Eculizumab for atypical haemolytic-uraemic syndrome. How long should we maintain it?☆

Eculizumab en el síndrome hemolítico urémico atípico. ¿Hasta cuándo mantenerlo?

To the Editor,

Atypical haemolytic uraemic syndrome (aHUS) is a thrombotic microangiopathy (TMA) mediated by uncommon and potentially fatal overaction of complement. The approval of eculizumab to treat aHUS has radically improved survival in this entity. The optimal duration of treatment in native kidneys remains the subject of debate.[1,2]

We present the case of a 26-year-old man, with no personal or family history of interest, who was transferred to our hospital due to acute oliguric renal failure requiring haemodialysis, severe anaemia and thrombocytopaenia. The blood test and blood smear performed were compatible with non-immune haemolytic anaemia.

Given the suspicion of TMA, we analysed ADAMTS13 activity, which was normal. PCR for SHIGA toxin and stool culture were negative. After exclusion of other secondary causes of TMA, the diagnosis of aHUS was established. Genetic study and study of complement factors were requested. We started vaccination against meningococcus B and ACW135Y, and prophylaxis with ciprofloxacin. A renal biopsy was performed in which glomeruli were observed with thickening of capillary walls, segmental and focal fibrinoid necrosis, abundant schistocytes, and crescent formation in 3 glomeruli. The arteriole walls presented fibrinoid necrosis and schistocytes, as well as intraluminal thrombi (Fig. 1).

Four days after admission, treatment was started with eculizumab 900 mg weekly for 1 month, showing good evolution with progressive normalisation of haematological parameters and, later, of renal function. After the second dose of eculizumab haemodialysis was no longer required, and the patient was discharged 21 days after starting treatment, with a creatinine level of 2.8 mg/dl (Fig. 2).

Fifteen days after discharge, the patient presented with pneumonia and an episode of decompensated heart failure requiring hospitalisation, where dilated cardiomyopathy was detected, which responded well to medical treatment. In the year following discharge, the patient has continued with eculizumab and presents stable renal function with a creatinine level of 2–2.5 mg/dl.

AHUS is a rare and serious disease with mainly renal involvement. Onset is generally abrupt, and it usually presents, as in our patient, with the triad of non-immune microangiopathic haemolytic anaemia, thrombocytopaenia and renal failure. Although renal involvement usually predominates, up to 20% of patients can present extrarenal manifestations, predominantly neurological, gastrointestinal and cardiac, due to the diffuse nature of the disease.[3,4]

The presence of complement gene mutations has been detected in approximately 40%–60% of patients with aHUS, and up to 10% have mutations in more than one gene.[2] In our patient, polymorphisms associated with risk of aHUS were detected in the membrane cofactor protein (MCP) gene, together with deletion in CFH3-CFHR1, both in heterozygosis, as well as the presence of anti-factor H antibodies. These antibodies are present in 5%–10% of patients with aHUS, with consequences similar to those of mutations in the FH gene, and they seem to be related to the onset or recurrence of the disease.[5] The presence of both polymorphisms, associated with the presence of anti-factor H antibodies, together with environmental factors that act as triggers, could justify the predisposition of this patient to develop aHUS (multiple hit theory).[2,6]

Genotypic–phenotypic characterisation of this syndrome has gradually improved thanks to the study of genetics and complement factors. Currently, one of the most debated issues is the duration of treatment with eculizumab.[7] This decision usually depends on the patient's risk of relapse, taking into account various factors such as the patient's age, partial or total recovery of renal function, the presence of extrarenal manifestations, and the result of the genetic study.[8]

Various case series report that in 20%–30% of patients eculizumab was interrupted in order to avoid meningococcal infections, side effects of the treatment, and the high cost of the therapy.[9] Approximately 20% of these patients

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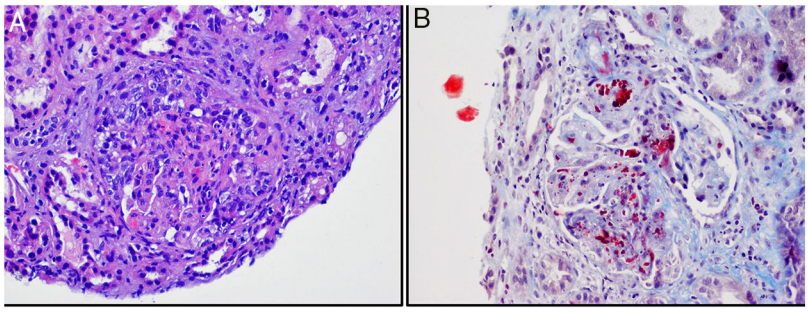

Fig. 1 – Renal biopsy. (A) Glomerulus with thickening of capillary walls, fibrinoid and crescent-shaped epithelial necrosis (haematoxylin–eosin). (B) Schistocytes in the mesangium, lumen and walls of the vessels (Masson's trichrome stain).

