

Comprehensive approach to paroxysmal nocturnal hemoglobinuria for the correct identification of patients who may benefit from switching from iC5 to iCP – expert consensus opinion

Abordaje integral de la hemoglobinuria paroxística nocturna para una correcta identificación de los pacientes que podrían beneficiarse del cambio de tratamiento de iC5 a iCP – consenso de opinión de expertos

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Abstract

Introduction: Paroxysmal nocturnal hemoglobinuria is a rare disease characterized by hemolytic anemia predominantly intravascular and cytopenias. Complement terminal C5 inhibitors (C5i) have significantly altered the treatment landscape. **Objective:** To facilitate the identification of patients with suboptimal response to C5i secondary to anemia and/or fatigue who may benefit from a therapeutic switch to proximal complement inhibitors (CPi). **Material and methods:** Narrative review with a collaborative methodology based on the clinical opinion of paroxysmal nocturnal hemoglobinuria experts, supported by scientific evidence. **Results:** First, diagnostic and treatment monitoring tests, differences between intravascular and extravascular hemolysis, and the utility of cytometric studies are detailed. A questionnaire for patients is proposed to identify the persistence of symptoms. Finally, the consequences of persistent anemia and/or chronic hemolysis are reviewed, along with recommendations for managing iron overload. **Conclusions:** Although C5i improves survival, treatment response is often suboptimal, which affects patients' quality of life. This document provides tools to identify patients with clinically significant hemolysis who may benefit from an CPi.

Keywords: Paroxysmal nocturnal hemoglobinuria. Intravascular hemolysis. Extravascular hemolysis. Proximal complement inhibitors. Erythroid clone. Iron overload.

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Resumen

Introducción: La hemoglobinuria paroxística nocturna es una enfermedad infrecuente que cursa con anemia hemolítica de predominio intravascular y citopenias. Los inhibidores de la fracción terminal C5 del complemento (iC5) supusieron un cambio radical en el tratamiento. **Objetivo:** Este documento pretende facilitar la identificación de pacientes con respuesta su-bóptima a iC5 por persistencia de anemia o fatiga que podrían beneficiarse del cambio terapéutico a inhibidores del complemento proximales (iCP). **Material y método:** Revisión narrativa con metodología colaborativa basada en la opinión clínica de expertos en hemoglobinuria paroxística nocturna, apoyada en evidencia científica. **Resultados:** Primero se detallan las pruebas que se deben realizar en el momento del diagnóstico y durante el tratamiento, las diferencias entre hemólisis intravascular y extravascular, y la utilidad del estudio citométrico. Se propone un cuestionario para los pacientes que permite identificar la persistencia de síntomas. Por último, se revisan las consecuencias de la persistencia de anemia o hemólisis crónica, así como las recomendaciones de manejo de la sobrecarga férrica. **Conclusiones:** A pesar de que los iC5 mejoran la supervivencia, la respuesta al tratamiento frecuentemente es subóptima, lo que afecta a la calidad de vida de los pacientes. Este documento aporta las herramientas para identificar pacientes con hemólisis clínicamente significativa que podrían beneficiarse de un iCP.

Palabras clave: Hemoglobinuria paroxística nocturna. Hemólisis intravascular. Hemólisis extravascular. Inhibidores del complemento proximales. Clon eritroide. Sobrecarga férrica.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal, nonmalignant, acquired disorder of pluripotent hematopoietic stem cells in which these cells acquire a somatic mutation in the PIG-A gene that results in a total or partial deficiency in the expression of membrane proteins anchored through glycosylphosphatidylinositol (GPI) molecules. This mutation renders these cells and their progeny – particularly erythrocytes – susceptible to the action of the complement system, leading to intravascular hemolysis (IVH). For clonal expansion of these cells to occur, a variable degree of bone marrow failure must coexist, which explains why PNH is closely linked to aplastic anemia.¹

It is a rare and severe disease with a heterogeneous course, ranging from spontaneous remissions to the development of bone marrow aplasia or myeloid neoplasms, or both. In the absence of treatment, affected patients have higher morbidity and mortality vs the general population of the same age and sex.¹

Although the typical clinical presentation consists of nonimmune hemolytic anemia, thrombosis, and cytopenias secondary to bone marrow failure, persistent IVH leads to symptoms related to nitric oxide (NO) depletion, such as dysphagia, abdominal pain, pulmonary hypertension, and erectile dysfunction. In addition, it causes hemoglobinuria and renal injury, leading to acute kidney disease that, if persistent, may progress to chronic kidney disease (CKD).² Among these manifestations, fatigue should be highlighted as particularly debilitating, significantly affecting quality of life, daily activity, and work productivity.³

The approval of the first inhibitor of the terminal complement fraction C5 (C5 inhibitor [C5i]) in 2007 represented a radical shift in the natural history of PNH,⁴ marking a turning point in the management of these patients by impacting not only clinical outcomes – improving anemia and transfusion dependence, renal and pulmonary function, reducing thrombotic risk, and enhancing quality of life – but also survival, which has become comparable to that of the general population within the same age range.^{4,5} However, the erythroid response is not uniform and is not always complete, with persistent anemia and fatigue in a high proportion of patients, sometimes due to residual IVH, although in most cases it is related to C3d-mediated extravascular hemolysis (EVH),⁶⁻⁹ a secondary effect of C5i. Bone marrow failure and other factors, such as CKD, should always be ruled out as causes of inadequate response.

The development of proximal complement inhibitors (CPI) has enabled, in many cases, complete erythroid recovery or, at least, recovery to the extent permitted by residual bone marrow function.¹⁰⁻¹²

The study endpoints defined by the expert panel to develop this document were:

- To clarify concepts and differences between EVH and IVH in patients with PNH on CPI.
- To assist in assessing the degree of PNH control in patients receiving C5i, both clinically and analytically, identifying those with a suboptimal response who may benefit from switching to proximal CPI.
- To expand knowledge on clonal size control by flow cytometry, as evaluation of the erythrocyte clone in

patients treated with C5i and CPi determines treatment efficacy.

