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ORIGINAL ARTICLE

Characteristics, management and outcomes of atypical haemolytic uraemic syndrome in kidney transplant patients: a retrospective national study

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ABSTRACT

Background. Kidney transplantation (KTx) is a strong trigger for the development of either recurrent or *de novo* atypical haemolytic uraemic syndrome (aHUS). According to previous studies, eculizumab (ECU) is effective for prophylaxis and for treatment of recurrence.

Methods. We evaluated the experiences of Spanish patients with recurrent and *de novo* aHUS associated with KTx, treated or not treated with ECU. In the *de novo* group, we classified patients as having early *de novo* (during the first month) or late *de novo* aHUS (subsequent onset).

Results. We analysed 36 cases of aHUS associated with KTx. All of the 14 patients with pre-KTx diagnosis of aHUS were considered to have high or moderate risk of recurrence. Despite receiving grafts from suboptimal donors, prophylactic ECU was effective for avoiding recurrence. The drug was stopped only in two cases with low–moderate risk of recurrence and was maintained in high-risk patients with no single relapse. There were 22 *de novo* aHUS cases and 16 belonged to the early *de novo* group. The median time of onset in the late group was 3.4 years. The early group had a better response to ECU than the late group, probably due to earlier diagnosis and use of the drug. No genetic pathogenic variant was detected in *de novo* aHUS cases, suggesting a secondary profile of the disease. ECU was stopped in all *de novo* patients with no relapses. ECU was well tolerated in all cases.

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Conclusions. Both groups (pre-aHUS and *de novo*) presented different clinical profiles, management approaches and outcomes. One should consider aHUS regardless of time after KTx. Genetic studies are crucial to stratify risks of relapse and to determine necessary lengths of treatment. We suggest short ECU treatment for *de novo* cases without pathogenic mutation and that ECU treatment be considered pre-emptively for patients with moderate or high risk of recurrence.

Keywords: aHUS de novo, aHUS atypical haemolytic uraemic syndrome, eculizumab, genetic study, kidney transplantation recurrence

INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is a rare but very serious disease. Uncontrolled activation of the complement system is clinically characterized by thrombotic microangiopathy and acute renal failure. It can lead to chronic renal insufficiency and other extrarenal manifestations, such as heart and brain complications [1].

Kidney transplantation (KTx) is a trigger for the development of aHUS, both as a recurrence of the disease or as a new-onset disease in grafts in patients with different causes of end-stage renal disease (ESRD). Known causes of *de novo* aHUS among KTx recipients include immunosuppressive drugs, ischaemia–reperfusion injury, antibody-mediated rejection and viral infections [2–7]. The risk of recurrence of aHUS in KTx recipients depends mainly on underlying alterations to the complement system [8–10]. Clinical guidelines recommend the use of prophylactic measures to prevent the recurrence of aHUS in all patients with primary aHUS who will receive KTx, except those with isolated mutations in membrane cofactor protein and those in whom anti-complement factor H (CFH) antibodies have been cleared from the circulation, because they are considered to be at low risk of recurrence [11]. However, recent publications and improvements in genetic testing have facilitated better assessment of recurrence risk [12] (see Figure 1 for the criteria used in this study).

Eculizumab (ECU; Alexion, New Haven, CT, USA), a humanized monoclonal antibody that prevents cleavage of the C5 molecule, which blocks activation of the terminal pathway and formation of the membrane attack complex (C5b-9), seems to be effective in both the prevention and treatment of aHUS relapse in KTx. Cases and short case series of aHUS associated with KTx have been published. Recently the global aHUS registry and the French registry published analyses of their data about the use of ECU in such patients [13–18]. Several cases of *de novo* aHUS after KTx have also been successfully treated with ECU [19, 20]. However, knowledge about the disease in this scenario is still scarce and is not sufficient to standardize criteria about the prophylactic and therapeutic management of aHUS in KTx [21]. Therefore, management remains a controversial issue and varies according to individual transplant centre protocols.

