Paroxysmal Nocturnal Hemoglobinuria Real-World Effectiveness of C5 Inhibitors and Cost Assessment

J.P. Burke, PhD[1], B. Sahli, PharmD[1], K. Broderick, PharmD[2], P.P. Gleason, PharmD[1,3]. [1]Prime Therapeutics LLC, Eagan, MN, United States; [2]Apellis Pharmaceuticals, Inc., Waltham, MA, United States; [3]University of Minnesota College of Pharmacy, Minneapolis, MN, United States.

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially life-threatening, chronic condition.[1-2] It can appear at any age and in any race or gender and is most often diagnosed in people in their early 30s.[3]
- In PNH, blood cells lack complement regulatory proteins, so the body recognizes these healthy red blood cells as damaged leading to uncontrolled activation of the complement cascade. It results in the destruction of oxygen-carrying red blood cells (hemolysis).[1-2]
- Hemolysis occurs in PNH through two mechanisms: intravascular hemolysis (IVH), mediated by complement protein C5, occurring inside the blood vessels; and extravascular hemolysis (EVH), mediated by C3, occurring in the liver and spleen.[1]
- Persistently low hemoglobin can result in frequent transfusions and debilitating symptoms such as severe fatigue and difficulty breathing (dyspnea).[1-4]
- Treatments include complement C5 inhibitors (C5I) eculizumab (ECU) and ravulizumab (RAV) which target IVH by inhibiting C5.[3,4,7] Bone marrow transplant is the only curative therapy; however, it carries many risks.[4]
- C5I PNH treatment goals include reduction in number of transfusions, improvement in hemoglobin levels, and reduction in debilitating symptoms.
- To overcome ongoing hemolysis in patients treated with C5I, clinicians may utilize blood transfusions or increase the dose of C5I beyond FDA label recommendations.[8,9]
- The real-world C5I therapy effectiveness, dosing, site of administration, and costs are not well documented.

OBJECTIVES

The primary objectives of this analysis were to:

- Determine unmet needs in members identified with PNH
- Examine C5I dosing patterns
- Determine C5I effectiveness by characterizing transfusion frequency and breakthrough hemolysis
- Describe commercially insured real-world total health care costs using administrative claims data

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2900 Ames Crossing Road, Eagan, MN 55121
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PATRICK GLEASON, 800.858.0723, ext. 5190
pgleason@primetherapeutics.com

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FIGURE 1

Attrition for Commercial Members Identified with PNH, from 1/1/2018-12/31/2019

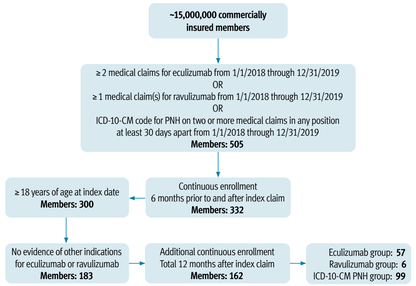


TABLE 1

Frequency of Complement Inhibitors and Transfusions in the Post-index Period in Commercial Members* Identified with PNH, from 1/1/2018-12/31/2019

	Eculizumab (n = 57)	Ravulizumab (n = 6)	Total (n = 63)
	mean (sd)	mean (sd)	mean (sd)
Index dose (mg)	1,068 (401)	2,070 (1,454)	N/A
	n (%)	n (%)	n (%)
New to complement inhibitor therapy	19 (33.3%)	6 (100%)	25 (39.7%)
Discontinuation	22 (38.6%)	3 (50%)	25 (39.7%)
	mean (sd)	mean (sd)	mean (sd)
Total claim count in post-index period	21.7 (8.2)	6 (2.6)	N/A
Total dose in post-index period, mg	23,533 (8,432)	18,240 (10,355)	N/A
Discontinuation	22 (38.6%)	3 (50.0%)	25 (39.7%)
Duration on therapy, days	268.3 (137.9)	272.7 (120.9)	268.7 (135.5)
Transfusions	n (%)	n (%)	n (%)
0	34 (59.6%)	4 (66.7%)	38 (60.3%)
1 to 3	11 (19.3%)	1 (16.7%)	12 (19.0%)
4+	12 (21.1%)	1 (16.7%)	13 (20.6%)

* ≥ 6 months of continuous enrollment in the pre-index period, 12 months of continuous enrollment in the post-index period, ≥ 18 years of age at the index date, and no evidence of atypical hemolytic uremic syndrome, generalized myasthenia gravis or neuromyelitis optica spectrum disorder in the identification period

N/A = not applicable

TABLE 2

Maintenance Dosing and Administration of Therapy Locations in the Post-index Period in Commercial Members* Identified with PNH, from 1/1/2018-12/31/2019

