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.
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.

MATERIALS AND METHODS

Study population, definitions and treatments

A diagnosis of aHUS was considered in patients who fulfilled the following criteria: platelet count <150 × 10^9/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...
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 recurrence.
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 (cCD)], and 4 from a donor after circulatory death Maastricht II [uncontrolled circulatory death donor (ucCD)]. 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 S1. Patients with aHUS in the native kidney receiving a kidney transplant

| ID | Risk assessmenta | Gender | Donor (age, years) | ECU preemptive | 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) | ucDCD            | No            | Yes, 2nd month           | ECU       | Yes             | Ongoing                  | No      | Alive (1.3)                 |
| 2  | Highb          | F (40) | BDD              | No            | Yes, 2 in second KTx     | TPE       | No              | As prophylaxis            | No      | Alive (0.8)                 |
| 3  | High           | M (46) | BDD              | No            | Yes, 10 years            | TPE + ECU | Yes             | Ongoing                  | No      | Alive (2.1)                 |
| 4  | Moderate       | M (34) | BDD              | No            | Yes                      | ECU       | Yes             | Ongoing                  | No      | Alive (0.9)                 |
| 5  | Moderate       | F (4)  | BDD              | No            | Yes                      | ECU       | Yes             | Ongoing                  | No      | Alive (0.9)                 |
| 6  | High           | F (24) | cCD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.5)                 |
| 7  | Moderate       | M (27) | BDD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.2)                 |
| 8  | High           | F (33) | URLD             | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.3)                 |
| 9  | Moderate       | F (27) | BDD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.0)                 |
| 10 | Moderate       | F (34) | EC BDD           | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.4)                 |
| 11 | Moderate       | F (26) | URLD             | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.2)                 |
| 12 | High           | F (22) | BDD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.0)                 |
| 13 | High           | M (54) | BDD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.4)                 |
| 14 | High           | M (17) | BDD              | Yes           | No                       | ECU       | Yes             | Ongoing                  | No      | Alive (1.3)                 |

aAccording to Kidney Disease: Improving Global Outcomes, with the exception that no genetic findings is considered low risk.
bPrevious recurrence confers high risk per se.
| ID | Risk assessment | 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 sCr (mg/dL) |
|----|----------------|---------------------|-----------|----------|-------------------|-----------------------------|-------|---------------|---------|-----------|-------------------|-------------|----------------|----------------|-----------------|-------------|----------------|--|----------------|
| 15 | Low F (46)     | M (38)              | Glom      | cDCD EC 3 | 13                | Tacro + cell ARR            | Yes   | No            | DGF/IM        | 9.9        | 91 14.6 6.8 5      | H response, no R | NA             | 5               | 26            | 21           | Complete (H+R) | No | Alive (2.5)    |
| 16 | Low F (46)     | M (34)              | Glom      | BDD EC 11 | 11                | Tacro                        | Yes   | Immediate     | DGF/IM        | 7.9        | 89 14.3 3 3        | H response, no R | 3              | 473             | No            | Alive (1.9)    | No | Alive (1.9)    |
| 17 | Low F (46)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | H response, no R | No | Alive (2.1)    |
| 18 | Low M (39)     | M (67)              | Glom      | BDD EC 2  | 2                 | UNK                          | Yes   | Immediate     | DGF/IM        | 7.8        | 69 16.3 5 5        | H response, no R | 30             | 14              | Complete (H+R) | No | Alive (1.8)    |
| 19 | Low F (46)     | M (34)              | Glom      | BDD EC 11 | 11                | Tacro                        | Yes   | Immediate     | DGF/IM        | 7.9        | 89 14.3 3 3        | H response, no R | 3              | 473             | No            | Alive (1.9)    | No | Alive (1.9)    |
| 20 | Low M (39)     | M (50)              | APKD      | ucDCD II 6  | 6                 | Same donor                   | Yes   | DGF/IM        | aHUS            | 7.7        | 33 11.2 4 4        | No            | NA             | 5              | 77            | Complete (H+R) | No | Alive (3.7)    |
| 21 | Low M (46)     | M (34)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 22 | Low M (39)     | M (50)              | APKD      | ucDCD II 6  | 6                 | Same donor                   | Yes   | DGF/IM        | aHUS            | 9.2        | 74 6.4 4 4        | No            | NA             | 5              | 77            | Complete (H+R) | No | Alive (3.7)    |
| 23 | Low M (46)     | M (34)              | Glom      | BDD EC 11 | 11                | Tacro                        | Yes   | Immediate     | DGF/IM        | 7.9        | 89 14.3 3 3        | H response, no R | 3              | 473             | No            | Alive (1.9)    | No | Alive (1.9)    |
| 24 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 25 | Low M (57)     | M (34)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 26 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 27 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 28 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 29 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |
| 30 | Low M (34)     | M (57)              | Glom      | BDD EC 5  | 5                 | Tacro                        | Yes   | Immediate     | DGF/IM        | 9.9        | 94 8.7 6 5        | H response, no R | 26             | 21              | Complete (H+R) | No | Alive (2.1)    |

