Transplantation and Atypical HUS

Neil Sheerin
Professor of Nephrology
Newcastle University
• Transplantation as a treatment for renal failure
• Transplantation in patients with Atypical HUS: what we know so far
• Transplantation in patients with Atypical HUS: Prospects for transplantation
Why have a transplant

• Kidney transplantation is considered the best treatment for most patients with renal failure
• Removes the burden of dialysis treatment
• Improved quality of life
  • Increased wellbeing
  • Reduction in symptoms
  • Improved cognition
  • Return to normal activities
• Increased life expectancy
Transplantation is not without its problems

- Immunosuppressive drugs are required for as long as the kidney is working
- Serious potential side effects
- Kidney transplants fail
Kidney transplant survival in the United Kingdom

Long-term graft survival after first kidney only transplant from donors after brain death, 1 January 1996 – 31 December 2008

Source: Transplant activity in the UK, 2009-2010, NHS Blood and Transplant

Year of transplant
(Number at risk on day 0)
- 1996-1998 (3285)
- 1999-2001 (2864)
- 2002-2004 (2747)
- 2005-2008 (2919)
Transplantation is not without its problems

- Immunosuppressive drugs are required for as long as the kidney is working
- Serious potential side effects
- Kidney transplants fail
- There is a waiting list for kidney transplantation
UK Transplant waiting list

Number of deceased donors and transplants in the UK, 1 April 2002 - 31 March 2012, and patients on the active transplant lists at 31 March

Source: Transplant activity in the UK, 2011-2012, NHS Blood and Transplant
Transplantation is not without its problems

- Immunosuppressive drugs are required for as long as the kidney is working
- Serious potential side effects
- Kidney transplants fail
- There is a waiting list for kidney transplantation
- Patients may be difficult to transplant
- Some disease that originally cause kidney failure can recur in a transplant
Transplanting patients with Atypical HUS

• Renal failure common often in young patients
• Kidney transplantation would be the recommended treatment
• Is transplantation an option?
• High rate of recurrence after kidney transplantation
  • 50-60% recurrence rate
  • 90% of grafts lost if recurrence occurs
Transplanting patients with aHUS

- Recurrence rate depends on which regulator gene is affected

<table>
<thead>
<tr>
<th></th>
<th>Transplants</th>
<th>% recurrence</th>
<th>% graft loss after recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor H mutations</td>
<td>42</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>Factor H antibodies</td>
<td>5</td>
<td>20</td>
<td>2/2</td>
</tr>
<tr>
<td>CFI mutations</td>
<td>12</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>MCP mutations</td>
<td>10</td>
<td>20</td>
<td>1/2</td>
</tr>
<tr>
<td>C3 mutations</td>
<td>7</td>
<td>57</td>
<td>80</td>
</tr>
<tr>
<td>CFB mutations</td>
<td>3</td>
<td>3/3</td>
<td>2/3</td>
</tr>
<tr>
<td>THBD mutations</td>
<td>1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
</tbody>
</table>

Noris and Remuzzi AJT 2010
When does recurrence occur?

Bresin E et al. CJASN 2006;1:88-99
renal transplantation alone is not recommended in [aHUS] patients known to have a factor H or factor I mutation.

In aHUS patients with a known mutation in either factor H or factor I consideration should be given either an isolated liver or a combined liver/kidney transplant as part of an internationally coordinated clinical trial.
Prospects for transplantation

- Combined liver and kidney transplantation
Liver transplantation in aHUS

- Potentially cure defect in cases where protein is synthesised in the liver
- Poor outcome in early transplants
- Uncontrolled complement activation at the time of the operation
- Better outcome with pre-operative plasma exchange to correct complement defect
- 15+ cases now reported with good outcome
- No recurrence reported
## Isolated renal transplantation vs combined liver kidney transplantation

<table>
<thead>
<tr>
<th></th>
<th>Surgical procedure</th>
<th>Lifelong immunosuppression</th>
<th>Renal graft survival</th>
<th>Protection against recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal transplantation</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Requires supplemental treatment</td>
</tr>
<tr>
<td>Combined liver kidney transplantation</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>complete</td>
</tr>
</tbody>
</table>
Protective effect of liver graft on kidney rejection

