from 28% to 38% in PNH and mainly affects cerebral, deep limb, or splanchnic veins. Thrombosis is the major factor affecting outcome.[7] Risk factors for thrombosis include older age, thrombosis at

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diagnosis, and the need of transfusions. Since 2004, reported approaches have used anticomplement agents, such as eculizumab, a C5 inhibiting recombinant humanized monoclonal antibody.[8–10] In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular hemolysis are blocked with eculizumab treatment. Chronic administration of eculizumab resulted in a rapid and sustained reduction in complement-mediated hemolytic activity, reduced mortality, reduced recurrence of thromboembolic events in all territories, including hepatic vein, cerebrovascular vein, mesenteric, and pulmonary vein thrombosis.[9–12] Initial studies have shown a significant impact of eculizumab on first or recurrent incident episodes of thrombosis in PNH patients: eculizumab reduced the thrombotic event incidence rate from 11–13 events per 100 patient-years to 2–14 events per 100 patient-years, a relative reduction of 81·8% ($p < .0005$).[12] Six-year overall survival was significantly improved in eculizumab patients (57% of whom had a previous thrombotic history) compared to historical controls. Fewer thrombotic events occurred during follow-up in the group of patients treated with eculizumab.[11] Yet, eculizumab-treated patients have died of VLD complications.[11] There is no study on the effect of eculizumab on the specific outcome of patients with a VLD. Thrombotic, bleeding, and liver complications in this specific setting need to be clarified.

We aimed to better characterize PNH/VLD patients including those currently treated with anticomplement agents, assessing the impact of eculizumab therapy on mortality, liver disease complications, and thrombotic or bleeding complications (including portal hypertension bleeding), in patients with BCS or PVT.

2 | PATIENTS AND METHODS

Methods and results are reported according to the STROBE statement.[13]

2.1 | Design and setting

We performed a retrospective study including patients with PNH and a diagnosis of BCS or PVT made between 1997 and 2019 in centers of the Vascular Liver Disease interest Group (VALDIG). Diagnosis of PNH preceded or followed diagnosis of VLD. The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board (IRB n 2003/21, Paris; France). Demographic and patient's data were collected at the diagnosis of VLD and during follow-up. Complications related to thrombosis, bleeding, portal hypertension, or blood disease were recorded.

2.2 | Definitions

BCS diagnosis was based on ultrasonography and/or multidetector computed tomography and/or magnetic resonance imaging and/or venography. Diagnostic criteria for PVT included recent portal and/or splenic and/or mesenteric venous thrombosis or portal cavernoma. PVT patients with cirrhosis or abdominal malignancies were not included. In the VALDIG group, patients with BCS were treated according a stepwise therapeutic strategy, since 1997.[1,5] The first step consists of anticoagulation therapy, specific therapy for underlying conditions, and medical or endoscopic management of liver-related complications. Recanalization of stenosis using angioplasty or stenting is routinely considered. In patients who do not respond to this first step therapy, transjugular intrahepatic portosystemic shunt (TIPS) is proposed and, as a fourth step, orthotopic liver transplantation (OLT). Patients with acute portal or mesenteric vein thrombosis are treated with anticoagulants since the 1990s.[3,6] Patients with chronic PVT are treated with anticoagulation when a severe thrombophilic factor is identified, and/or past history of mesenteric infarction or personal or family history of deep vein thrombosis or on a case-to-case basis for others.[1,14,15] Anticoagulants therapy is based on low-molecular-weight heparin during the acute phase, or in patients with high-bleeding -risk situations, switch to warfarine derivatives in stabilized conditions.[1,4,5,15]

PNH diagnosis was based on the detection of GPI-deficient white blood cells (WBCs) by the flow cytometry assay. To avoid biases related to the evolution of flow cytometry techniques, a threshold of 5% was used to define a PNH clone. As previously proposed, PNH were categorized as follows[7]: the classic PNH subcategory includes patients with clinical evidence of intravascular hemolysis but no evidence of other defined bone marrow failure criteria (neutrophils and platelets were per criteria higher than 1500/L and 120 000/L, respectively). Aplastic anemia-PNH syndrome (AA-PNH syndrome) subcategory includes patients who were diagnosed with PNH (with a PNH clone at diagnosis) and with, at least, 2 or 3 peripheral blood cytopenias (hemoglobin <100 g/L, platelets $<80 \times 10^9$/L, neutrophils <1000/L). Patients who did not fulfill the last two groups' criteria were assigned to a third group of patients called intermediate PNH: this category includes patients with myelodysplastic (MDS) and myeloproliferative neoplasm (MPN).

