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ORIGINAL RESEARCH

Real-World Healthcare Resource Utilization (HRU) and Costs of Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Receiving Eculizumab in a US Population

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ABSTRACT

Introduction: To evaluate the economic burden and treatment patterns of patients with paroxysmal nocturnal hemoglobinuria (PNH) treated with eculizumab, a C5 inhibitor, who were defined as blood transfusion-dependent (TD) versus blood transfusion-free (TF) in the US population.

Methods: Patients aged at least 12 years with at least two claims for eculizumab infusion (first claim was the index date) were identified from the IBM® MarketScan® Research Databases (April 1, 2014–September 30, 2019). The overall PNH eculizumab user cohort was stratified into the TD cohort (i.e., at least one claim for blood transfusion within 6 months following any eculizumab infusion, including on the infusion date) or the TF cohort (i.e., all non-TD patients). Treatment patterns, healthcare resource utilization (HRU), and costs were evaluated and compared during follow-up (i.e., index date to end of enrollment or data availability).

Results: Of 151 patients in the overall cohort (mean age 36.7 years; 55.6% female), 55 were TD (mean age 35.1 years; 67.3% female) and 96 were TF (mean age 37.6 years; 49.0% female). A total of 61% of patients (TD, 66%; TF, 58%) discontinued eculizumab, with TD patients having a shorter median time to discontinuation (TD, 0.5 years; TF, 0.9 years). TD patients had more all-cause hospitalizations than TF patients ($p < 0.05$). TD patients incurred higher all-cause direct medical costs (adjusted cost difference = $247,848) and medical-related absenteeism costs (adjusted cost difference = $4186) than TF patients (all $p < 0.05$), largely driven by hospitalizations. Similar trends were observed for PNH-related HRU and costs.

Conclusions: The economic burden of patients with PNH treated with eculizumab is greater among those dependent on blood transfusions.

Keywords: Paroxysmal nocturnal hemoglobinuria; Eculizumab; Blood transfusion; Treatment patterns; Healthcare resource utilization; Medical costs; Absenteeism; Economic burden; Retrospective study

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Key Summary Points

Why carry out this study?

Many patients with paroxysmal nocturnal hemoglobinuria (PNH) experience ongoing symptoms that necessitate blood transfusions even during treatment with eculizumab; however, real-world studies on the burden of transfusion-dependent (TD) eculizumab users compared to transfusion-free (TF) eculizumab users are currently lacking.

To address this knowledge gap, we conducted a retrospective, longitudinal cohort study evaluating the economic burden and treatment patterns of TD versus TF eculizumab users based on nationally representative, administrative claims data from a US population.

What was learned from this study?

TD eculizumab users, who comprised more than 36% of the overall study sample, showed evidence of greater disease severity (e.g., high rates of aplastic anemia), earlier discontinuation of eculizumab treatment, higher resource utilization, and higher direct medical costs and medical-related absenteeism costs driven by increased hospitalizations, compared to those who were TF.

The findings suggest that blood transfusion dependence may serve as an important indicator of uncontrolled disease and high economic burden among patients with PNH.

In future research investigating PNH management strategies, an improved understanding of the risks and burden among TD eculizumab users may help to inform novel therapies targeting this patient population.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14748699.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and chronic clonal hematopoietic stem cell disorder that affects 12–13 per 1,000,000 individuals in the USA [1, 2]. PNH is characterized by the destruction of blood cells via the complement system due to the absence of protective proteins at their cell surface, resulting in symptoms such as hemolytic anemia, thrombosis, bone marrow failure, abdominal pain, and hemoglobinuria [1, 3]. PNH is an acquired disease that can affect individuals of any age group, with the average age of diagnosis in the early 30s [4]. If it is not adequately managed, PNH may severely compromise patients' quality of life and lead to premature mortality [5, 6].

The current standard of care for PNH is complement-targeting therapy. In 2007, eculizumab, a humanized monoclonal antibody that inhibits terminal complement C5 activation, became the first complement-targeting therapy approved for the treatment of patients with PNH [7]. The labelled dosage of eculizumab is 600 mg/week for the first 4 weeks (induction phase), 900 mg for the fifth dose 1 week later, and 900 mg every 2 weeks thereafter (maintenance phase) [7]. In clinical trials, eculizumab was well tolerated and demonstrated significant reductions in complement-mediated hemolysis, as well as associated symptoms [8–13].

Despite the demonstrated efficacy of eculizumab [8–13], significant unmet needs persist among patients with PNH who receive this treatment in real-world clinical practice. Approximately 11–27% of patients receiving labelled dosages of eculizumab experience breakthrough hemolysis (BTH), defined as elevated concentrations of lactate dehydrogenase (LDH) following a prior LDH reduction [12, 14, 15]. Patients who experience BTH while

receiving eculizumab may require blood transfusions or increases in the dosage or dosing frequency of eculizumab. However, these clinical management strategies often fail to adequately control PNH [14]. In a long-term extension study of patients who had previously participated in PNH clinical trials, 50% of patients experiencing BTH were unable to achieve symptom control despite eculizumab dosage modifications [12]. Furthermore, 18% of all patients continued to require transfusions through the end of the study. Additionally, evidence suggests that transfusions may be associated with a range of transfusion-related adverse events and may not be an appropriate treatment option among patients with PNH experiencing anemia, thrombocytopenia, or coagulopathy [16, 17].

Despite eculizumab treatment, PNH is associated with considerable healthcare resource utilization (HRU) due to hospitalizations, as well as frequent workplace absenteeism [5]. Notably, preliminary results from the prospective observational International PNH Registry study demonstrated that initiation of eculizumab was associated with increased rates of hospital admissions and healthcare provider visits [18]. However, there is a paucity of information describing HRU, as well as healthcare costs associated with PNH and eculizumab treatment in real-world clinical practice in the USA. In one recent study based on a cost model, the management of BTH was associated with substantial costs driven by eculizumab dosage adjustments, hospitalizations, and blood transfusions [19], suggesting that the economic burden of PNH may be particularly high among patients who continue to experience ongoing symptoms and transfusion dependence after the initiation of eculizumab.

In light of this recent evidence, there is a need to better understand the economic burden of patients with PNH receiving eculizumab who may continue to experience ongoing disease activity necessitating blood transfusions. Therefore, the present study evaluated the treatment patterns of patients with PNH post-initiation of eculizumab and compared the HRU and costs of blood transfusion-dependent (TD) eculizumab users and blood transfusion-free (TF) eculizumab users in real-world clinical practice in the USA.

METHODS

Data Source

Administrative claims data from the IBM® MarketScan® Research Databases (Commercial Database, Medicare Supplemental and Coordination of Benefits Database, Multi-State Medicaid Database, and Lab Results Database) spanning from January 1, 2014 to September 30, 2019 were utilized. All database records were de-identified and certified as fully compliant with US patient confidentiality requirements outlined in the Health Insurance Portability and Accountability Act (HIPAA). Since this study relied exclusively on de-identified patient records and did not involve the collection, use, or dissemination of individually identifiable data, institutional review board approval was not required.

