Soyon Lee | Soyon.lee@novartis.com

Evaluation of the Healthcare System Burden Associated with Intravenous Treatment for Paroxysmal Nocturnal Hemoglobinuria

Brian P. Mulherin[1], Daniel Winokur[2], Abdulraheem Yacoub[3], Soyon Lee[4], Ver Bilano[5], Glorian P. Yen[4], Anumaxine Geevarghese[4], Jincy Paulose[4], Annie Guerin[6], Dominick Latremouille-Viau[6], Gayatri Marathe[6], Anem Waheed[7]

[1] Hematology Oncology of Indiana, Indianapolis, Indiana, USA; [2] UMass Memorial Health Care, University of Massachusetts Medical School, Worcester, Massachusetts, USA; [3] KU Medical Center, The University of Kansas, Kansas City, Kansas, USA; [4] Novartis Pharmaceutical Corp, East Hanover, New Jersey, USA; [5] Novartis Pharmaceuticals UK Ltd, London, United Kingdom; [6] Analysis Group, Inc., Montréal, Quebec, Canada; [7] Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

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KEY FINDINGS & CONCLUSIONS

The study revealed **complexities associated with IV treatment with ravulizumab for PNH** from a healthcare system perspective.

Given the resource and time-intensive nature of IV treatment for patients and providers, alongside infusion centers operating at full capacity, the integration of an oral treatment like iptacopan could **increase infusion center capacity and enhance scheduling flexibility** for managing other concurrent conditions.

As physicians may not have complete visibility into certain treatment preparation and administration procedures, further studies are warranted to **understand the burden of IV treatment** from the perspective of additional healthcare personnel (nurses, pharmacists) and the patient perspective. A second phase of this study is planned, involving interviews with nurses and pharmacists.

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening disorder with ongoing hemolysis that may cause thrombosis and bone marrow failure [1]
- Treatments for PNH in the US include complement inhibitors (Ci) such as C5 inhibitors, intravenous (IV) eculizumab (FDA-approved: 2007)
  and IV ravulizumab (FDA-approved: 2018), a subcutaneous (SQ) C3 inhibitor pegcetacoplan (FDA-approved: 2021), with most recent options iptacopan, an oral complement factor B inhibitor (FDA-approved: 2023), and danicopan as an add-on to C5 inhibitors (FDA-approved: 2024)
- Following the introduction of ravulizumab, patients with PNH treated with an IV C5 inhibitor tend to be initiated on ravulizumab or switched from eculizumab to ravulizumab [2]; Data on the use of more recent PNH treatments are limited
- For IV ravulizumab, the recommended dosing regimen consists of a loading dose, followed by maintenance doses once every 8-week, starting 2 weeks after the loading dose administration, with IV administration by a healthcare provider [3]
  - Physicians may modify the dosing schedule with more frequent infusions, particularly in case of breakthrough hemolysis to re-reach disease control [3]
- For oral iptacopan, the recommended dosage is 200 mg orally twice daily with or without food (capsules of 200 mg) [4]
- IV infusion, such as ravulizumab, can have significant implications for treatment administration resources, including time and costs. From a healthcare system perspective, it can be both human and materials resource-intensive [5]
- In contrast, oral therapies, such as iptacopan, could offer the advantage of patients taking their medications without requiring the same level
  of institutional resources (including personnel time and materials required for infusion)

OBJECTIVE

With availability of the novel oral therapy iptacopan for paroxysmal nocturnal hemoglobinuria (PNH) since December 2023, to delineate steps in the IV treatment workflow with ravulizumab from a healthcare system perspective and identify steps potentially simplified with the adoption of this oral therapy

METHODS

- This qualitative cross-sectional study consisted of individual in-depth semi-structured interviews with five US hematologists between October and December 2023 (prior to iptacopan FDA-approval)
  - Eligible physicians were interviewed remotely using a semi-structured interview guide via Microsoft Teams
  - An initial 60-minute interview and a 30-minute follow-up interview were conducted with each physician
- Participating physicians were from large medical centers (academic and community-based) experienced in treating PNH patients with IV ravulizumab
  - Had completed medical subspecialty training in hematology
  - Had treated or were currently treating patients with PNH and were responsible for treatment decisions for patients with PNH
  - Had prescribed IV ravulizumab to patients with PNH
- Detailed information was collected on the workflow for IV treatment with ravulizumab including patient reception, treatment preparation, treatment administration, post-administration monitoring, and additional steps for treatment reimbursement
- The interview data were analyzed to identify steps in the IV treatment workflow, leading to the development of a process map, covering treatment decision/planning to outpatient IV administration
- Physicians' perspectives on process complexities related to IV treatment and steps that could be simplified through the adoption of an oral therapy such as iptacopan were collected
- An IRB exemption was received for the conduct of this study