- To provide guidance on the most appropriate follow-up for patients with PNH receiving either C5i or CPi.
- To inform about long-term complications associated with persistent EVH in patients treated with C5i.

Method

This work corresponds to a consensus document structured following a narrative review and developed by a group of clinical experts in PNH, with the aim of generating educational and informative material for healthcare professionals who are not specialists in this condition. It is based on clinical practice and expert opinion, supported by the available scientific literature and developed through a collaborative methodology.

This work is not based on a systematic review nor does it include statistical analyses. However, it reflects the accumulated experience of clinical experts and provides a practical perspective supported by the available evidence.

The expert panel consisted of seven professionals with clinical experience in the diagnosis and management of PNH, from different national hospital centers and specialized units, including hospitals from the main regions of Spain. This geographic diversity allowed the inclusion of different regional perspectives, enriching the analysis. The selection of experts was based on their clinical and scientific trajectory in this disease, as well as their different professional roles within the field of hematology, ensuring broad coverage of approaches and experiences. All of them have participated in expert committees, previous publications, and the care of patients with PNH.

The content was developed between March and December 2024 through a mixed process combining face-to-face working sessions and individual development:

- In an initial phase, during an in-person meeting, the key sections to be addressed in the document and their hierarchy were agreed upon, including all the necessary information for proper identification of patients with PNH.
- The proposed contents included: diagnostic test panels, follow-up algorithm, differentiation between IVH and EVH, physician – patient communication, data on iron overload, and long-term anemia.

- Each expert drafted one or more sections according to their field of expertise, performing an exhaustive literature review and focusing the content based on their clinical practice.
- Individual contributions were reviewed and discussed by the experts in an online meeting in which the collected information was contrasted according to each professional's experience, and all recommendations (with at least 80% consensus among experts) were incorporated into the final document.
- In a final joint in-person meeting, the definitive document was presented and fully validated by consensus.

Recommendations were grouped into 3 sections:

- 1) tests and assessments for diagnosis and follow-up,
- 2) physician – patient communication, and
- 3) identification, consequences, and management of secondary complications of anemia and chronic hemolysis.

Results

Tests and assessments for diagnosis and follow-up

INITIAL EVALUATION OF THE PATIENT WITH PNH (PRETREATMENT)

Clinical suspicion of PNH requires diagnostic confirmation by high-sensitivity flow cytometry and an appropriate patient evaluation, which includes a complete examination and a broad panel of tests aimed particularly at assessing hemolysis, the degree of bone marrow failure, and damage to different target organs to establish treatment indication.¹³⁻¹⁸

Table 1 summarizes the tests to be performed at diagnosis, classified according to their level of recommendation.

In addition to laboratory evaluation, the following radiologic assessment adapted to the patient's clinical context and aimed at detecting potential disease complications is recommended:¹³

- Doppler echocardiography when pulmonary hypertension is suspected, with further evaluation by pulmonary computed tomography (CT) angiography or cardiac catheterization if signs are detected.
- Abdominal Doppler ultrasound to detect thrombosis in hepatic, splenic, and mesenteric territories, with CT angiography or abdominal magnetic resonance imaging (MRI) considered optional.

Table 1. Recommended laboratory and imaging tests for the diagnosis and follow-up of patients with paroxysmal nocturnal hemoglobinuria¹³

Tests	Diagnosis and follow-up of PNH
Required	Complete blood count with reticulocytes
	Biochemistry including LDH and fractionated bilirubin
	Renal function assessment in serum and 24-hour urine
	Haptoglobin
	Direct antiglobulin test (Coombs test)
	Iron profile, vitamin B12, and folic acid
	Bone marrow study including cytogenetic and molecular analysis*
	PNH clone in leukocytes and erythrocytes
Optional	Free plasma Hb (if available)
	Hemosiderinuria and/or confirmation of hemoglobinuria due to discrepancy between urinalysis and sediment
	ProBNP or NT-proBNP
	Thrombophilia studies and D-dimer
	Erythropoietin levels
	HLA typing
Recommended	Echocardiogram
	MRI
	Hepatic Doppler ultrasound

*Recommended in all cases and mandatory if other associated cytopenias are present.

Hb: hemoglobin; HLA: human leukocyte antigen; PNH: paroxysmal nocturnal hemoglobinuria; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; ProBNP: pro-brain natriuretic peptide; MRI: magnetic resonance imaging.

Based on available scientific evidence.

- Cranial MRI with CT angiography according to radiologic indication in the presence of neurologic symptoms, to rule out thrombosis.
- MRI with hepatic iron assessment in heavily transfused patients and MRI with renal iron assessment in patients with signs of CKD.

FOLLOW-UP OF PATIENTS WITH PNH (POSTTREATMENT)

Among the available tests for patient evaluation during disease follow-up are biomarkers for monitoring complement inhibitor therapy, classical laboratory parameters mainly aimed at assessing the type and

intensity of hemolysis, and monitoring of the PNH clone by flow cytometry.^{13,15}

Laboratory parameters and algorithm for hemolysis evaluation

In the absence of treatment, classic PNH is characterized by IVH with marked elevations of lactate dehydrogenase (LDH) and consumption of haptoglobin with minimal bilirubin elevation. This IVH, in addition to causing anemia and hemoglobinuria, leads to symptoms related to smooth muscle dystonia secondary to nitric oxide depletion, such as abdominal pain, dysphagia, dyspnea, and erectile dysfunction, and is also associated with an increased risk of thrombosis.^{13,19,20} IVH decreases or disappears except during episodes of breakthrough hemolysis, in which it reappears abruptly together with the previously described symptoms, associated with a marked increase in LDH levels and a decrease in hemoglobin. Intercurrent breakthrough IVH may be attributed to suboptimal complement inhibition, either due to pharmacokinetic causes^{20,21} (low levels of the inhibitory drug) or pharmacodynamic causes, due to increased complement activation secondary to triggering events such as infection or inflammation.^{15,20,22-24}

