Renal transplantation and Hemolytic Uremic Syndrome: What’s new?

Julien Zuber
Renal Transplantation, Necker Hospital

26/04/2010
- Recurrent vs de novo HUS -

- Post-renatal transplant HUS is classically split into **two separate entities**:  
  - recurrence of non-infection-related HUS (atypical HUS)  
  - de novo HUS (in 1 to 5% of renal transplant recipients)

- The risk of recurrence depends on the mechanisms involved:  
  - **typical** (infection-related) HUS has a **low rate** of recurrence (<1%)  
  - **atypical** HUS may recur **in up to 100%** of patients, in whom the alternative pathway of the complement system is deregulated

- Alternative complement pathway -
- Alternative complement pathway -

- Paradigm for post-transplant HUS -

de novo HUS

- Genetic Susceptibility
  - 30%
  - Alternative Complement Pathway Deregulation
    - Mutation, Polymorphism
    - Anti-FH Auto-antibodies
  - 60%

- Environmental factors

Donor genetic background

MCP

Endothelial Injuries
1. Immunosuppressive drugs
2. Virus
3. Ischemia-reperfusion lesions
4. Rejection

Recurrent HUS

Zuber submitted
Post-transplant aHUS recurrence
- Membrane vs Circulating factor -

High risk (70-90%)
- Membrane vs Circulating factor -

High risk (70-90%)

Low risk (15-20%)
A mutation in CFH was found in 20 to 30% of aHUS

Noris NEJM 2009
- Mutation in CFH -

- Quantitative deficiency
  - Reduced FH level
  - Uncontrolled activation in fluid phase
  - Membrano-proliferative GN (homozygous and heterozygous mutations)

- Functional deficiency
  - Normal FH level
  - Uncontrolled activation on endothelium surface
  - HUS (heterozygous mutation)

- Mutation in CFH -

- Recurrence rate is comprised between 70 and 90%
  - In 2006 a meta-analysis reported 36 renal transplantations in 27 aHUS patients with a mutation in CFH. **Recurrence occurred in 74%**
  - In two *French series*, the recurrence frequency was **80%** in 5 children and **75%** in 16 adults, who had received 6 and 17 renal transplants, respectively

- Recurrence was responsible for **graft loss in 60%** of these patients

- Mutations affecting the **first 15 SCR** are associated with a **lower risk** for recurrence **than** mutations affecting the **last SCR 19 and 20** (44 vs 76%)

- Anti-Factor H autoantibodies

- In 5 to 10% of aHUS patients, anti-CFH Ab are readily detected
- aHUS associated with anti-CFH Ab occurred primarily between 4 and 12 years of age
Genetic susceptibility to anti-FH Ab

- Anti-FH Ab are tightly associated with homozygous deletion of CFHR1
  - in 3 to 8% of controls
  - in 14 to 23% of aHUS patients
  - in >90% of aHUS with anti-CFH Ab

- Anti-Factor H autoantibodies

● The risk of recurrence of aHUS in patients with anti-CFH Ab is not well understood.

● The risk of recurrence correlates positively with anti-CFH Ab titer
  ● Absence of recurrence despite lack of specific treatment in patients with low or undetectable anti-CFH titer
  ● Enhanced complement activation in vitro correlated with increased anti-CFH titers

Le Quintrec AJT 2009, Strobel NDT 2010, Moore Blood 2010
A mutation in *CFI* was found in 2 to 12% of aHUS.
Mutations in *CFI* gene are more frequently associated with quantitative deficiency than functional deficiency.
Renal transplantation in aHUS patients with CFI mutations has been also associated with a high recurrence rate and poor prognosis.

The reported cases in the literature consist in 15 renal transplants, received by ten patients. Twelve (80%) failed consecutively because of HUS recurrence.

