Thrombotic microangiopathy and transplantation

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15. Transplantations-Workshop
vom 06.12.2013 - 08.12.2013

15. TRANSPLANTATIONS-WORKSHOP
06.12. bis 08.12.2013

Transplantationszentrum
Chirurgische Universitätsklinik
Ärztlicher Direktor: Prof. Dr. Dr. h. c. U. T. Hopt
Abteilung Nephrologie
Medizinische Universitätsklinik
Ärztlicher Direktor: Prof. Dr. G. Walz

Parkhotel Adler, Hinterzarten
Thrombotic microangiopathy (TMA) is a disorder characterized by an acute syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and variable signs of organ (kidney) injury due to platelet thrombosis in the microcirculation.

Tsai HM et al. Kid Int 2006; 70:16-23
Benz K et al. Curr Opin Nephrol Hypertens 2010;19:242-47
Chronic Uncontrolled Complement Activation Leads to Endothelial and End Organ Damage

Clinical Consequences:
- Blood clotting
- Platelet consumption
- Mechanical hemolysis
- Vessel occlusion
- Inflammation
- Ischemia
- Systemic organ complications

Loss of Natural Inhibitors Leads to Chronic Uncontrolled Complement Activation

Proximal

- Lectin Pathway
- Classical Pathway
- Alternative Pathway

Immune Complex Clearance
Microbial Opsonization

C3

C3 + H2O –

ALWAYS ACTIVE & REGULATED

(Crónic)

Natural Inhibitors:
Factor H, I, MCP, CD55

Natural Inhibitor:
CD59

Amplification

C5

Anaphylaxis
Inflammation
Thrombosis

Consequences

- Potent Anaphylatoxin
- Chemotaxis
- Proinflammatory
- Leukocyte/Monocyte Activation
- Endothelial Activation
- Prothrombotic

C5a

- Cell Lysis
- Proinflammatory
- Platelet Activation
- Leukocyte/Monocyte Activation
- Endothelial Activation
- Prothrombotic

C5b-9

Membrane Attack Complex

Consequences

- Cell Destruction
- Inflammation
- Thrombosis

Consequences

Chronic Progressive TMA Causes
Systemic Life-threatening Clinical Complications

**Cardiovascular**
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy

**Renal**
- Elevated creatinine
- Edema, malignant hypertension
- Renal failure
- Dialysis, transplant

**Systemic Thrombosis, Inflammation, Occlusion of Small Vessels**

**CNS**
- Confusion
- Seizures
- Stroke
- Encephalopathy

**Gastrointestinal**
- Liver necrosis
- Pancreatitis
- Colitis, Diarrhea
- Nausea/vomiting
- Abdominal pain

**Pulmonary**
- Dyspnea
- Pulmonary edema
- PE

**Blood**
- Hemolysis
- Thrombocytopenia
- Fatigue
- Transfusions

**Impaired Quality of Life**
- Fatigue
- Pain/Anxiety
- Reduced mobility

Pathology of Thrombotic Microangiopathy (TMA)

- Pathological lesion
- Thrombus (clot) formation in microvasculature (small vessels)
- Multiple clots lead to ischemia (deficiency of blood flow to an organ or tissue) and organ dysfunction

Microangiopathic Hemolysis
- Presence of schistocytes

Causes of Systemic Thrombotic Microangiopathy

SYSTEMIC THROMBOTIC MICROANGIOPATHY:
- Multiple thromboses and inflammation throughout the body
- Cell surface and fluid phase complement inhibitors
- aHUS
- STEC-HUS
- TTP
- Genetic defect in complement regulation
- Shiga toxin
- Severe deficiency of ADAMTS13 activity
- Direct complement activation
- Interferes with Complement regulation
- Endothelial damage
- Uncleaved long VWF multimeric strings
- Chronic uncontrolled complement activation
- Platelet, white blood cell, and endothelial cell activation

Thrombotic microangiopathy: Pathogenesis

Loss of Natural Inhibitors Leads to Chronic Uncontrolled Complement Activation

SECONDARY TMA

aHUS  -----------  STEC-HUS

GENETIC PREDISPOSITION
Mutations - SNPs
(FH, FHRP, FI, C3, MCP)

ENDOTHELIAL INJURIES
Thrombotic microangiopathy and transplantation

TMA-Tx

De Novo

Recurrence

STEC-HUS

aHUS
Thrombotic microangiopathy and transplantation

Differential Diagnosis

**De Novo HUS**
- aHUS: Recurrence
- No history HUS
- Only graft involved – sCr
- Mild - Progressive
- Histology (TMA)
  - No hematological TMA
  - Secondary: CNI – mTORi
- Viral infections
- ABMR – Severe IRI
  - Reversible – Correct F/U