Treatment of patients with PNH using C5i produces another type of iatrogenic hemolysis that, unlike IVH, is predominantly extravascular. C5 blockade leads to the deposition of C3 fragments (particularly C3d) on the membrane of GPI-deficient erythrocytes due to persistence of the C3 activation loop and deficiency of CD55.^{6,23,24}

These opsonized erythrocytes become targets for macrophages of the reticuloendothelial system, leading to EVH. The clinical impact is variable and unpredictable because the amount of C3 fragment deposition on erythrocytes does not correlate with levels of hemoglobin dependence or transfusion requirements.²⁴ In these patients, persistent reticulocytosis is observed (if adequate bone marrow reserve is present).^{21,23} with minimal elevation of LDH, but with an increase in indirect bilirubin due to intracellular hemoglobin degradation.^{8,23} In the absence of hemoglobinuria, symptoms derived from smooth muscle dystonia, or thrombosis. This iatrogenic EVH may reduce the clinical benefits of C5i. In fact, nearly 80% of patients treated with C5i continue to have anemia, including approximately one third who do not achieve transfusion independence.⁷⁻⁹ This has been an important driver for improving the performance

of C5i and for the development of proximal complement inhibitors.¹⁰⁻¹²

Figure 1 illustrates an algorithm for the evaluation of patients with clinical PNH receiving complement inhibitors. It details the laboratory parameters that allow assessment of disease activity and treatment response, as well as monitoring hemolysis, both IVH and EVH.^{13,14,17} Other biomarkers that could help in the clinical management of patients with PNH, such as AH50 or CH50, require complex methodologies that are not always available, and therefore their applicability in clinical practice remains limited.¹⁵

MONITORING OF GPI-DEFICIENT CELL CLONE (PNH CLONE)

Follow-up of patients with PNH involves integrating clinical-biological evaluation with clone monitoring.^{18,25} The frequency of assessments depends on symptoms, the degree of hemolysis, clone size, and administered treatment.^{12,15,17,26}

In follow-up studies, it is necessary to evaluate clone size (in leukocytes and erythrocytes) compared with previous measurements and to include this assessment in the flow cytometry report, always indicating, whenever possible, the interval for the next study. Analysis of the erythroid clone has proven to be a useful tool for monitoring the efficacy of proximal complement inhibitor therapy, allowing rapid and objective assessment.^{15,17} The size of the erythroid clone is affected by both IVH and EVH, and a greater increase in clone size is expected when proximal inhibitors are administered, as they block both types of hemolysis, unlike terminal inhibitors, which only control the intravascular mechanism.²⁵ These objective results, together with their rapid evaluation by flow cytometry, make this test a preferred option for assessing the efficacy of complement inhibitor drugs, especially proximal agents.

Overall, monitoring of the PNH clone and hemolysis parameters in untreated patients should be performed every 6 months within the first 2 years after detection, with subsequent annual assessments if the disease remains stable.^{15,16,26} If treatment with CPi has been initiated or modified, the frequency of monitoring should be increased to every 2-6 months, adapting the interval according to clinical status, clone evolution, and response to the administered inhibitor.^{13,15,16,26} Finally, the clone should be reassessed whenever clinical or laboratory changes suggestive of disease

activity, progression, or modification of inhibitor therapy are observed.^{13,15,26}

In patients with hemolysis, those receiving transfusions, or in the absence of bone marrow failure, evaluation of PNH clone size in reticulocytes is particularly useful, as these cells are not affected by hemolysis or transfusions, unlike erythrocytes.¹⁷

Table 2 details the laboratory and radiologic tests, as well as their recommended frequency, for the follow-up of patients with PNH on CPi.^{13,15,16,26}

Physician-patient dialogue

As important as laboratory parameters is speaking with patients and exploring their symptoms, both at the time of diagnosis and after initiation of C5i. It is necessary to correctly identify patients who are not adequately controlled with C5i by evaluating a series of questions together with different laboratory parameters (such as hemoglobin level), as these patients may benefit from switching to proximal CPi.¹⁰ For this purpose, it is ideal to conduct a structured interview with pre-defined questions that explore all clinical aspects of the disease.

For the selection of these questions, we can rely on those used in classic patient-reported quality-of-life questionnaires, such as the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) and the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-C30 (EORTC QLQ-C30), which are used in other conditions and, although they include items not relevant for patients with PNH, have also been validated in this disease.²⁷ We may also use newer, more specific questionnaires for PNH, such as the Paroxysmal Nocturnal Hemoglobinuria Symptom Questionnaire (PNH-SQ), which assesses the presence, severity, and daily variation of 10 PNH-related symptoms and may be useful in clinical trials.²⁸

Recently, a new instrument (Quality-of-Life Questionnaire, QLQ) has been developed in phase III, specific for aplastic anemia and PNH (QLQ-AM/PNH), as a patient-reported outcome measure in these diseases, although psychometric evaluations are still ongoing.²⁹ This tool includes 54 questions and may be used in clinical trials and studies of the disease.³⁰ The QLQ-AM/PNH aims to better adapt to the needs of patients with these ultra-rare diseases, with good internal consistency already validated.³⁰