	Eculizumab (n = 57) n (%)	Ravulizumab (n = 6) n (%)
Maintenance dosing per label-recommended treatment, n (%)	29 (55.8%)	-----**
Higher than standard	20 (38.5%)	-----
Lower than standard	0 (0.0%)	-----
Unknown***	8 (14.0%)	-----
Administration of therapy locations, n (%)		
Hospital Outpatient	8 (14.0%)	3 (50.0%)
Office	32 (56.1%)	3 (50.0%)
ER	0 (0.0%)	0 (0.0%)
In-home	8 (14.0%)	0 (0.0%)
Other	9 (15.8%)	0 (0.0%)

* ≥ 6 months of continuous enrollment in the pre-index period, 12 months of continuous enrollment in the post-index period, ≥ 18 years of age at the index date, and no evidence of atypical hemolytic uremic syndrome, generalized myasthenia gravis or neuromyelitis optica spectrum disorder in the identification period; **Because RAV is weight-based and weights were not available, maintenance dosing relative to label recommendation was not calculated; ***7 members in the ECU group did not reach maintenance dosing and/or switched therapy. **** Members with a 25% greater or lesser than expected maintenance dose claims were defined as NOT having standard of care treatment. The standard care of treatment was calculated on a mg/day basis while members were on maintenance therapy. The maintenance dose was established after accounting for the initial loading doses (5 for ECU). Once a member was on maintenance therapy, they were followed to the earliest of discontinuation date or the end of the study period (365 days). Members were categorized by whether they had higher than standard (>80 mg/day), standard and lower than standard (<48 mg/day) care treatment.

TABLE 3

Breakthrough Hemolysis in the Post-index Period in Commercial Members* Identified with PNH from 1/1/2018-12/31/2019

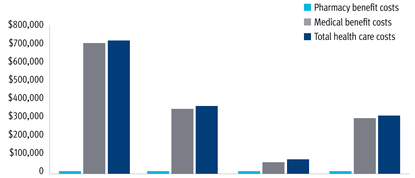
Characteristics	Eculizumab (n = 57)	Ravulizumab (n = 6)	ICD-10-CM D59.5, no Index C5I (n = 99)
Number of episodes, n (%)			
0	43 (75.4)	5 (83.3)	83 (83.8)
1	5 (8.8)	1 (16.7)	11 (11.1)
2	4 (7)	0	1 (1)
3+	5 (8.8)	0	4 (4)
Mean number of episodes, mean (sd)	0.8 (2.1)	0.2 (0.4)	0.3 (0.7)
Costs per episode, mean (sd)	$16,826 ($38,572)	$250 (0)	$49,127 ($145,470)
Total costs of all episodes, mean (sd)	$12,693 ($55,259)	$42 ($102)	$13,398 ($78,363)
Hospitalization, mean (sd)	$12,299 ($54,648)	0 (0)	$13,210 ($78,319)
ER, mean (sd)	$394 ($1,032)	$42 ($102)	$188 ($698)

* ≥ 6 months of continuous enrollment in the pre-index period, 12 months of continuous enrollment in the post-index period, ≥ 18 years of age at the index date, and no evidence of atypical hemolytic uremic syndrome, generalized myasthenia gravis or neuromyelitis optica spectrum disorder in the identification period, sd = standard deviation, ER = emergency room, C5I = complement C5 inhibitor drug therapy

ICD-10-CM D59.5, no Index C5I is the member population identified with a paroxysmal nocturnal hemoglobinuria (PNH) diagnosis and no C5I drug claims history at the time of Index PNH medical claim diagnosis identified.

FIGURE 2

All-cause Health Care Costs in the Post-index Period in Commercial Members* Identified with PNH, from 1/1/2018-12/31/2019



* ≥ 6 months of continuous enrollment in the pre-index period, 12 months of continuous enrollment in the post-index period, ≥ 18 years of age at the index date, and no evidence of atypical hemolytic uremic syndrome, generalized myasthenia gravis or neuromyelitis optica spectrum disorder in the identification period

The eculizumab, ravulizumab and ICD-10 PNH diagnosis groups are mutually exclusive groups.

ICD-10-CM D59.5, no Index C5I is the member population identified with a paroxysmal nocturnal hemoglobinuria (PNH) diagnosis and no C5I drug claims history at the time of Index PNH medical claim diagnosis identified.

** ≥ 2 medical claims in the ID period at least 30 days apart with an ICD-10 code of D59.5 in any position

METHODS

All analyses were conducted using integrated medical and pharmacy claims data from approximately 15 million commercially insured members.