Temporality of PNH and VLD was categorized as PNH before VLD, PNH after VLD, and contemporary diagnoses when PNH was diagnosed within a month of VLD diagnosis (before or after).

Eculizumab therapy was first available in 2007. In a sensitivity analysis, we considered only patients with a VLD diagnosis made after 2007 (after first availability of eculizumab).

Eculizumab regimen used the standard 4-week initial phase followed by the standard maintenance phase.[9] In patients for whom there seemed to be an inefficacy on hematological manifestations, complement blockade could be assessed and regimen modified in case of insufficient complement blockade.[16]

2.3 | Endpoints

Primary endpoint was mortality. Secondary outcomes were as follows: new venous thrombosis (including deep vein thrombosis, new

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splanchnic vein thrombosis, cerebral thrombosis, and TIPS thrombosis) occurring after VLD diagnosis; arterial ischemic event (arterial stroke, myocardial infarction, and obliterating arteriopathy), bleeding event including upper gastrointestinal bleeding (UGIB) or other severe bleeding, bacterial infection, and liver complications (including spontaneous bacterial peritonitis [SBP], UGIB, hepato-renal syndrome, hepatic encephalopathy, or ascites [resolved or recurrent]). Ascites resolution was assessed among patients with ascites at VLD diagnosis and ascites recurrence, among patients with ascites resolution.

2.4 | Follow-up

Patients were followed according to local practice from the date of VLD diagnosis until death or last visit of follow-up or 10 years follow-up (predefined as the most clinical significant period) after VLD diagnosis, whichever occurred first. For five patients with BMT, follow-up was censored at the date of BMT (the patient being therefore considered as cured).

2.5 | Investigations for thrombotic risk factors

Patients were tested according to previously reported methods for the following thrombotic risk factors[4,5]: factor V R 506 Q mutation (factor V Leiden); G 20210 A factor II gene mutation; *JAK2*^{V617F}, mutations, deficiencies in protein C, protein S, or antithrombin (regarded as primary deficiencies only in conjunction with a prothrombin index ≥80%); PNH; and antiphospholipid antibodies. Oral contraceptive use was considered as a thrombotic risk factor when taken within the 3 months preceding diagnosis of VLD.[17]

2.6 | Statistical analysis

Data were described using median (interquartile range) or number (proportion) as appropriate. In order to account and control for immortal time bias,[18,19] we defined exposed and unexposed person-time by using start and end date of eculizumab. Incidence rates for individual outcomes were calculated by dividing the incident number of events by the number of person-years (PY) over the corresponding period (either exposed or unexposed period). Incidence rate ratio (IRR) was estimated by Poisson's regression with their 95% confidence interval (95% CI). In a sensitivity analysis, patients diagnosed and managed after 2007 (i.e., the opportunity of having eculizumab therapy) were analyzed separately.

We compared survival and new thrombotic event from our PNH/VLD cohort to Envie2 cohort. Envie 2 cohort prospectively followed-up 147 consecutive incidental non-PNH patients with BCS diagnosed between October 2003 and October 2005 in nine European countries from the same valdig group, until June 2009 in an extended follow-up study.[20] To compare both groups, we censored the event (death and/or new thrombosis) at 6 years. Survival curves were obtained using the Kaplan–Meier methods and compared using the log-rank test.

Analyses were performed using the R software (The R Foundation for Statistical Computing Plateform), version 4.0.

Author list has been performed according to valdig rules.

Number of patients from

France: $N = 50$ (Clichy/Saint Louis $n = 29$, Besançon $n = 2$, Bordeaux $n = 2$, Clermont Ferrand, $n = 2$, Lille $n = 2$, Lyon $n = 2$, Marseille $n = 2$, Poitiers $n = 1$, Toulouse $n = 3$, Rouen $n = 2$,Tours $n = 2$, Brest $n = 1$, Caen $n = 1$).

Spain: Barcelona $N = 4$, Madrid $n = 1$.

India: Mumbai $n = 3$.

Italy: Roma $n = 3$.