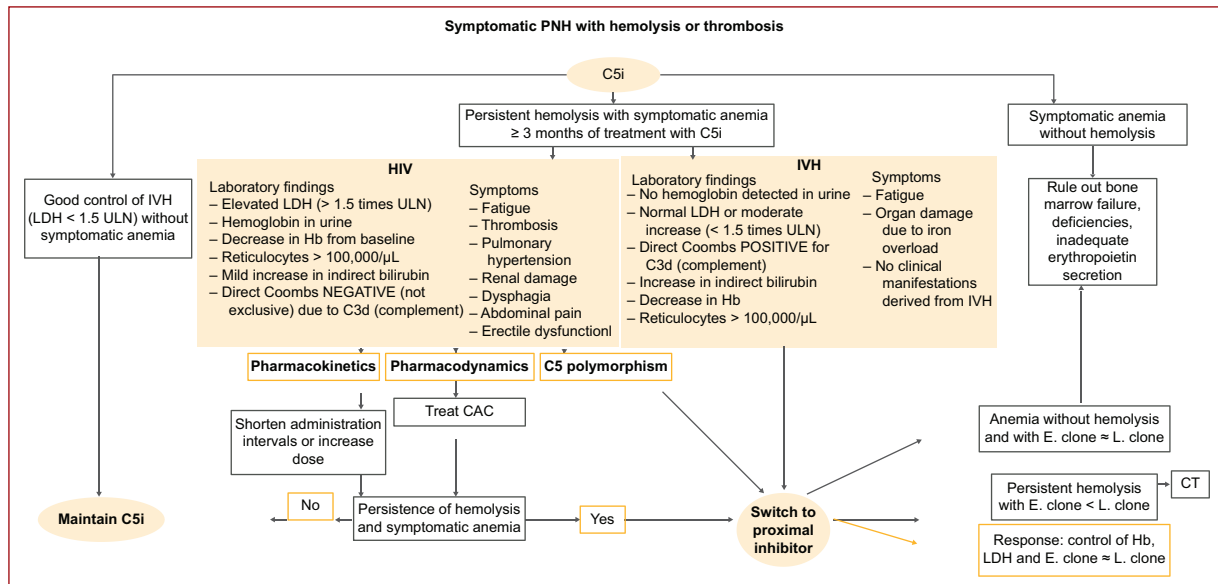


Figure 1. Algorithm for the evaluation of patients with clinical paroxysmal nocturnal hemoglobinuria (PNH) on C5i therapy (adapted from Villegas et al.,¹³ Fattizzo et al.,¹⁴ Kulasekararaj et al.,¹⁵ Bodo et al.,¹⁹ Kulasekararaj et al.,²² and Szlendak et al.²⁶). CAC: complement amplifying condition; E. clone: erythroid clone; L. clone: leukocyte clone (neutrophils and monocytes); CT: clinical trial; Hb: hemoglobin; EVH: extravascular hemolysis; IVH: intravascular hemolysis; C5i: complement component 5 inhibitor; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Table 2. Monitoring of C5i therapy

Monitoring schedule	C5i	Proximal C5i
At each analytical check (first 4 weeks)	Complete blood count with reticulocytes	Complete blood count with reticulocytes
	Biochemistry including LDH and fractionated bilirubin	Biochemistry including LDH and fractionated bilirubin
	Urinary Hb (if available)	D-dimer
	D-dimer	DAT for C3d* until negativization
At least every 3 months	DAT for C3d*	Renal function study in serum and 24-hour urine
	Renal function study in serum and 24-hour urine	Erythroid PNH clone until equal to leukocyte clone
At least every 6 months	Iron metabolism	Iron metabolism
	Folic acid and vitamin B12 levels	PNH clone [†] (leukocytes and erythrocytes)
	PNH clone [†] (leukocytes and erythrocytes)	-
At least every 12 months	Abdominal Doppler ultrasound	Abdominal Doppler ultrasound
	Echocardiogram	Echocardiogram
	NT-proBNP	NT-proBNP
	PNH clone [†] (leukocytes and erythrocytes) if stable disease	PNH clone [†] (leukocytes and erythrocytes) if stable disease
	MRI	MRI if elevated ferritin

*Assessment of extravascular hemolysis.

[†]Flow cytometry.

Hb: hemoglobin; PNH: paroxysmal nocturnal hemoglobinuria; C5i: complement inhibitors; C5i: C5 inhibitors; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; DAT: direct antiglobulin test (Coombs test); MRI: magnetic resonance imaging.

Adapted from Villegas et al.,¹³ Kulasekararaj et al.,¹⁵ Patriquin et al.,¹⁶ and Szlendak et al.²⁶

Based on the questions included in the QLQ-AA/PNH³⁰ and other questionnaires, we propose a questionnaire (Table 3) that includes specific aspects related to fatigue and anemia, excluding symptoms associated with other cytopenias. It is essential to specifically explore fatigue, as it is a central symptom in PNH that significantly affects overall well-being, interfering with daily activities and work productivity, and is present not only in untreated patients but also in a significant proportion of those receiving C5i.^{9,31} In addition, assessment of neurological symptoms is included, as fatigue affects cognitive function, particularly concentration and memory; therefore, questions should address all these aspects.³¹ The final block of questions explores symptoms related to hemolysis, both IVH and EVH. This questionnaire may be administered during the medical consultation or provided beforehand for patient review and subsequent discussion with the physician.

