Editorial

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Advancements in PNH treatment: crovalimab's clinical efficacy

Eisha Shoaib, MBBS[a], Filzah Imam, MBBS[a], Mahnoor Khan, MBBS[a], Mohammed H. Jaber Amin, MBBS[b,*]

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening hematologic disease that is characterized by the destruction of red blood cells, leading to a range of severe symptoms and complications. Recent advancements in drug therapies have significantly improved the prognosis for PNH patients. This editorial comprises the impact of PNH drugs, focusing on eculizumab and ravulizumab and comparing them to the recently approved complement inhibitor, crovalimab, which targets the complement system to prevent hemolysis. The discussion includes an analysis of clinical trial data and patient outcomes. The editorial mainly addresses emerging therapies, like crovalimab, that promise to offer more comprehensive, complete blockage of the complement system and low-dose solutions, reducing the treatment hassle while simultaneously appealing to a wider range of patients.

Keywords: C5 inhibitor, COMMODORE trials, complement system, crovalimab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, non-malignant hematologic clonal disease caused by a mutation in the X-linked PIGA gene in hematopoietic stem cells. This results in defective glycosylphosphatidylinositol (GPI) synthesis, preventing regulatory proteins like CD55 and CD59 from attaching to erythrocytes, thus impairing complement regulation[1]. Evidence suggests the global prevalence and incidence of PNH to be 10–20 cases per million and 1–1.5 cases per million, respectively[2]. Commonly, PNH presents as hemolytic anemia, hemoglobinuria, fatigue, and dyspnea. Additionally, thrombosis, renal insufficiency, and, in advanced stages, bone marrow failure may occur[1].

The three PNH subtypes are classic PNH (normal counts, large clone, high hemolysis), aplastic PNH (10–50% clone, mild hemolysis, low counts), and subclinical PNH (1–10% clone in myelodysplasia/aplasia, no hemolysis)[3]. The two primary effective approaches for PNH are the use of complement C5 inhibitors and allogeneic hematopoietic stem cell transplantation (allo-HSCT). The specific treatment depends on the characteristics and clinical manifestation of the individual PNH cases. Complement C5 inhibitor represents the current standard of care for classic PNH[3].

[a]Karachi Medical and Dental College, Karachi, Pakistan and [b]Faculty of Medicine, Alzaiem Alazhari University, Khartoum, Sudan

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*Corresponding author. Address: Faculty of Medicine, Alzaiem Alazhari University, Khartoum 11111, Sudan. Tel.: +249 119 303 629.
E-mail: mohammesjaber123@gmail.com (M.H. Jaber Amin).

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Among C5 inhibitors, eculizumab and ravulizumab were approved for PNH in the US, EU, and Japan[4]. Eculizumab has been the standard since 2007, with ravulizumab approved in 2018[3].

Eculizumab is a monoclonal antibody that prevents serious complications of chronic PNH-related hemolysis and can even improve renal function. However, some patients may have incomplete responses due to factors like insufficient RBC production or rare genetic variations[3]. A cohort study showed eculizumab given every 2 weeks in a standard 900 mg dose to be ineffective for all patients as 49% showed hemolytic activity resulting in 34–51% of patients needing regular transfusions[4]. Many of these continue to show such activity during this treatment, possibly from underdosing causing incomplete C5 blockage[3]. This often led to increasing doses in (20–40%) patients[4].

Ravulizumab, a modified version of eculizumab, offers comparable therapeutic benefits and safety for PNH. The key advantage is its 4-fold longer half-life, allowing less frequent 8-week dosing compared with eculizumab[3].

The only curative treatment for PNH is allo-HSCT. However, it carries the risk of morbidity, mortality, and HLA donor incompatibility, leading to graft-versus-host disease in a substantial proportion of patients[3].

Crovalimab is another C5 complement inhibitor. It works as an anti-C5 sequential monoclonal antibody recycling technology (SMART) antibody that efficiently binds and disposes of the complement protein C5 while enhancing its own recycling process via the neonatal Fc receptor(FcRn)[3]. Crovalimab is highly soluble[3] and was designed for prolonged self-administration of subcutaneous small-volume doses in PNH[4].