**Medical history HUS/TMA**
- Systemic involvement
- Severe – Abrupt
- AKI – ARF
- Hematological TMA
- Histology (TMA)
  - No precipitation factors
  - Irreversible – Lost graft

*J. Zuber et al. / Transplantation Reviews 27 (2013) 117–125*
Thrombotic microangiopathy and transplantation

aHUS – RENAL TRANSPLANTATION

- Treatment
- Prevention (recurrence)
Post-transplant aHUS recurrence
Eculizumab binds with high affinity to C5

- Terminal complement - C5a and C5b-9 activity blocked

- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex clearance
  - Microbial opsonization

- **Approved:** PNH and aHUS

Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation

J. Zuber\textsuperscript{a, *}, M. Le Quintrec\textsuperscript{b}, S. Krid\textsuperscript{c}, C. Bertoye\textsuperscript{d}, V. Gueutin\textsuperscript{e}, A. Lahoche\textsuperscript{f}, N. Heyne\textsuperscript{g}, G. Ardissino\textsuperscript{h}, V. Chatelut\textsuperscript{i}, L.-H. Noël\textsuperscript{d}, M. Houman\textsuperscript{j}, P. Niaudet\textsuperscript{c}, V. F. Bacchi\textsuperscript{k}, E. Rondeau\textsuperscript{l}, C. Legendre\textsuperscript{a}, and C. Loirat\textsuperscript{m} for the French Study Group for atypical HUS
Improvement in renal function with eculizumab treatment in both trials

- In patients with progressing TMA
- In patients with long disease duration and CKD
## Trial 002 (Progressing TMA)
### Patients baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients with native kidneys (N=10)</th>
<th>Patients with a transplant (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean, range)</td>
<td>28 (17-68)</td>
<td>37 (21-47)</td>
</tr>
<tr>
<td>No identified complement mutation or anti-CFH antibodies (%)</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Mean time from clinical manifestation of HUS to screening (months) (SD)</td>
<td>0.67 (0.47)</td>
<td>1.71 (1.4)</td>
</tr>
<tr>
<td>Mean eGFR at baseline (SD)</td>
<td>27.0 (14.8)</td>
<td>17.1 (12.9)</td>
</tr>
</tbody>
</table>
Clinical Report

Rescue therapy with eculizumab in a transplant recipient with atypical haemolytic-uraemic syndrome

Carlos E. Durán, Miquel Blasco, Francisco Maduell and Josep M. Campistol
(28/10/2009): DIAGNOSIS: thrombotic microangiopathy, COMPATIBLE WITH RECURRENCE OF aHUS. NO EVIDENCE OF REJECTION.
<table>
<thead>
<tr>
<th></th>
<th>Result</th>
<th>Reference intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>79</td>
<td>(65–110)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>29/A</td>
<td>(6–25)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.82/A</td>
<td>(0.30–1.30)</td>
</tr>
<tr>
<td>Glomerular filtration rate (MDRD), mL/min / 1.73 m²</td>
<td>45.02</td>
<td></td>
</tr>
<tr>
<td>For MDRD equation, calculation assumes patient is white</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum haptoglobin, g/L</td>
<td>1.070</td>
<td>(0.320–1.810)</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>854/A</td>
<td>(20–400)</td>
</tr>
<tr>
<td>Transferrin, g/L</td>
<td>2.0/B</td>
<td>(2.2–3.6)</td>
</tr>
<tr>
<td>Iron binding capacity, mg/L</td>
<td>2.81</td>
<td></td>
</tr>
<tr>
<td>Transferrin saturation, serum, %</td>
<td>31.67</td>
<td></td>
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<tr>
<td><strong>Haematology</strong></td>
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<tr>
<td>Leucocytes, 10⁹/L</td>
<td>6.86</td>
<td>(4.00–11.00)</td>
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<tr>
<td>Red blood cells, 10¹²/L</td>
<td>4.79</td>
<td>(3.90–5.50)</td>
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<tr>
<td>Haemoglobin, g/dL</td>
<td>14.3</td>
<td>(12.0–17.0)</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.450</td>
<td>(0.360–0.510)</td>
</tr>
</tbody>
</table>

MDRD, Modification of Diet in Renal Disease
An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document

Elevated clinical suspicion of post-transplant TMA
(non-immune haemolytic anaemia + thrombocytopenia + graft dysfunction)

Individualised evaluation of the need for renal biopsy

History of aHUS-caused TCRF
Probable recurrence (complete differential diagnosis)
Evaluate early use of eculizumab