Identification, consequences, and management of complications of persistent anemia and chronic hemolysis
Long-term effects of anemia

There is limited evidence on how chronic anemia affects patients with PNH and the complications it triggers.^{9,31-34} Anemia results in a reduced capacity for oxygen transport to tissues, which over time leads to multiorgan involvement, including cardiac injury, cognitive impairment, and renal failure.^{32,33,35} In patients with non-hematologic diseases, the association between anemia and an increased risk of mortality and hospitalization due to cardiovascular complications is well established, particularly in patients with CKD or heart failure.³⁶⁻³⁸ By increasing cardiac output to compensate for reduced oxygen delivery to peripheral tissues, anemia leads to left ventricular hypertrophy as well as arterial remodeling, a process that results in compensatory intimal thickening and arteriosclerosis. The association between anemia and left ventricular hypertrophy is well established in patients with CKD, regardless of whether they are undergoing dialysis.³⁸ In patients with heart failure, chronic anemia is a predictor of clinical deterioration and mortality.³⁶ This is particularly relevant in older patients, in whom anemia increases frailty and, consequently, the risk of falls and fractures.³⁷ Furthermore, chronic anemia is associated with persistent fatigue, which negatively affects quality of life, worsens mood, and reduces daily activity.^{9,31,33} Even

Table 3. Questionnaire for symptomatic evaluation of patients with paroxysmal nocturnal hemoglobinuria

Asthenia	Have you felt tired lately?
	Have you had difficulty getting out of bed?
	Do you need to rest during the day?
	Do you have difficulty standing for long periods?
	Do you have difficulty climbing stairs?
	Have you felt exhausted for several days after exertion?
	Does this fatigue limit your ability to work?
	Does this fatigue limit your ability to maintain a normal pace of life?
	Does this fatigue limit your ability to perform more strenuous activities such as sports?
	Do you find it burdensome to ration your energy?
Neurological symptoms	Have you had difficulty concentrating?
	Have you felt irritable?
	Do you feel a sense of dizziness or confusion?
	Have you experienced memory loss?
Other symptoms	Have you experienced shortness of breath at rest?
	Have you experienced shortness of breath when climbing stairs?
	Have you noticed darker or reddish urine?
	Have you noticed yellowing of your skin?
	Have you had unexplained colicky abdominal pain or chest pain?
	Have you had difficulty swallowing food or liquids?
	Have you experienced erectile dysfunction?

All questions have the following response options: never, sometimes, almost always, or always.
Based on available scientific evidence.

patients adequately treated with C5i continue to experience chronic fatigue, leading to impaired quality of life compared with the reference population.^{31,33} A real-world study in patients treated with C5i found that 35% of respondents presented anemia-related symptoms, such as fatigue, dyspnea, headache, difficulty concentrating, and sleep disturbances.⁹ In a study of transfusion-dependent patients with another hemolytic anemia, beta-thalassemia, pre-transfusion hemoglobin levels < 9 g/dL were associated

with a 9.3% increase in mortality (70% of deaths were due to vascular causes), compared with those with levels > 10.5 g/dL.³⁹ Similarly, mortality is significantly higher when hemoglobin is < 10 g/dL, with cardiac involvement accounting for a considerable proportion of deaths.³⁹

From these data, it can be extrapolated that correcting anemia due to EVH in patients with PNH should be a therapeutic goal, both to improve quality of life and to reduce complications.

Complications derived from chronic hemolysis

When discussing complications of chronic hemolysis, it is necessary to differentiate between those derived from IVH and those derived from EVH.

The differences observed between EVH and IVH, represented in **figure 2**, are as follows:

- Complications derived from IVH:^{1-3,31} these are due to the release of intravascular hemoglobin, subsequent NO depletion, endothelial damage, increased thrombotic risk, and renal clearance of free hemoglobin. These complications lead, in the long term, to pulmonary hypertension and CKD. Pulmonary hypertension, in turn, causes dyspnea disproportionate to the degree of anemia and cardiac dysfunction. CKD may progress to the need for dialysis and significantly reduces patient survival. Regarding thrombosis, although its origin in PNH is multifactorial, the release of free hemoglobin and NO depletion contribute to a prothrombotic state, which is the main cause of death in untreated patients with PNH. Treatment with CPi (C5i and CPi) aims to eliminate complications derived from IVH.
- Complications derived from EVH:^{6,8,24} these occur in patients on C5i. C3d-opsonized erythrocytes are phagocytosed by splenic and hepatic macrophages.⁶ Unlike IVH, hemoglobin does not circulate freely or undergo renal excretion; therefore, hemoglobinuria and NO depletion do not occur. Due to hemoglobin metabolism, there is an increase in bilirubin, predominantly in the indirect fraction. The mechanisms involved are illustrated in **figure 3**.⁴⁰

Chronic EVH represents a sustained erythropoietic stimulus, which is responsible for secondary iron overload detected in treated patients, unlike untreated patients, in whom iron deficiency due to hemoglobinuria predominates.⁴¹⁻⁴³ Iron overload may lead to organ damage, particularly affecting the liver, although other organs such as the kidneys and heart may also be involved. This iron overload may be clinically significant

and require chelation therapy, similar to what occurs in patients with other chronic hemolytic anemias.⁴² Of note, the use of chelating agents may cause renal damage,⁴¹ in addition to adverse effects such as abdominal pain, diarrhea, and skin rash.

Patients with chronic anemia often present decreased bone density and develop early osteoporosis.⁴⁴ Although erythropoietic expansion has been identified as one of the main triggers, it is not the only cause, since in older patients without underlying disease, anemia itself is a risk factor for bone fractures.⁴⁴ The InCHIANTI study demonstrated that lower hemoglobin levels and anemia were associated with reduced bone density, particularly in cortical bone.⁴⁵ Although bone density impairment has not been specifically studied in patients with PNH, in those receiving long-term C5i therapy who present chronic EVH, it represents a potential complication that should be considered, especially in older adults and postmenopausal women.

Iron overload

Iron deficiency is associated with the development of renal siderosis; the kidney becomes damaged by the excretory burden of IVH products.⁴¹⁻⁴³ In these patients, hepcidin – the main regulator of iron metabolism through control of iron uptake (and storage) – is decreased in response to increased erythropoiesis; however, renal iron loss prevents its accumulation.⁴¹⁻⁴³ Therefore, in these patients it is necessary to monitor iron profile parameters and reticulocytes, bearing in mind that iron deficiency may aggravate anemia.