In the French multi-centric adult series, recurrence occurred in 5 out of 11 renal transplantations (45%) performed in 10 patients (Jablonski ASN congress 2009).
In the 23 patients with mutation in *CFI* in the French cohort:

- 7 (30%) have an **additional genetic susceptibility** factor to HUS such as mutation in *CFH, MCP, CFB* or *C3*
- 5 (21%) have an homozygous deletion of *CFHR1*

Patients with a complete deletion of the *CFHR1* gene had a significantly higher risk of bad prognosis compared with those with isolated *CFI* mutation.
Heterozygous mutation in MCP gene was found in **10 to 15 %** of aHUS.

Given the transmembrane location of MCP, a **low risk of recurrence after renal transplantation** and a poor response to plasma therapy are expected.

However, among 15 renal transplantations performed in 12 recipients with mutation, **3 recurrences have been reported** (20%).

- Mutation in MCP -

The expression of MCP by graft endothelium is driven by the donor genome. How to explain recurrence?

- **Endothelial chimerism**: graft endothelial cells may be partially replaced by circulating endothelial cells of donor origin.

- MCP mutation might be associated with **another unknown genetic abnormality**.
Among the 7 aHUS patients in whom a mutation in THBD was identified, post-transplant recurrence was reported in one of them (14%) …

<table>
<thead>
<tr>
<th>Patient</th>
<th>AA change</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

… although the graft should bear a wild-type THBD molecule, limiting the risk of recurrence
Gain-of-function mutation in C3

Unable to bind MCP and FH

Heterozygous mutation in C3 gene was found in 10% of aHUS

Noris NEJM 2009
Gain-of-function mutation in C3

Among aHUS patients with **C3 mutations**, recurrence was reported in 5 out of 12 renal transplantations (42%).

Whether production of wild type C3 by the graft might account for a reduced rate of recurrence compared with **CFH** and **CFI** is a tempting but speculative hypothesis.

Gain-of-function mutation in *CFB*

- Heterozygous mutation in *CFB* gene was found in 1% of aHUS
- Four renal transplantations have been performed in 3 aHUS patients with *CFB* mutations. **All four (100%) failed secondary to HUS recurrence**

Goicoechea de Jorge PNAS 2007, Roumenina Blood 2009
- In the era of Complement genetics -

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein Affected</th>
<th>Main Effect</th>
<th>Frequency</th>
<th>Response to Short-Term Plasma Therapy</th>
<th>Long-Term Outcome</th>
<th>Outcome of Kidney Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H</td>
<td>No binding to endothelium</td>
<td>20–30</td>
<td>Rate of remission: 60% (dose and timing dependent)</td>
<td>Rate of death or ESRD: 70–80%</td>
<td>Rate of recurrence: 80–90%</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>Factor HR1, R3</td>
<td>Anti-factor H antibodies</td>
<td>6</td>
<td>Rate of remission: 70–80% (plasma exchange combined with immunosuppression)</td>
<td>Rate of ESRD: 30–40%</td>
<td>Rate of recurrence: 20%</td>
</tr>
<tr>
<td>MCP</td>
<td>Membrane cofactor protein</td>
<td>No surface expression</td>
<td>10–15</td>
<td>No definitive indication for therapy</td>
<td>Rate of death or ESRD: &lt;20%</td>
<td>Rate of recurrence: 15–20%</td>
</tr>
<tr>
<td>CFI</td>
<td>Factor I</td>
<td>Low level or low cofactor activity</td>
<td>4–10</td>
<td>Rate of remission: 30–40%</td>
<td>Rate of death or ESRD: 60–70%</td>
<td>Rate of recurrence: 70–80%</td>
</tr>
<tr>
<td>CFB</td>
<td>Factor B</td>
<td>C3 convertase stabilization</td>
<td>1–2</td>
<td>Rate of remission: 30%</td>
<td>Rate of death or ESRD: 70%</td>
<td>Recurrence in one case</td>
</tr>
<tr>
<td>C3</td>
<td>Complement C3</td>
<td>Resistance to C3b inactivation</td>
<td>5–10</td>
<td>Rate of remission: 40–50%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Rate of recurrence: 40–50%</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>Rate of remission: 60%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Recurrence in one case</td>
</tr>
</tbody>
</table>

Noris NEJM 2009
A complex polygenetic disease

- The **penetrance** for mutations in \textit{CFH}, \textit{CFI}, \textit{MCP}, \textit{C3}, \textit{CFB} and \textit{THBD} is estimated at **50%**.