Switzerland: Bern $n = 1$.

3 | RESULTS

3.1 | Patient characteristics

PNH cohort patients' characteristics are shown in Table 1 and Table S1. Sixty-two patients (33 women, 53%) were included, including 50 with BCS, and 12 with PVT, with a median age of 35 (28–48) years at the time of VLD diagnosis. Median follow-up after VLD diagnosis was 4.7 years (1.2–9.5). In 13 patients, PNH was diagnosed after VLD, with a median interval of 0.2 (0–1.7) years. In 4 patients, PNH was diagnosed at the time of VLD diagnosis, and in 45 patients, PNH was diagnosed before VLD diagnosis with a median interval of 3.6 (1.3–7.1) years (Table S2). Venous and arterial thrombosis elsewhere at diagnosis had occurred in 34 patients (54%) including 8 (13%) cerebral thrombosis. In the non-PNH Envie 2 cohort, venous and arterial thrombosis elsewhere at diagnosis had occurred in 11%, including 2.7% cerebral thrombosis.

JAK2^{V617F} myeloproliferative neoplasm was detected in 7% of patients with PNH-VLD and 32% in non-PNH Envie2 cohort.

Sixty patients (97%) were treated with anticoagulants for a median duration of 4.7 [1.3–9.9] years. Agents were vitamin K antagonists (VKA) in 4 (6.7%) patients, low molecular weight heparin in 10 (16.7%) patients, LMWH followed by VKA antagonists in 43 (71.7%) and other in 3 (5%). The two patients who were not treated with anticoagulants had severe thrombocytopenia (<40 000 platelets) or/and active bleeding at diagnosis.

3.1.1 | PNH characteristics

Median clone size among neutrophils was 80% (70–90), hemoglobin 10 (8–11) g/dl, and LDH 736 (482–1744) IU/L; the size of clone was not different over time, before and after 2007 (Table S3); 21 patients (37%) had classic PNH, 12 (21%) had aplastic anemia-PNH syndrome (AA-PNH syndrome), and 23 (41%) had intermediate PNH. Among intermediate PNH, 7 had a diagnosis of MDS and 3 a diagnosis of MPN, others not fulfilled the diagnosis of AA-PNH.

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TABLE 1 Characteristics at vascular liver disease (VLD) diagnosis, risk factors for thrombosis, and VLD treatments

	PNH cohort ($n = 62$)	Non-PNH Envie2 cohort ($N = 147$)
Age, years	35 (28–48)	38.5 (28–51)
Female	33 (53)	83 (57)
Delay symptoms—VLD diagnosis >6 months (N, %)	22 (39)	NA
≥1 inconclusive imaging before VLD diagnosis	33 (64)	NA
Inherited thrombophilia		
Factor V gene mutation	1 (2)	13 (9)
Factor II gene mutation	0	1 (1)
PC or PS, AT deficiency	3 (7)	11 (8)
Acquired thrombophilia		
JAK2^{V617F} myeloproliferative neoplasms	3 (7)	47 (32)
Antiphospholipid antibody syndrome	3 (7)	5 (3)
Multiple risk factors	1 (2)	4 (3)
Clone size %, IQR	80 (70–90)	–
Hemoglobin g/dl	10 (8–11)	8.9 (8–10)
LDH IU	736 (482–1744)	110 (80–1500)
Platelets, G/L	101 (61–162)	249 [162–38]
PNH type		
Aplastic	12 (21)	–
Classic	21 (38)	–
Intermediate	23 (41)	–
Serum bilirubin, μmol/L	30 (16–53)	31.9 (19–48)
Serum albumin, g/L	35 (28–38)	33.5 (29–38)
Ascites	33 (53)	122 (84)
Esophageal varices	18 (36)	42 (59)
Upper GI bleeding (UGIB)	4 (7)	6 (4)
Hepatic encephalopathy	3 (5)	12 (8)
Spontaneous bacterial peritonitis	3 (5)	1 (0.7)
Sepsis	13 (21)	1 (15)
Venous thrombosis elsewhere	25 (40)	10 (9)
Mesenteric or splenic infarction	3 (5)	14 (13)
Cerebral thrombosis	8 (13)	4 (3)
Arterial ischemic event*	9 (15)	6 (4)
Treatments		
Anticoagulation	60 (97)	126 (86)
Stent	3 (5)	14 (12)
TIPS	16 (26)	48 (32)

Note: Values are *n* (%) or median (interquartile range). Arterial ischemic event includes arterial stroke, myocardial infarction, and obliterating arteriopathy.

