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# CURRENT AND EMERGING TREATMENT FOR PAROXYSMAL NOCTURNAL HEMOGLOBINURIA, WITH EMPHASIS ON THE COMPLEMENT INHIBITOR IPTACOPAN AND DANICOPAN

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## ABSTRACT

Paroxysmal nocturnal haemoglobinuria (PNH) is a life-threatening and rare haematological disease that is defined by the intravascular haemolysis due to the autoimmune system mediated destruction of the red blood cells causing some of the symptoms of fatigue, impotence and thrombosis. Until recently, treatments for PNH were restricted and the usual management of PNH include using anticomplement component 5 (C5) monoclonal antibodies like eculizumab or ravulizumab with a primary aim of controlling symptoms and averting threat. Though, there exists newer drugs such as iptacopan and danicopan which is a new, oral complement factor B inhibitor and factor D inhibitors respectively, for PNH patients.

**KEYWORDS:** Iptacopan, Danicopan, Paroxysmal nocturnal haemoglobinuria (PNH).

## INTRODUCTION

PNH is a chronic, rare acquired hematological condition that affects 1 to 1.5 million people globally. In hematopoietic stem cells, it is brought on by a somatic mutation in the phosphatidylinositol glycan A (PIGA) gene.[1–4] Although PNH can be diagnosed at any age, persons in their early 30s are the most likely to have it.[1,3] The hallmark of the typical presentation of PNH is sudden, episodic (paroxysmal), nocturnal hemoglobinuria—the passage of the RBC breakdown product into the urine—occurring at night. However, not all PNH patients have frank hemoglobinuria, and hemoglobin in the urine may not always be apparent to the naked eye. Although PNH symptoms differ from person to person, extreme

fatigue is the most prevalent symptom.[1] PNH can manifest clinically as bone marrow failure, thrombosis propensity, and chronic complement-mediated hemolysis.[5]

Paroxysmal nocturnal hemoglobinuria (PNH) is unique among hemolytic anemias in two ways. First and foremost, an anomaly that is not specific to erythrocytes underlying the pathobiology of PNH. Instead, PNH affects hematopoietic stem cells. Second, the faulty mechanism in PNH is acquired rather than inherited, setting it apart from all other intrinsic red cell disorders.[6]

**PATHOPHYSIOLOGY**: The PIGA mutations that result in PNH lead to partial or complete loss of enzyme function, which ultimately results in the lack of all GPI-anchored protein production, either completely or almost.[6] A glycolipid moiety capable of anchoring over 150 distinct proteins to the surface of cells.[7] More than 20 of the membrane-bound proteins that make up this moiety's functionally varied group are expressed on human hematopoietic lineage cells.[6]

The complement regulating proteins, CD59 (membrane inhibitor of reactive lysis; MIRL) and CD55 (decay accelerating factor; DAF) are absent on red blood cells (RBCs) (1). CD59, a 19,000 molecular weight glycoprotein, binds directly to the membrane attack complex and stops the fixation of C9 thus preventing the formation of lytic holes. Hemolysis is the major cause of morbidity and mortality in PNH and the absence of this protein leads to chronic complement-mediated intravascular hemolysis. The 68,000 molecular weight glycoproteins, CD55 is known to enhance the rate at which the membrane-bound C3 convertase is cleared. Thus, CD55 consumption diminishes the amount of C3 that is cleaved and CD59 consumption reduces the number of MAC formed. Between the two, CD59 is considered to be more vital in the respect to protection of cells from the complement.[8] PNH cells lack of CD55 and CD59 causes hemolysis; both intravascular and extravascular hemolysis; inflammation; platelet activation, and thrombosis.[7] Intravascular hemolysis in PNH patients in high doses or for a long time leads anemia, hemoglobinuria and other pathogenic effects of plasma-free hemoglobin such as thrombosis, abdominal pain, dysphagia, erectile dysfunction and pulmonary hypertension.[9]

**CURRENT TREATMENT OPTIONS:** Some of the supportive therapeutic approaches implemented to PNH in the past, and still being used, include transfusion support, anticoagulation or the chronic use of corticosteroids and narcotics which lead to extremely

low quality of life and high-risk profile. PNH has received a major breakthrough in the past decade with the approval of complement inhibitors like eculizumab and later ravulizumab.[9] Eculizumab is the biosimilar of a humanized monoclonal antibody which selectively targets and binds to the human complement protein C5 thereby preventing the generation of the pro-inflammatory and prothrombotic C5a, and the C5b that leads to the formation of the membrane attack complex.[3] Eculizumab decreases intravascular hemolysis, and can either decrease or remove the requirement of transfusions, enhance anemia, fatigue, and quality of life for patients with PNH.[9] However, these treatments entail other complications that demand the administration of intravenous infusions and come with high health costs together with logistical problems.[10] In addition, some patients still exhibit low-level hemolysis and other symptoms as a result of incomplete complement blockade.[11]