- At least 10\% of patients have a combination of two mutations.

- **Genetic polymorphisms** in \textit{CFH}, \textit{MCP}, \textit{CFHR1}, \textit{C4bBP} could influence the development and severity of disease.

In families with inherited mutation-related aHUS, affected individuals frequently harbor additional genetic factor for HUS, while healthy carriers of the mutation do not.

A complex polygenic disease

Esparza-Gordillo Mol Immunol 2006
De novo HUS
“Environmental theory”

Immunosuppressive drugs
- CNI (Endothelin-1)
- m-TOR inhibitor (VEGF)

Acute rejection
- AMR +++
- ACR

Endothelial injury

I/R injury
- Toll-like receptors
- Complement

Virus
- CMV
- VZV
- Parvovirus B19

Genetic susceptibility to *de novo* HUS

A mutation in *CFH* or *CFI* was found in 7 out of 24 (29%) patients with *de novo* HUS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cause of ERSD</th>
<th>Mutation</th>
<th>Protein domain</th>
<th>Mutation characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NAS</td>
<td>p.Asn516Lys (c.1548T&gt;A)</td>
<td>SCR9</td>
<td>SCR9 is implicated binding of CFH to the C3c and heparin</td>
</tr>
<tr>
<td>2</td>
<td>CrGN</td>
<td>p.Gln950His (c.2850G&gt;T)</td>
<td>SCR16</td>
<td>SCR16 is implicated binding of CFH to C3b/C3d, as well as to endothelial cells. Q950H has been reported in one patient with aHUS (28)</td>
</tr>
<tr>
<td>3</td>
<td>CrGN</td>
<td>p.Lys1186His (c.3557A&gt;C)</td>
<td>SCR 20</td>
<td>SCR20 is highly implicated binding of CFH to C3b/C3d, as well as to endothelial cells</td>
</tr>
<tr>
<td>CFI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>IgAN</td>
<td>p.Ser90Asn (c.269G&gt;A); S72N</td>
<td>FIMAC</td>
<td>Associated with a reduced CFI concentration seem to result in quantitative defect</td>
</tr>
<tr>
<td>1</td>
<td>NAS</td>
<td>p.Gly162Asp (c.485G&gt;A); G144D</td>
<td>CD5</td>
<td>Associated with a reduced CFI concentration seem to result in quantitative defect</td>
</tr>
<tr>
<td>5</td>
<td>NAS</td>
<td>p.Ile416Leu (c.426A&gt;C); I398L</td>
<td>SP</td>
<td>Associated with a normal CFI concentration; presumed functional deficiency has not yet been defined; reported in one patient with aHUS (4)</td>
</tr>
<tr>
<td>6</td>
<td>Und</td>
<td>p.Ile306Val (c.916A&gt;G); I288V</td>
<td>LDLRA-2</td>
<td>Associated with a normal CFI concentration; presumed functional deficiency has not yet been defined</td>
</tr>
<tr>
<td>3</td>
<td>CrGN</td>
<td>p.Ile340Thr (c.1019T&gt;C); I322T</td>
<td>Between Heavy and light chain</td>
<td>I322T has been reported in one patient with aHUS (32) Complete loss C3b cofactor activity (33)</td>
</tr>
<tr>
<td>7</td>
<td>MPGN</td>
<td>IVS12 + 5 (c.1536 + 5 G&gt;T)</td>
<td>Spice defect</td>
<td>Previously reported in patients with aHUS (4,6)</td>
</tr>
</tbody>
</table>