Identification of Commercial Members with PNH

- Members with PNH evidence based on claims indicating PNH treatment or PNH diagnosis claims evidence from Jan. 1, 2018-Dec. 31, 2019 (2-year identification [ID] period) were identified using combined pharmacy and medical claims data. Three mutually exclusive groups were created: ECU and RAV groups based on members first claim for C5I and a third group identifed by PNH diagnosis without C5I claim history. Members were selected based on the following characteristics:
- PNH Treatment group identification
  - ≥ 2 ECU infusion claims; the index date was defined as the date of the first ECU infusion
  - ≥ 1 RAV infusion claim; the index date was defined as the date of the first RAV infusion

  OR
- PNH Diagnosis group identification
  - PNH diagnosis defined as an ICD-10-CM code (D59.5) on two or more medical claims in any position at least 30 days apart in the ID period; the date of the first medical claim with PNH evidence was defined as the index date

ECU and RAV groups were based on the member's first claim for a C5I. For members with an ECU or RAV claim AND evidence of PNH diagnosis, their index date was based on their first ECU or RAV infusion.

To be included in the analyses, members must also have had:

- ≥ 6 months continuous enrollment prior to the index date (pre-index period)
- 12 months continuous enrollment after the index date (post-index period)
- ≥ 18 years of age at the index date

Members were excluded based on the following criteria:

- The presence of another indication for ECU or RAV (including index date) defined as one or more medical claims with an ICD-10-CM code from the conditions below in any position during the identification period.
  - Atypical hemolytic uremic syndrome (D59.3)
  - Generalized myasthenia gravis (G70.xxx)
  - Neuromyelitis optica spectrum disorder (G36.0)

Outcomes Measurements

- **Standard of care treatment –** For ECU, the expected dosage is 600mg weekly for the first 4 weeks, followed by 900mg for the 5th dose 1 week later, then 900mg every 2 weeks (maintenance). For RAV (weight-based; pediatric and adult), the expected dosage is a loading dose (600mg–3000mg) followed 2 weeks later by a weight-based maintenance dose every 4 to 8 weeks.[6,7]

Members utilizing ECU with a 25% greater or lesser than expected maintenance dose claims were defined as NOT having standard of care treatment. The standard care of treatment is calculated on a mg/day basis while members are on maintenance therapy. The maintenance dose was established after accounting for the initial loading doses (5 doses for ECU).

Time between doses was also assessed in members with greater than one claim after their loading doses. A mean time between doses was calculated for each member.

- **Transfusions –** The number of transfusions in the post-index period was determined. Because of the difficulty in determining the presence of multiple transfusions on a single day using claims data, all transfusions on a single day were considered a single episode. Members were stratified by whether they have 0, 1 to 3, or 4+ transfusions in the post-index period. The time from the index date to the first transfusion and the time between the first and second transfusions was calculated.
- **Breakthrough hemolysis (BTH) –** was defined as the presence of one or more ICD-10-CM codes for abdominal pain, anemia (excluding aplastic anemia), chronic kidney disease (CKD), dysphagia, dyspnea, erectile dysfunction, fatigue, infection, sepsis, respiratory infection, kidney infection, urinary tract infection (UTI), pulmonary, hypertension, thrombosis in any of the 5 positions on a medical claim AND PNH-related hospitalization or ER visit. If BTH was defined via a hospitalization, then the episode was extended through the entire length of the hospitalization. Costs related to BTH were evaluated for in total and on a per episode basis. Costs for BTH included medical claims costs related to the ER visits or hospitalizations for claims defined above as BTH.
- **Discontinuation –** was defined as an index therapy gap during the post-index period. For ECU (given every 14 days), a member with a gap of more than 28 days between administrations was considered to have discontinued therapy. For RAV (given every 56 days), discontinuation was defined as a member with a gap of more than 112 days between administrations. Members were not considered discontinued if they switched to RAV from ECU within 28 days of their last ECU claim or to ECU from RAV within 112 days of their last RAV claim. Time to discontinuation (duration on therapy) was also determined.
- **Health care utilization and site of care –** Health care utilization was broken out by hospitalization, emergency room (ER) and office visits. Site of care (office, hospital outpatient, or home infusion) was determined using the medical claim place of service code to categorize place of C5I therapy.
- **Health care costs –** Health care costs in the post-index period were determined. The total cost of care included all pharmacy and medical claims and includes member share and plan paid allowed amounts. The costs were broken out by medical costs and pharmacy costs. C5I costs were further broken out by site of care.
- Age, gender and proportion of members new to therapy (no claim for a C5I in the pre-index period) were examined for descriptive purposes.

Statistical Analyses

- Descriptive analyses were used.

RESULTS

Identification of Analytic Population — Commercial Members with PNH (Figure 1)

- A total of 505 commercial members with a pharmacy claim for ECU or RAV or an ICD-10-CM code for PNH were identified from Jan. 1, 2018 to Dec. 31, 2019.
- After applying the continuous enrollment and age criteria and excluding members with evidence of another indication, 162 commercial members met analysis criteria: 57 in the ECU group, 6 in the RAV group, and 99 in the ICD-10-CM PNH group.
- The mean index age of the members was 43.0 years; 61.9% were female, and 39.7% were new to C5I therapy (data not shown).