Abbreviations: AT, antithrombin; LDH, lactate dehydrogenase; PC, protein C; PNH, paroxysmal nocturnal hemoglobinuria; PS, protein S; TIPS, transjugular intrahepatic portosystemic shunt; VLD, vascular liver disease.

3.1.2 | Patients with BCS

In patients with BCS, hepatic venous outflow obstruction was due to occlusion of one, two, and 3 hepatic veins in 7, 7, and 33 patients, respectively, associated or not to obstruction of the suprahepatic segment of the inferior vena cava in five patients (-Table S1). Fifteen (31%) out of the 50 patients with BCS also had a PVT, four had an obstruction of the mesenteric vein (one had a mesenteric infarction with small bowel resection), and eight of the splenic vein. Duration between symptoms and BCS diagnosis was longer than 6 months in 17 (37%) patients. One, two, and three inconclusive imaging of the liver were performed respectively in 20, 7, and 1 patients before diagnosis of BCS was eventually confirmed. Ten patients underwent a liver biopsy. In one patient, imaging was inconclusive, whereas liver biopsy found a "small vessel BCS."

Thirty-one (65%) had ascites; 16 (38%) esophageal varices (four variceal bleeding). Median Child-Pugh score, Clichy score, and Rotterdam score at diagnosis were respectively of 10 (8–11), 6 (5–7), and 1.2 (0.1–1.31).

3.1.3 | Patients with PVT

Mesenteric vein obstruction was present in 6 (60%), splenic infarction in 1, and mesenteric infarction with bowel resection in one patient (-Table S1). At diagnosis, two patients had esophageal varices, and none had bled.

3.1.4 | Therapeutic management an outcome

All BCS patients received a stepwise therapeutic strategy, including anticoagulation ($n = 49$, 98%), hepatic venous angioplasty/stenting ($n = 3$; 6%), and TIPS ($n = 16$, 32%). No patient had liver transplantation.

In comparison of survival and new thrombotic events between our PNH/VLD cohort to non-PNH Envie 2 cohort, with similar therapeutic strategy, survival was not significantly different with a median follow-up of 4.1 [1.33–4.93]. Conversely, thrombosis-free survival was significantly lower in PNH patients compared to non-PNH patients. Six-year thrombosis-free survival was 70%, 95% CI [0.60–0.83] for PNH cohort and 83%, 95%IC [0.70–1.00] for non PNH Envie 2 patients, ($p < .001$), Figure 1A,B.

Patients diagnosed and managed with VLD before and after 2007 were comparable in terms of initial severity and management (Table S3).

Out of the 62 patients, 42 (68%) patients received eculizumab, including 29 within the first 4 months after VLD diagnosis; 34/42 (80%) had BCS, and 8/42 (20%) had PVT. Eculizumab administration was delayed in eight patients with a median delay of 4.2 (3.4–5.9) years. In 4 of these 8 patients, diagnosis of PNH was reached after the diagnosis of VLD. Eculizumab median exposure time was 40.05 [9.33–72.55] months. All had eculizumab until death or bone