Le Quintrec AJT 2008
Who should be investigated and how?
# Recommended investigations

<table>
<thead>
<tr>
<th>Target</th>
<th>Test</th>
<th>Method</th>
</tr>
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<tbody>
<tr>
<td>CFH and CFH related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFH gene</td>
<td>Coding sequence analysis</td>
<td>Direct sequencing</td>
</tr>
<tr>
<td>CFH-CFHR1 hybrid gene</td>
<td></td>
<td>MLPA</td>
</tr>
<tr>
<td>CFHR1-CFHR3 deletion/duplication</td>
<td></td>
<td>MLPA/PCR</td>
</tr>
<tr>
<td>CFH protein</td>
<td>CFH serum levels</td>
<td>ELISA/RID</td>
</tr>
<tr>
<td></td>
<td>Anti-CFH antibodies</td>
<td>ELISA</td>
</tr>
<tr>
<td></td>
<td>CFH activity</td>
<td>Hemolytic assay</td>
</tr>
<tr>
<td>CFHR1 protein</td>
<td>CFHR1-CFHR3 in serum</td>
<td>Western Blot</td>
</tr>
<tr>
<td></td>
<td>CFHR1 serum levels</td>
<td>ELISA</td>
</tr>
<tr>
<td>MCP</td>
<td></td>
<td></td>
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<td>MCP gene</td>
<td>Coding sequence analysis</td>
<td>Direct sequencing/MLPA</td>
</tr>
<tr>
<td>MCP protein</td>
<td>MCP expression on leukocytes</td>
<td>FACS</td>
</tr>
<tr>
<td>CFI</td>
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<td></td>
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<td>CFI serum levels</td>
<td>ELISA</td>
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<td>CFB protein</td>
<td>CFB/Bb serum levels</td>
<td>ELISA/RID/nephelometry</td>
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<td></td>
<td></td>
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<td>C3 gene</td>
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<td>C3 protein</td>
<td>C3/C3a/C3d in serum, plasma</td>
<td>ELISA, nephelometry</td>
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Recommended investigations

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<td>CFH-CFHR1 hybrid gene</td>
<td>MLPA</td>
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<tr>
<td>CFH protein</td>
<td>CFHR1-CFHR3 deletions</td>
<td>MLPA</td>
</tr>
<tr>
<td>CFHR1</td>
<td></td>
<td>MLPA</td>
</tr>
<tr>
<td>MCP</td>
<td></td>
<td>ELISA/RID/nephelometry</td>
</tr>
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<td>MCP gene</td>
<td></td>
<td>ELISA/RID/nephelometry</td>
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<td>MCP protein</td>
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<td>ELISA/RID/nephelometry</td>
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<td>CFI</td>
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<td>ELISA/RID/nephelometry</td>
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<td>C3 gene</td>
<td>C3/C3a/C3d in serum, plasma</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td>C3 protein</td>
<td></td>
<td>ELISA, nephelometry</td>
</tr>
</tbody>
</table>

- All atypical HUS
- De novo post-transplant HUS
- Typical HUS

Chronic, severe, recurrent forms

Saland JASN 2009
List of laboratories

R. Smith
Iowa City

V. Fremeaux-Bacchi
Paris

T. Goodship
Newcastle upon Tyne

P. Zipfel
Jena

S. Rodriguez de Cordoba
Madrid

M. Noris
Ranica

Therapeutics: aims and tools?
CNI avoidance?

● The benefit of CNI-free protocol in post-transplant HUS remains controversial. These discrepant findings could be explained by:

  ➔ Limited number of patients receiving CNI-free treatment
  ➔ The most frequent CNI-free protocol relied on SRL-based regimen

● However, a maintenance regimen based on belatacept, instead of CNI, has shown promising results


SRL-induced downregulation of VEGF predisposes to TMA
Plasma therapy

- In recurrent forms, **curative plasma exchange therapy has failed in most studies**, including the French adult series, to hamper pejorative evolution

- Therefore **preemptive plasma therapy** has been proposed for patients with aHUS-related ESRD.