## ORAL COMPLEMENT INHIBITORS: IPTACOPAN AND DANICOPAN

The newest addition of oral complement inhibitors is a major advancement in the management of PNH with indication that it can be more effective and easier to use compared to earlier intravenous drugs.[12]

Iptacopan (LNP023) is an orally active Factor B inhibitor which selectively targets the AP of complement activation.[13] Iptacopan thus selectively blocks Factor B that is required in the generation of the C3 convertase (C3bBb) so that the amplification of the complement cascade above C5 is reversed.[14] The bonus to this mechanism is that it gives allowance to modulate both intravascular and extravascular hemolysis, which is a concern seen with C5 inhibitors.[15] Iptacopan has been tested in the landmark clinical trials APPOINT-PNH and APPLY-PNH which suggest that it can decrease hemolysis and improve hematologic markers in the process, thus indicating possible usage as a sole agent or combined with other therapy forms.[16,17]

• **APPOINT-PNH Trial:** This was Phase 3 trial and it compared the effects that iptacopan had on PNH patients who had never received complement inhibitors. The study revealed that iptacopan gave a rapid and continued improvement in the condition whereby a considerable number of the patients treated with iptacopan became transfusion independent and attained the normal normal range of the hemoglobin level.[17]

• **APPLY-PNH Trial**: This was a Phase 3 trial meant for patients with PNH who were transfer from C5 inhibitors because of inefficiency. Compared to persistent C5 inhibition,

iptacopan proved to have better haemolysis control and reduced fatigue and enhanced quality of life.[16]

On the other hand, Danicopan also known as ALXN2040 is an oral Factor D inhibitor.[13] As mentioned earlier, danicopan prevents Factor D, which in turn inhibits the formation of the alternative pathway C3 convertase that means that danicopan acts at a different step than eculizumab.[12] Several clinical trials have established that danicopan when administered in conjunction with eculizumab results in a substantial reduction in the haemolysis of PNH patients particularly those with suboptimal response to the former.[15]

## CLINICAL EFFICACY AND SAFETY OF IPTACOPAN AND DANICOPAN

Different clinical trials that have been undertaken on iptacopan show that it is effective.[18] Moreover, iptacopan was shown to reduce lactate dehydrogenase (LDH), a marker of haemolysis as well as improve the haemoglobin levels of PNH patients to levels that are equivalent to the current management therapies in the Phase 2 trial with a similar safety profile of the therapy. These results were similarly evident in the Phase 3 APPOINT-PNH trial, which established that iptacopan is capable of controlling hemolysis and improving the patients' condition, including attaining the state of transfusion independence. However, this is also true with other agents, where iptacopan has been demonstrated as a monotherapy useful as an oral agent instead of intravenous C5 inhibitors.[17]

Likewise, danicopan has been examined in patients with inadequate response to C5 inhibition together with eculizumab.[13] The Phase 2 study findings showed that danicopan helps to decrease breakthrough hemolysis and increase the levels of hemoglobin enabling eculizumab dose attenuation.[12] Concerning the safety profile, moderate to severe adverse events were rare while the majority of them were considered to be mild to moderate in severity.[15]

## CONCLUSION

Iptacopan and danicopan are expected to have a large impact on the therapeutic response of PNH in the near future. The use of these agents in oral formulations responds to a need for better and more convenient ways to have better outcomes, less fatigue, fewer transfusions, and better health in general. In addition, these drugs work farther upstream of C5 to control the complement cascade and thereby provide a more versatile mechanism of combating hemolysis potentially leading to improved patient outcomes.

The fact that iptacopan can be used as a monotherapy brings convenience in the management of patients especially when it comes to lifelong intravenous infusions. However, its efficacy while in combination with eculizumab makes it an option that can be given to patients who develop breakthrough hemolysis while on C5 inhibitors only. However, the high cost of the approach and the necessity to have further testing for safety in the future could present the issues. Further researches are awaited for even more developments to PNH treatment in the future since best treatments for every patient with this condition should be achieved.

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