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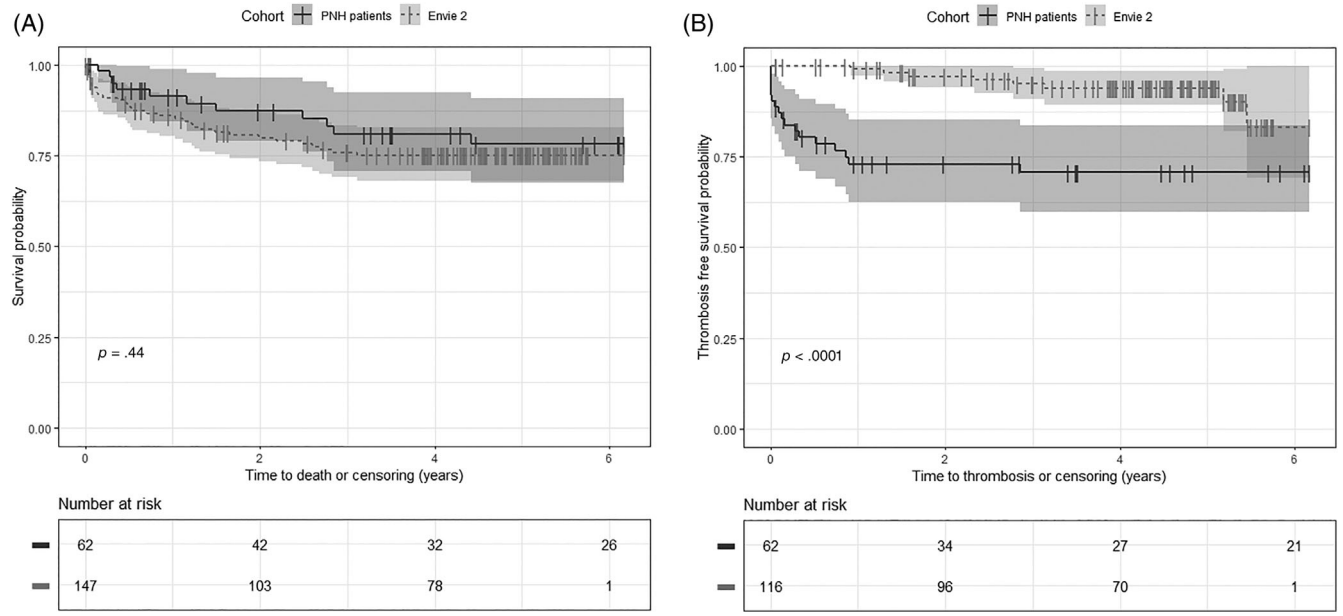

FIGURE 1 Comparison of survival and new thrombotic events between our PNH/VLD cohort to non-PNH Envie 2 cohort (A) PNH cohort and Envie 2 non PNH VLD patient's survival and (B) PNH cohort and Envie 2 non PNH VLD patient's thrombosis free survival

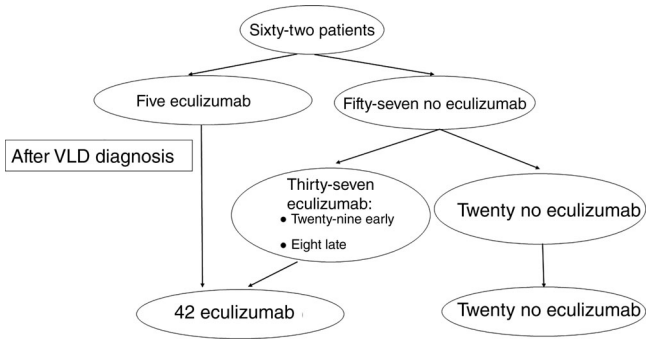

FIGURE 2 Eculizumab therapy according to Budd-Chiari syndrome (BCS) or portal vein thrombosis (PVT) diagnosis

marrow stem cell transplantation or patient's interruption ($n = 1$). Eculizumab therapy according to BCS or PVT diagnosis is described Figure 2.

3.1.5 | Outcomes

Hepatic or portal vein recanalization was obtained in 12 patients, all on anticoagulation therapy. Overall, 17 (27%) patients died (eight died from severe liver disease complications, four from infection and multiple organ failure, three from cancer or leukemia, and two cerebral bleeding), and 15 of them had persistent ascites and portal hypertension at the time of death. The mortality was significantly lower with eculizumab therapy (Table 2): 2.6 versus 8.7 per 100 PY, IRR 0.30 95% CI (0.10–0.92) (p value = .035).

During follow-up, there were 25 venous thrombosis, including eight TIPS thrombosis and one cerebral thrombosis. New venous thrombosis, in the splanchnic or extrasplanchnic veins, occurred less frequently in patients during exposure time to eculizumab: 2.62 versus 14.2 per 100 PY, IRR 0.22 (0.07–0.64).

