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A 15-year, single institution experience of anticoagulation management in paroxysmal nocturnal hemoglobinuria patients on terminal complement inhibition with history of thromboembolism

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To the Editor:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal disorder of hematopoietic stem cells manifesting as hemolytic anemia, marrow failure, smooth muscle dystonia and thrombosis. Deficiency of the glycosylphosphatidylinositol anchored complement regulatory proteins CD55 and CD59, due to somatic mutation of the phosphatidylinositol glycan A gene, leads to complement-mediated lysis of PNH erythrocytes and activation of platelets, monocytes and granulocytes.[1] Eculizumab and the newer, four-times longer half-life drug, ravulizumab are humanized monoclonal antibodies that interfere with the cleavage of complement C5 and have changed the natural history of PNH.

Prior to therapeutic complement inhibition, thromboembolism (TE) was the leading cause of death in PNH.[2] Complement inhibitors are highly effective in reducing TE. In the combined clinical trials of eculizumab, Hillmen et al. found that eculizumab led to an 85% relative reduction in TE, but many patients remained on concomitant anticoagulation for both primary and secondary prophylaxis.[3] In another study by Kelly et al., 58% of patients were on anticoagulation at initiation of eculizumab and 45% of patients stopped primary prophylaxis with anticoagulation, but only one patient stopped anticoagulation for secondary prophylaxis.[4] No thrombotic events were observed. Correlative laboratory data also supports

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that eculizumab decreases plasma markers of thrombosis, such as levels of prothrombin fragment F1+2, D-dimer and plasmin-antiplasmin complexes, and endothelial cell activation, such as tissue plasminogen activator, von Willebrand factor and tissue factor pathway inhibitor.[5] Primary prophylactic anticoagulation has not proven to be beneficial with the use of complement inhibitors, however, there is no data on how to manage anticoagulation in the setting of secondary prophylaxis. Whether indefinite anticoagulation adds to secondary prevention of thrombosis in patients well controlled on terminal complement inhibition without additional risk factors remains an unanswered management dilemma in PNH, an important question since the median age of PNH is less than 50 years-old and many have baseline thrombocytopenia.[1, 6]

We identified 22 PNH patients evaluated at Johns Hopkins Hospital over a 15-year period from 2005–2020 with a history of TE, who were treated with C5 inhibition. Patients who met the following criteria were included: documented PNH clone in two cell lineages as assessed by flow cytometry; treatment with C5 inhibition for > six months; history of TE; and 18 years or older at data collection. TE was confirmed by imaging or based on high clinical suspicion at the discretion of the treating hematologist. Eculizumab and ravulizumab were dosed at standard maintenance doses of 900 mg every 14 ± 2 days and 3300 mg every eight weeks, respectively, except in five patients who received higher doses of eculizumab due to breakthrough hemolysis. Anticoagulation included warfarin, direct-acting oral anticoagulants and low molecular weight heparin at therapeutic doses at the discretion of the treating physician. The study was approved by the Institutional Review Board of Johns Hopkins Hospital.

We evaluated thrombosis rates for the periods pre-C5 inhibition and following initiation of anti-C5 therapy in patients on complement inhibition alone and in those who remained on concomitant anticoagulation. The pretreatment patient-years (pre-C5 inhibition) included all TE events between diagnosis of PNH and treatment with a terminal complement inhibitor. The period on C5 inhibition was defined as the time from treatment initiation with C5 inhibition through last follow-up or bone marrow transplant. We considered patients as being treated with C5 inhibitor monotherapy if they were never treated with anticoagulation or discontinued anticoagulation and remained on a C5 inhibitor alone. In the “C5 inhibitor monotherapy group,” we counted only the years since initiation of C5 inhibition and discontinuation of anticoagulation.

The incidence of TE was calculated as TE events per patient-years. We compared paired observations for thrombosis rates pre-treatment and while on C5 inhibition (with or without concomitant anticoagulation) using the exact Poisson method. Two-sided exact mid-P values are provided and $P<0.05$ is considered significant.

Eighteen patients were treated with C5 inhibition alone without therapeutic anticoagulation including 12 patients who discontinued anticoagulation after initiation of the C5 inhibitor and six patients who never received anticoagulation or could not tolerate anticoagulation. Four patients were treated with a C5 inhibitor and maintained on indefinite anticoagulation. The patients who continued on indefinite anticoagulation either had additional hypercoagulable risk factors (n=2; one patient with antiphospholipid syndrome

and one with a strong family history of venous thromboembolism) or continued due to patient or physician preference (n=2).

Patient and TE characteristics are presented in Table I. The median number of years from PNH diagnosis to initiation of anti-C5 treatment was 4 (range, 0–14) years in the C5 inhibitor monotherapy patients and 3.5 (range, 0.5–8) years in the patients maintained on indefinite anticoagulation. The median time on treatment with C5 inhibition was similar between the groups (10 versus 9.5 years). The median time on anticoagulation in the group on C5 inhibitor monotherapy was 4 (range, 0–132) months, whereas patients maintained on indefinite anticoagulation were treated with anticoagulation for a median of 9 (range, 4–19) years. Patients in whom anticoagulation was stopped once on complement inhibition overlapped anticoagulation and the C5 inhibitor for a median of 6 (range, 0–132) months. Ten of the 12 patients in whom anticoagulation was discontinued were treated with anticoagulation for at least 3 months consistent with treatment for acute venous thromboembolism. The decision to stop anticoagulation was at the discretion of the treating clinician reflective of patient preference and bleeding risk.