Here we present the Spanish experience of KTx-associated aHUS. This is the third largest series of cases published so far. It includes not only patients with aHUS as their cause of ESRD who have received KTx, but also cases of KTx patients who have developed *de novo* aHUS. The description and analysis of our cohort, especially regarding presentation, the genetic and functional profile of the complement system and the prophylactic and therapeutic use of ECU, can help to expand our knowledge of aHUS in the context of KTx.

Risk assessment for aHUS recurrence after Tx

High risk:
- Previous recurrence
- Presence of *CFH*, *C3* or *CFB* pathogenic variant
- *CFH:CFHR-1* rearrangements

Moderate risk:
- Presence of *CFI* pathogenic variant
- Presence of *CFH*, *C3*, *CFB* or *CFI* uncertain significance variant
- Homozygosity for *CFH-H3* risk polymorphism
- Anti-FH autoantibodies

Low risk:
- Isolated *MCP* pathogenic variant
- *DGKE* pathogenic variant
- *THBD* pathogenic variant
- Loss of anti-FH autoantibodies
- No genetic findings
- Secondary aHUS

FIGURE 1: Risk assessment for aHUS recurrence after transplantation.

MATERIALS AND METHODS

Study population, definitions and treatments

A diagnosis of aHUS was considered in patients who fulfilled the following criteria: platelet count $<150 \times 10^3/\mu L$ or a decrease of >25% from baseline values, microangiopathic haemolytic anaemia and serum creatinine (sCr) level greater than the upper limit of the normal range, together with a negative Coombs test, normal activity of a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats (ADAMTS-13) and negative Shiga toxin detection [22]. If possible, the diagnosis was confirmed via renal biopsy.

The patients were classified according to the moment of onset of aHUS. The pre-emptive group included patients with a diagnosis of aHUS in their native kidneys who received KTx. The *de novo* post-KTx group comprised those patients who had their first episode of aHUS after KTx. Within this group the patients were subdivided according to the time of onset of the disease: those with a debut in the first month post-transplant were classified as having early *de novo* aHUS and those with a subsequent presentation as having late *de novo* aHUS (Figure 2). We reviewed clinical data from medical records and asked clinicians for detailed information about the ESRD diagnoses leading patients to dialysis. In particular, we searched for clinical pictures like abrupt ESRD onset, hypertensive emergencies or haematology patterns that could hint at unnoticed aHUS.

Cases of acute antibody-mediated rejection with a histological pattern of thrombotic microangiopathy and those with any other type of solid organ transplant were excluded from the study.

This study was supported by the public health transplant research net and approved by the institutional review board of the University Hospital Puerta de Hierro, Madrid, Spain. The study group made calls to every transplant centre asking

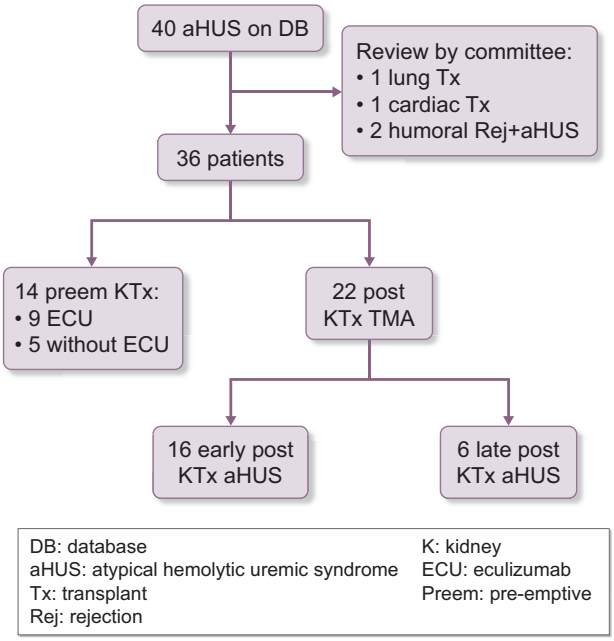

FIGURE 2: Patient flow chart.

them to include aHUS cases via the Transplant Working Group of the Spanish Society of Nephrology (SENTRA) and the Spanish Renal Research Network (REDinREN). Every case that fulfilled the selection criteria was included, no matter what the transplantation vintage, treatment or outcomes were. All of the aHUS cases in the *de novo* group were recorded between 2013 and 2017. During this 5-year period, 14 401 KTx procedures were performed in Spain and the mean prevalence of patients with CKD with functioning grafts was 29 676 patients/year.