RESULTS

Physician Characteristics

- Of the 5 participating physicians, the majority worked in an academic center (80%) with 10-14 years of experience
- On average, physicians saw 10 patients with PNH in the past 12 months, of which they prescribed treatment to 8 patients

Main Results

- The process map delineated multiple steps from treatment decision to administration, inclusively (**Figure 1**)
  - The total time required from treatment decision to administration was ~2-4 weeks, which included the time required for insurance approval (from 2 days to 2-3 weeks)
    and the time spent by patients at each infusion center visit (3-4 hours)
  - If patients have manual or physical jobs, then they may need to take a full day off of work during day of treatment administration

- **Steps that would be alleviated by an oral treatment, such as iptacopan, include treatment scheduling and administration at infusion centers**

Physician Perspective on Treatments

Main challenges related to IV treatment with ravulizumab:

VACCINATIONS

- Vaccinations are generally handled by specialty pharmacies and availability can be limited in community-based settings
- Ravulizumab administration may be delayed if vaccines are not up to date; such delays sometimes occur because physicians may not always have visibility on the status of vaccination boosters (requirement of REMS) in the EMR system

TREATMENT SCHEDULING

- Scheduling flexibility is limited as infusion centers operate at full capacity, exacerbated by staffing constraints within the center. Securing available chairs for patients can be challenging, potentially resulting in treatment delays, which is not recommended.
- There have been instances of patients with PNH experiencing dose delays with some centers prioritizing cancer patients, suggesting a need for enhanced education at infusion centers regarding PNH treatment

INSURANCE APPROVAL

- There are delays in treatment initiation due to issues with insurance approvals, necessitating the drafting of appeal letters to insurance providers for approval
- There are delays in obtaining off-label doses, for example, for breakthrough hemolysis (BTH), due to added complexity of obtaining insurance approvals
- Inpatient treatment of patients with urgent needs relies on the medications stocked at the hospital pharmacy (e.g., eculizumab)

PATIENT TIME COMMITMENT

- The lack of flexibility in selecting infusion centers, coupled with the complexity of switching or finding an alternative center, poses significant challenges
- Patients typically continue receiving treatment at the initial infusion center, with some traveling long distances, even requiring flights, every 8 weeks for their appointments
- Patients often structure their lives around their treatment administration appointments. Some may prefer to schedule their treatments for an entire year, which can be burdensome for the center due to reduced flexibility

Introduction of the oral therapy, iptacopan:

- Eliminates the need for treatment scheduling, thereby easing the burden on infusion centers and healthcare providers
- Reduces the patient's travel burden, as they no longer need to visit an infusion center every 8 weeks, minimizing loss of workdays
- Alleviates the inconvenience of lab tests by allowing them to be conducted at a facility closer to the patient's home, although the frequency of testing remains unchanged
- Requires healthcare providers to be involved in additional patient education, adverse event monitoring, and treatment compliance monitoring; adherence to the oral treatment will be crucial
- May only be available in select specialty pharmacies and may have to be shipped to the patient's home
- Maintains a similar frequency of physician visits for disease control and treatment efficacy monitoring. Clinic visit frequency may vary based on physician preference, with more frequent visits typically occurring during the first 6 months of treatment, gradually decreasing as the patient stabilizes and gains experience

Figure 1. Treatment workflow of outpatient IV administration of ravulizumab for PNH