  - **Successful in 10 renal transplant recipients** (4, 3 and 1 with mutations in \( CFH \), \( CFI \) and \( C3 \), respectively and 2 with anti-FH Ab)

  - Achievement of a **metastable state** which would not preclude a delayed recurrence, after either a reduction in plasma support or an infection
Preemptive Plasma therapy

- **Aug 1998**: late-onset aHUS in a **42 year-old female**
- **Sept 1998**: starts hemodialysis

- **Mar 2000**: 1st deceased-donor renal transplantation
  - HUS recurrence at 5 months post-transplant
  - Intensive plasma therapy (PE and plasma infusions)

- **Feb 2004**: Return to hemodialysis

- **2006-2007**: Identification of a **new mutation in C3 gene**

![Diagram showing mutation K155Q in C3 gene]
Preemptive Plasma therapy

Mar 2007: 2\textsuperscript{nd} deceased-donor renal transplantation (51 year-old)

<table>
<thead>
<tr>
<th>Renal biopsy</th>
<th>Normal</th>
<th>Normal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine levels (µmol/L)</td>
<td>75</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>FPI</td>
<td>15 ml/kg/dy</td>
<td>10 ml/kg/15dy</td>
<td>10 ml/kg/30dy</td>
</tr>
<tr>
<td>PE</td>
<td>1 EP/7dy</td>
<td>1 EP/15dy</td>
<td></td>
</tr>
</tbody>
</table>
Example 2

Preemptive Plasma therapy

- aHUS disease started at **6 years of age**
- She already had experienced 4 RT before the current one
- HUS has recurred in 3 out of 4 previous RT
- high titers of anti-FH Ab were readily detected, associated with \( \Delta_{CFHR1-3} \)}
Rituximab and/or Cyclophosphamide

Kwon NDT 2008, Boyer AJKD 2010
Combined liver and kidney transplantation

- The two first combined liver and kidney transplantations failed.

**Fatal non function of the liver graft** might result from I/R-induced massive shedding of heparan sulfate and uncontrolled complement activation leading to intra-graft TMA

Native liver | Failed liver graft
---|---
C5b-C9
Heparan Sulfate

Remuzzi Lancet 2002, Remuzzi AJT 2005
New and successful protocol

12 LKT with this protocol
- 10 succeed, 2 failed
- Benefit/risk balance should be considered for every case
- Preferential indication
  - CFH and CFI mutations already reported to the registry as being associated with recurrence

Dialysis
- Better before plasma exchange in all cases
- Mandatory before plasma exchange in cases with evidence of complement activation (e.g., angioedema) during dialysis

Plasma exchange
- A minimum of 1.5 Vol of FFP is exchanged within 4 to 6 h of surgery
- Exchange must be repeated if surgery is delayed

Plasma infusion
- 10 to 20 ml/kg body wt FFP is infused intraoperatively after native hepatic explant
- Additional plasma may be given as clinical need dictates

Surgery
- Split or whole liver transplantation is indicated
- Adequate liver mass must be provided (minimum 2% liver to recipient mass ratio)
- Auxiliary liver transplantation is not recommended
- Living-related donation is not recommended

Monitoring
- Posttransplantation liver function should be judged by coagulation profile
- In cases of inadequate liver function, plasma exchange in conjunction with standard

Posttransplantation anticoagulation
- Low molecular weight heparin at prophylactic dosages (e.g., enoxaparin 0.5 mg/kg twice daily)
- Aspirin (2 mg/kg per d up to 80 mg/d)
- To be continued for 3 mo

Immunosuppression
- Per standard practice of each center
- mTOR inhibitors are not encouraged
Eculizumab Soliris®