Study Design and Population

A retrospective longitudinal cohort design was used. The index date was defined as the date of the first eculizumab infusion occurring on or after April 1, 2014 with at least 3 months of continuous eligibility prior (baseline period). The follow-up period spanned from the index date until the end of continuous healthcare plan enrollment or end of data availability, whichever occurred first.

Patients who were at least 12 years of age at the index date were deemed eligible if they had at least two medical claims for an infusion of eculizumab (HCPCS code J1300) between April 1, 2014 and September 30, 2019 with at least 3 months of continuous eligibility prior to the index date. Patients were excluded if (a) they had at least one medical claim for an infusion of eculizumab any time prior to the index date or (b) at least one diagnosis of another indication for eculizumab during the baseline period or on the index date (i.e., atypical hemolytic uremic syndrome, generalized

myasthenia gravis, and neuromyelitis optica spectrum disorder). Because the ICD-9 diagnosis code for PNH is an imprecise, broad code that encompasses other related diagnoses, this so-called inclusion by exclusion principle as shown in exclusion criterion (b), in which patients were excluded if they had at least one diagnosis of another indication of eculizumab, rather than a conventional approach of including patients with at least one diagnosis of PNH helps improve specificity of the treated population and to ensure that eculizumab was given for the indication of PNH. The overall PNH population treated with eculizumab (i.e., the overall eculizumab user cohort) was stratified into the TD cohort (i.e., at least one medical claim for blood transfusion within 6 months following any eculizumab infusion, including on the infusion date) or the TF cohort (i.e., all remaining patients who did not meet the criterion of the TD cohort).

Outcomes

Patient characteristics that were measured at baseline included demographics (i.e., age, gender, region, and insurance plan type), clinical characteristics (i.e., Quan-Charlson comorbidity index [Quan-CCI] [20], Elixhauser comorbidities [21], PNH-related comorbidities, symptoms, and treatments), HRU, and healthcare costs.

Study outcomes measured at follow-up included treatment patterns, HRU, and healthcare costs.

Treatment patterns of interest included the number of eculizumab infusions and the time between infusions calculated overall and stratified by treatment phase, as specified in the US Food and Drug Administration (FDA)-approved product labeling, including the induction phase (i.e., first 4 weeks of treatment) and maintenance phase (i.e., the fifth week of treatment and onward) [7]. The proportion of patients with eculizumab discontinuation and time to discontinuation were evaluated, where discontinuation was defined as a gap of more than 42 days between two infusions (i.e., 14-day exposure period + 28-day grace period between infusions) or from the last infusion to the end of follow-up [2]. Additionally, the number of blood transfusions and iron chelation therapies was assessed during follow-up.

All-cause and PNH-related HRU outcomes were evaluated, including frequency of hospitalizations, emergency room (ER) visits, outpatient (OP) visits, and other visits, as well as hospitalization days. A medical service claim was considered to be PNH-related if it was associated with an ICD-9-CM or ICD-10-CM diagnosis of PNH in any position.

All-cause and PNH-related direct medical costs included the costs of hospitalizations, ER visits, blood transfusions, other OP visits, and other visits. Other visit costs included costs of visits with laboratory medical claims, or home services and hospice visits. All-cause and PNH-related medical-related absenteeism costs included the costs of hospitalization-related absenteeism, ER-related absenteeism, and OP-related absenteeism and were evaluated among patients less than 65 years of age. Computed sick leave costs were based on length of stay (i.e., 1 day of absenteeism per hospitalization or half-day per ER/OP/other visit) × daily wage; five-sevenths of the total sick-leave hours were used in the calculation to account for weekend visits. Patients' mean wage was valued at $26 based on data collected by the US Department of Labor, Bureau of Labor Statistics, 2019 for all occupations [22].

Statistical Analysis

Patient characteristics and treatment patterns were assessed using descriptive statistics, and patient characteristics during baseline were compared between TD and TF cohorts using standardized differences (std. diff), with greater than 20% indicating substantial differences. Time to eculizumab treatment discontinuation was evaluated with Kaplan–Meier analysis. The incidence rates of all-cause and PNH-related HRU were reported per person year (PPY) over the follow-up period as the frequency of events divided by the total person-years; adjusted incidence rate ratios (IRR) were estimated using multivariate Poisson regression models adjusting for baseline characteristic differences.

Mean all-cause and PNH-related direct medical costs and medical-related absenteeism costs were evaluated per person per year (PPPY) during follow-up from the payer perspective and inflated to USD 2020; adjusted mean cost differences were estimated using multivariate generalized linear models with gamma distribution and log-link, adjusting for baseline characteristic differences. For HRU and costs, 95% confidence intervals (95% CI) and *p* values were generated using non-parametric bootstrap procedures. All analyses were performed using SAS Enterprise Guide Version 7.1 (SAS Institute, Cary, NC, USA).

RESULTS

Of 849 patients that had at least two medical claims for infusion of eculizumab between April 1, 2014 and September 30, 2019, a total of 151 patients were included in the overall eculizumab user cohort (Fig. 1). Among patients in the overall eculizumab user cohort, 55 patients (36.4%) were TD and 96 patients (63.6%) were TF.

Baseline Characteristics

Patient demographic and clinical characteristics at baseline are presented in Table 1. Mean age of patients in the overall eculizumab user cohort was 37.6 years. In the overall eculizumab user cohort, 55.6% of patients were female, 32.5% were from the South, and 76.8% were insured through a commercial insurance plan. Patients in the TD cohort were more likely to be female and from the South than patients in the TF cohort (female 67.3% vs 49.0%, std. diff = 37.8%; South: 40.0% vs 28.1%, std. diff = 25.3%).

Patients in the TD cohort had a higher mean Quan-CCI score compared to patients in the TF cohort (mean 1.2 vs 0.9, std. diff = 16.5%), suggesting more severe disease. Consistent with this finding, a higher proportion of patients in the TD cohort compared to the TF cohort had a diagnosis for aplastic anemia (63.6% vs 42.7%, std. diff = 42.9%). The most frequent PNH-related symptoms in the TD and TF cohorts were anemia (other than aplastic anemia and PNH; 63.6% vs 64.6%, std. diff = 2.0%) and viral and bacterial infections (38.2% vs 31.3%, std. diff = 14.6%). In terms of PNH-related treatments, a higher proportion of patients in the TD cohort compared to the TF cohort received a PNH-related blood transfusion during their baseline period (70.9% vs 17.7%, std. diff = 126.8%). Further, corticosteroid therapy was higher in the TD cohort compared to the TF cohort (45.5% vs 32.3%; std. diff = 27.3%). As shown in the Supplementary Material, the most frequent Elixhauser comorbidities in the TD and TF cohorts were coagulopathy (49.1% vs 30.2%, std. diff = 39.3%), hypertension (32.7% vs 27.1%, std. diff = 12.4%), and deficiency anemias (27.3% vs 21.9%, std. diff = 12.6%).