![Graph showing time to initial acute rejection](image)

- **Time to initial acute rejection**
- **Incidence of acute rejection**
- **p < 0.05**

Queen Elizabeth Hospital, Birmingham
Prospects for transplantation

• Combined liver and kidney transplantation
• Treatment with Eculizumab
  • Treatment if the disease recurs in the transplant
Eculizumab use in aHUS post-transplantation

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>28 (17-68)</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>29 (5)</td>
</tr>
<tr>
<td>Mutations identified, % (n)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (4)</td>
</tr>
<tr>
<td>1</td>
<td>53 (9)</td>
</tr>
<tr>
<td>2+</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Dialysis, % (n)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>Kidney transplant, % (n)</td>
<td>41 (7)</td>
</tr>
<tr>
<td>Median number of plasma interventions 7 days prior</td>
<td>6 (0 to 7)</td>
</tr>
<tr>
<td>to eculizumab (range)</td>
<td></td>
</tr>
</tbody>
</table>
Prospects for transplantation

- Combined liver and kidney transplantation
- Treatment with Eculizumab
  - Treatment if the disease recurs in the transplant
  - Prevention of aHUS in a patient undergoing kidney transplant
Preventing recurrent aHUS

- Prophylactic treatment with Eculizumab makes successful kidney transplantation possible
- There are case reports of Eculizumab being used in this way
- Should be effective at preventing disease
What treatment regime should be used?

First dose given prior to transplant

900mg/wk

Wk1 Wk5

1200 mg every 2 weeks
Who needs treatment?

• Is it possible to stratify risk of recurrence?
• Low risk patients who may not need treatment
  • MCP mutation
  • Previous autoantibodies
• High risk patients who definitely need treatment
  • Previous graft lost due to recurrent disease
  • Factor H mutations
  • Gain of function mutations
• Is there an intermediate group that may need a limited period of treatment?
How long do you need to give eculizumab?

• There is a high risk group who need life long treatment
• There may be a lower risk group who can stop after a period of treatment
• Most recurrences occur early
• Prophylactic Eculizumab during this high risk period and subsequent withdrawal
• Monitor closely for evidence of recurrence
  • What test
  • How often would you need to test
• Economic case, perhaps necessity, to consider these questions
Living donation in aHUS

• Increasing numbers of living donor transplants are being performed
• 64 living donor kidney transplants in Newcastle last year
• Almost 50% of transplants
• Best treatment for patients with renal failure
  • Timely availability of kidney
  • Guarantee of a kidney with good function
  • Better outcomes compared with waiting list transplants
• Living donation should be a first line treatment in aHUS
Living related donation in aHUS

- Can you use a kidney from a relative of a patient with aHUS?
- Could the relative have the mutation?
- Would this put the donor at risk of developing aHUS?
Living related donation in aHUS

Living donor transplantation

Non-related donor available

- Proceed as for cadaveric transplants
  - Warn of risk to donor

Related donor available

- Is the disease causing mutation known in the recipient
  - Yes
    - Does the potential carry this mutation – or other mutation on full screening
      - No
      - Yes
  - No
    - Cannot proceed
Transplanting sensitised patients

- Sensitised patients have antibodies against their donor
- They cause damage to the graft by activating complement
- Historically if these antibodies were present the transplant could not be performed
- The antibodies can now be removed to allow transplantation
- Data suggests that Eculizumab combined with limited antibody removal is very effective
- Transplantation of sensitised patients with aHUS may therefore be possible
- This would require – at present – a living donor
Key messages

- Kidney transplant using standard protocols is not recommended for the majority of patients with aHUS
- Eculizumab is effective in treating aHUS that develops after a transplant
- Combined liver and kidney transplant is an option that should be considered
- Eculizumab prophylaxis can allow safe transplantation for patients with aHUS
- Living donation should be considered as it offers better outcomes
- Specific considerations for related donors
Future prospects

Effective treatment of aHUS will stop people from developing renal failure, avoiding the need for transplantation.

But:
- Late presentation
- Delayed recognition
- Availability of treatment
Transplantation will have an important, although diminishing, role in the treatment of aHUS