Treatment. We defined the standard dose of ECU as the administration of an initial dose of 900 mg/week for 4 weeks, followed by doses of 1200 mg every 2 weeks. Plasma exchange therapy was discontinued in all patients once they started ECU. All patients received a meningococcal vaccine and antibiotic prophylaxis according to label instructions. The duration of ECU therapy was determined by the treating physician based on the patient's response and individual characteristics.

Outcomes. Normalization of platelet and haemoglobin counts in combination with the disappearance of haemolysis markers was considered to be a complete haematological response. Complete renal response was defined as the recovery of renal function compared with baseline sCr or, in cases of aHUS in the immediate post-transplant phase, as the normalization of graft function (eGFR >60 mL/min) estimated by the Modification of Diet in Renal Disease equation. A partial renal response was defined as a >25% reduction of the peak sCr value without reaching previous baseline sCr or, in cases of early aHUS, as partial recovery of graft function.

Statistical analysis

Quantitative data are shown as median and interquartile range (IQR) as appropriate. Qualitative data are shown as frequencies or percentages. Values of sCr, haemoglobin and platelets are depicted in the corresponding tables of each group.

RESULTS

Pre-emptive management

We identified 14 patients who received KTx after a diagnosis of aHUS in the native kidney. The median age at the onset of disease was 26.5 years (IQR 23.5–33.3) and 30.5 years (IQR 28.9–31.5) at the time of KTx. The average time from the first episode until KTx was 4.4 years. The median follow-up after KTx was 5.8 years (IQR 4.1–12.5). The individual characteristics of each patient are detailed in Table 1. Functional and genetic studies of the complement system were performed for all patients. Patients were classified according to their risk of relapse, as shown in Figure 1 and Supplementary data, Table S1. Eight patients were considered to be at high risk and six patients at moderate risk of recurrence. A detailed description of how the genetic findings for each individual patient were interpreted in terms of risk recurrence is provided in the Supplementary data.

A pre-emptive ECU strategy was used in nine patients, all with high or moderate risk of recurrence. Patients received grafts from different types of donors, but only two were from an unrelated living donor (URLD). The most common pre-emptive treatment was that recommended by the European Renal Association–European Dialysis and Transplant Association guidelines, which was the peri-transplant administration of a dose of 1200 mg. In only one patient was an extra dose of 900 mg administered 24 h after transplantation. ECU was suspended in two of the four patients with moderate risk of

Table 1. Patients with aHUS in the native kidney receiving a kidney transplant

ID	Risk assessment[a]	Gender (age, years)	Time from aHUS (years)	Donor	ECU, pre-emptive	aHUS relapse, time post-KTx	Relapse Rx	Kidney remission	Time on ECU status (days)	Relapse	Pat status and last Cr (mg/dL)
1	High	M (27)	4.0	ucDCD	No	Yes, 2nd month	ECU	Yes	Ongoing	No	Alive (1.3)
2	High[b]	F (40)	1.1	BDD	No	Yes, 2 in secondTx (4 years and 4 months)	TPE	No	As prophylaxis inthird KTx	No	Alive (0.8)
3	High	M (46)	1.3	BDD	No	Yes, 10 years	TPE+ECU	Yes	Ongoing	No	Alive (2.1)
4	Moderate	M (34)	6.4	BDD	No	No				No	Alive (0.9)
5	Moderate	F (4)	3	BDD	No	No				No	Alive (0.9)
6	High	F (24)	3.1	cDCD	Yes	No			Ongoing	No	Alive (1.5)
7	Moderate	M (27)	1.2	BDD	Yes	No			Closed (30)	No	Alive (1.2)
8	High	F (33)	5.0	URLD	Yes	No			Ongoing	No	Alive (1.3)
9	Moderate	F (27)	2.6	BDD	Yes	No			Closed (361)	No	Alive (1.0)
10	Moderate	F (34)	4.3	EC BDD	Yes	No			Ongoing	No	Alive (1.4)
11	Moderate	F (26)	2.5	URLD	Yes	No			Ongoing	No	Alive (1.2)
12	High	F (22)	4.5	BDD	Yes	No			Ongoing	No	Alive (1.0)
13	High	M (54)	1.7	BDD	Yes	No			Ongoing	No	Alive (1.4)
14	High	M (17)	21.3	BDD	Yes	No			Ongoing	No	Alive (1.3)

