Can we safely perform Kidney Transplants in patients with aHUS?

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Disclosures

None!!

Objectives

- Know that aHUS is a rare and deadly disease
- Know that the recurrence of the disease after kidney transplantation is very high
- Know that the therapeutic options for recurrence are very limited
- Know that the new drug Eculizumab might offer hope
Case

- 61-year-old Caucasian male, who had ESKD due to HUS/TTP, currently on dialysis was referred for kidney transplant
- Otherwise, very healthy and physically fit and high functioning member of society
- After further research into his condition, it was revealed that he had aHUS

What is aHUS?

Thrombotic Microangiopathies

<table>
<thead>
<tr>
<th>TTP</th>
<th>Hemolytic Uremic Syndrome</th>
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<td>Typical – Diarrheal Secondary</td>
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<td>Infection</td>
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<td>Drug Toxicity</td>
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<td>Other States</td>
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<td>Atypical/Non Diarrheal/Primary</td>
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<td>Complement Gene</td>
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<td>Mutations</td>
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<td>Antibodies to Complement Factors</td>
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aHUS

- Genetic, chronic, progressive inflammatory disease
- Caused by mutation (inherited or acquired) in the complement regulatory cascade
- Continuous uncontrolled activation of complement leading to platelet, leukocyte and endothelial cell activation
- Manifestations include TMA, multi organ system involvement (most notably kidneys)
- Approximately 40% of patients either die or progress to ESRD during the first clinical manifestation

Case

- Received a kidney transplant at our institution and did not have the CFH mutation
- Received a modified immunosuppressive regime of Alemtuzumab, and MPA and prednisone (no CNI) and Sirolimus after a week.
- Course was complicated by lymphocele and proteinuria
- Biopsy revealed ATN with regenerating tubules
Course after Transplantation

- Recurrence is the norm (50-70%), and this happens within the first year
- Risk factors
  - Older age at presentation
  - Shorter duration between disease onset and ESRD
  - Use of living kidney donors
  - Administration of CNI
- Most patients lose their allograft despite aggressive measures


Case

- A decision was made to give him Eculizumab, and received a total of 2 doses within the first 3 months
- At month 4, the creatinine increased from 2.1 to 11 over the course of a month
- Repeat biopsies revealed thrombotic microangiopathy, and BK virus nephropathy and also hemolytic anemia
- Plasma exchange was resumed for several treatments and also received IVIg

Treatment

- Supportive (blood pressure, volume overload, transfusions etc)
- Plasma Exchange or Plasma Infusion
- Eculizumab
The role of Eculizumab

- Eculizumab has an Orphan Drug status for the treatment of PNH, aHUS and most recently NMO
- So, the expectations in a clinical trial for such a drug:
  - Less number of patients
  - Sponsored by the drug company (that manufactures/markets the drug)
  - Soft clinical end points
  - Less duration of follow up
  - Uncertain long term side effects

Eculizumab: Mechanism of Action

Eculizumab is a recombinant, fully humanized hybrid IgG2/IgG4 monoclonal antibody directed against human complement component C5. It hence inhibits the cleavage of C5 to C5a and C5b by the C5 convertase thus preventing the development of C5b-9 complex (MAC).

Does it prevent/treat recurrence after transplantation?
The Literature

- Too many case reports
- Used Eculizumab as rescue therapy
- The drug was not used as recommended
- No adequate follow up
- The most glaring issue was the cost of the drug
NEJM Study: Terminal Complement Inhibitor Eculizumab in aHUS

- Two studies in one
- 37 patients were enrolled (17 and 20)
- Trial 1: Primary end point was increase in the platelet count
- Trial 2: Primary end point was TMA event free status
- Significant improvement of all secondary end points in both trials


NEJM Study: Terminal Complement Inhibitor Eculizumab in aHUS

- Inhibition of complement mediated TMA
- 15 kidney transplant recipients were included
- Improved the health related QOL
- No serious toxicity or infection related events occurred

Proposed Dosing (for adults)

- First dose prior to transplant (900 mg)
- Then on Day 7, 14 and 21 (900 mg each)
- Then, every 2 weeks after that (1200 mg)
- It is unclear when to stop the drug
- Also, it is recommended that patients are vaccinated with meningococcal vaccine at least 2 weeks prior to the drug infusion

Case

- He underwent intermittent dialysis, and immunosuppression was decreased due to BKVN
- However, the kidney disease progressed and eventually was declared ESKD in June 2013
- He developed hematuria 2 months later, and had a transplant nephrectomy

What next for our patient?

- He will be worked up again for another transplant
- Currently on dialysis and doing well
- Will be transplanted at a center which has agreed to use the medication prior to transplant and the suggested doses subsequently
Summary

• aHUS is a rare and deadly disease and the treatment options are limited
• Kidney transplant outcomes “were” poor
• Eculizumab might be an attractive option to treat the disease process and as an option after kidney transplantation
• Cost of the drug is definitely an issue (~ $5000 per 300 mg vial)
• Transplantation should be considered only by those centers which are willing to assume the costs that are incurred by the drug

Future thoughts on Eculizumab

• Could be useful in any complement mediated disease states
  – Antibody mediated rejection
  – Some types of glomerular diseases
  – Neuromyelitis Optica
• It is very essential to keep the cost of the drug in mind

THANK YOU!!