Meningococcemia in vaccinated patient under treatment with eculizumab☆

Infección meningocócica en paciente vacunado y en tratamiento con eculizumab

The increase in susceptibility to meningococcal infections in patients with paroxysmal nocturnal haemoglobinuria and use of eculizumab amounts to 0.5 episodes/year/100 patients. We present the case of a 23-year-old man diagnosed with paroxysmal nocturnal haemoglobinuria (PNH) in 2008 and being treated with eculizumab (ECM) since January 2010. In 2011, he had signs and symptoms of sepsis due to *Neisseria meningitidis (N. meningitidis*) serogroup B, a serogroup not covered by the tetravalent conjugated vaccine (A, C, W137, Y) that he received (Menveo®). From then on he was treated with ECM, with no new admissions or need for transfusions. In October and November 2014, he was administered 2 doses of the vaccine against *N. meningitidis* serogroup B (Bexsero®) according to a recommended regimen. Then, 10 months after the vaccine had been administered, the patient visited the emergency department and was admitted to the ICU with pharyngeal discomfort, left earache associated with myalgia and a fever of 40 °C. He had severe hypotension and tachycardia despite receiving serotherapy, as well as coagulopathy and acute renal failure. BP: 94/36 mmHg; HR 132 bpm; temperature 40.5 °C. Clinical chemistry: procalcitonin 83.25 ng/ml; lactate 6.3 mmol/l; creatinine 2 mg/dl; urea 58 mg/dl; sodium 132.7 mmol/l; potassium 3.2 mmol/l. Venous blood gas: pH 7.34; pCO_2 35 mmHg; pO_2 31 mmHg; HCO_3 18.9 mmol/l. CBC: Hb 10.1 g/dl; haematocrit 32.1%; 3170 leukocytes/μl and 149,000 platelets/μl. On admission, blood cultures were obtained and treatment with noradrenaline and imipenem was started. At 24 h of incubation, positivity was detected in the blood cultures and Gram staining was performed in which Gram-negative diplococci were observed. The Siemens MicroScan WalkAway 40® automated microdilution system identified it as *N. meningitidis*, which agglutinated to serogroup B. Treatment was started with cefotaxime at a dose of 2 g IV/4 h with favourable progression. On discharge, he continued treatment with ECM and he was advised to take oral prophylaxis with penicillin V until his next check-up with his physician.

A meningococcal carrier study was performed on samples obtained from pharyngeal swabs which turned out to be negative.

The strain was sent to the Spanish National Centre for Microbiology (CNM) in Majadahonda (Madrid) to perform genotypic characterisation and molecular study of the antigens included in the 4CMenB vaccine (Bexsero®). The multilocus sequence typing (MLST) study showed that the sequence type was ST-11505, which is associated with the clonal complex ST-41/44. In addition, the strain contained the NHBA antigen (allele 1/peptide 2), the same variant as that included in the vaccine.

ECM is the treatment of choice for patients with PNH. It reduces haemolysis, decreases transfusion requirements and improves quality of life in these patients. It is a monoclonal antibody that targets the C5 complement fraction. It blocks excision of C5a and C5b and prevents generation of the membrane attack complex, thereby increasing the risk of infections due to encapsulated bacteria, especially *N. meningitidis*. Therefore, vaccination at least 2 weeks before starting treatment is recommended.[1,2] Apart from receiving treatment with ECM, our patient did not have any other added risk factor (asplenia or serious spleen dysfunction). He received 2 doses of vaccine against meningococcus B 10 months before he developed meningococcal sepsis. This was enough time to generate a vaccine response. Some studies suggest that vaccination with 4CMenB induces the production and activation of memory T cells at optimal levels, but could fail to maintain a population of memory B cells that is sufficient in terms of size and functionality.[3]

Bexsero® is the only vaccine against *N. meningitidis* serogroup B currently authorised in the European Union and available in Spain. It is a recombinant vaccine obtained through "reverse vaccinology" that contains 3 subcapsular meningococcus B antigens (*N. meningitidis* adhesin A or NadA, the protein which binds to complement factor H or GNA2091-fHbp and the *Neisseria* antigen which binds to heparin or NHBA-GNA1030) combined with the outer membrane vesicles (OMVs) of the *N. meningitidis* strain NZ 98/254, which expresses serotype 1.4 of membrane protein porin A (PorA).[4,5]

However, the different meningococcal strains are known to vary widely in terms of surface expression of these antigens, and therefore in non-susceptibility to the vaccine. A study conducted in Europe on more than 1000 meningococcus B isolates in 2007 and 2008 showed that, depending on the country of origin, 73%-87% of these strains had a *Meningococcal Antigen Typing System* (MATS) profile that was susceptible to the vaccine. In Spain there are studies placing this figure around 69%.[6]

The molecular techniques performed at the Spanish National Centre for Microbiology (CNM) showed that our strain did not have the NadA antigen (quite common in the strains circulating in our geographical area). It had the fHbp antigen (variant 2/subfamily A), a variant other than the one included in the vaccine (variant 1/subfamily B) and contained the same variant of the NHBA antigen present in the vaccine (allele 1/peptide 2). This caused us to consider a potential failure in efficacy of Bexsero®.

Given the low incidence of the disease and the great deal of variability among the circulating meningococcus strains, it is difficult to conduct studies with a statistically significant sample size. In the absence of conclusive data on the efficacy, immunogenicity and effectiveness of Bexsero® in patients diagnosed with PNH and being treated with ECM, it will be necessary to wait for population data to become available once its use has been instituted.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Urbano-Ispizua A, Gaya A, Colado E, López M, Arrizabalaga B, Vicente V, et al. Diagnosis and treatment of nocturnal paroxismal hemoglobinutia. Med Clin (Barc). 2011;136:121–7.
2. Eculizumab. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf [accessed 30.09.15].
3. Cruz SC, Souza SL, Cruz AC, Silva GP, Milagres LG. Humane antibody and memory B and T-cell responses after primary and booster inmunisation against *Neisseria meningitidis B*. Vaccine. 2011;29:7387–94.
4. Gil A, Barranco D, Batalla J, Bayas JM, Camping M, Gorrotxategi Gorrotxategi P, et al. Prevención de la enfermedad meningocócica por el serogrupo B mediante una vacuna de cuatro componentes. Rev Pediatr Aten Primaria. 2014;16:108.e55–74.
5. Bai X, Findlow J, Borrow R. Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles. Expert Opin Biol Ther. 2011;11:969–85.
6. Vogel U, Taha MK, Vazquez JA, Findlow J, Claus H, Vogel U, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in

☆ Please cite this article as: Hernando Real S, Vega Castaño S, Pajares García R. Infección meningocócica en paciente vacunado y en tratamiento con eculizumab. Enferm Infecc Microbiol Clin. 2017;35:200–201.

Europe: a qualitative and quantitative assessment. Lancet Infect Dis. 2013;13:416–25.

Susana Hernando Real[a,*], Silvia Vega Castaño[a], Rafael Pajares García[b]

[a] *Sección de Microbiología, Hospital General de Segovia, Segovia, Spain*
[b] *Servicio de Medicina Intensiva, Hospital General de Segovia, Segovia, Spain*

* Corresponding author.
E-mail address: shernando@saludcastillayleon.es (S. Hernando Real).

Received 9 October 2015
Accepted 18 February 2016

2529-993X/