[a]According to Kidney Disease: Improving Global Outcomes, with the exception that no genetic findings is considered low risk.
[b]Previous recurrence confers high risk *per se*.
[C]r: creatinine; EC: extended criteria; F: female; ID: identifier; M: male; Pat: patient; Rx: therapy; Tx: transplant.

recurrence without relapse: one in the second month and the other 1 year after KTx. All other patients continued ECU treatment until the end of follow-up. None of the patients relapsed under ECU treatment.

The other five patients received KTx without ECU prophylaxis. Three of them had recurrences between 2 months and 10 years after KTx. Two of these three patients received rescue treatment with ECU, reaching full recovery. The one who did not receive rescue ECU therapy lost the graft, as well as a second graft due to disease recurrence. Finally, this patient received a third transplant with prophylactic ECU, which had a favourable evolution. The first two transplants were performed before ECU became available.

De novo post-transplant aHUS

We classified the 22 patients with *de novo* post-KTx aHUS into two subgroups according to the time of disease onset: early (in the first month post-KTx) or late (beyond the first year). A total of 16 cases (12 men) were included in the early *de novo* post-transplant aHUS group, with a median age of 51.5 years (IQR 42.8–64.3). All of them had received a deceased donor kidney: 11 from a brain-dead donor (BDD), 1 from a donor after circulatory death Maastricht III [controlled circulatory death donor (cDCD)] and 4 from a donor after circulatory death Maastricht II [uncontrolled circulatory death donor (ucDCD)]. Two of the Maastricht II cases shared the same donor, which suggests complement activation due to damage in ischaemia–reperfusion. The majority of patients (15 of 16) received tacrolimus (Astellas Pharma, Tokyo, Japan) at the time of the aHUS episode and 3 of them also received a mammalian target of rapamycin (mTOR) inhibitor (Everolimus, Novartis, Basel, Switzerland). In most cases treatment had only been given 48 h before onset. Clinicians did not report any cases of high blood levels of tacrolimus or mTOR inhibitor during the 4 days before aHUS onset. In 11 patients the aHUS was histologically confirmed. One patient also presented an acute cellular rejection. No other possible triggers were identified beyond the transplant itself or the immunosuppression. It is noteworthy that five patients had intermediate renal function before the onset of aHUS. In four patients a genetic study was performed, and all were assessed as having a low risk of recurrence. The series is detailed in Table 2 and Supplementary data, Table S1.

The majority of patients (13) were initially treated with therapeutic plasma exchange (TPE), achieving haematological remission in all cases but one. However, only two patients achieved total renal recovery and two cases had partial renal response. Eight of the nine cases who did not have a renal response received rescue ECU therapy, along with three patients who received initial treatment with ECU without TPE. The median time from the onset of the disease until the beginning of the drug was 11.5 days (IQR 5.0–21.3) and treatment was maintained for a median of 21 days (IQR 14–17) with 21 days as the mean. ECU was withdrawn in all cases. Renal response was achieved in all but one patient: eight had complete remission and two had a partial renal response. The median time to starting ECU treatment of patients with complete response was shorter (5 days) compared with patients with a partial or no response (22 days). Likewise, the length of the treatment period was shorter in the group with a partial or no response (median 21 days versus 49 days).