Other secondary end-points (bleeding, arterial ischemic lesions, ascites resolution and recurrence, infection, and liver complications) were less common in patients exposed versus nonexposed period, although not reaching statistical significancy (Table 2). All patients but one have continued long-term eculizumab therapy until bone marrow stem cell transplantation or death. In eight patients, the dose of eculizumab was temporally increased to 1200 mg/every 2 weeks, due to inefficacy on hematological manifestations and on complement blockade: among them, six patients had ascites and four had a TIPS. At the end of follow-up, one of these eight patients was deemed to require BMT because of severe bone marrow failure. This patient had persisting moderate ascites despite functional TIPS (porto caval gradient below 8 mm Hg). One patient stopped eculizumab during follow-up and had recurrent thrombosis despite anticoagulation. Eight (13%) patients underwent hematopoietic stem cell transplantation for aplastic anemia, including four who were previously treated with eculizumab.

Twenty-six (42%) still needed regular blood transfusion at the end of follow-up versus 50 (81%) at diagnosis. Eighteen patients have had severe infection during follow-up, which was synchronous to venous thrombosis episode in 3.

When restraining analyses of primary and secondary outcomes to the "after 2007 period," era of eculizumab therapy, we observe significant reduced venous thrombosis and arterial events and a trend in favor of eculizumab efficacy on survival. (Table S4).

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TABLE 2 Complications during follow-up

Complication	Exposure	Number of event	Person-years (PY)	Incidence rate per 100 PY	IRR (95% CI)
Death	**Yes**	**4**	**152.6**	**2.62**	**0.30 (0.10–0.92)**
	No	**13**	**148.7**	**8.74**	
Bleeding	Yes	5	152.6	3.28	0.41 (0.14–1.15)
	No	12	148.7	8.07	
Liver complications[a]	Yes	4	152.6	2.62	0.43 [0.13–1.41]
	No	9	148.7	6.05	
Infection	Yes	6	152.6	3.93	0.53 [0.2–1.44]
	No	12	148.7	8.07	
Arterial ischemic event	Yes	1	152.6	0.66	0.16 (0.02–1.35)
	No	8	148.7	5.38	
Venous thrombosis[b]	**Yes**	**4**	**152.6**	**2.62**	**0.22 (0.07–0.64)**
	No	**21**	**148.7**	14.12	
Among 33 patients with ascites					
Ascites resolution[c]	Yes	13	80.9	16.1	0.29 [0.08–1.05]
	No	11	86.8	12.7	
Among 24 patients with resolved ascites					
Recurrent ascites[d]	Yes	1	71.5	1.40	0.97 [0.06–15.5]
	No	5	69.3	7.21	

Bold entries correspond to complications that were statistically significantly different according to eculizumab therapy exposure.
[a]Hepatic encephalopathy/ hepatorenal syndrome/péritonitis/ascites.
[b]Venous thrombosis included deep vein thrombosis, new splanchnic vein thrombosis, cerebral thrombosis, and transjugular intrahepatic portosystemic shunt (TIPS) thrombosis occurring after Budd-Chiari syndrome (BCS) or portal vein thrombosis (PVT) diagnosis.
[c]For ascites resolution, analyses were performed among patients with ascites at BCS or PVT diagnosis.
[d]For recurrent ascites, analyses were performed among patients with ascites resolution.

4 | DISCUSSION

The most important result from this multicentric cohort is the significant impact on mortality and recurrent thrombotic events of eculizumab in patients with severe VLDs and PNH, while conversely, we did not characterize a significant impact of eculizumab on the incidence of liver or portal hypertension complications. To avoid immortal bias, which may arise in cohort studies of drug effects, we have used incidence rates of exposition to assess the effect of eculizumab on endpoints.[18,19] The drawback of this methodology is that the study spans over a long period of time (1997–2019), with eculizumab available only after 2007. Nevertheless, this period has the advantage that VLD management otherwise than eculizumab administration was stable over time among the Valdig group. Indeed, management of BCS or PVT was homogeneous, in terms of anticoagulation therapy for all BCS or PVT patients, and "BCS therapeutic strategy" in BCS within the Valdig group.[4,5] Indeed, most of these centers routinely record VLD patients in a registry for BCS or PVT so called the VALDIG registry and manage the patients according to a protocol implemented for Envie 1 and 2 studies.[4,5,20] It is also important to note that BCS or PVT patients were comparable before and after 2007, in terms of extension of thrombosis, severity of PNH, severity of VLD (number of BCS and/or PVT), and in BCS patients, prognosis indexes. Finally, when restricting the analysis from 2007, Eculizumab has similarly a significant impact on thrombosis and arterial complications and trends to be significant on survival. The positive effect of eculizumab on vascular thrombotic events is already well established for all sites of venous thrombosis, due to the reduction of relapse as well as to the direct effect on the prothrombotic conditions, which may account for fatal complications of the vascular events. In these studies, the mean past history thrombotic event rate at inclusion was 19%–43%.[8,9,11] Our study focused on vascular liver thrombosis, where all patients (100%) had recent hepatic or portal venous thrombosis, 50% had portal hypertension complications at diagnosis, and 26% occurred during follow-up, and 97% were treated with antithrombotic therapy. Our results on the role of eculizumab in VLD patients confirm a similar positive effect in the splanchnic territory, mainly due to its impact to reduce thrombosis recurrence. Preliminary results presented in 2012 also support this hypothesis in VLD: survival after eculizumab therapy was a 100% in 19 BCS patients, after a median follow-up of 7 years with eculizumab therapy, recurrent thrombosis did not occur in 6/19 patients after eculizumab late therapy, while three had recurrent thrombosis prior eculizumab administration.[21] Although it could have been a hypothesis that patients described with other causes for VLD would be at higher risk for thrombosis, this risk was not increased in the 11 patients with another cause.