Patients on C5 inhibitor monotherapy had 25.91 events/100 patient-years prior to C5 inhibition (25 events) versus 1.45 events/100 patient-years post-C5 inhibition and off anticoagulation (two events) (P <0.001) (Supplemental Table I). In the four patients who were treated with a C5 inhibitor and indefinite anticoagulation, there were 38.71 events/100 patient-years prior to the C5 inhibitor (six events) and 5.41 events/100 patient-years after (two events) (P =0.01). This corresponds to a relative reduction of 94.4% in patients on C5 inhibitor monotherapy and 86.0% in patients on concomitant anticoagulation and C5 inhibition. TE events that occurred prior to C5 inhibitor therapy included intra-abdominal and cerebrovascular locations, whereas following treatment with a C5 inhibitor, thrombosis occurred in more common locations, such as deep vein thrombosis (DVT) and pulmonary embolism. Three of the four TE events occurring in patients on C5 inhibitors were provoked (2 associated with major surgeries and bilateral DVTs attributed to uterine compression), whereas only one pretreatment event was considered provoked, associated with a venous access device. Two gastrointestinal bleeding events, one meeting ISTH criteria for major bleeding, occurred among two patients on anticoagulation alone.

Our data suggest that discontinuation of anticoagulation for secondary prevention of TE in PNH patients well controlled (lactate dehydrogenase < 1.5 times the upper limit of normal) on terminal complement inhibition may be safe. Further, discontinuation of anticoagulation may be advantageous in reducing bleeding risk and complications of thrombocytopenia resulting from comorbid bone marrow failure or liver disease.[2] Our rate of TE in patients on C5 inhibition and no anticoagulation (1.45 events/100 patient-years) was similar to that reported in patients on eculizumab +/− anticoagulation (1.07 events/100 patient-years[3] and 0.8 events/100 patient-years[4]). Our study looks specifically at patients with a history of TE as opposed to all PNH patients, which may select for patients with higher granulocyte clones and a thrombotic form of PNH.[1] Our median period on C5 inhibition and off anticoagulation was also longer than previously reported.

To our knowledge, this is the largest reported series of PNH patients with a history of thrombosis who discontinued anticoagulation. No randomized clinical trials exist to address whether anticoagulation can be discontinued in PNH patients on terminal complement inhibition. This question ideally would be answered using this modality, however, given the rarity of PNH, it is unlikely that such a trial will be performed. Further, registry data in PNH may lack the longitudinal follow-up to address this question. The limitations of this study include its single center, retrospective design. In addition, anticoagulation compliance was not routinely collected. We describe a relatively small number of patients, owing to the rarity of this disease, however, we report a long duration of follow-up for the majority of patients.

Anticoagulation remains the mainstay of treatment for acute TE. C5 inhibition should be initiated expeditiously after a thrombotic event, as anticoagulation alone is ineffective in preventing recurrence of complement-mediated TE. This study supports the idea that untreated PNH is a provoking factor for TE and select patients may not require indefinite anticoagulation if well controlled on complement inhibition and there are no other persistent provoking risk factors for TE. We recommend overlapping anticoagulation and complement inhibition for three to six months following the acute thrombotic event unless contraindicated due to bleeding risk and/or thrombocytopenia. The potential additional benefit of continued anticoagulation in reducing thrombosis must be weighed against the risk of bleeding on an individual basis after an informed discussion with patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

PNH patient and thromboembolism characteristics.

Patient Group	Patients treated with C5 inhibitor monotherapy (n=18)	Patients treated with C5 inhibitor and indefinite anticoagulation (n=4)
History of aplastic anemia, no.	7	0
Sex, no.		
Male	11	1
Female	7	3
Race		
Caucasian	14	1
Black	4	3
Median age at PNH diagnosis (range)	23.5 years (10–50)	41 years (36–61)
Median PNH granulocyte clone at TE diagnosis (range)	96% (73–100)	87.8% (78–99)
Median disease duration pre-C5 inhibition (range)	4 years (0–14)	3.5 years (0.5–8)
Median time on anti-C5 treatment (range)	10 years (0.5–15)	9.5 years (5–13)
Median time on anticoagulation (range)	4 months (0–11 years)	9 years (4–19)
Location of TE events prior to C5 inhibition, no. [†]		
DVT	1	1
pulmonary embolism	1	1
abdominal vein	11	2
dermal	1	-
small bowel	3	-
cerebrovascular	3	2
IVC	1	-
renal vein	2	-
ureter	1	-
tonsillar	1	-
Location of TE events on C5 inhibitor, no.		
DVT	2[‡]	1[§]
pulmonary embolism	-	1

[†] 28/31 TE events occurred not on anticoagulation.

[‡] Not on concurrent anticoagulation. Two lower extremity deep vein thromboses (DVT) around major surgeries, hip replacement and liver transplant, respectively.

[§] 1 bilateral DVT attributed to uterine compression.