The median follow-up period from KTx was 3.1 years (IQR 1.9–3.9). None of the patients in this group had subsequent recurrence of aHUS.

The remaining six patients, with a median age of 58.5 years (IQR 45.6–61.3), developed aHUS much later, always after the first year following KTx, with a median of 3.4 years (IQR 2.4–8.7). The median follow-up period after KTx was 6.8 years (IQR 5.2–11.2).

Three of the grafts came from standard-criteria BDDs, two from expanded-criteria BDDs and one from a URLD. All patients were receiving tacrolimus at the onset of aHUS, one in combination with an mTOR inhibitor. In addition, as additional triggers, four infectious processes, two acute cellular rejections and one malignant tumour were identified. In five patients a kidney

Table 2. Patients with early *de novo* post-transplant aHUS

ID	Risk assessment[a]	Gender (age, years)	Aetiology	KTx type	KTx to aHUS (days)	Trigger for aHUS (MD criteria)	Tacro	DGF/immediate	Biopsy	Hb (g/dL)	Platelets (10^3/μL)	sCr (mg/dL)	TPE (sessions)	TPE rResponse	aHUS to ECU (days)	ECU Rx (days)	ECU response	Relapse	Patient status and last Cr (mg/dL)
15		M (38)	Glom	ucDCD II	7	SLE	Yes	DGF	aHUS	8.6	57	8.2	No	NA	22	58	H response, partial R response, not dialysis	No	Alive (3. 3)
16		M (50)	APKD	ucDCD II	6	Same donor	Yes	DGF	aHUS	7.7	33	11.2	No	NA	5	77	Complete (H+R)	No	Alive (3. 2)
17		M (39)	Inters	ucDCD II	6	Same donor	Yes	DGF	aHUS	9.2	74	6.4	No	NA	5	77	Complete (H+R)	No	Alive (3.7)
18	Low	F (44)	UNK	BDD	13	Tacro+	T/E	Immediate function	ND	8.7	51	3.6	4	No response	3	7	Complete (H+R)	No	Alive (1.4)
19	Low	M (44)	APKD	BDD	2	UNK	No	DGF	aHUS	6.9	35	10.2	6	H response, no R	10	241	Complete (H+R)	No	Alive (1.5)
20		M (46)	UNK	ucDCD II	4	Tacro	Yes	DGF	aHUS	9	55		6	H response, no R	19	7	Complete (H+R)	No	Alive.. nephrectomy,[b] on dialysis
21	Low	M (34)	Glom	BDD	11	Tacro	Yes	DGF	aHUS	7.9	89	14.3	3	H response, no R	3	473	Complete (H+R)	No	Alive (1.9)
22		M (67)	VasNAE	BDD EC	2	UNK	Yes	Immediate function	aHUS	7.8	69	16.3	5	H response, no R	30	14	Complete (H+R)	No	Alive (1.8)
23		M (65)	Glom	BDD EC	5	Tacro	Yes	DGF	aHUS+ cell ARR	9.9	42	8.7	6	H response, no R	NA	21	Complete (H+R)	No	Alive (2.1)
24	Low[c]	M (55)	Glom	BDD EC	5	Tacro+	Yes	DGF	aHUS	9.1	94	6.8	5	H response, no R	26	21	H response, no R (dialysis)	No	Alive, on dialysis
25		M (57)	Glom	cDCD EC	3	Tacro	Yes	DGF	aHUS	7.7	53	8.2	5	H response, no R	13	14	H response, partial R response, not dialysis	No	Alive (2.5)
26		F (66)	Inters	BDD EC	6	Graft preservation	T/E+	DGF	aHUS	9.6	57	7.8	4	H response, no R				No	Alive (2.3)
27		M (74)	UNK	BDD EC	5	Tacro	Yes	DGF	ATN	10.7	53	5.8	5	H response, partial R response, not dialysis				No	Alive (2.0)
28		M (53)	UNK	BDD EC	6	Tacro	Yes	Immediate function	ND	7.3	45	4.9	5	H response, partial R response, not dialysis				No	Alive (2.8)
29		F (64)	Glom	BDD EC	4	Tacro	T/E	Immediate function	ND	9	42	9.3	6	Complete (H+R)				No	Alive (1.7)
30		F (30)	Glom	BDD	4	Tacro	Yes	Immediate function	ND	7.9	50	6.4	5	Complete (H+R)				No	Alive (1.4)