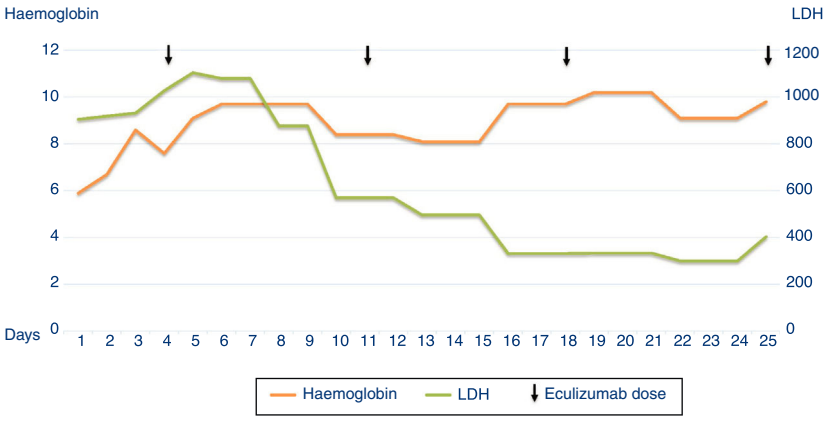

Fig. 2 – Evolution of the patient's haemoglobin and LDH.

present recurrence of TMA.[5] It is crucial to monitor patients for early identification of recurrence and resumption of treatment. Despite the fact that most patients returned to their baseline status after eculizumab was resumed, it would be necessary to take into account the subclinical renal damage to which the patient is exposed with each relapse, and the subsequent progression of renal disease.[10]

Our patient showed significant haematological and renal involvement, and although he had already presented symptoms 2 weeks before admission, early start of treatment with eculizumab was key in his good evolution. Given this presentation, the persistence of chronic kidney disease and the subsequent development of extrarenal cardiac manifestations, we decided to continue with the treatment. More observational studies and a more complete collection of data on the interruption of treatment and its consequences would improve decision-making in this regard.

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Does vitamin D influence hepatitis B surface antibodies in non-vaccinated patients on haemodialysis?☆

¿Influye la vitamina D en los anticuerpos de superficie de la hepatitis B en pacientes no vacunados en hemodiálisis?

The prevention of hepatitis B virus infection is one of the main goals in haemodialysis (HD) centres. Vaccination is recommended, but only 50%–85% of patients develop antibodies (HBsAb) but in less quantities and shorter permanence over time.[1–3] This response is worse in patients with reduced renal function, older and malnourished patients[1,2] or those with vitamin D (VD) deficiency[3] which is common in dialysis patients.[3,4] We are aware of seasonal variations in VD, but variations of HBsAb titres have not hitherto been described.

In the HDHD NephroCare Fresenius Medical Care centre (FMC)-Reus, we conducted a retrospective observational study with the aim of assessing the relationship between VD and HBsAb. We divided the study into 2 annual semesters, terminating in April and October, when most of the laboratory determinations were obtained and which, in turn, coincided with the lowest and highest annual sun exposure. Nonvaccinated patients were included, before or during their stay in the centre, had at least 1 determination of HBsAb in each consecutive period, and one determination of 25-hydroxycholecalciferol. Vaccinated patients were excluded, in addition to those with laboratory results with non-numerical values and patients on holiday. The data was obtained over 40 months, from July 2014 to October 2017.

We obtained results in 20 patients: 90 determinations (between 2 and 9, an average of 5 determinations per patient). HBsAb levels were between 8 and 635 UI/ml, with a mean value of 151 ± 161 UI/ml. Ten patients (50%) had mean values higher than 100 UI/l. Due to the limited size of the study population, the values of the monthly medians were influenced by the entry of patients with different antibody levels. For example, the entry in November of one patient with levels of 566 UI/ml increased the mean estimated for that month. The values were grouped by semesters regardless of the year in which they were obtained, observing an insignificant increase of levels in the warm semester (Table 1). The 25-hydroxycholecalciferol results were obtained from 94 determinations (between 2 and 8, an average of 5 determinations per patient). The values of 25-hydroxycholecalciferol were significant higher during the warm semester (Table 1).

The action of VD against infections earned Dr Ryberg Finsen the Noble Prize in 1903.[5] We now know that VD deficiency is associated with an increase in the rate and poor prognosis of infectious diseases[3,4,6,7] and absence of response to treatment of viral hepatitis with more chronic liver disease and hepatocellular carcinoma.[8] We also know that sun exposure is associated with the viral response to treatment of hepatitis C,[9] and that VD status is related to the persistence of HBsAb 20 years after primary vaccination.[7] The supplementation with VD in dialysis patients reduces respiratory infections and peritonitis in peritoneal dialysis patients.[4]

Most immune cells produce CYP27B1, express VD receptors (VDR), and are regulated by VD via the endocrine, autocrine

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