In patients with PNH on C5i therapy, IVH is largely controlled, preventing the passage of free hemoglobin to the kidney; consequently, renal siderosis and iron loss do not occur.⁴¹⁻⁴³ In fact, the variable degree of EVH makes iron metabolism more similar to that observed in chronic extravascular hemolytic anemias, such as hereditary spherocytosis and thalassemias.^{46,47} This results in a shift in iron metabolism, from iron deficiency to increased iron stores, with a risk of visceral hemosiderosis due to increased intestinal iron absorption secondary to decreased hepcidin levels.^{42,43} This phenomenon is well documented in the literature on PNH,^{41-43,46,47} although no published data establish in detail the underlying pathophysiologic mechanisms or evaluate the impact of hepatic iron overload risk in patients treated with CPi. There is evidence supporting the importance of monitoring hepatic iron overload by MRI rather than ferritin levels in these patients,⁴¹⁻⁴³ as well as changes in

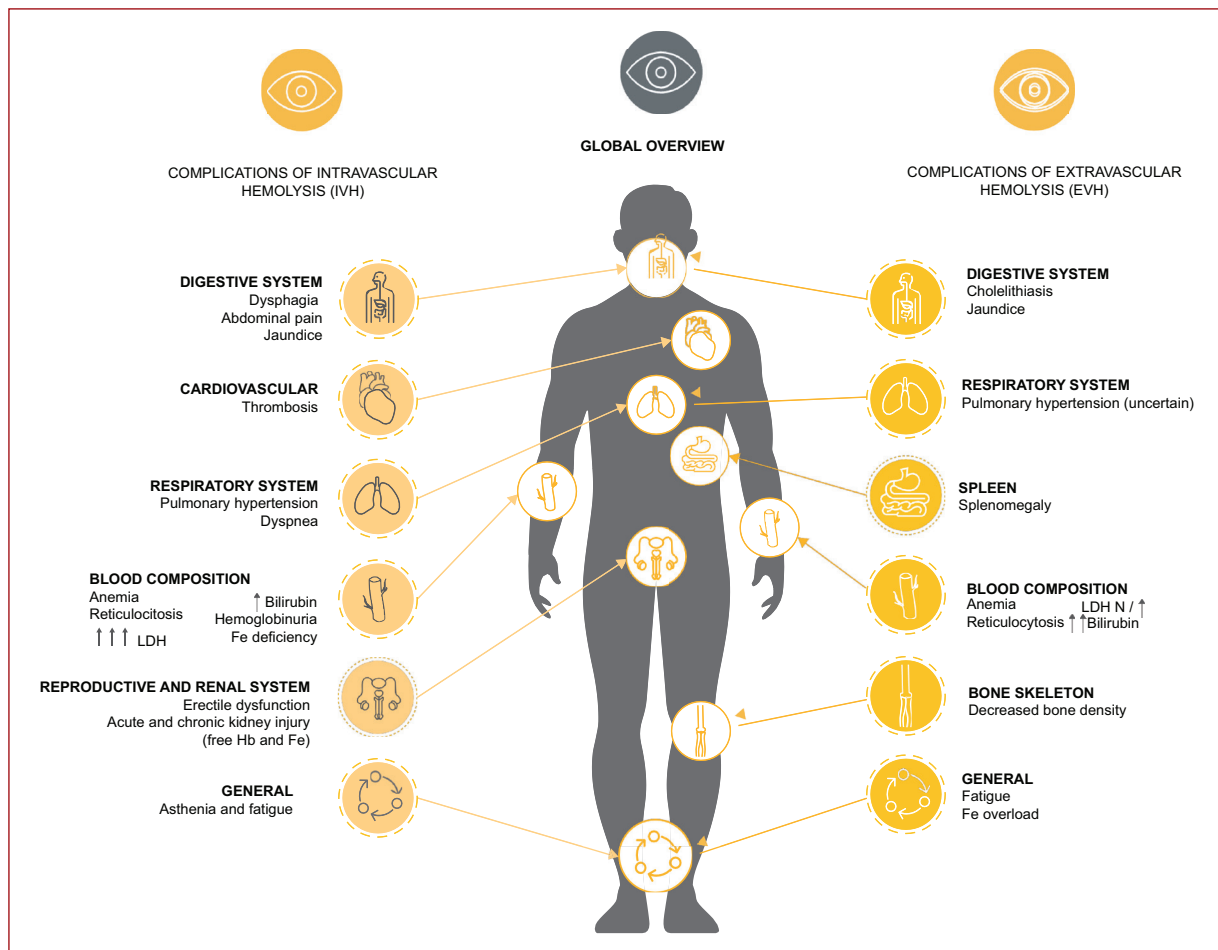


Figure 2. Comparative diagram of long-term complications of intravascular and extravascular hemolysis (*adapted from scientific evidence*). Fe: iron; Hb: hemoglobin; LDH: lactate dehydrogenase; N: normal.

iron metabolism patterns before initiation of C5i therapy.^{42,43} There is no information regarding the effect of proximal CPi on iron overload; however, since they do not induce EVH, it can be hypothesized that they would prevent iron overload due to erythropoietic stimulation. Therefore, in patients on anticomplement therapy (specifically C5i), serum ferritin levels should be monitored and hepatic and cardiac MRI should be performed, using thalassemia models as a reference.^{48,49} Table 4 summarizes normal and pathological values obtained by hepatic and cardiac MRI, as well as the recommended frequency of monitoring. For initiation and follow-up of chelation therapy, similar strategies to those used in thalassemia are recommended.^{48,49}

Discussion

We consider it essential for physicians treating patients with PNH to understand how to perform

appropriate follow-up, how to identify patients with a suboptimal response, when to suspect that lack of response is due to EVH, and how to detect it.