[a]According to Kidney Disease: Improving Global Outcomes, with the exception that no genetic findings is considered low risk.
[b]Due to kidney cancer.
[c]Low risk (none present in the KTx).
+: discontinued; APKD: autosomal polycystic kidney disease; ATN: acute tubular necrosis; cell ARR: cellular acute renal rejection; DGF: delayed graft function; DM: diabetes mellitus; EC: extended criteria; F: female; Glom: glomerulonephritis; Hb: haemoglobin; Inters: interstitial nephropathy; M: male; MD: medical doctor; ND: not done; T/E: tacrolimus and everolimus; SLE: systemic lupus erythematosus; UNK: unknown; VasNAE: vascular nephropathy.

biopsy had been performed, confirming the diagnosis of aHUS. Genetic studies were performed for four patients. All patients were classified as having a low risk of recurrence (Table 3 and Supplementary data, Table S1).

All of these patients received ECU as second-line treatment after unsuccessful treatment with TPE. In this group, ECU was initiated later than in the previous group [median time from the outbreak to the start of the drug was 27 days (IQR 21–32)]. In two cases, complete recovery of renal function was achieved and one had a partial renal response, whereas three patients lost their grafts. The group with partial or absent responses had shorter average treatment times (27.5 versus 203 days). The median follow-up period following the aHUS episode was 2.5 years and no patient presented with disease recurrence.

In all groups of patients, ECU was well tolerated and no infections or other severe adverse events were reported.

DISCUSSION

We assessed the Spanish experience of aHUS associated with KTx. This is one of the largest series to date with an accompanying genetic study that was performed in a single reference centre and has the longest follow-up period reported so far. Our study provides a better understanding of the disease in the KTx environment and describes clinical profiles, treatments, efficacy, safety and outcomes. We distinguished patients with a pretransplant diagnosis of aHUS who received KTx from those with *de novo* aHUS after KTx and highlighted important differences in onset, management and outcomes. We also emphasized the importance of performing functional and genetic studies of the complement system to stratify the risk of relapse in order to enable better therapeutic decisions to be made.

The risk of recurrence of aHUS after KTx in patients with previous aHUS as the cause of ESRD is high [2–10]. Therefore the Kidney Disease: Improving Global Outcomes guidelines stratify patients by their risks and recommend the use of prophylactic therapy before KTx for every patient with high or moderate risk of recurrence [11]. As shown in Figure 1, we used this risk classification strategy, adding some criteria that were discussed in the consensus meeting but are not written in the guidelines, such as homozygosity for CFH-H3 risk polymorphisms or variants of unknown significance. We also considered patients without any findings in the genetic study to have low rather than moderate risks of recurrence, based on the expertise of our national reference genetic laboratory.

Our study supports the efficacy and safety of ECU prophylaxis in patients with a high or moderate risk of recurrence. Even so, the Dutch group has reported good results without preemptive use of ECU, but in a very favourable scenario with optimal conditions to avoid the recurrence of aHUS. Their model is based on the minimization of tacrolimus, a very short ischaemia time and the use of optimal grafts from URLDs [23]. All these factors contribute to minimizing the activators of the complement system that act as triggers for recurrence. On the other hand, the follow-up period in their study was quite short, only 2 years, while in our series we described recurrence after as many as 10 years. We demonstrate that recurrence can occur at any time after KTx in patients with pathogenic mutations of genes involved in the complement system.

