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Eculizumab as a treatment for atypical hemolytic uremic syndrome secondary to carfilzomib☆

Síndrome hemolítico urémico atípico secundario al uso de carfilzomib tratado con eculizumab

Dear Editor,

Carfilzomib is a proteasome inhibitor drug with antiproliferative and pro-apoptotic activity. It is one of the drugs used in the treatment of refractory multiple myeloma.[1–4] The onset of atypical haemolytic uremic syndrome (aHUS) associated with the use of carfilzomib is a complication previously described in the literature.[5–10] We describe a case of aHUS secondary to carfilzomib effectively treated with eculizumab.

This case involves a 71-year-old woman with refractory Bence-Jones Kappa multiple myeloma treated with carfilzomib, daratumumab and dexamethasone (KdD). The patient was admitted to the Haematology Department due to onset of malaise and fever 2 days after receiving the second cycle of KdD. Despite negative microbiology results, her blood pressure increased to over 180/100 mmHg on the fourth day. Blood tests found a decrease in haemoglobin of up to 6.8 g/dl and in platelets of up to 12,000, with an increase in LDH of up to 900 IU/l, accompanied by a deterioration of renal function, with serum creatinine levels of 2.6 mg/dl. Suspecting thrombotic microangiopathy (TMA), treatment with prednisone (1 mg/kg/day) and fresh plasma was started, with no improvement, and the patient was referred to the Nephrology Department for assessment.

Studies performed by the Nephrology Department showed 5–6% schistocytes per field on peripheral blood smear, no signs of malignant arterial hypertension on fundoscopy, undetectable haptoglobin in blood, and negative direct Coombs test. ADAMTS13 test was normal (ADAMTS13 > 50%). Other causes of aHUS and typical haemolytic uraemic syndrome (*STEC-HUS*) were ruled out, and genetic studies were not performed due to the high suspicion of a pharmacological cause. Carfilzomib was discontinued and treatment with eculizumab was started after administration of meningococcal prophylaxis with oral penicillin. Plasmapheresis was not performed due to the poor status of the patient and to avoid the comorbidity associated with the technique. One week after the third dose of eculizumab, serum creatinine levels had normalised (1.1 mg/dl) without the need for any haemodialysis sessions, and schistocytes had disappeared. From a haematological point of view, partial improvement was observed in haemoglobin and platelet levels, probably due to the underlying disease, although no schistocytes were found. The patient received 3 weekly doses of 900 mg of eculizumab, which was discontinued after improvement of renal function and stabilisation of haemolysis parameters.

Based on the accumulated evidence relating to the pathogenesis of this condition, we wonder whether treatment with

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Table 1 – Review of cases of TMA associated with the use of carfilzomib.

Reference	Number of cases	Clinical presentation	Drug used	Measure taken	Outcome
Chen et al.[5]	4	HUS	Carfilzomib	Withdrawal of the drug	Outcome1 Haemodialysis
Yui et al.[6]	11	HUS	8 Carfil-zomib 3 Borte-zomib	Withdrawal of the drug 4 plasma-pheresis 3 Eculizumab	2 did not recover
Qaqish et al.[7]	2	HUS TMA kidney biopsy	Carfilzomib	Withdrawal of the drug Plasmapheresis	Outcome
Lodhi et al.[8]	1	HUS	Carfilzomib	Withdrawal of the drug Plasmapheresis	Outcome
Sullivan et al.[9]	1	HUS	Carfilzomib	Withdrawal of the drug	Outcome
Hobeika et al.[10]	1	HTN and proteinuria TMA kidney biopsy	Carfilzomib	Withdrawal of the drug	Outcome

eculizumab is justified. In the years since it was released, carfilzomib has been associated with several cases of TMA[5–10] (Table 1). The mechanism by which the damage occurs is thought to be related to the accumulated dose or to an alloimmune effect. Some authors suggest, however, that proteasome inhibitors decrease production of vascular endothelial growth factor (VEGF) by inhibiting the activity of proteins that regulate its genetic transcription. This results in endothelial and podocyte damage similar to that caused by anti-VEGF drugs.[6,8] The latter is the most plausible of the 3 proposed mechanisms, since aHUS has occurred in patients who have only received 2 doses, as in our case, and not in other patients with higher cumulative doses. Likewise, the alloimmune mechanism is an unlikely culprit, given the context of administration of a plasma cell depleting drug in patients that are highly immunosuppressed due to previous chemotherapy and, as in our case, do not respond to immunosuppressive treatment (prednisone).