According to national PNH guidelines,¹³ first-line therapy in patients with hemolytic PNH (LDH > 1.5 times the upper limit of normal) and signs of high disease activity remains C5i,^{4,5} which have improved clinical outcomes and achieved survival comparable to that of the general population in patients without significant bone marrow failure.^{4,5} However, the erythroid response rate to C5i is variable and not always complete, partly due to bone marrow failure or, more frequently, due to the development of C3d-mediated EVH.⁶⁻⁹ Approximately 80% of patients treated with C5i remain anemic, including those who are transfusion dependent.⁷⁻⁹

Proximal CPi are drugs that inhibit the complement system at the level of C3 (pegcetacoplan¹⁰) or upstream in the cascade (iptacopan at factor B¹¹, danicopan at factor D¹²), thereby controlling IVH without inducing

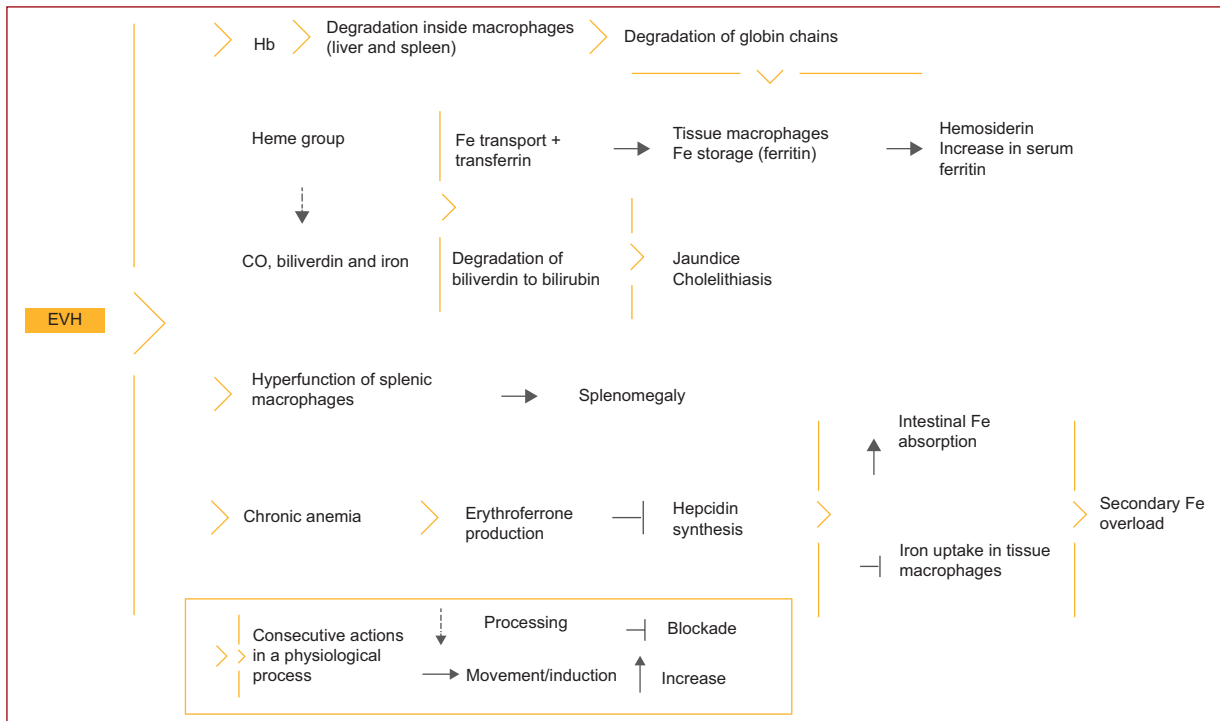


Figure 3. Diagram of complications derived from extravascular hemolysis (EVH) (adapted from Dingli et al.,⁹ Petz and Garratty,⁴⁰ and Risitano et al.).⁴² CO: carbon monoxide; Fe: iron; Hb: hemoglobin.

EVH by preventing C3d deposition on erythrocyte membranes. This explains the high degree of erythroid response and clinically significant effects on fatigue observed with these agents compared with C5i.¹⁰⁻¹² Similarly, awareness should be raised regarding the long-term complications of persistent anemia and chronic hemolysis. The objective of this document is to help identify patients who may benefit from switching therapy from a C5i to a proximal CPi.

Regarding the tests and assessments that should be performed in patients, both at diagnosis and during follow-up after treatment initiation, these must include monitoring of the PNH clone in leukocytes and erythrocytes, along with tests for evaluating hemolysis (both intravascular and extravascular), bone marrow failure, and assessment of the various organs that may be affected at baseline or during disease progression.^{13,15,16,25} In most patients, clones persist over time, although both expansion and regression may be observed.¹⁸ The emergence of PNH clones and their potential progression during disease evolution highlight the importance of adequate clone monitoring to improve clinical management.¹⁸ Furthermore, erythroid clone size is influenced by both IVH and EVH, and an increase in clone size is expected when response to CPi is

effective, making its assessment essential during follow-up in patients receiving this type of therapy.^{13,15}

Overall, in patients with PNH not receiving anticomplement therapy, laboratory tests and PNH clone monitoring should be performed every 6 months within the first 2 years, followed by annual assessments if the patient remains clinically stable.^{13,15,16,25} The frequency should be increased when CPi therapy is initiated or modified, and reassessment should always be performed when clinical or laboratory findings suggest disease progression.^{13,15,16,25}

In addition to laboratory parameters and PNH clone monitoring, imaging studies may be necessary depending on the patient's clinical context and emerging complications.¹³

The second aspect addressed in this document focuses on physician–patient dialogue. A study involving 255 patients with PNH reported more frequent and severe symptoms than those perceived by their hematologists, emphasizing the importance of improving physician–patient communication to optimize clinical management of this disease.⁵⁰ This demonstrates that suboptimal response cannot be assessed solely through laboratory parameters. To achieve a comprehensive and objective evaluation, various quality-of-life

Table 4. Assessment of iron overload by hepatic and cardiac magnetic resonance imaging