Treatment Patterns

The mean observation period was 1.6 years for the overall eculizumab user cohort (TD, 1.6 years; TF, 1.6 years). During the maintenance phase, patients in the overall eculizumab user cohort had a median of 8 eculizumab infusions. Patients in the TD cohort had a lower median number of eculizumab infusions compared those in the TF cohort (TD, 5 infusions; TF, 8 infusions), suggesting that eculizumab treatment alone may not have been sufficient for disease management among TD patients (Table 2). Further, only 29% of eculizumab users (TD, 21%; TF, 33%) had on average 14 days between maintenance eculizumab infusions, indicating that a large proportion of patients with PNH were not dosed per label [7]. A total of 61% of patients (TD, 66%; TF, 58%) discontinued eculizumab treatment, with TD patients having a shorter median time to treatment discontinuation (TD, 0.5 years; TF, 0.9 years; Fig. 2). The mean (range) number of blood transfusions was 3 (0, 54) among patients in the overall eculizumab user cohort (TD, 8.5; TF, not applicable).

HRU

Patients in the TD cohort had 2.95 times more all-cause hospitalizations, 4.58 times more all-

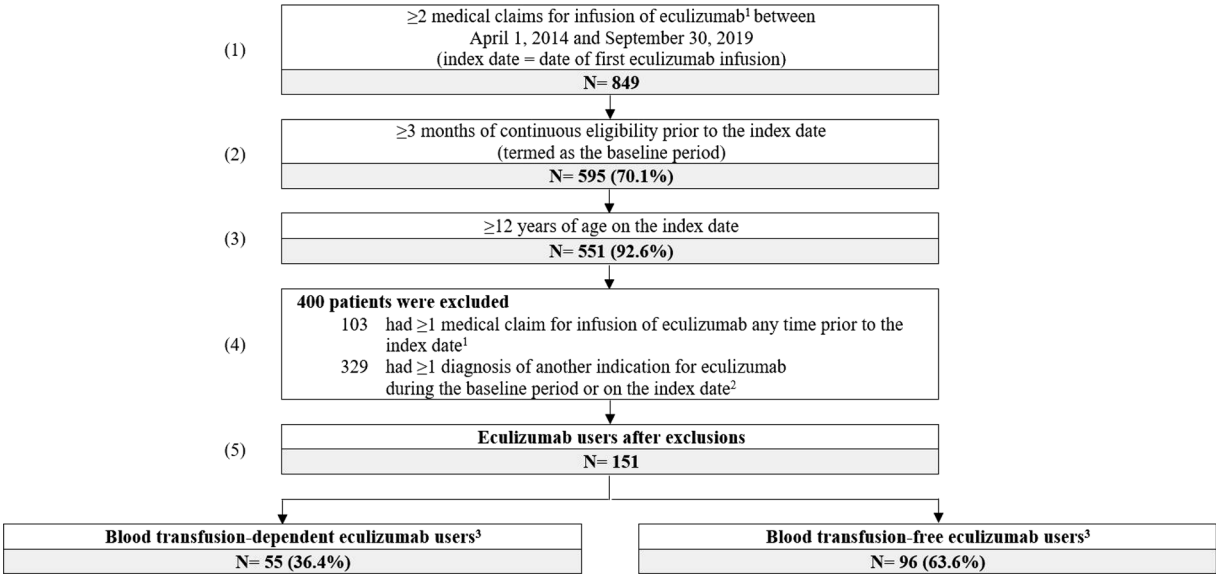


Fig. 1 Patient disposition for eculizumab cohort. ICD-10-CM International Classification of Diseases, 10th Revision, Clinical Modification; PNH paroxysmal nocturnal hemoglobinuria. [1]Eculizumab was identified using the HCPCS procedure code J1300. [2]Other indications of eculizumab include atypical hemolytic uremic syndrome (ICD-9-CM, 283.11; ICD-10-CM, D59.3), generalized myasthenia gravis (ICD-9-CM, 358.0x; ICD-10-CM, G70.0x), and neuromyelitis optica spectrum disorder (ICD-9-CM, 341.0; ICD-10-CM, G36.0). [3]Defined as patients with at least one medical claim for blood transfusion within 6 months after an eculizumab infusion, including on the infusion date

cause hospitalization days, and 1.43 more all-cause OP visits compared to those in the TF cohort (all $p < 0.05$; Fig. 3a). Patients in the TD cohort also had 2.99 times more PNH-related hospitalizations and 5.30 times more PNH-related hospitalization days compared to patients in the TF cohort (all $p < 0.05$; Fig. 3b).

Direct Medical Costs

Patients in the TD cohort incurred significantly higher all-cause hospitalization costs compared to those in the TF cohort ($168,783 vs $20,275, adjusted cost difference = $144,210, $p < 0.001$),[1] which led to significantly increased all-cause direct medical costs ($409,591 vs $189,778, unadjusted cost difference = $219,813; adjusted cost difference = $247,848, $p = 0.004$). Blood transfusion costs also contributed to higher all-cause direct medical costs among patients in the TD cohort compared to those in the TF cohort ($30,542 vs $0; Fig. 4a).[2] The most frequent diagnoses associated with a hospitalization among patients in the TD cohort with a hospitalization were PNH (42%), fever (39%), and sepsis (33%), of which the most expensive hospitalizations were associated with a diagnosis of infection, aplastic anemia, or sepsis.

Patients in the TD cohort had higher PNH-related hospitalization costs compared to patients in the TF cohort ($41,609 vs $3001, adjusted cost difference = $34,113, $p = 0.01$) and comparable PNH-related total medical costs ($142,743 vs $101,653, adjusted cost difference = $51,202, $p = 0.258$; Fig. 4a). Furthermore, higher PNH-related comorbidity and symptoms costs were observed among patients

[1] Hospitalization costs included all costs incurred in an inpatient setting, excluding inpatient blood transfusion costs. Outpatient costs included all costs incurred in an outpatient setting excluding outpatient blood transfusion costs, IV administration costs, and eculizumab infusion costs.

[2] Blood transfusion costs included all costs incurred during an inpatient or outpatient blood transfusion.

