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Original Investigation

# Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series

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**Background:** The development of complement inhibitors has greatly improved the outcome of patients with atypical hemolytic uremic syndrome (aHUS), making kidney transplantation a more feasible option. Although prophylactic eculizumab therapy may prevent recurrent disease after transplantation, its necessity for all transplant recipients is debated.

**Study Design:** A case series.

**Setting & Participants:** Patients with aHUS who underwent living donor kidney transplantation after 2011 at 2 university centers, prospectively followed up with a protocol of eculizumab therapy limited to only recipients with documented posttransplantation recurrent thrombotic microangiopathy. In addition, the protocol emphasized lower target level tacrolimus and aggressive treatment of high blood pressure.

**Outcomes:** Recurrence of aHUS, kidney function, acute kidney injury.

**Results:** We describe 12 female and 5 male patients with a mean age of 47 years. 5 patients had lost a previous transplant due to aHUS recurrence. 16 patients carried a pathogenic or likely pathogenic variant in genes encoding complement factor H, C3, or membrane cofactor protein, giving a high risk for aHUS recurrence. Median follow-up after transplantation was 25 (range, 7-68) months. One patient had aHUS recurrence 68 days after transplantation, which was successfully treated with eculizumab. 3 patients were treated for rejection and 2 patients developed BK nephropathy. At the end of follow-up, median serum creatinine concentration was 106 (range, 67-175) μmol/L and proteinuria was negligible.

**Limitations:** Small series and short duration of follow-up.

**Conclusions:** Living donor kidney transplantation in aHUS without prophylactic eculizumab treatment appears feasible.

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***INDEX WORDS:*** Atypical hemolytic uremic syndrome (aHUS); prophylactic therapy; plasmapheresis; eculizumab; living donor; kidney transplantation; recurrence; complement; mutation; variant; thrombotic microangiopathy (TMA); drug costs; end-stage renal disease (ESRD); case series.

**Editorial, p. 754**

Thrombotic microangiopathy (TMA) is the term used to define the clinical syndrome characterized by microangiopathy, hemolysis, thrombocytopenia, and acute kidney injury. The differential diagnosis is wide ranging. Atypical hemolytic uremic syndrome (aHUS) is used to describe TMA affecting mainly the kidney in the absence of associated disease. Rare variants in complement genes are detected in 40% to 60% of these patients. These genetic abnormalities lead to uncontrolled activation of the alternative complement pathway and consequent endothelial damage. In the past, the outcome of patients with aHUS was dismal, with most patients reaching end-stage renal disease despite the use of plasmapheresis therapy. Kidney transplantation in patients with aHUS was not very successful due to the high recurrence rate and negligible efficacy of plasma therapy on transplant survival.[1] The introduction of the complement inhibitor eculizumab has significantly improved the prognosis of patients with aHUS,[2] also after kidney transplantation.[3]

Recently, a KDIGO (Kidney Disease: Improving Global Outcomes) conference was held concerning the use of eculizumab in aHUS.[4] The KDIGO work group recommends using eculizumab prophylaxis in case of a high recurrence risk after transplantation. Patients carrying a pathogenic variant and those with a previous early recurrence are considered high risk (50%-100% recurrence risk). In patients with a moderate recurrence risk (no pathogenic variant identified, isolated CFI

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variants, gene variants of unknown significance, or persistently low anti-CFH autoantibody titer), the decision to use eculizumab prophylaxis or plasma exchange is left to the treating physician. Although in patients with aHUS in native kidneys, eculizumab therapy may be discontinued, lifelong therapy is advised after kidney transplantation.[4,5] Firm evidence to support the need for prophylactic and/or lifelong eculizumab therapy in transplant recipients is lacking; the mentioned recommendations are based on expert opinion. Although the recurrence rate is high after kidney transplantation, a substantial number of patients do not develop a recurrence.[1,6] The risk for recurrence varies according to the genetic variant, but may also be influenced by environmental triggers such as ischemia-reperfusion injury or immunosuppressive drugs.[7]

The high costs of eculizumab warrant its responsible use. Therefore, in 2011, we adopted an alternative strategy for kidney transplantation in patients with aHUS in which no prophylactic eculizumab therapy is given and the reduction of triggers for aHUS is emphasized. The protocol dictated the preferential use of living kidney donors, use of low-dose calcineurin inhibitor (CNI) therapy, strict blood pressure control, and use of drugs that should limit endothelial injury. Previously, we described our experience in 4 patients.[8] We now provide data for a larger cohort with extended follow-up from 2 university medical centers in the Netherlands.