Secondary aHUS should be treated by withdrawing the causative agent.[1,2] In some series, plasmapheresis has been used, with no clear benefit for symptoms.[6,7] In many cases, TMA is resolved by withdrawing the drug. However, as shown by the review published by Cavero et al., early use of eculizumab may be effective in cases of refractory TMA in which impaired renal function persists or worsens, or in life-threatening situations.[2] Recent studies have shown that the alternative pathway of the complement system is temporarily activated in cases of secondary aHUS. Based on this evidence, the new classification of thrombotic microangiopathies proposed in the KDIGO guidelines[1] now includes all secondary TMAs with ADAMTS13 > 10% activity in the context of aHUS. Therefore, in cases of secondary aHUS that does not improve despite withdrawal of the causative agent, we recommend early, short-term administration of eculizumab.

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Translumbar and transhepatic haemodialysis catheters: A viable option☆

Catéteres translumbares y transhepáticos para hemodiálisis: una opción viable

Dear Editor,

The objective of this study was to share our hospital's experience regarding non-conventional vascular access: translumbar catheters (TLCs) and transhepatic catheters (THCs) in haemodialysis (HD) patients.

A retrospective study was conducted during the period 2009–2015, and a total of 40 catheters were inserted in 24 HD patients: 26 TLCs and 14 THCs. All patients had previously been diagnosed with stenosis of the superior vena cava and femoral arteries by fluoroscopy. Tunnelled catheters were used for the TLC (Medcomp® 14 F × 55 cm) and THC (Medcomp® 14 F × 28 cm). This study was reviewed and approved by the Ethics Committee of the Hospital Nacional Alberto Sabogal and authorised by the *Instituto de Evaluación de Tecnologías Sanitarias e Investigación* [Institute for Evaluation of Health Technologies and Research] (IETSI) of EsSalud. The survival analysis was performed in June 2016.

Data analysis was performed using the StataCorp Stata/SE 10 program.

Twenty-four patients were assessed. In two patients the placement of the catheter was unsuccessful. Therefore, they were not included in the analysis (Table 1). Thirteen patients (59.1%) were female. The average age of these patients was 59.2 (range: 30–83). In 13 patients (56.5%) only a TLC was inserted, in 8 (34.8%) only a THC and in 2 (8.7%) both types of catheter were inserted. The median follow-up time for these patients was 591 days (283–2372) in the TLC group, 235.5 days (35–1329) in the THC group and 659.5 days (429–890) in the group with both types of catheters. The most common cause of chronic kidney disease (CKD) was nephroangiosclerosis (43.5%), followed by an unknown cause (34.8%) and diabetes mellitus (17.4%). There was only one case of lupus nephritis as a cause of CKD. In total, 13 patients died during the study period, 8/15 (61.5%) in the TLC group, 4/8 (50.0%) in the THC group and 1/2 (50%) in the group which received both catheters. There were no significant differences in the follow-up times for these three groups. No patient died due to the direct cause of catheter placement. However, one patient died 30 days after placement of a THC as he presented with a hepatic haematoma. This was the only death in the placement of a non-conventional venous access.

At the end of follow-up, nine patients were still alive, seven of whom had a functioning catheter at that time, and two went on to undergo peritoneal dialysis. In the group of those who died, eight died with the catheter functioning, three with the catheter not functioning and two had gone on to receive peritoneal dialysis. The cause of death was cardiovascular in five patients, followed by sepsis in four, respiratory failure in three and a case of hepatic bleeding in one patient with a THC (Table 1).

As regards the catheters, a total of 40 were inserted in the 22 patients included in this study (Table 2). The TLC site was used on 26 occasions (65%), while the THC site was used on 14 occasions (35%). Regarding the reasons to remove the catheter, we can indicate that the first reason was dysfunction or thrombosis (60%), followed by infection (20%) and exposed cuff (15%).

The Kaplan–Meier estimate survival curve for catheter survival shows a slightly greater survival for TLCs compared to THCs, but this difference is not significant (Fig. 1).

The univariate Cox regression analysis for catheter survival shows an HR of 1.50 (0.67–3.39) for THCs compared to TLCs. When performing the multivariate analysis, the final model delivered a marginally statistically significant HR for the removal of the catheter for a THC 1.86 (0.88–3.88) compared to a TLC.

The overall results of our study have similarities with the median follow-up results, as well as those for complications.[1–9]

TLCs have a greater survival and a lower HR for removal risk than THCs, and, despite the fact that these findings are

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