Table 1 Baseline characteristics of the overall eculizumab user and of eculizumab users stratified by blood transfusion dependence status

Characteristics	Overall eculizumab user cohort	TD cohort	TF cohort	Std. diff.[a,b] TD vs TF	
	N = 151	*N* = 55	*N* = 96	(%)	
Observation period,[c] years, mean ± SD [median]	1.6 ± 1.3 [1.2]	1.6 ± 1.3 [1.4]	1.6 ± 1.4 [1.1]	–	
Demographic characteristics[d]					
Age, years, mean ± SD [median]	36.7 ± 16.4 [36.0]	35.1 ± 17.5 [30.0]	37.6 ± 15.8 [39.5]	15.2	
Gender, female, *n* (%)	84 (55.6)	37 (67.3)	47 (49.0)	37.8	*
Region, *n* (%)					
South	49 (32.5)	22 (40.0)	27 (28.1)	25.3	*
Unknown	30 (19.9)	11 (20.0)	19 (19.8)	0.5	
Northeast	28 (18.5)	8 (14.5)	20 (20.8)	16.5	
Midwest	25 (16.6)	4 (7.3)	21 (21.9)	42.3	*
West	19 (12.6)	10 (18.2)	9 (9.4)	25.8	*
Insurance plan type, *n* (%)					
Commercial	116 (76.8)	40 (72.7)	76 (79.2)	15.1	
Medicaid	29 (19.2)	11 (20.0)	18 (18.8)	3.2	
Medicare	6 (4.0)	4 (7.3)	2 (2.1)	24.8	*
Clinical characteristics[e]					
Quan-CCI,[f] mean ± SD [median]	1.0 ± 1.8 [0.0]	1.2 ± 1.9 [0.0]	0.9 ± 1.7 [0.0]	16.5	
PNH-related comorbidities, *n* (%)					
Aplastic anemia	76 (50.3)	35 (63.6)	41 (42.7)	42.9	*
Myelodysplastic syndrome	15 (9.9)	7 (12.7)	8 (8.3)	14.4	
PNH-related symptoms, *n* (%)					
Anemia (other than aplastic anemia and PNH)	97 (64.2)	35 (63.6)	62 (64.6)	2.0	
Viral and bacterial infections	51 (33.8)	21 (38.2)	30 (31.3)	14.6	
Abdominal pain	35 (23.2)	15 (27.3)	20 (20.8)	15.1	
Dyspnea	26 (17.2)	10 (18.2)	16 (16.7)	4.0	
Chronic kidney disease	21 (13.9)	8 (14.5)	13 (13.5)	2.9	
Fatigue	21 (13.9)	6 (10.9)	15 (15.6)	13.9	
Thrombosis	13 (8.6)	2 (3.6)	11 (11.5)	29.9	*
Pulmonary hypertension	2 (1.3)	0 (0.0)	2 (2.1)	20.6	*

Table 1 continued

Characteristics	Overall eculizumab user cohort	TD cohort	TF cohort	Std. diff.[a,b] TD vs TF	
	N = 151	*N* = 55	*N* = 96	(%)	
Dysphagia	1 (0.7)	1 (1.8)	0 (0.0)	19.3	
Erectile dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	0.0	
PNH-related treatments, *n* (%)					
Blood transfusions	56 (37.1)	39 (70.9)	17 (17.7)	126.8	***
Corticosteroid therapy	56 (37.1)	25 (45.5)	31 (32.3)	27.3	*
Anticoagulants	39 (25.8)	18 (32.7)	21 (21.9)	24.5	*
Immunosuppressants	16 (10.6)	9 (16.4)	7 (7.3)	28.4	*
Iron therapy	5 (3.3)	3 (5.5)	2 (2.1)	17.8	
Iron-chelation therapy	2 (1.3)	2 (3.6)	0 (0.0)	27.5	*
Androgen therapy	1 (0.7)	0 (0.0)	1 (1.0)	14.5	
All-cause HRU					
Patients with HRU, *n* (%)					
Hospitalizations	55 (36.4)	28 (50.9)	27 (28.1)	47.9	*
ER visit	29 (19.2)	14 (25.5)	15 (15.6)	24.5	*
OP visit	147 (97.4)	53 (96.4)	94 (97.9)	9.3	
Number of HRU events, mean ± SD [median]					
Hospitalizations	0.6 ± 1.0 [0.0]	0.9 ± 1.2 [1.0]	0.4 ± 0.8 [0.0]	52.9	**
Length of stay, days	4.2 ± 10.5 [0.0]	6.5 ± 14.7 [2.0]	2.9 ± 6.9 [0.0]	30.7	*
ER visits	0.3 ± 0.8 [0.0]	0.4 ± 1.0 [0.0]	0.2 ± 0.7 [0.0]	26.2	*
OP visits	10.3 ± 7.7 [8.0]	11.6 ± 9.4 [9.0]	9.5 ± 6.5 [7.5]	26.5	*
PNH-related HRU[g]					
Patients with HRU, *n* (%)					
Hospitalizations	21 (13.9)	11 (20.0)	10 (10.4)	26.9	*
ER visit	4 (2.6)	4 (7.3)	0 (0.0)	39.6	*
OP visit	90 (59.6)	31 (56.4)	59 (61.5)	10.4	
Number of HRU events, mean ± SD [median]					
Hospitalizations	0.2 ± 0.5 [0.0]	0.3 ± 0.7 [0.0]	0.1 ± 0.4 [0.0]	33.5	*
Length of stay, days	1.3 ± 4.6 [0.0]	1.6 ± 4.6 [0.0]	1.2 ± 4.6 [0.0]	10.5	
ER visits	0.0 ± 0.3 [0.0]	0.1 ± 0.5 [0.0]	0.0 ± 0.0 [0.0]	35.2	*
OP visits	2.8 ± 4.1 [1.0]	3.2 ± 5.3 [1.0]	2.5 ± 3.1 [1.0]	16.0	

Table 1 continued

Characteristics	Overall eculizumab user cohort	TD cohort	TF cohort	Std. diff.[a,b] TD vs TF	
	N = 151	*N* = 55	*N* = 96	(%)	
All-cause healthcare costs,[h] US$ 2020, mean ± SD [median]					
Total healthcare costs	73,141 ± 123,042 [20,923]	110,622 ± 160,444 [42,289]	51,667 ± 89,401 [14,775]	45.4	*
Medical costs	59,927 ± 118,354 [12,952]	98,736 ± 155,123 [33,624]	37,693 ± 84,071 [8359]	48.9	*
Hospitalization costs	40,106 ± 102,785 [0]	70,024 ± 140,668 [2994]	22,966 ± 67,959 [0]	42.6	*
ER visit costs	631 ± 2439 [0]	1084 ± 3591 [0]	371 ± 1370 [0]	26.2	*
OP visit costs	19,029 ± 49,647 [5012]	27,336 ± 54,543 [9566]	14,270 ± 46,239 [3819]	25.8	*
IV administration costs	189 ± 887 [0]	230 ± 1047 [0]	166 ± 786 [0]	6.9	
Pharmacy costs	13,024 ± 35,016 [281]	11,656 ± 29,918 [576]	13,808 ± 37,755 [258]	6.3	
PNH-related healthcare cost,[g,h] US$ 2020, mean ± SD [median]					
Total healthcare costs	13,220 ± 45,766 [1056]	19,340 ± 46,854 [2035]	9714 ± 45,003 [854]	21.0	*
Medical costs	12,653 ± 45,650 [628]	18,542 ± 46,547 [1100]	9279 ± 45,025 [569]	20.2	*
Hospitalization costs	5651 ± 27,724 [0]	12,705 ± 44,238 [0]	1609 ± 7474 [0]	35.0	*
ER visit costs	109 ± 888 [0]	298 ± 1461 [0]	0 ± 0 [0]	28.9	*
OP visit costs	6893 ± 36,893 [173]	5538 ± 16,522 [165]	7670 ± 44,635 [183]	6.3	
IV administration costs	89 ± 566 [0]	157 ± 861 [0]	50 ± 282 [0]	16.7	