- Fully humanized monoclonal anti-human C5 Ab, whose mean elimination half-life is roughly 10 days

- Has become the **treatment of choice for Paroxysmal Nocturnal Hemoglobinuria**
  - 4 prospective studies with 195 patients
  - dramatically decreases need in red blood cell packs
  - reduces incidence of thrombotic events
  - meningococcal septicemia in 2 out of 195 patients

Hillmen NEJM 2005, Brodsky Blood 2008
Promising new avenue for aHUS treatment

- 25 patients treated in off-label studies
- 15 were presented: 7 children / 8 adults
- 9 and 6 involved native and transplanted kidneys, respectively
- $CFH (n=4), C3 (n=1)$, no mutation identified (n=10)
- **HUS remission was achieved in 100% of cases**
- 8/15 (53%) still under treatment

Four clinical trials of eculizumab in HUS patients

- the 4 studies have achieved the Company’s enrollment targets
- a total of roughly 35 adult and adolescent patients with HUS
Eculizumab for post-RT HUS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Indication</th>
<th>Recurrence to anti-C5 interval</th>
<th>Remission</th>
<th>Therapeutic scheme</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH Y475S</td>
<td>Curative Plasma resistant</td>
<td>5 days</td>
<td>Yes</td>
<td>Single dose (600 mg)</td>
<td>8 months</td>
</tr>
<tr>
<td>CFH S1191L</td>
<td>Curative Plasma dependent</td>
<td>10 months</td>
<td>Yes</td>
<td>Complete protocol</td>
<td>6 months</td>
</tr>
<tr>
<td>CFH W1183C</td>
<td>Curative Plasma resistant</td>
<td>10 days</td>
<td>Yes</td>
<td>Complete protocol</td>
<td>6 months</td>
</tr>
<tr>
<td>C3 R592Q</td>
<td>Curative Plasma dependent</td>
<td>14 months</td>
<td>Yes</td>
<td>Complete protocol</td>
<td>7 months</td>
</tr>
<tr>
<td>No</td>
<td>Curative Plasma resistant</td>
<td>9 days</td>
<td>Yes</td>
<td>Single dose (600 mg)</td>
<td>7 months</td>
</tr>
</tbody>
</table>
Eculizumab

Example 3

- **1987:** early-onset aHUS in a **6 month-old female**
  starts peritoneal dialysis

- **1990:** 1<sup>st</sup> deceased-donor renal transplantation
  HUS recurrence within the following days
  Intensive plasma therapy poorly tolerated

- **1995:** Return to hemodialysis
Example 3

2006: Identification of two heterozygous mutations in CFH

S1191L  V1197A
Example 3

**Eculizumab**

**Serum creatinine levels (µmol/L)**

**Platelets (µm³)**

Days post-transplant: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16

Renal graft biopsy

Eculizumab

PI

PE
Conclusions

- Alternative complement pathway deregulation is involved in 60% of aHUS cases and in 30% of de novo post-transplant HUS.

- aHUS related to mutations in genes encoding circulating complement regulators has a high recurrence rate following renal transplantation.

- So far, post-transplant recurrence of aHUS has been associated with an extremely poor prognosis.

- Innovative therapeutic avenues have emerged, including preemptive plasma therapy, combined LKT and anti-C5 Ab, which are extremely promising for the prevention or even the cure of aHUS recurrence.
Acknowledgements

Thank you for your attention
Acknowledgements

Chantal Loirat        V. Frémeaux-Bac

Patrick Niaudet
Georges Deschenes
Véronique Baudouin
AL Sellier Leclerc
Theresa Kwon
Olivier Boyer
Marina Charbit
Genevieve Guest
François Bouissou
Hubert Nivet
Corine Alberti
Marie-Alice Macher
Bernard Boudailliez
Sophie Gie
Michel Tsimaratos
Michel Fischbach
Denis Morin

Thank you for your attention