## METHODS

### Study Design

Two university medical centers in the Netherlands (Radboud University Medical Center in Nijmegen and University Medical Center Groningen in Groningen) participated in the study. Since 2011, all adult patients with aHUS diagnosed who underwent kidney transplantation were managed prospectively according our protocol. For this analysis, we retrospectively analyzed the data for patients who received a living donor kidney. Medical records were reviewed from kidney transplantation until last follow-up (April 1, 2017). Obtained data included demographics, previous history, variants in complement genes, immunosuppressive therapy, clinical data after transplantation, laboratory parameters, aHUS recurrence, and other complications affecting kidney function after transplantation. Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Recorded blood pressure is a manual office blood pressure measurement; when this was not available, automated home blood pressure measurements were used. Recurrence of aHUS was suspected by the presence of clinical evidence of TMA and confirmed by kidney transplant biopsy. In accordance with Dutch law, this study was exempted from formal approval by the ethics committee and the need for informed consent due to its retrospective nature.

### Transplantation Protocol

In 2011, when eculizumab therapy became available, we implemented a new strategy for the transplantation in patients with aHUS. Before 2011, kidney transplantations were performed with some reluctance because of the often unfavorable prognosis. The new strategy included the preferential use of living kidney donors, an immunosuppressive regimen based on basiliximab prophylaxis (20 mg on days 1 and 4), and triple therapy consisting of low-dose tacrolimus (starting dose, 0.03 mg/kg twice daily; target blood levels of 4-5 μg/L for the first 30 days, and 5-7 μg/L thereafter), prednisone (starting dose, 100 mg/d on days 1-3, thereafter 25 mg/d and tapering to 0.1 mg/kg/d [or to 5 mg/d in Groningen] at 3 months after transplantation), and high-dose mycophenolate mofetil (starting dose, 1,000 mg twice daily; target area under the curve, 40-60 mg/mL/h [or trough levels of 3 mg/mL in Groningen]), strict blood pressure control (target, <130/80 mm Hg), and the early use of statins and angiotensin-converting enzyme (ACE) inhibition. Details have been described.[8] This protocol differs from our standard kidney transplantation protocol in patients with other causes of kidney failure (specifics are provided in Item S1, provided as online supplementary material). Prophylactic vaccinations against meningococcal infection were administered before transplantation in most patients in view of the potential need for rescue eculizumab therapy. Patients were closely monitored during follow-up: daily for the first 2 weeks, twice weekly for the next 2 to 4 weeks, and weekly thereafter until 4 months after transplantation. Subsequently, the follow-up interval was gradually extended to every 6 weeks at 12 months and every 3 months after 2 years. Patients were instructed to perform home blood pressure measurements; in case of high blood pressure, the antihypertensive dose could be adjusted without a hospital visit or patients could be seen earlier at the outpatient clinic. Patients were instructed to contact their physician in case of symptoms or signs compatible with aHUS recurrence (ie, generalized malaise, high blood pressure, hematuria, edema, oliguria, dyspnea, and jaundice) or in case of potential triggers of aHUS, such as infections or pregnancy. During routine follow-up visits, blood and urine samples were collected for measurement of kidney function (creatinine and eGFR), hemolysis parameters (hemoglobin, thrombocytes, and lactate dehydrogenase [LDH]), and proteinuria. Haptoglobin was measured in case of a suspected recurrence and infrequently during routine visits.

Eculizumab therapy was started when signs of TMA occurred. In case of decreased kidney function, a kidney biopsy was performed for the purpose of diagnosing the cause of kidney injury

**Table 1.** Patient Characteristics at Kidney Transplantation

| Patient No.[a] | Sex | Age at current Tx, y | Donor | HLA Mismatch |
|---|---|---|---|---|
| 1 | F | 35 | LR | 3 |
| 2 | F | 29 | LR | 2 |
| 3 | F | 54 | LU | 4 |
| 4 | M | 46 | LU | 6 |
| 5 | F | 40 | LU | 5 |
| 6 | M | 58 | LU | 3 |
| 7 | F | 63 | LU | 5 |
| 8 | F | 24 | LU | 5 |
| 9 | M | 68 | LR | 3 |
| 10 | F | 40 | LU | 4 |
| 11 | F | 65 | LU | 5 |
| 12 | M | 30 | LU | 6 |
| 13 | F | 35 | LU | 4 |
| 14 | F | 52 | LU | 2 |
| 15 | M | 43 | LU | 0 |
| 16 | F | 56 | LU | 4 |
| 17 | F | 56 | LU | 1 |

Abbreviations: F, female; LR, living related; LU, living unrelated; M, male; Tx, transplantation.

[a]Patients 1 to 4 were previously described.[8]