Table 1 continued

Characteristics	Overall eculizumab user cohort	TD cohort	TF cohort	Std. diff.[a,b] TD vs TF
	N = 151	*N* = 55	*N* = 96	(%)
Pharmacy costs[i]	478 ± 1515 [0]	641 ± 1948 [0]	385 ± 1201 [0]	15.8

ER emergency room, *IV* intravenous, *OP* outpatient, *PNH* paroxysmal nocturnal hemoglobinuria, *Quan-CCI* Quan-Charlson comorbidity index, *SD* standard deviation, *Std. diff* standardized difference, *TD* blood transfusion-dependent eculizumab user cohort, *TF* blood transfusion-free eculizumab user cohort, *US$* United States dollar

*Standardized differences greater than 20%; **standardized differences greater than 50%; ***standardized differences greater than 80%. Standardized differences of 20%, 50%, and 80% suggest small, medium, and large differences, respectively [31]

[a] For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the blood transfusion-dependent eculizumab users and non-blood transfusion-dependent eculizumab users by the pooled standard deviation of both groups. The pooled standard deviation is the square root of the average of the squared standard deviations

[b] For dichotomous variables, the standardized difference is calculated using the following equation where *P* is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$

[c] Defined as the period from the index date (i.e., date of first eculizumab infusion) to the earliest of end of continuous healthcare plan enrollment or end of data availability (September 30, 2019)

[d] Evaluated at the index date (i.e., date of first eculizumab infusion)

[e] Evaluated during the 3-month baseline period, not including the index date

[f] Reference: Quan et al. [32]

[g] A medical service claim was considered to be PNH-related if it is associated with an ICD-9-CM or ICD-10-CM diagnosis of PNH in any position

[h] Costs are from the payer's perspective and are inflated to $US 2020 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor

[i] PNH-related pharmacy costs included only medications specific to PNH treatment

in the TD cohort compared to those in the TF cohort (PNH-related comorbidity costs: adjusted cost difference = $137,637, $p = 0.010$; PNH-related symptoms costs: adjusted cost difference = $203,475, $p < 0.001$).

Medical-Related Absenteeism Costs

Patients in the TD cohort had significantly higher all-cause medical-related absenteeism costs compared to the TF cohort ($7756 vs $3830, adjusted cost difference = $4186, $p < 0.001$), including higher all-cause hospitalization-related absenteeism costs ($2958 vs $501, adjusted cost difference = $2413, $p < 0.001$) and higher all-cause OP-related absenteeism costs ($4720 vs $3250, adjusted cost difference = $1493, $p = 0.006$; Fig. 4b). Significantly higher PNH-related medical-related absenteeism costs were also observed among patients in the TD cohort compared to those in the TF cohort ($3388 vs $1705, adjusted cost difference = $1463, $p = 0.016$), including higher hospitalization-related absenteeism costs ($1697 vs $87, adjusted cost difference = $1534, $p < 0.001$; Fig. 4b).

DISCUSSION

This USA-based real-world study demonstrated that, overall, patients with PNH initiated on eculizumab had substantial unmet clinical needs and posed a considerable economic

Table 2 Treatment patterns of the overall eculizumab user and of eculizumab users stratified by blood transfusion dependence status

Treatment patterns	Overall eculizumab user cohort *N* = 151	TD cohort *N* = 55	TF cohort *N* = 96
Observation period,[a] years, mean ± SD [median]	1.6 ± 1.3 [1.2]	1.6 ± 1.3 [1.4]	1.6 ± 1.4 [1.1]
Eculizumab infusions[b]			
Number of eculizumab infusions, median (IQR)			
Overall	11.0 (5.0–34.0)	9.0 (5.0–29.0)	11.5 (6.5–34.5)
Induction phase[c]	4.0 (2.0–4.0)	4.0 (2.0–4.0)	4.0 (2.0–4.0)
Maintenance phase[d]	8.0 (3.0–30.0)	5.0 (2.0–24.0)	8.0 (3.0–32.0)
Time between eculizumab infusions, days, median (IQR)[e]			
Overall	13.7 (11.2–19.4)	13.6 (9.9–19.4)	13.8 (11.7–19.2)
Induction phase[c]	7.0 (7.0–8.3)	7.0 (7.0–8.6)	7.0 (7.0–8.3)
Maintenance phase[d]	14.4 (13.7–21.2)	14.5 (13.4–21.9)	14.4 (13.7–20.5)
Average time between infusions during maintenance phase, *n* (%)			
< 14 days	30 (21.9)	13 (27.7)	17 (18.9)
14 days	40 (29.2)	10 (21.3)	30 (33.3)
15–21 days	34 (24.8)	11 (23.4)	23 (25.6)
> 21 days	33 (24.1)	13 (27.7)	20 (22.2)
Patients with eculizumab discontinuation[e], *n* (%)	92 (60.9)	36 (65.5)	56 (58.3)
Duration of eculizumab treatment until discontinuation, days, mean ± SD [median][f]	204.5 ± 275.0 [87.5]	154.9 ± 234.6 [87.0]	236.4 ± 295.7 [87.5]
Time to discontinuation using Kaplan–Meier analysis, years, median	0.7	0.5	0.9
Blood transfusions			
Number of blood transfusions, mean (min, max)	3.1 (0.0, 54.0)	8.5 (1.0, 54.0)	–
Patients with ≥ 1 blood transfusion during follow-up period, *n* (%)	55 (36.4)	55 (100.0)	0 (0.0)
Iron chelation therapy			
Number of iron chelation therapy, mean (min, max)	0.2 (0.0, 11.0)	0.5 (0.0, 11.0)	–

Table 2 continued

Treatment patterns	Overall eculizumab user cohort *N* = 151	TD cohort *N* = 55	TF cohort *N* = 96
Patients with ≥ 1 iron chelation therapy during follow-up period, *n* (%)	4 (2.6)	4 (7.3)	0 (0.0)

IQR interquartile range, *SD* standard deviation

[a] Defined as the period from index date (i.e., date of first eculizumab infusion) to the earliest of end of continuous healthcare plan enrollment or end of data availability (September 30, 2019)