Frequency of Complement Inhibitors and Transfusions in the Post-index Period (Table 1)

- The mean index dose in the ECU group was higher than the FDA label recommended maintenance dose of 900mg at 1068mg. The mean per member claim count in the post-index period was 21.7 in the ECU group and 6.0 in the RAV group.
- 22 (38.6%) of the 57 members in the ECU group and 3 (50.0%) of 6 members in the RAV group discontinued therapy.
- Mean duration on therapy was similar in the two groups.
- A total of 39.6% of members on therapy had at least one transfusion in the post-index period while 20.6% had 4 or more transfusions.

Maintenance Dosing and Administration of Therapy Locations (Table 2)

- 38.5% of members in the ECU group had higher than label recommended treatment in the post-index period.
- Regarding duration between infusions, the mean time between infusions was 15.0 days for ECU and 52.3 days for RAV.
- The most common ECU administration site of care on the index claim was the provider's office. In the RAV group, administration site of care was evenly split between the provider's office and hospital outpatient settings.
- It should be noted that the mean cost/mg for ECU infusions was substantially higher in the hospital outpatient setting relative to the provider's office or home setting (data not shown).

Breakthrough Hemolysis Frequency and Costs (Table 3)

- 14 (24.6%) of the 57 members in the ECU group had at least one BTH episode compared to 1 (16.7%) of 6 in the RAV group and 16 (16.2%) of 99 in the ICD-10-CM PNH group.
- The mean cost per BTH episode was substantially higher if a hospitalization was involved ($12,299 vs. $394).

All-cause Health Care Costs and Health Care Utilization (Figure 2)

- Total health care costs in the post-index period were highest in the ECU group ($729,683) followed by the RAV ($371,648) and ICD-10-CM PNH ($79,295) groups.
- All C5I claims were billed through the medical benefit and, thus, all costs were included in the medical costs. C5I costs accounted for 87.1% and 74.4% of total health care costs in the ECU and RAV groups, respectively. Medical costs accounted for over 99% of total health care costs.
- Non-index medication costs were similar across the three groups.
- Health care utilization was determined in the post-index period.
  - The proportion of members with a hospitalization was 24.6%, 33.3% and 26.3% in the ECU, RAV and PNH ICD-10-CM groups, respectively.
  - The proportion of members with an ER visit was 29.8%, 16.7% and 12.1% in the ECU, RAV and PNH ICD-10-CM groups, respectively.
  - The proportion of members with a provider office visit was 98.2%, 83.3% and 98.0% in the ECU, RAV and PNH ICD-10-CM groups, respectively.

Cost of Higher than Standard Dosing

- Members with above standard dosing had a median C5I cost per day of $3,767 compared to $1,669 in members receiving standard dosing, a 2.25 times greater median daily medication cost.

LIMITATIONS

- Pharmacy claims include assumptions of members' actual drug use and diagnoses.
- The data used in this study was limited to a commercial population, and results may not be generalizable to Medicare or Medicaid populations.
- Costs in this analysis are limited to health care claim expenses. However, PNH also results in significant indirect and societal costs.[8,10]
- RAV was approved during the identification period (12/21/2018),[2,11] thus, limiting the RAV sample size for analysis. The results may not be representative of the current RAV and ECU PNH treatment patterns.
- The optimal measure of BTH would include laboratory measures of lactate dehydrogenase (LDH) along with clinical symptoms and may not be fully captured in the present analysis given coding limitations.
- 12 of the 57 members in the ECU group did not have a medical claim with an ICD-10-CM code for PNH and, thus, their PNH diagnosis is not definite.
- Since individual weights were not available and RAV dosing is weight-based, standard-of-care based on dosage was not calculated for the RAV group.
- There were 4 of 99 members with a PNH diagnosis and no C5I drug claims history at the time of index PNH medical claim diagnosis who subsequently had a C5I drug claim during the 12-month post-index period.

CONCLUSIONS

- Among 15 million commercially insured members meeting analytic criteria, we found that 61% of members identified with PNH were untreated with a C5I. These findings are the first to explore PNH C5I treatment rate in the U.S. commercially insured population.
- Of potential concern are the following real-world C5I treatment findings:
  - 1 in 5 had ≥ 4 transfusions
  - 4 of 10 discontinued therapy
  - 1 of 4 had claims indicating BTH
  - 4 of 10 members treated with ECU received higher than label dosing the billed claims
- With RAV PNH approval, further C5I therapy real-world cost assessments are imperative.
- These real-world findings highlight unmet needs among members with PNH treated with a C5I. Through integrated medical and pharmacy benefits real-world analytics, insurers can assess medication value and inform management decisions.

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