

PNH

AA-MDS Patient Conference
Raleigh-Durham
July, 2016
Advances in PNH Treatment: What's on the
Horizon

How is PNH treated?



Treatment of PNH

- Who needs to be treated?
- With what?
- Does everybody respond?
- What is on the horizon?

PNH – Who needs to be treated?

- Patients with blood clots
- Patients with symptomatic anemia from hemolysis
- Patients with severe bone marrow failure

The Treatment “Grey zone”

- Patients with hemolysis who are not symptomatic
 - Can we prevent long term complications such as blood clots, renal failure, or pulmonary hypertension?

How do we treat PNH -hemolysis

Transfusion
Iron, folic acid
Steroids
Eculizumab

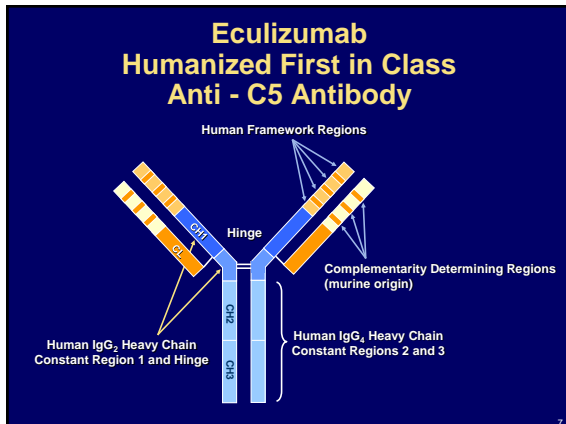
TRIUMPH- Transfusion Reduction Efficacy and Safety Clinical Investigation, A Randomized Multi-Center, Double-Blind, Placebo-Controlled Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

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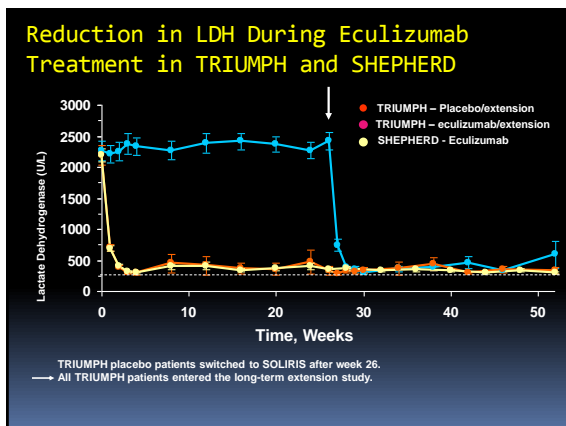
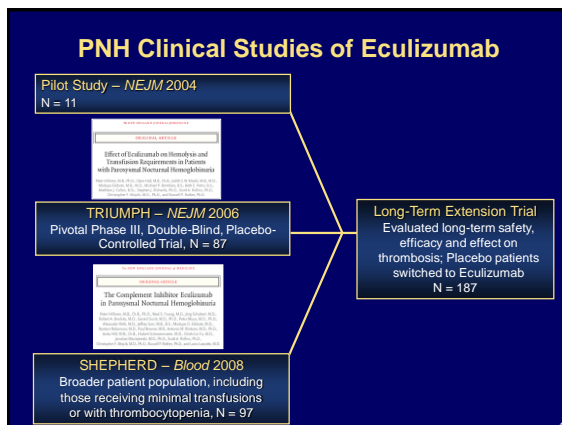


- ### What does Eculizumab do?
- Quickly and effectively blocks complement activation at C₅.
 - Blocks hemolysis and related effects
 - Stops hemoglobinuria
 - Markedly reduces transfusion requirements
 - Hemoglobin / hematocrit may not return to "normal"
 - Other long term effects?