Hepatic MRI*	
< 1.8 mg Fe/g liver tissue	Normal range in healthy population
1.8-3.2 mg Fe/g liver tissue	Minimal iron overload, borderline normal. Lower limit for chelation therapy
3.2-7.0 mg Fe/g liver tissue	Mild to moderate iron overload. Optimal range for chelation therapy
7.0-15.0 mg Fe/g liver tissue	Increased risk of complications associated with hemosiderosis
> 15.0 mg Fe/g liver tissue	High risk of cardiac disease and premature death
Frequency of hepatic monitoring	
Patients within optimal range (3-7 mg Fe/g liver tissue)	Every 1-2 years
Patients > 7 mg Fe/g liver tissue	≥ 1 per year, or more frequently
Cardiac MRI (T2 sequence)	
≥ 20 ms	No evidence of cardiac iron, low risk of hemosiderotic cardiomyopathy
10-19 ms	Mild to moderate iron deposition, low risk of hemosiderotic cardiomyopathy
6-9 ms	Severe cardiac iron overload. Risk of HF increases markedly as T2 decreases
< 6 ms	50% risk of developing HF within 1 year (without intensification of chelation therapy)
Frequency of cardiac monitoring	
T2 > 20 ms (no cardiac iron, low risk of HF)	Every 2 years
T2 10-19 ms (low to moderate cardiac iron)	Annually
T2 < 10 ms (high cardiac iron)	Every 6 months

*Conversion factor: 1 mg Fe = 17.889 μ mol.
 HF: heart failure; MRI: magnetic resonance imaging.
 Adapted from *Taher et al.*⁴⁸ and *Wood.*⁴⁹

questionnaires have been reviewed, including nonspecific instruments used in PNH studies (FACIT-Fatigue and EORTC QLQ-C30²⁷) and disease-specific tools (PNH-SQ²⁸ and QLQ-AM/PNH).^{29,30} Based on these questionnaires, we propose a set of questions with particular focus on fatigue as a key symptom, neurological involvement, and other hemolysis-related symptoms, to facilitate a structured clinical interview. This approach aims to identify patients with inadequate disease control and to assess their evolution to determine those who may benefit from a therapeutic switch, thereby optimizing clinical management.

In the final section of this work, we address the consequences and management recommendations for complications secondary to anemia and chronic hemolysis. It is noteworthy that there is limited evidence in the scientific literature regarding the impact of chronic extravascular anemia in patients with PNH, as well as its associated complications.^{33,34} It is well documented that patients treated with C5i continue to experience fatigue due to persistent anemia,^{9,31} and that iron

metabolism shifts from iron deficiency at diagnosis to iron overload secondary to chronic erythropoietic stimulation, which over time may lead to organ damage (hepatic, cardiac, and renal).^{9,31,41-43} However, in patients with PNH, the degree of cardiac or renal involvement due to chronic anemia has not been extensively or systematically described, as it has in other oncologic or non-hematologic diseases.^{35-38,44} Other complications, such as cholelithiasis (with or without pancreatitis), jaundice, splenomegaly, pulmonary hypertension, and osteopenia, are extrapolated from other chronic hemolytic anemias with EVH. It is important to recognize and assess these potential complications to better evaluate the possibility of therapeutic modification.

Regarding iron overload, this is a complication derived from EVH in patients on C5i, whose impact in PNH has not yet been fully documented, although it may contribute to morbidity and mortality.^{15,46} The recommendations provided in this document for its diagnosis, follow-up, and management have been extrapolated from other conditions with greater clinical

experience in iron overload management (such as hemoglobinopathies and thalassemias),^{46,47} and may be helpful in patients with PNH.

The main limitation of this work lies in the fact that it is a narrative review based on expert clinical experience and opinion, supported by the available scientific literature and developed through a collaborative methodology. Although the expert group has extensive demonstrated clinical experience in the diagnosis and management of PNH, these remain recommendations based on personal experience and literature review. Despite this methodological limitation, the proposed objectives were achieved.

Conclusions

Although treatment with C5i has enabled patients with PNH to achieve normal survival, in the absence of bone marrow failure, the response to treatment is often suboptimal, which entails long-term risks and affects patients' quality of life. This document provides tools to identify patients with a suboptimal response to C5i who present EVH, as well as organ damage secondary to persistent anemia and the development of iron overload. To this end, analytical parameters, a structured symptom-related questionnaire, and differential aspects in treatment evaluation between inhibitors acting at different levels of the complement cascade have been included.

Authors' contributions

All authors made substantial contributions to the content of the document. All authors critically reviewed the manuscript for important intellectual content, approved the final submitted version, and take responsibility for all aspects of the work. As coordinator and lead author of the study, M. Morado-Arias actively participated in manuscript drafting and in the revision of the first draft.

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Conflicts of interest

A. Contento-Gonzalo has received honoraria from Sobi, Roche, Alexion, and Novartis as an expert advisor and speaker at conferences. A.P. González-Rodríguez has received honoraria from Sobi, Novartis, and Alexion for participation as an expert advisor and speaker at conferences. A. Sempere-Talens has received honoraria from Sobi, Novartis, Roche, and Alexion for participation as an expert advisor and speaker at conferences. C. González has received honoraria from Sobi, Novartis, and Samsung for participation as an expert advisor and speaker at conferences. M. Ballesteros-Andrés has received honoraria from Sobi, Novartis, Roche, and Alexion for participation as an expert advisor and speaker at conferences. M.T. Gómez-Álvarez has received honoraria from Sobi, Novartis, Roche, and Alexion for advisory roles and speaking engagements. M. Morado-Arias has received honoraria from Sobi, Novartis, Roche, and Alexion for participation as an expert advisor and speaker at conferences. The authors declare full editorial independence in the preparation of this article.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples; therefore, it does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used for the writing or content creation of this manuscript.

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