TMA with no history of aHUS
Plasma exchanges + removal of CNI
Evaluate eculizumab in resistant cases

Secondary TMA
AHR
CMV
BK virus
Aetiological treatment
Thrombotic microangiopathy and transplantation

aHUS – RENAL TRANSPLANTATION

- Treatment
- Prevention (recurrence)
Table 3. Clinical characteristics of patients with atypical haemolytic uraemic syndrome based on complement abnormality

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Nefrologia 2013;33(1):27-45
Pre-transplant assessment of post-transplant recurrence risk relies on genetics

71 grafts in 57 patients with complete complement investigation

- No mutation and no at risk CFH haplotypes, n=16, "Controls"
- No mutation but 2 at risk CFH haplotypes, n=7
- CFI mutation, n=11
- CFH mutation, n=22
- C3/CFB gain of function mutation, n=7

Le Quintrec et al, Am J Transplant 2013
aHUS - Prevention of post-RT recurrence

Options to prevent post-RT recurrence:

- Combined hepatic–renal transplantation
- Renal transplant + plasma exchange
- Renal transplant + eculizumab
Successful Liver-Kidney Transplantation in Two Children With aHUS Caused by a Mutation in Complement Factor H

H. Jalanko\textsuperscript{a, *}, S. Peltonen\textsuperscript{b}, A. Koskinen\textsuperscript{c,f},
J. Punttila\textsuperscript{a}, H. Isoniemi\textsuperscript{d}, C. Holmberg\textsuperscript{a},
A. Pinomäki\textsuperscript{e}, E. Armstrong\textsuperscript{e}, A. Koivusalo\textsuperscript{d},
E. Tukiainen\textsuperscript{d}, H. Mäkisalo\textsuperscript{d}, J. Saland\textsuperscript{g},
G. Remuzzi\textsuperscript{h}, S. de Cordoba\textsuperscript{i}, R. Lassila\textsuperscript{e},
S. Meri\textsuperscript{c,f} and T. S. Jokiranta\textsuperscript{c,f}
Experience with liver or combined liver / kidney transplantation in aHUS patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Peri- and post-transplant morbidity</th>
<th>Transplant outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined liver and kidney transplant</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Loirat et al. 2012</td>
<td>Cerebral ischaemia related to vena cava syndrome</td>
<td>Fatal</td>
<td>–</td>
</tr>
<tr>
<td>Remuzzi et al. 2005</td>
<td>Irreversible liver failure with extensive vascular thrombosis</td>
<td>Fatal</td>
<td>–</td>
</tr>
<tr>
<td>Saland et al. 2009b</td>
<td>Hepatic artery thrombosis, hepatic encephalopathy</td>
<td>Fatal</td>
<td>–</td>
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<tr>
<td>Loirat et al. 2012</td>
<td>No morbidity reported</td>
<td>Fatal</td>
<td>–</td>
</tr>
<tr>
<td>Loirat et al. 2012</td>
<td>Liver failure and hepatic necrosis</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Saland et al. 2009b</td>
<td>Severe post-transplant hypertension</td>
<td>Survived</td>
<td>2 yrs post Tx</td>
</tr>
<tr>
<td>Jalanko et al. 2008</td>
<td>Generalised seizures associated with high blood pressure</td>
<td>Survived</td>
<td>8 months post Tx</td>
</tr>
<tr>
<td>Jalanko et al. 2008</td>
<td>Hypertension, polyuria, electrolyte loss</td>
<td>Survived</td>
<td>Mild hemiplegia at 14 months post Tx</td>
</tr>
<tr>
<td>Remuzzi et al. 2002</td>
<td>Severe hepatic encephalopathy requiring re-transplantation</td>
<td>Survived</td>
<td>Died 3 yrs post Tx</td>
</tr>
<tr>
<td>Wilson et al. 2011</td>
<td>Biliary stricture and acute pancreatitis</td>
<td>Survived</td>
<td>1 yr post Tx</td>
</tr>
<tr>
<td>Sanchez-Corral 2010</td>
<td>No morbidity reported</td>
<td>Survived</td>
<td>~2-3 yrs post Tx</td>
</tr>
<tr>
<td>Koskinen et al. 2011</td>
<td>No morbidity reported</td>
<td>Survived</td>
<td>3 yrs post Tx</td>
</tr>
<tr>
<td>Saland et al. 2009a</td>
<td>No morbidity reported</td>
<td>Survived</td>
<td>Unknown</td>
</tr>
<tr>
<td>Saland et al. 2006</td>
<td>No major morbidity</td>
<td>Survived</td>
<td>28 months post Tx</td>
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<tr>
<td><strong>Liver transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haller et al. 2010</td>
<td>Hypertensive encephalopathy, superior vena cava obstruction</td>
<td>Survived</td>
<td>2 yr post Tx</td>
</tr>
<tr>
<td>Cheong et al. 2004</td>
<td>Infection associated with immunosuppression</td>
<td>Survived</td>
<td>Died 11 months after Tx</td>
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<tr>
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<td>Survived</td>
<td>Unknown</td>
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aHUS - Prevention of post-RT recurrence