Furthermore, we achieved effective prophylaxis with ECU despite using grafts from suboptimal donors, such as extended-criteria BDDs and even cDCDs and ucDCDs. Although the acceptance of suboptimal grafts allows us to improve the accessibility of KTx and reduce the risk associated with remaining on dialysis and on the waiting list, this strategy does not always offer the best conditions, such as the ones reported in the Dutch study.

A controversial issue is the potential advantage of preventive use of ECU starting from the moment of transplantation to avoid recurrence over the course of rescue therapy after aHUS develops. There are no randomized studies in this regard, but recent registry and retrospective studies have reported a better prognosis for those receiving prophylaxis than rescue therapies [12, 17, 21]. In addition, for some patients in our cohort, predominantly in the late *de novo* aHUS group, rescue ECU therapy did not always achieve complete recovery of renal function. Finally, we must consider the possibility of subclinical histological damage of the graft after aHUS recurrence, even if sCr returns to baseline. This harmful effect could reduce the long-term survival of the graft.

There is no consensus regarding how long prophylactic ECU should be maintained. In our series, pre-emptive ECU was maintained in all but two cases, both with moderate genetic risk of recurrence. To date, no randomized study has clarified this issue, either in patients receiving KTx or in native kidneys. Fakhouri *et al.* [24] reported a high incidence of recurrence after ECU withdrawal in patients with mutations in CFH who had suffered aHUS in native kidneys and with only 2 years of follow-up. In our opinion, the same recommendations should be applied for KTx kidneys as for native kidneys. Although some authors recommend withdrawing ECU prophylactic therapy at some point based on the potentially high burden, we recommend that this option only be considered for patients with low–moderate risk of recurrence. However, more clinical evidence is needed.

Our *de novo* group included patients with ESRD arising from any other cause other than aHUS who developed an episode of aHUS after KTx. We distinguished between early and late onset to emphasize differences between the two situations and to raise awareness that the risk of aHUS, although reduced, still exists beyond the first months after transplantation. It is well known that early detection and treatment have relevant prognostic implications [25]. Lack of awareness leads to delayed diagnosis and use of ECU and is associated with a worse renal response, which might additionally be aggravated by the presence of chronic graft damage at the time of onset. Therefore it is important to keep the possibility of late-onset aHUS in mind during the diagnosis of any long-term KTx recipient with impaired renal function and haematological abnormalities after the first few years following transplantation.

In our cohort, ECU was well tolerated and demonstrated its superiority over TPE, leading to remission in patients with *de novo* aHUS. The usual real-world scenario seems to be the use of a short course of TPE as a primary treatment in order to gain a haematological response, usually without complete renal remission, which could be achieved with ECU as a second step. Our experience and the previously published findings favour the early use of ECU, because TPE therapy is not harmless and because delaying ECU administration may lead to suboptimal outcomes.

We searched carefully for evidence of clinical pictures like abrupt ESRD onset, hypertensive emergencies or haematology patterns that could hint at the presence of unnoticed aHUS and found no single case with these data. In all *de novo* post-transplant aHUS cases, at least one trigger could be identified. Genetic analyses were available for only 4 of the 16 patients included in this group and failed to identify genetic mutations, indicating they were secondary aHUS cases. Without genetic