[b] Eculizumab was identified using the HCPCS procedure code J1300

[c] The induction phase was defined as the first 4 weeks of eculizumab treatment

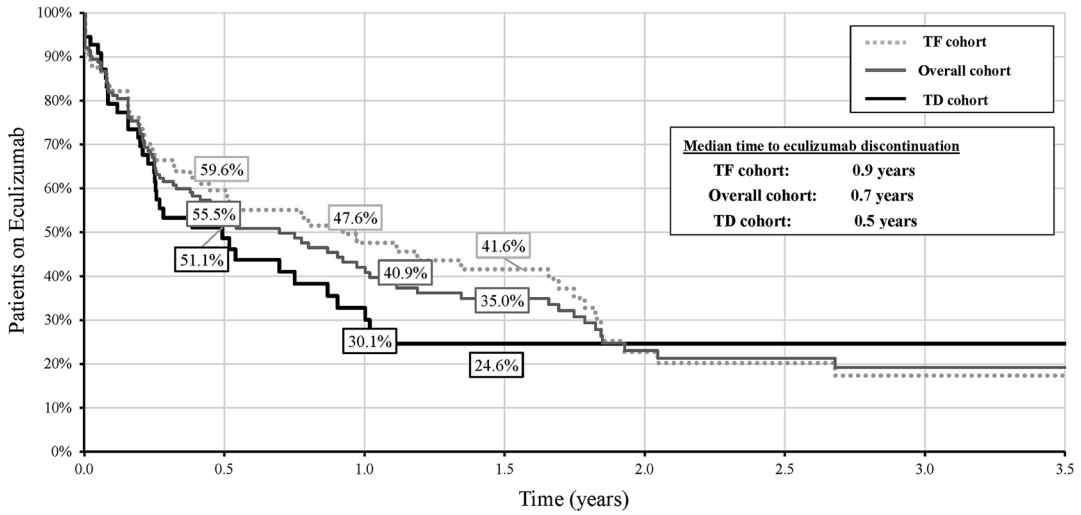
[d] The maintenance phase was defined as the fifth week of eculizumab treatment and onwards

[e] Discontinuation was defined as a gap of more than 42 days between infusions or the last infusion and the end of follow-up (i.e., the earliest of end of continuous healthcare plan enrollment or end of data availability)

[f] Duration of treatment was calculated among the subset of patients discontinuing treatment

burden on the US healthcare system. Further, this clinical and economic burden was significantly greater among TD eculizumab users relative to TF eculizumab users. TD eculizumab users comprised 36% of the overall sample, indicating that the disease activity may not be well controlled and was consistent with prior studies, where between 36% to 49% of patients with PNH treated with eculizumab were still transfusion-dependent in the long term [8, 12, 23]. Moreover, these patients had more than four times the number of hospitalization days compared to TF eculizumab users, emphasizing the substantial unmet need despite treatment with eculizumab. On the basis of time between dosing intervals, more than 70% of eculizumab-treated patients with PNH in this study were not dosed per label, and two-thirds of patients discontinued eculizumab within an average of a 1.5-year timeframe. Discontinuation of eculizumab may be attributed to complications resulting in adverse events, the development of comorbid diseases (i.e., aplastic anemia, myelodysplastic syndrome) [12], or the high cost of the therapy [24], which in turn may have contributed to the lower number of infusions among TD eculizumab users (5 vs 8 infusions). Findings indicate that blood transfusion dependence added significantly to both the direct medical and medical-related absenteeism cost burden of patients with PNH initiated on eculizumab, particularly with respect to increased hospitalizations and related costs due to PNH, fever, and sepsis. For example, the present study reported over 2-fold higher annual direct medical costs among patients in the TD cohort compared to the TF cohort after treatment with eculizumab, which has implications for US payers since most commercially insured patients (82.7% in 2019) [25] are likely to maintain their coverage for a period of 1–3 years.

The present study provides novel additional insights into the characteristics and treatment patterns of the PNH population. To date, the International PNH Registry, the largest worldwide observational study of patients with PNH, has served as a comprehensive source of real-world information for researchers to draw upon [5, 6, 18]. Consistent with the present study, rates of PNH-related comorbidities and symptoms have been found to be high among the PNH Registry population, with aplastic anemia observed in approximately 50% of patients at baseline [5, 6]. The present study expanded upon these findings by showing that TD eculizumab users had higher rates of aplastic anemia than TF eculizumab users (63.6% vs 42.7%), suggesting that blood transfusion dependence is associated with a greater burden of disease



Number of TF Patients

At-risk	96	40	24	20	9	7	4	3
Failed	0	35	42	45	53	54	55	55

Number of Patients (Overall Cohort)

At-risk	151	60	36	27	13	11	6	5
Failed	0	61	74	80	88	89	90	90

Number of TD Patients

At-risk	55	20	12	7	4	4	2	2
Failed	0	26	32	35	35	35	35	35

Fig. 2 Kaplan–Maier rates of discontinuation for eculizumab users stratified by blood transfusion dependence[1–6]. TD transfusion-dependent, TF transfusion-free. [1]Observation period was defined as the period from the index date (i.e., date of first eculizumab infusion) to the earliest of end of continuous healthcare plan enrollment or end of data availability (September 30, 2019). [2]The induction phase was defined as the first 4 weeks of eculizumab treatment (i.e., the 28-day starting period beginning on the index date). [3]The maintenance phase was defined as the fifth week of eculizumab treatment and onwards. [4]Assessed among patients with at least two eculizumab infusions during the entire follow-up period (overall), induction (N = 127) or maintenance phase (N = 137), respectively. [5]Discontinuation was defined as a gap of more than 42 days between infusions or the last infusion and the end of follow-up (i.e., the earliest of end of continuous healthcare plan enrollment or end of data availability). [6]Duration of treatment was calculated among the subset of patients discontinuing treatment

relative to the general PNH population. Further, given the highly variable symptomatic presentation of PNH [3, 14], differences in blood transfusion dependence status may also partly explain the clinical heterogeneity of this patient population. Patients in the TD eculizumab user cohort also had higher rates of coagulopathy than TF eculizumab users (49.1% vs 30.2%), which may be attributed to the higher use of anticoagulants among TD eculizumab users (32.7% vs 21.9%). It is important to note that the PNH Registry population also differs from the present study population in certain respects. For instance, patients in the PNH Registry are older compared to patients in the present study (mean age 45 vs 37 years), which may in turn be associated with greater disease severity. Moreover, the PNH Registry includes patients across multiple countries unlike the current study, which was focused on patients in the USA, and may contribute to differences in treatment patterns. Further, the PNH Registry assessed patient characteristics and outcomes based on physician assessments and medical records whereas the present study utilized administrative claims data. Thus, results may vary between studies because of differences in the data sources and coding methods used.