Options to prevent post-RT recurrence:

- Combined hepatic–renal transplantation
- Renal transplant + plasma exchange
- Renal transplant + eculizumab
aHUS - Prevention of post-RT recurrence

RT + eculizumab/PE: living or deceased donor?

• Living donor:
  – Risk of recurrence
  – Future problems for donor
  – Anticipated treatment with eculizumab
  – Excellent renal function

• Deceased donor:
  – Risk of recurrence
  – Long-time WL
  – ECD
  – No previous treatment with eculizumab

RT, renal transplant
Options to prevent post-RT recurrence:

- Combined hepatic–renal transplantation
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Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation


Case Report

Renal Transplantation Under Prophylactic Eculizumab in Atypical Hemolytic Uremic Syndrome With CFH/CFHR1 Hybrid Protein

S. Krid, LT. Roumenina, D. Beury, M. Charbit, O. Boyer, V. Frémeaux-Bacchi and P. Niaudet

hemolytic anemia, thrombocytopenia and acute renal failure. Most cases of HUS are associated with diarrhea and caused by enterohemorrhagic E. Coli (typical HUS). Atypical forms of HUS represent 5% of HUS cases in children. Ge-
Patient history and presentation

- Female patient, aged 24 years, diagnosed with aHUS in April 2008
- Patient received PE and corticosteroids
  - No improvement in kidney function → progressed to ESRD
- Renal replacement therapy with haemodialysis initiated 1 month later

aHUS, atypical Haemolytic Uraemic Syndrome; ESRD, end-stage renal disease; PE, plasma exchange
Complement and genetic analysis

- Low levels of complement C3
- Normal levels of C4, CFH and CFI
- Normal MCP levels in lymphocytes
- No evidence of anti-CFH autoantibodies
- Normal ADAMTS13 activity: 90%
- Heterozygous mutation (c.3497C>T) in the C terminus region of CFH gene identified
  - Inherited from her asymptomatic mother
  - Father had no relevant aHUS risk factors

*C3, complement component 3; C4, complement component 4; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein*

**Table 3.** Clinical characteristics of patients with atypical haemolytic uraemic syndrome based on complement abnormality

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Kidney transplantation

- September 2011: living donor kidney transplantation; father donor
- Immunosuppression: mycophenolate mofetil, steroids, sirolimus and antithymocyte globulin
- Patient received an initial dose of eculizumab (900 mg) - 1 week prior to the transplant
  - Meningococcal vaccination 6 weeks before starting eculizumab
  - Patient received a further 1200 mg eculizumab during surgery
  - Eculizumab was continued at 900 mg/week for 4 weeks, then 1200 mg every 2 weeks
- Patient received prophylactic antibiotic during the first 3 months post-transplantation
Laboratory findings following transplantation

- Creatinine (mg/dL):
  - Post-transplantation:
    - Day 0: 8
    - Days 30 to 360: 2

- LDH (U/L):
  - Post-transplantation:
    - Day 0: 600
    - Days 30 to 360: 400

Eculizumab infusion:
- Eculizumab 900 mg
- Eculizumab 1200 mg

LDH, lactate dehydrogenase
Laboratory findings following transplantation

- **Platelets (10⁹/L)**
  - Eculizumab infusion
  - Eculizumab 900 mg
  - Eculizumab 1200 mg

- **Haptoglobin (g/L)**

<table>
<thead>
<tr>
<th>Days</th>
<th>Platelets</th>
<th>Haptoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30</td>
<td>450</td>
<td>0.8</td>
</tr>
<tr>
<td>60</td>
<td>400</td>
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<td>90</td>
<td>350</td>
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<td>120</td>
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<td>150</td>
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<td>1.6</td>
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<td>180</td>
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<tr>
<td>210</td>
<td>150</td>
<td>2.0</td>
</tr>
<tr>
<td>240</td>
<td>100</td>
<td>2.2</td>
</tr>
<tr>
<td>270</td>
<td>50</td>
<td>2.4</td>
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<tr>
<td>300</td>
<td>0.0</td>
<td>2.6</td>
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<tr>
<td>330</td>
<td>0.2</td>
<td>2.8</td>
</tr>
<tr>
<td>360</td>
<td>0.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