Table 3. Patients with late *de novo* post-transplant aHUS

ID	Risk assessment[a]	Gender (age, years)	Aetiology	KTx type	KTx to aHUS (days)	Tacro	DGF/ immediate	Trigger for aHUS (MD criteria)	Biopsy	Hb (g/dL)	Platelets (10^3/μL)	Cr (mg/dL)	TPE (sessions)	TPE response	aHUS to ECU (days)	ECU Rx (days)	ECU response	Relapse	Patient status and last Cr (mg/dL)
31		F (41)	Glom	BDD	732	T+/E+	Immediate	Infection	ND	8.7	48	2.8	22	H response, no R	32	49	Complete (H+R)	No	Alive (1.9)
32	Low	M (62)	DM	BDD	3,799	Yes+	Immediate	Tumour versus tacro	aHUS				10	H response, no R	32	357	Complete (H+R)	No	Alive (2.1)
33	Low H	F (62)	VasNAE	BDD EC	4,542	Yes	DGF	Infection	aHUS	8.6	113	5	2	H response, no R	10	14	Partial R response, no dialysis	No	Alive, on dialysis
34		M (35)	Inters	UR LD	811	Yes	Immediate	Tacro	aHUS				17	H response, no R	22	7	No R, dialysis	On dialysis	Alive, on dialysis
35	Low	F (59)	Inters	BDD	1,126	Yes+	Immediate	Infection and cellular rejection	aHUS+cell ARR	7.7	42		30	No response	48	43	No R, dialysis	ReTx and no relapse	Alive, on dialysis AliveReTx (1.0)
36	Low	F (58)	UNK	BDD EC	1,343	Yes	NA	Infection and cellular rejection	aHUS+cell ARR	7.4	31	5.8	9	No response	21	41	No R, dialysis	On dialysis	Alive, on dialysis

[a]According to Kidney Disease: Improving Global Outcomes, with the exception that no genetic findings is considered low risk.

+: discontinued; cell ARR: cellular acute renal rejection; Cr: creatinine; DGF: delayed graft function; DM: diabetes mellitus; EC: extended criteria; F: female; Glom: glomerulonephritis; H: haematological; Hb: haemoglobin; inters: interstitial nephropathy; M: male; MD: medical doctor; NA: not applicable; ND: not done; R: renal; tacro: tacrolimus; T/E: tacrolimus and everolimus; UNK: unknown; VasNAE: vascular nephropathy.

studies, we cannot be certain about the remaining 12 patients, although most of them were probably also secondary aHUS cases. This presumption is supported by the absence of recurrence after remission, as previously described in other series [19, 26]. Therefore, unlike patients with primary aHUS, for such *de novo* post-transplant aHUS cases (once they have been confirmed to be secondary aHUS cases), the withdrawal of treatment seems reasonable after remission is consolidated.

In our series, the majority of patients received ECU for an average of 3 months to achieve remission with no subsequent relapses after withdrawal. Unfortunately, genetic study data were not available for all patients, such as those with aHUS prior to KTx. The low accessibility, time delay and cost of such studies seem to discourage nephrologists, who handle treatment based on clinical response. We strongly recommend that genetic studies be conducted for all cases of aHUS associated with KTx, which is already current clinical practice in aHUS associated with pregnancy [11, 27], to identify pathogenic variants that may help to define the prognosis, required length of therapy and future plans for retransplantation.

Our study has limitations due to its retrospective nature and low statistical power regarding the analysis prognostic factors and ability to draw statistically significant conclusions. Obviously there was no control group and an underreport bias cannot be totally ruled out. To overcome this, we sent a call to every centre from the REDInREN public research network and the Transplant Working Group of the Spanish Society of Nephrology. Moreover, electronic patient database systems have enabled us to recover detailed clinical data for complete follow-up periods. aHUS associated with KTx is a rare disease, which makes conducting a conventional study difficult. Our aHUS cohort related to KTx has one of the longest follow-up periods reported to date. It is the third largest published series, and unlike the global registry, we also included patients who were not treated with ECU, thus covering more clinical and therapeutic scenarios.

CONCLUSIONS

Our study shows the importance of including aHUS in the differential diagnosis of any functional impairment after KTx. Both recurrence of aHUS and *de novo* aHUS may appear after the first months following transplantation. Early detection and treatment determines the prognosis of the graft. In our experience, treatment with ECU is effective in most cases and well tolerated in all. An accurate functional and genetic study of the complement system is crucial to predict the risk of recurrence. In primary aHUS with moderate or high risk of recurrence, it seems reasonable to use prophylaxis with ECU and maintain such treatment at least in patients at high risk, whereas in patients with *de novo* aHUS without genetic mutation it seems reasonable to suspend the drug after achieving remission of the disease. More studies, especially clinical trials, are needed to shed more light on these issues.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

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