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

- **AAccording to Kidney Disease: Improving Global Outcomes, with the exception that no genetic findings is considered low risk.
- **Due to kidney cancer.
- **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, VanNAE: 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 haematological patterns that could hint at the presence of unnoticed aHUS and found no single case with these data. In all de novo posttransplant 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 post-transplant aHUS

| Patient status | aHUS (days) | Tacro (mg/dL) | ECU to aHUS (days) | Hb (g/dL) | Platelets (10^9/L) | Risk assessment | TPE (sessions) | TPE response | aHUS to ECU (days) | Rx (days) | TPE response | aHUS to ECU (days) | Rx (days) |
|---------------|-------------|---------------|-------------------|-----------|-----------------|----------------|---------------|--------------|-------------------|-----------|--------------|-------------------|-----------|
| Gender (age, years) | Aetiology | Trigger | KTx to DGF for aHUS | MD criteria | Biopsy | Endpoint | Graft | Artefact | Cellular rejection | Cell ARR | Arrangement | Incidence | Treatment |
| 31 Low M (41) | Glom | Immediate infection | ECU 722 | Yes | 3 | H response, no R | 7 | Complete (H+R) | No | Alive | 49 | 0.9 | 49 | Complete (H+R) |
| 32 Low F (62) | DM | Immediate infection | ECU 3,799 | Yes | 3 | H response, no R | 10 | Complete (H+R) | No | Alive | 357 | 0.1 | 0.1 | Complete (H+R) |
| 33 Low F (62) | VasNAE | Immediate Tumor | ECU 4,542 | Yes | 3 | H response, no R | 14 | Partial R response | No | Alive | 10 | 0.1 | 10 | Partial R response |
| 34 Low M (35) | Inter | Tubular injury | ECU 1,126 | Yes | 3 | H response, no R | 7 | No response | No | Alive | 43 | 0.1 | 43 | No response |
| 35 Low F (59) | Inters BDD 1,126 | Yes | Complete (H+R) | No | R | alive | 48 | No response | No | Alive | 41 | 0.1 | 41 | No response |