Warning

WARNING: SERIOUS MENINGOCOCCAL INFECTION

- Eculizumab increases the risk of meningococcal infections
 - Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of eculizumab
 - Revaccinate according to current medical guidelines for vaccine use
 - Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary

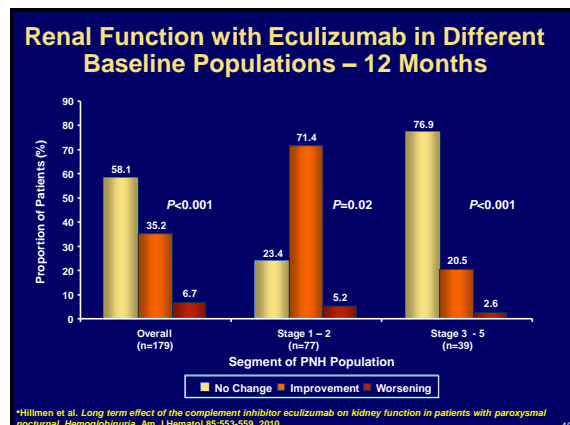
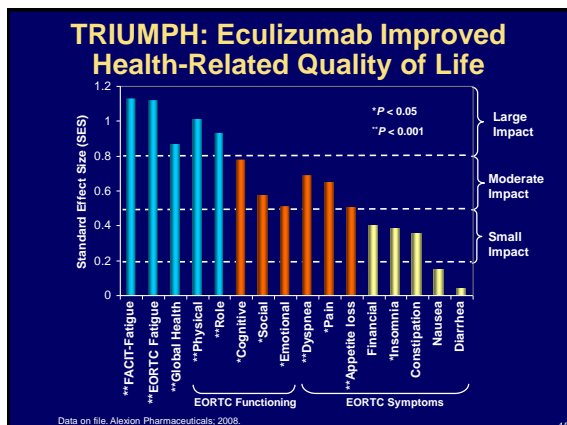
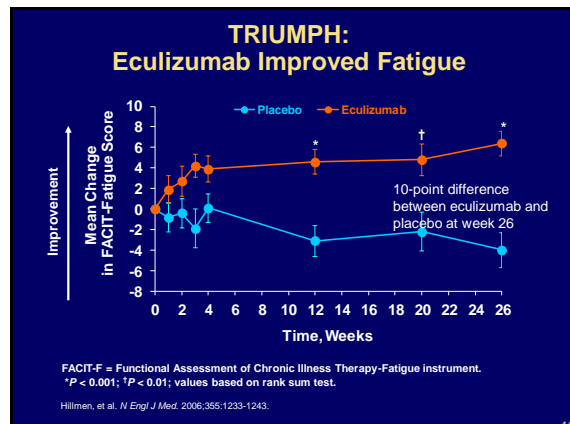
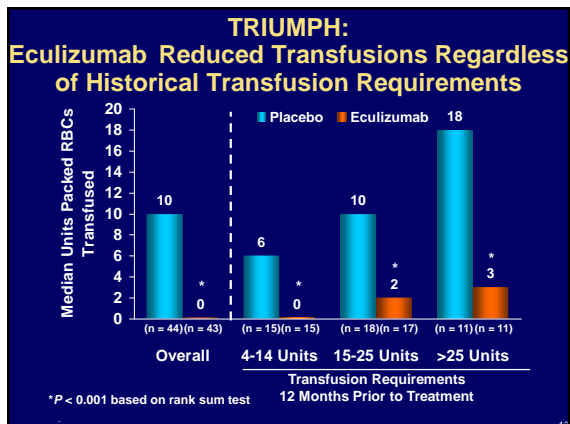


TRIUMPH: Results

All 1^o and 2^o endpoints met with statistical significance

Parameter	Placebo (n = 44)	Eculizumab (n = 43)
LDH levels at end of study, median (U/L) (range)	2,167 (1183 - 5643)	239* (142 - 2984)
Packed RBC units transfused per patient, median (range) †	10 (2 - 21)	0* (0 - 16)
Transfusion avoidance, %	0	51*
Patients with stabilized hemoglobin levels, †	0	49*
Free hemoglobin at end of study, median, (mg/dL) (range)	62 (0.7 - 386)	5* (3 - 194)

*P < 0.001; †denotes co-primary endpoints



What eculizumab does not do

- Probably does not help bone marrow failure (improve other low blood counts)
- Completely correct anemia
- Teach you how to play the violin if you have never played before