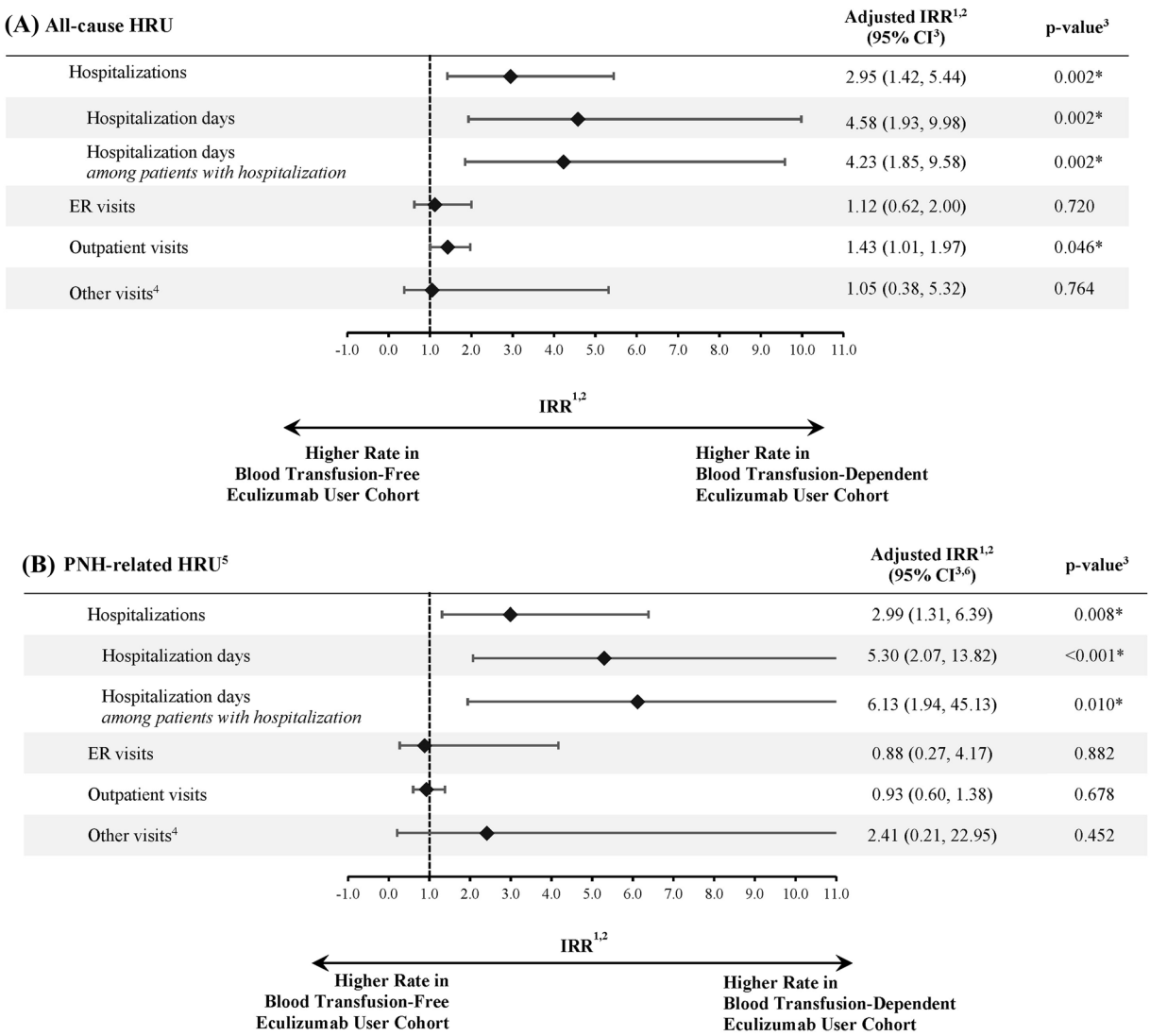


Fig. 3 Health resource utilization of transfusion-dependent patients compared to transfusion-free patients among eculizumab users. *$p < 0.05$. CI confidence interval, ER emergency room, HRU healthcare resource utilization, IRR incidence rate ratio, PNH paroxysmal nocturnal hemoglobinuria. [1]The rate was calculated as the frequency of HRU divided by the total person-years. [2]Adjusted incidence rate ratios were estimated using multivariate Poisson models adjusting for baseline covariates. [3]The 95% confidence intervals and p values were generated using non-parametric bootstrap procedures using 999 replications. [4]Included visits with laboratory medical claims, or home services and hospice visits. [5]A medical service claim was considered to be PNH-related if it is associated with an ICD-9-CM or ICD-10-CM diagnosis of PNH in any position. [6]Any 95% CI with an upper bound exceeding 11.0 has been truncated in the figure for PNH-related HRU

Although real-world data on the treatment patterns of patients with PNH initiated on eculizumab is currently limited, available findings appear to corroborate the results obtained in the present study. In a prior retrospective study using Marketscan data [2], only a minority of patients newly diagnosed with PNH were initiated on eculizumab, and among these patients, at least 30% discontinued eculizumab within the first year of treatment. Similarly, in the present study, an estimated 61% of patients discontinued eculizumab treatment during a

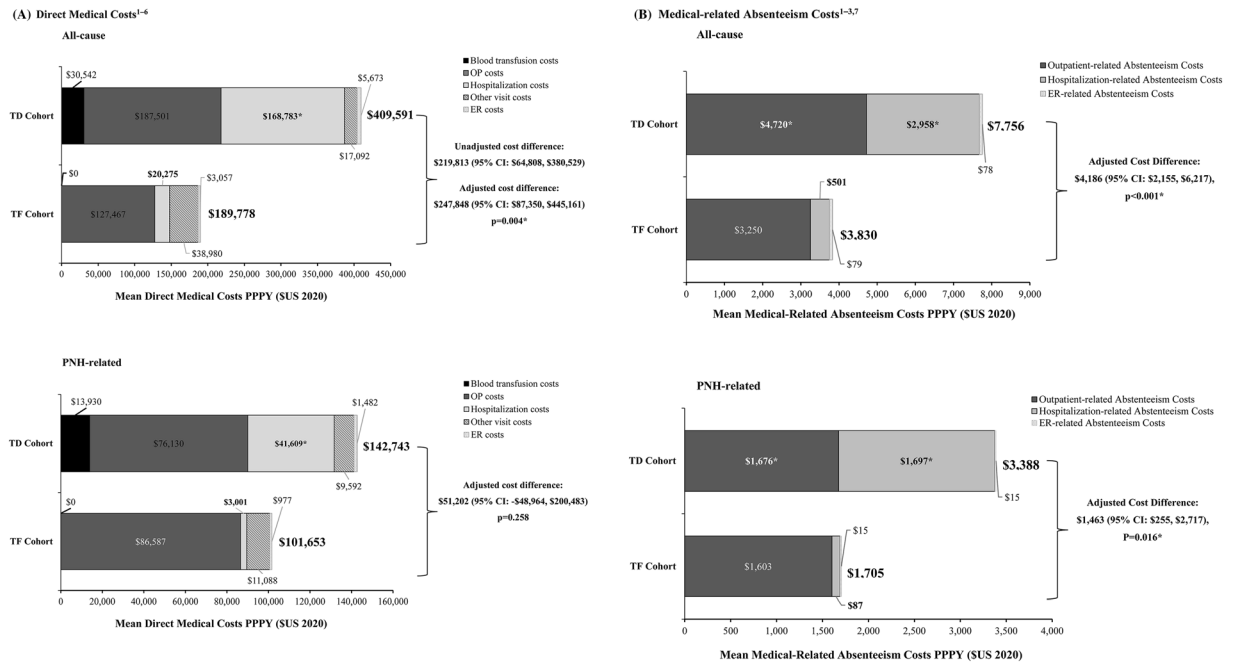


Fig. 4 Healthcare costs of eculizumab users stratified by blood transfusion dependence status. $^{*}p < 0.05$. CI confidence interval, ER emergency room, HRU healthcare resource utilization, OP outpatient, PNH paroxysmal nocturnal hemoglobinuria, PPPY per patient per year, TD transfusion-dependent, TF transfusion-free. [1]Costs are from the payer's perspective and are inflated to $US 2020 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor. [2]Adjusted cost differences were estimated using multivariate generalized linear models with gamma distribution and log-link. Covariates included gender and aplastic anemia. [3]The 95% confidence intervals and p values were generated using non-parametric bootstrap procedures using 999 replications. [4]Hospitalization costs included all costs incurred in an inpatient setting, excluding inpatient blood transfusion costs. Outpatient costs included all costs incurred in an outpatient setting excluding outpatient blood transfusion costs, IV administration costs, and eculizumab infusion costs. [5]Blood transfusion costs included all costs incurred during an inpatient or outpatient blood transfusion. [6]Other visits included visits with laboratory medical claims, or home services and hospice visits. [7]Evaluated among patients aged less than 65 years ($N = 144$)