PNH/VLD patients differ from non-PNH VLD patients in thrombotic extent characteristics: thrombosis mainly affects small hepatic

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vessels, sometimes difficult to characterize, and associates multiple splanchnic veins sharing similar severe complications such as mesenteric vein infarction. Cerebral venous thrombosis is a frequent complication, not so frequently encountered in patients with VLD in the absence of PNH. Combining PVT and BCS in this study was noteworthy, as it has previously been shown that PNH mainly affects thrombosis in small vessels, sometimes difficult to characterize,[22] and associates multiple splanchnic veins sharing similar severe complications such as mesenteric vein infarction.[23] This study also confirms that other causes, such as myeloproliferative neoplasms or antiphospholipid syndrome, can be associated in VLD patients, and that diagnosing one cause should not jeopardize a complete screening of all causes, especially now that we know that treating PNH is efficient on VLD course. It is also interesting to note that eight patients were deemed to require increased doses of eculizumab to reduce hemolysis and obtain complement inhibition as previously shown.[16] This study demonstrates that treating the underlying cause favorably impacts on survival in VLD patients. Actually, a treatable cause for thrombosis is common in VLD patients, including, for example, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, or Behcet's disease, collectively found in 50%–80% of patients with BCS, and 40–60% of patients with PVT.[1] The management of causes and their treatment could have a major effect on the course of liver disease. Yet, studies on this point are scarce.[24] Despite eculizumab treatment, management of VLD events and complications remains challenging, as recurrences are possible and complement blockade not always efficient with standard regimen. Still, few patients died despite eculizumab therapy. The impact of persisting ascites in the ability to efficiently block complement with eculizumab needs to be investigated.

Prospective studies are warranted to evaluate if an early initiation of eculizumab (before 2 weeks) or new anticomplement therapies and complement blockade monitoring will help to avoid the use of stent and TIPS and prevent severe VLD in these patients. This is of particular importance in PNH patients that will develop an aplastic anemia or an MDS/AML in 30% and 15% of cases, respectively, at 15 years and could be candidates for bone marrow transplantation in those situations.

To conclude, patients with PNH and VLD are at higher risk of recurrent thrombosis than non-PNH patients. We show that recurrent thrombotic risk is much lower in PNH-VLD patients with eculizumab therapy; although as previously suggested, it still exists in very few patients with other possible local or general co-factors for thrombosis. The management of these events associated to portal hypertension complications remains challenging, and recurrences are possible. Close follow-up is still needed in these patients who may still have severe, lethal complications. Assessing new anticomplement agents currently in clinical development impact could be an alternative in these situations.

ACKNOWLEDGMENT

We want to thank Kamal Zekrini kamal.zekrini@aphp.fr and Dahia Secour Sekour dahia.sekour@aphp.fr for their collaboration for the French national network for vascular liver diseases.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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How to cite this article: Plessier A, Esposito-Farèse M, Baiges A, et al. Paroxysmal nocturnal hemoglobinuria and vascular liver disease: Eculizumab therapy decreases mortality and thrombotic complications. *Am J Hematol*. 2022;97(4): 431-439. doi:10.1002/ajh.26474

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