Treatment Decision & Planning
Patient Prep
Treatment Preparations
Laboratory
Clinic
Treatment
Pharmacy
Patient diagnosed with PNH
Ongoing, routine labs and monitoring
Symptoms and lab values indicate that treatment for PNH is required
Select therapy based on patient's condition
Patient stable enough for outpatient therapy
Select standard Order Set in EMR
Physician may consult pharmacist
Pharmacist places order
Physician signs order
Patient education regarding diagnosis
Vaccinations
Antibiotics
Discuss treatment with Patient
Patient consent
Patient education regarding treatment
Scheduling request
Some patients receive a port
Insurance pre-authorization
Financial consultation with patient
Triggers scheduling of treatments and labs
Nursing/ infusion center has contact with physician
Infusion scheduler locates dates
Coordinate schedules with patient
Multiple treatment dates may be scheduled ahead of time
Patient may verify schedule on day of treatment
Typical tests for PNH include: CBC, CMP, LDH, haptoglobin, reticulocyte count
Patient may have routine tests for other conditions
Labs are drawn on day of treatments and clinic visits
Physician typically sees patient before treatment
Time lapse from Treatment Required to First Outpatient:
• Minimum of 2 weeks
• Can be as long as 3 – 4 weeks
Patient travels to infusion center
Patient checks in at reception
Samples are drawn for laboratory tests
Patient in waiting room
Move patient to the infusion area
Take patient vitals and move to chair
Nurse will verify and access patient
Nurse reviews orders and labs in EMR
Nurse retrieves treatment
Prep for administration
Administer IV ravulizumab
Post-administration (no waiting)
Patient leaves chair and goes to checkout
Patient done
Receives order in EMR
Pharmacy tech prepares treatment
Stages/ sends treatment to infusion room
IV administration time: ~30 – 45 minutes
Total chair time: ~80 – 120 minutes
Total time in the Infusion Center: ~3 – 4 hours
Legend
High-level steps related to diagnosis and monitoring of PNH; outside the scope of the study
Treatment decision, treatment planning, and treatment orders
Activities related to physical interactions with the patient and include vaccinations, antibiotics, access port, and drawing blood for laboratory tests. It does not include any of the IV treatment steps
Administrative-type steps related to preparations for treatment and include insurance pre-authorization, financial, scheduling, and patient coordination
Laboratory activities
Physician exam or clinic on the day of treatment
Patient movement before and after treatment
Treatment administration steps within the infusion area
Pharmacy activities
Steps that would be alleviated with the adoption of oral therapy, iptacopan

Notes:

1. Patient is stable when they are not in immediate danger of hemolysis; 2. Physicians may sign one order for all treatments. However, this is EMR dependent, and some physicians may sign or verify the order on the day of treatment; 3. Physicians will typically see the patient once during treatment planning; 4. Vaccinations may be given at the center or at an off-site pharmacy; 5. Vaccinations may require boosters every 3-5 years; 6. Vaccinations and antibiotics are the same for any complement inhibitor; 7. All patients will receive vaccinations, but the use of antibiotics may be more selective. Antibiotics may be given if the physician decides to start treatments within two weeks of vaccination or before vaccinations are administered; 8. Ports are not common for ravulizumab, since it is administered every 8 weeks and the patient population is younger; 9. Pre-authorization will typically take 1-2 days but can take as long as 2-3 weeks; 10. REMS certification is required to prescribe ravulizumab, mainly due to the risk of meningococcal infection; 11. As PNH is not a common condition, some nursing/infusion centers may reach out to the physician with questions; 12. For some centers, the scheduling process may be automated; 13. Home infusion may be an option under specific circumstances (e.g., stable and experienced patients, accessible via insurance plan/state) but is not commonly used. If home infusion is used, the physician may not have visibility of the process; 14. There are no laboratory tests specific to the selected therapy. However, patients receiving ravulizumab may be tested for Ferritin or Iron levels periodically; 15. It is common for PNH patients to have other diseases requiring physician care, testing, and monitoring; 16. Infusion centers may not be convenient for patients, including travel to the centers, parking, and logistics; 17. Patients receive a first dose (i.e., loading dose) and then a maintenance dose every 8 weeks starting 15 days after the loading dose. The regimen is consistent for outpatient infusions; 18. Patients can receive a dose after 7 weeks if they have a scheduling conflict, but it is not recommended to push the dose to 9 weeks; 19. One physician chose to see patients on non-treatment days to reduce their time in the center on the day of treatment; 20. During the first 6 months of treatment, physicians may see patients at least once per month during clinics. Once the patient becomes stable, they may see them less frequently and/or a nurse practitioner may see the patient; 21. Nurse reviews lab results, but there are no holding parameters for ravulizumab; 22. Drug availability can be an issue, depending on the size of the center and if the dose is required outside the regularly scheduled 8-week dose; 23. There is no post-administration monitoring or waiting period for ravulizumab. Some nurses may ask the patient to wait for a brief period for their first dose only.

LIMITATIONS

- Interviews were conducted with physicians only; nurses and pharmacists may have access to more detailed information regarding the preparation and administration of the IV treatment
- Treatment workflow for IV ravulizumab administration was limited to outpatient settings and may not be representative of all US practices
  - The workflow cannot be generalized to inpatient, emergency department, or home health service settings, which would also require personnel time and materials

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