According to the phase 1/2 COMPOSER study, crovalimab administered in small amounts subcutaneously (1–4 ml) showed excellent tolerability and acceptable safety, maintaining sustained and complete inhibition of the terminal complement pathway[4]. Crovalimab targets a different part of the C5 protein than other approved drugs, potentially making it more effective for a wider range of patients[4]. The COMPOSER trial demonstrated that four patients who switched from 1200 mg of eculizumab to crovalimab maintained clinical stability. One transfusion-

dependent patient became transfusion-independent on a 4-week schedule of crovalimab. The trial concluded that a dose of 680 mg crovalimab, administered subcutaneously every 4 weeks, appears to be effective and safe with a low treatment burden, even for patients tolerating higher doses of eculizumab. Crovalimab treatment led to notable improvements in fatigue, physical functioning, and overall quality of life. It effectively suppressed complement activation and showed better results compared to other C5 inhibitors in treatment-naive patients. The annualized breakthrough event rate for crovalimab in the COMPOSER trial was 0.13, which compares favorably to 0–0.14 for ravulizumab and 0.06-0.46 for eculizumab in recent phase 3 studies. Despite crovalimab's post hoc analysis, it still shows promise in the reduction of breakthrough events[4].

COMMODORE 3 trial met both primary endpoints of hemolysis control and transfusion avoidance and also showed that crovalimab is effective and well-tolerated in complement inhibitor-naive PNH patients. The safety profile of crovalimab matched that of other C5 inhibitors[5]. Crovalimab rapidly controlled hemolysis, reducing plasma LDH levels to $\leq 1.5\times$ ULN by week 3 and maintaining this through week 25. The transfusion avoidance rate was 51%, consistent with other C5 inhibitors, despite a high proportion of patients with advanced bone marrow disease. A post hoc analysis showed that even patients not achieving full transfusion avoidance still had reduced transfusion needs[5].

The phase 3 COMMODORE 2 study evaluated crovalimab against eculizumab in C5 inhibitor-naive adults with PNH, including 135 patients on crovalimab and 69 on eculizumab. The results proved crovalimab noninferior to eculizumab in controlling hemolysis and avoiding transfusions; however, both treatments improved patient-reported outcomes, with 65.6% of crovalimab-treated patients reaching near normal fatigue levels compared with 43.6% with eculizumab. Biomarker analysis revealed greater inhibition of terminal complement activity with crovalimab. Overall, crovalimab was preferred for its convenience, efficacy, and patient preference[6].

The tolerability profile of crovalimab was similar to eculizumab, with corresponding results in both C5 inhibitor-naïve and experienced patients, in accordance with pooled phase 3 COMMODORE studies[6]. Amidst the 377 crovalimab and 111 eculizumab patients, adverse event (AE) rates were 522/100 patient-years (PYs) for crovalimab and 583/100 PYs for eculizumab. Crovalimab resulted in a lower number of serious infections (7.4/100 PYs) compared with eculizumab (14.1/100 PYs). Decreased WBC and neutrophil counts, upper respiratory infections, and COVID-19 were some of the common AEs noted[6]. There have been transient immune complex reactions seen in 18% of patients switching from eculizumab to crovalimab. No concerns regarding renal functions were noticed with crovalimab, indicating its potential significance for aHUS treatment[6].

Conclusion

2024 is the year of significant regulatory approvals for crovalimab as China and Japan approved it for PNH treatment on 6th February and 24th March, respectively[6]. Crovalimab, showing promising results in the above-mentioned trials, has made its way into the USA recently by being approved by the FDA as a novel drug under the name 'Piasky' on 20th June 2024[7]. This detailed editorial can assure healthcare professionals about the clinical efficacy, long-term benefits, and safety profile of crovalimab as it will enhance patient care and improve the quality of life of PNH-affected individuals in a shorter period of time.

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Mohammed Hammad Jaber Amin; Faculty of Medicine, Alzaiem Alazhari University, Khartoum, Sudan.

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