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Cartas al director

## Biosimilar eculizumab and meningococcal meningitis: the importance of strengthening health education

Eculizumab biosimilar y meningitis meningocócica: la importancia de reforzar la educación sanitaria

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Dear Director:

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder characterized by hemolytic anemia, bone marrow failure, and frequent thrombotic events. Exact prevalence data is not available, although it has been described globally. Until 2007, treatment was symptomatic: transfusions, anticoagulants, and management of aplasia. In 2007, Eculizumab, a monoclonal antibody targeting human complement protein C5, was designated as an orphan drug for PNH. Currently, there are two biosimilars of Eculizumab authorized for PNH in Spain: Bekemv<sup>®</sup>, since April 2023, and Epysqli<sup>®</sup>, since June 2023, with the former being the most cost-effective and the one used in our hospital.

Meningococcal infection is a rare adverse effect, according to the product's prescribing information. The efficacy of vaccination in patients with complement deficiencies is not well established, and while vaccination for serogroups A, C, W, Y, and B is recommended at least 2 weeks prior to the first dose, the immune response may be suboptimal in immunocompromised patients. Therefore, it is crucial to monitor patients for early signs of meningococcal infection<sup>(1)</sup>.

We present the case of a 41-year-old male diagnosed with PNH in 2007 and treated with Eculizumab since 2013. He received Soliris<sup>®</sup> until 2023, followed by Bekemv<sup>®</sup>, with a declining clone in the latest flow cytometry assessment. A panel comprising FLAER, CD157, CD45, CD64, CD10, and CD59 was employed, revealing the presence of a PNH clone in the neutrophil (10.4%), monocyte (14.7%), and erythrocyte compartments (6.8%). Meningococcal vaccination was appropriately administered (Nimenrix<sup>®</sup>, Bexsero<sup>®</sup>). His medical history includes hospitalization in 2021 for bacteremia due to *Neisseria meningitidis*, treated with cefotaxime with a favorable outcome. On November 17, 2024, he presented to the emergency department with odynophagia, arthralgia, myalgia, vomiting, petechiae on the upper and lower extremities, and a 24-hour fever of 40°C that did not respond to paracetamol. He was transferred to the Intensive Care Unit after initiating treatment with vancomycin, cefotaxime, ampicillin, and dexamethasone. A diagnosis of meningococcal meningitis (serogroup B) was confirmed by cerebrospinal fluid analysis (Gram stain and polymerase chain reaction) and blood culture antibiotic was switched to ceftriaxone), with prerenal renal failure and coagulopathy.

In the inpatient ward, Eculizumab was reinitiated after 16 days of hospitalization, as recommended by the Hematology Department. The patient was discharged on December 8, 2024, with antibiotic prophylaxis using ciprofloxacin 500 mg daily for a year, with subsequent reassessment. Warning signs for meningococcal infection were reinforced with a multidisciplinary approach.

The adverse drug reaction (ADR) was reported from the Pharmacy Department to the Spanish System of Pharmacovigilance of Human Medicines. Causality between meningitis and Eculizumab was evaluated using the Naranjo algorithm, classifying the ADR as probable. Table 1 presents a summary of published cases in the scientific literature regarding this ADR in PNH<sup>(2-5)</sup>.

This is the first reported case of meningococcal meningitis linked to biosimilar eculizumab. Patient education on immunization updates and early symptom recognition is critical<sup>(4)</sup>, particularly given a prior episode of drug-related meningitis, as noted by Real S et al.<sup>(3)</sup>, or a delay in presenting to the Emergency Department.

The heightened susceptibility to *Neisseria meningitidis*, a Gram-negative bacterium, observed in patients undergoing C5 blockade therapy is attributed to a reduction in the formation of the membrane attack complex (MAC). Eculizumab-associated meningitis may occur despite vaccination. This raises the question of whether current patient education practices are sufficient and whether they should be improved by fostering greater patient engagement.

**Table 1.** Published clinical cases of meningitis associated with Eculizumab in PNH

Reference	Gender and age	Year of treatment initiation	Appropriate meningococcal vaccination	Year of admission	Bacterial species and serogroup	Eculizumab reintroduction	Antimicrobial prophylaxis at discharge	Previous eculizumab associated meningitis episodes	Healthcare education	Outcome
Algadoa JT et al (2012) <sup>(2)</sup>	1 woman 45 years old	2008	Yes	Not indicated	<i>Haemophilus influenzae B</i>	Not indicated	Not indicated	Not indicated	Not indicated	Recovery
Hernando Real S et al (2017) <sup>(3)</sup>	1 man 23 years old	2010	No	2011	<i>Neisseria meningitidis</i> sero- group B	Yes	Oral Penicillin V	Yes	Not indicated	Recovery
Mc Namara LA et al (2017) <sup>(4)</sup>	n=16 (n=10 HPN) Mean age: 30 years old	2008-2016	n=14 Yes n=2 No	2008-2016	<i>Neisseria meningitidis</i> *	Not indicated	Not indicated	Not indicated	Not indicated	n=1 Exitus n=15 Recovery
Nolfi-Donagan D et al. (2018) <sup>(5)</sup>	1 woman 16 years old	Not indicated	Yes	2016	<i>Neisseria meningitidis</i> sero- group B	--	--	Not indicated	Not indicated	Exitus

\*Patients with Meningitis: n=6.

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