mean follow-up period of approximately 1.5 years. When stratifying patients by blood transfusion dependence status, the present study found that TD eculizumab users were less likely to be dosed per label (TD, 21%; TF, 33%) and went on to have a shorter median time to treatment discontinuation (TD, 0.5 years; TF, 0.9 years).

The current study helps to provide additional context to previous findings regarding the HRU burden of patients with PNH. Prior studies relying on the PNH Registry [5] and those relying on Marketscan data [2] have reported a substantial HRU burden among patients with PNH irrespective of treatment, particularly for hospitalizations. However, only one prior study to date has investigated the HRU burden among patients with PNH post-initiation of eculizumab compared to pre-initiation. Preliminary results shared at the European Hematology Association 22nd Annual Congress [18] showed that treatment with eculizumab failed to decrease the rate of healthcare provider visits and hospitalizations compared to before. Thus, treatment with eculizumab may not be sufficient to control disease among patients with PNH, although further studies are needed to confirm this. The present study expands upon these findings by providing evidence of a greater unmet clinical need among

TD eculizumab users, as evidenced by approximately three times more all-cause hospitalizations and more than four times more all-cause hospitalization days compared to TF eculizumab users, which translates into higher all-cause hospitalization costs among TD eculizumab users.

Despite evidence of a high burden of disease, there is currently a dearth of information available on the direct medical costs associated with PNH, particularly among eculizumab users. The present study helps to close this knowledge gap by providing evidence of the significant direct medical costs incurred by TD eculizumab users, which are driven primarily by hospitalization costs, with blood transfusions representing a further cost burden. More specifically, the annual incremental medical costs to the healthcare system due to HRU, including blood transfusions, hospitalizations, and OP/ER visits, were an estimated average of $219,813 per year for every TD eculizumab user compared to TF eculizumab users, not including PNH-related drug costs for which TD eculizumab users had a shorter duration of treatment. In one recent study by Tomazos et al. [14], a cost model was used to quantify the economic burden of BTH management among patients with PNH receiving eculizumab. Consistent with the present study, substantial costs were estimated for eculizumab users due to the ongoing management of BTH (costs ranging from $51,716 to $186,107 PPPY), including expenses for eculizumab dosage adjustments, hospitalizations, and blood transfusions [19]. However, given that this study relied on data modeling rather than empirical data analyses, certain underlying assumptions may not be generalizable to the real-world clinical setting. A further limitation of the model was that it did not account for differences in PNH management costs based on blood transfusion dependence status.

Patients with PNH are known to suffer from impaired quality of life and disease-related fatigue [5, 6]. Additionally, TD patients require intravenous treatment administration at infusion clinics, which may require a considerable amount of their time [26]. As a result, it is not surprising that a substantial proportion of patients cite PNH as a major factor contributing to their workplace absenteeism [5, 18]. To our knowledge, the present study findings represent the first evidence of a significant increase in medical-related absenteeism costs among TD eculizumab users compared to TF eculizumab users, driven by greater hospitalization-related absenteeism costs and OP-related absenteeism costs.

Taken together, the substantial direct medical costs and medical-related absenteeism costs associated with PNH further suggest that disease activity may not be well controlled despite treatment with eculizumab, and that the burden of disease appears greater among TD eculizumab users relative to TF eculizumab users. However, some case studies have shown that treatment with eculizumab may contribute to a reduction of morbidity prior to and complications following allogeneic hematopoietic stem cell transplantation among patients with PNH [27, 28]. Additional research is needed to further delineate the use of eculizumab in the setting of transplantation.

The present study was subject to certain limitations. First, the ICD-9 diagnosis code for PNH is a broad code, encompassing other related diagnoses. To minimize imprecision in selecting patients with PNH into the study, the study cohort was selected on the basis of an inclusion by exclusion principle, in which patients were excluded if they had at least one diagnosis of another indication of eculizumab. As a result, the number of patients with PNH may be underestimated if a patient had a diagnosis for PNH as well as another indication of eculizumab. Another limitation of this study was the lack of available information in the data source regarding mortality and the reasons for discontinuation of eculizumab. Competing risk of death is an important consideration in time-to-event analyses of older patients (e.g., median age of 80 years) [29] and older age at enrollment is a risk factor for mortality among patients with PNH [30]. However, the present study evaluated clinical outcomes (i.e., discontinuation of eculizumab) in a younger PNH population with a lower risk of near-term death. Therefore, mortality was likely to have a lesser impact on the analysis. Common limitations of administrative claims-based studies include the potential

misclassification of clinical outcomes due to the misspecification of diagnosis, procedure, or drug codes, as well as billing inaccuracies and missing data due to miscoding of diagnoses. However, the aforementioned limitations were expected to affect all cohorts equally and, therefore, were not likely to have biased the comparative analyses. Additionally, definitions of visit types (e.g., IP, OP) vary among claim database analyses. The lack of standardization may add bias in the attribution of visit type-specific costs, but this limitation was unlikely to impact the total cost analysis presented. As in all observational studies, confounding adjustments can only account for factors that are observable and recorded in the database.

CONCLUSIONS

Patients with PNH initiated on eculizumab, a C5 inhibitor, have a substantial burden of disease, which translates into considerable healthcare costs from the payer perspective. Study findings further suggest that blood transfusion dependence status may be associated with greater clinical and economic burden among patients with PNH. More than one-third of patients with PNH treated with eculizumab remained transfusion-dependent despite eculizumab treatment and incurred substantial HRU and costs compared to TF eculizumab users, including three times more all-cause hospitalizations and more than four times more all-cause hospitalization days, which further translated into an annual average of nearly $248,000 in higher direct medical costs. Taken together, these findings suggest that the current PNH standard of care may be insufficient. Novel therapeutic options are required to reduce the considerable burden of patients with PNH, especially among patients dependent on blood transfusions.

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Compliance with Ethics Guidelines. All database records were de-identified and certified as fully compliant with US patient confidentiality requirements outlined in the Health Insurance Portability and Accountability Act (HIPAA). Since this study relied exclusively on de-identified patient records and did not involve the collection, use, or dissemination of

individually identifiable data, institutional review board approval was not required.

Data Availability. The datasets generated and analyzed during the current study are not publicly available because they were used pursuant to a data use agreement. The data are available through requests made directly to IBM.

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