**aAccording 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.**

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**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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REFERENCES
1. Noris M, Remuzzi G. Atypical haemolytic-uremic syndrome. N Engl J Med 2009; 361: 1676–1687
2. Ruggenenti P. Post-transplant haemolytic-uremic syndrome. Kidney Int 2002; 62: 1093–1104
3. Ponticelli C, Banfi G. Thrombotic microangiopathy after kidney transplantation. Transpl Int 2006; 19: 789–794
4. Damman J, Schuurs TA, Ploeg RJ et al. Complement and renal transplantation: from donor to recipient. Transplantation 2008; 85: 923–927
5. Zuber J, Le Quintrec M, Krid S et al. Atypical haemolytic uraemic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol 2011; 7: 23–35
6. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med 2014; 371: 654–666
7. Garg N, Rennke HG, Pavliakos M et al. De novo thrombotic microangiopathy after kidney transplantation. Transplant Rev (Orlando) 2018; 32: 58–68
8. Bresin E, Daina E, Noris M et al. Outcome of renal transplantation in patients with non-Shiga toxin-associated haemolytic uremic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol 2006; 1: 88–99
9. Caprioli J, Noris M, Brioschi S et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood 2006; 108: 1267–1279
10. Noris M, Remuzzi G. Managing and preventing atypical haemolytic uremic syndrome recurrence after kidney transplantation. Curr Opin Nephrol Hypertens 2013; 22: 704–712
11. Goodship TH, Cook HT, Fakhouri F et al. Atypical haemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney Int 2017; 91: 539–551
12. Zuber J, Frimat M, Caillard S et al. Use of highly individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical haemolytic uremic syndrome. J Am Soc Nephrol 2019; 30: 2449–2463
13. Miller RB, Burke BA, Schmidt WJ et al. Recurrence of haemolytic-uraemic syndrome in renal transplants: a single-centre report. Nephrol Dial Transplant 1997; 12: 1425–1430
14. Zuber J, Le Quintrec M, Krid S et al. Eculizumab for atypical haemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant 2012; 12: 3337–3354
15. Legendre CM, Campistol JM, Feldkamp T et al. Outcomes of patients with atypical haemolytic-uremic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. Transpl Int 2017; 30: 1275–1283
16. Milan Manani S, Virzi OM, Giuliani A et al. Haemolytic uremic syndrome and kidney transplantation: a case series and review of the literature. Nephron 2017; 136: 245–253
17. Siedlecki AM, Ibel N, Vande Walle J et al. Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome. Kidney Int Rep 2018; 4: 434–446
18. Alpay N, Ozcelik U. Renal transplantation in patients with atypical hemolytic uremic syndrome: a single center experience. Transplant Proc 2019; 51: 2295–2297
19. Cavero T, Rabasco C, López A et al. Eculizumab in secondary atypical haemolytic uremic syndrome. Nephrol Dial Transplant 2017; 32: 466–474
20. Java A, Edwards A, Rossi A et al. Cytomegalovirus-induced thrombotic microangiopathy after renal transplant successfully treated with eculizumab: case report and review of the literature. Transpl Int 2015; 28: 1121–1125
21. Gonzalez Suarez ML, Thongprayoon C, Mao MA et al. Outcomes of kidney transplant patients with atypical haemolytic-uremic syndrome treated with eculizumab: a systematic review and meta-analysis. J Clin Med 2019; 8: 919
22. Campistol JM, Arias M, Ariceta G et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia 2015; 35: 421–447
23. Duineveld C, Verhave JC, Berger SP et al. Living donor kidney transplantation in atypical hemolytic uremic syndrome: a case series. Am J Kidney Dis 2017; 70: 770–777
24. Fakhouri F, Fila M, Provoost F et al. Pathogenic variants in complement genes and risk of atypical haemolytic uremic syndrome relapse after eculizumab discontinuation. Clin J Am Soc Nephrol 2017; 12: 50–59
25. Fakhouri F, Hourmant M, Campistol JM et al. Terminal complement inhibitor eculizumab in adult patients with atypical haemolytic uremic syndrome: a single-arm, open-label trial. Am J Kidney Dis 2016; 68: 84–89
26. Le Clech A, Simon-Tillaux N, Provoost F et al. Atypical and secondary haemolytic uremic syndromes have a distinct presentation and no common genetic risk factors. Kidney Int 2019; 95: 1443–1452
27. Huerta A, Arjona E, Portoles J et al. A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome. Kidney Int 2018; 93: 450–459