- Graph showing platelet and haptoglobin levels over time with Eculizumab infusions indicated.
Clinical course following transplantation

- Rapid improvement in kidney function
- Biopsies taken at 2 weeks, 3 and 12 months post-surgery:
  - Minimal chronic vascular changes
  - No signs of rejection or disease activity
- 26 months post-transplantation (Nov'13):
  - Patient continues to receive maintenance therapy with eculizumab every 2 weeks
  - Normal graft function: sCr 0.8 mg/dL – CrCl 75 mL/min
  - No proteinuria
  - Haematological parameters remain normal (normal haemoglobin)
  - No opportunistic infections or surgical complications
1. Post-transplant TMA is a frequent clinical situation, associated with different endothelial aggressiveness factors.

2. Differential diagnosis must be considered between de novo HUS and aHUS recurrence.

3. Polymorphisms or mutations in complement regulating genes have been described in patients with de novo post-transplant HUS.

4. The incidence of post-transplant aHUS recurrence depends on the different gene mutations (15% MCP; 80% soluble factors).
5. Recurrence of aHUS is generally associated with poor prognosis and follow-up (graft failure).

6. Treatment of aHUS recurrence in transplant patients must be similar to the native kidneys. Eculizumab must be the first option, as soon as possible.

7. Prevention of aHUS recurrence is mandatory in some associated mutations (CHF/CIF/C3). Combined liver and kidney transplantation or the prophylactic use of Eculizumab seem the best strategies to prevent post-transplant recurrence.
BACK-UP SLIDES
Suggested protocol for eculizumab prophylaxis for renal transplant in aHUS

Candidates for renal transplantation with aHUS-related ESRD

Deceased-donor renal transplantation

Recipient risk assessment

Living-donor renal transplantation

Living non-related donor

Living related donor

Donor risk assessment

Low risk of recurrence

- Isolated MCP mutation
- Long-term negative anti-CFH antibody

No prophylaxis

Moderate risk of recurrence

- Isolated CFI mutation
- No identified mutation
- Mutation with unknown effect
- Persistent low-titre anti-CFH antibody

Prophylactic eculizumab or PE*

High risk of recurrence

- Previous early recurrence in the same individual or within the family
- Mutations in CFH, NAHR in CFH region, gain-of-function mutations in C3 and CFB

Prophylactic eculizumab‡

PE or eculizumab-conditioned CLKT‡

Prophylactic eculizumab

PE or eculizumab-conditioned CLKT

No prophylaxis

Low risk

- The donor does not harbour the mutation found in the recipient that has an indisputable role in the disease pathogenesis

Living related donor RTx may be permitted

High or moderate risk

- The donor shares a genetic susceptibility factor to aHUS with the recipient
- No mutations have been identified in either the donor or the recipient

Living related donor RTx should not be performed

PE: plasma exchange

### Kidney Transplant Does Not Address the Cause of aHUS

<table>
<thead>
<tr>
<th>Affected Protein</th>
<th>Outcome of Kidney Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor H</td>
<td>Percent of patients with ongoing TMA: 80-90%</td>
</tr>
<tr>
<td>CFHR1, R3</td>
<td>Percent of patients with ongoing TMA: 20%</td>
</tr>
<tr>
<td>MCP</td>
<td>Percent of patients with ongoing TMA: 15-20%</td>
</tr>
<tr>
<td>Factor I</td>
<td>Percent of patients with ongoing TMA: 70-80%</td>
</tr>
<tr>
<td>Factor B</td>
<td>Ongoing TMA in one published case</td>
</tr>
<tr>
<td>C3</td>
<td>Percent of patients with ongoing TMA: 40-50%</td>
</tr>
<tr>
<td>THBD</td>
<td>Ongoing TMA in one published case</td>
</tr>
</tbody>
</table>

More than 90% of these patients experienced graft loss, most within the first year\(^2\)

Investigations are Required to Unmask Other Causes of TMA

Thrombotic microangiopathy: Pathogenesis

Loss of Natural Inhibitors Leads to Chronic Uncontrolled Complement Activation

**Driving force**

- **CFH/CFHR1**
- **CFH**
- **C3**
- **CFB**

- Isolated **CFI**
  - Positive anti-CFH Ab
  - Homozygous *gtgt* CFH
  - Combined **MCP**

- Isolated **MCP**
  - Negative anti-CFH Ab

**Triggers**

- Brain death
- I/R injury
- Rejection
- Infections
- IS drugs