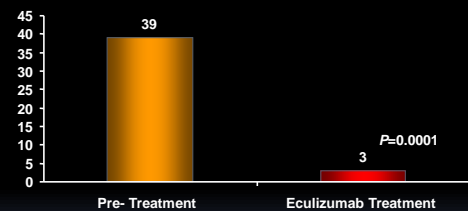
Downside of Eculizumab treatment

- Increased risk of meningococcal infections
 - All patients must be vaccinated
 - All patients educated on signs and symptoms of meningitis and what to do
 - All patients given cards describing this
- Cost
- Possible coating of red cells with C₃ complement leading to their destruction (extravascular) and anemia
- Inconvenience
 - Must be given intravenously every 12-14 days

How do we treat or prevent blood clots?

Coumadin prophylaxis
 Acute treatment with lytic agents
 Anticoagulation therapy
 Bone marrow transplantation
 Eculizumab

Effect of Eculizumab on Thrombosis



■ 92% Fewer thrombotic events with Eculizumab treatment

There were fewer thrombotic events with Eculizumab treatment than during the same period of time prior to treatment.

Hilmen P, et al. Blood. 2007;110: 4123-4128

How do we treat bone marrow failure?

Stimulating agents such as erythropoietin
 Immunosuppressive agents (ATG, cyclosporine A)
 Bone marrow transplantation

PNH – Suboptimal Responders to Eculizumab

- Definition of a suboptimal responder
- Reasons for suboptimal responses
 - Metabolism of eculizumab
 - Bone marrow failure
 - Polymorphisms in C₅
 - C₃ coating of red cells

Suboptimal responders – Metabolism, breakthrough

- Some will metabolize the eculizumab antibody quicker.
- Current recommendation is to increase the frequency to every 12 or 13 days.
- Current practice is to increase the dose to 1200 mg every 2 weeks.

Suboptimal responders – Bone marrow failure

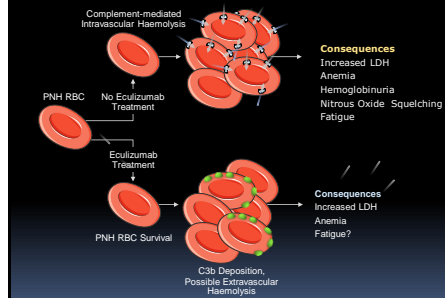
- Some PNH patients clearly have bone marrow failure with poor production of red cells.
- Usually see a low reticulocyte count in addition to other blood counts (WBC, platelets) being lower.
- May respond to erythropoietin (EPO)
- May need some immunosuppressive therapy
 - Prednisone, Cyclosporine, ATG

Suboptimal responders – Polymorphisms

- 11 Japanese patients with a polymorphism of C5
- Polymorphism occurs at the site where eculizumab binds to C5
- Poor response to eculizumab
- Same polymorphism also found in Han Chinese population.

Nishimura J, et al. Genetic variants in C5 and poor response to eculizumab. *N Engl J Med* 370: 632-639, 2014

Suboptimal Responders: C3 Coating and Extravascular Haemolysis

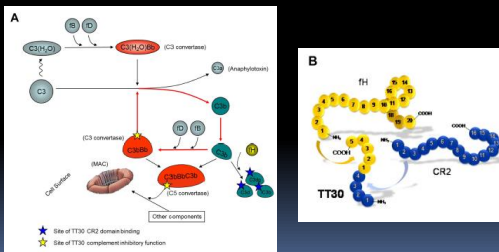


1. Hill, A et al. *Haematologica* 2010; 95:567-573. 2. Risitano, AM. *Blood* 2009;113:4094-4100. 3. Hillman P et al. *N Engl J Med*. 1995;333:1253-1258.

Design and development of TT30, a novel C3d-targeted C3/C5 convertase inhibitor for treatment of human complement alternative pathway-mediated diseases

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PNH - What is on the horizon?

- New C5 inhibitors
 - New antibodies against different C5 epitopes
 - Naturally occurring inhibitors of C5
 - siRNA inhibitors of hepatic C5 production
- C3 inhibitors
- Eltrombopag for bone marrow failure

Thank you.
Any questions?

