

Advances in PNH Treatment: What's on the Horizon

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THE NEW ENGLAND JOURNAL OF MEDICINE

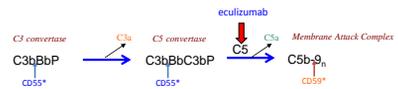
ORIGINAL ARTICLE

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Neal S. Young, M.D., Jörg Schubert, M.D., Robert A. Brodsky, M.D., Gerard Socié, M.D., Ph.D., Petra Muus, M.D., Ph.D., Alexander Röth, M.D., Jeffrey Szer, M.B., B.S., Modupe O. Elebute, M.D., Ryotaro Nakamura, M.D., Paul Browne, M.B., Antonio M. Risitano, M.D., Ph.D., Anita Hill, M.B., Ch.B., Hubert Schrezenmeier, M.D., Chieh-Lin Fu, M.D., Jaroslaw Maciejewski, M.D., Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., Russell P. Rother, Ph.D., and Lucio Luzzatto, M.D.

N Engl J Med 2006;355:1233-43

Alternative Pathway of Complement Activation on Erythrocytes

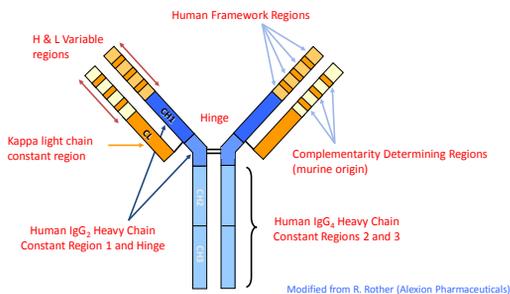


*GPI-anchored complement regulatory proteins deficient in PNH

Complement Activation



SOLIRIS (eculizumab) Humanized Anti-C5 Antibody



What Does Eculizumab Do?

- Blocks Intravascular Hemolysis
 - Reduces transfusion requirements
 - Prolongs transfusion interval
- Ameliorates symptoms associated with chronic and acute intravascular hemolysis
 - Malaise, lethargy, fatigue, asthenia
 - Abdominal pain, dysphagia, male impotence
- Ameliorates the thrombophilia of PNH

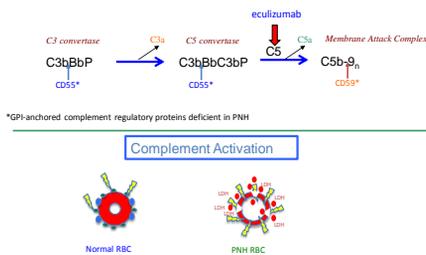
What Doesn't Eculizumab Do?

- Block Extra-Vascular Hemolysis
 - Mediated by complement opsonization of RBCs
- Completely eliminate transfusion requirements in all patients
- Eliminate anemia
- **Affect the underlying disease process**
 - Clonal hematopoiesis
 - Bone marrow failure
 - Effective therapy because *PNH is not a malignant clonal disease*

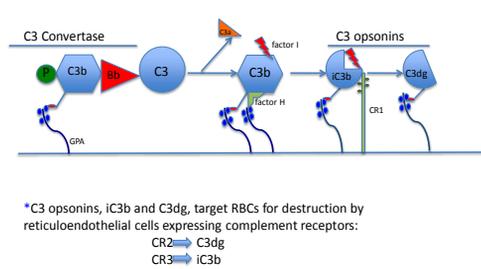
Suboptimal Response to Eculizumab

- A small minority of patients with classic PNH experience only modest improvement in constitutional symptoms
- Although serum LDH concentration returns to normal or near normal in all PNH patients treated with eculizumab, anemia and reticulocytosis persists in most patients with classic PNH and some remain transfusion dependent

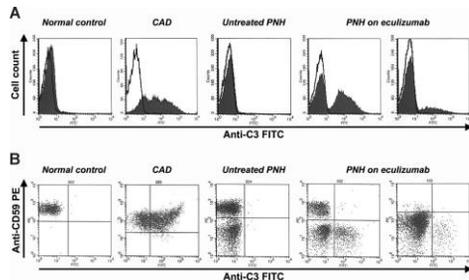
Alternative Pathway of Complement Activation on Erythrocytes



Generation of C3 Opsonins* on Erythrocytes

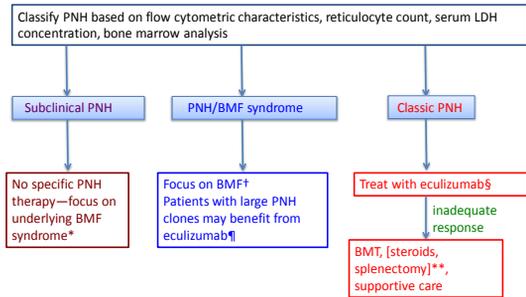


Complement C3 Binding to PNH RBCs in Patients Treated with Eculizumab

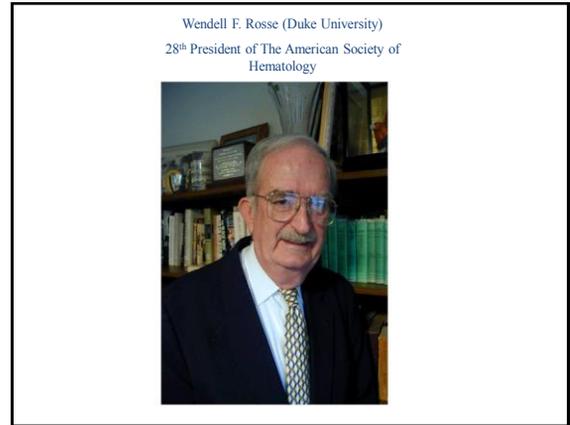
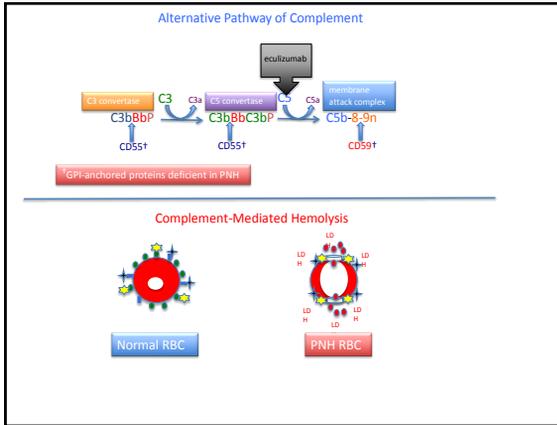


Risitano et al. *Blood* 2009 113:4094-4100

Management of PNH Based on Disease Classification



BMF, bone marrow failure (aplastic anemia and low risk MDS); BMT, bone marrow transplant
 *Some, but not all, studies suggest a favorable response to immunosuppressive therapy (IST)
 †BMT eradicates the PNH clone, and typically, treatment with IST does not affect PNH clone size
 ‡~10% of patients with PNH/BMF have PNH clone size >50%
 §Some patients respond to Danazol as first line therapy
 ***Cautiously consider for patients with clinically significant extravascular hemolysis



What's on the Horizon for Treatment of PNH

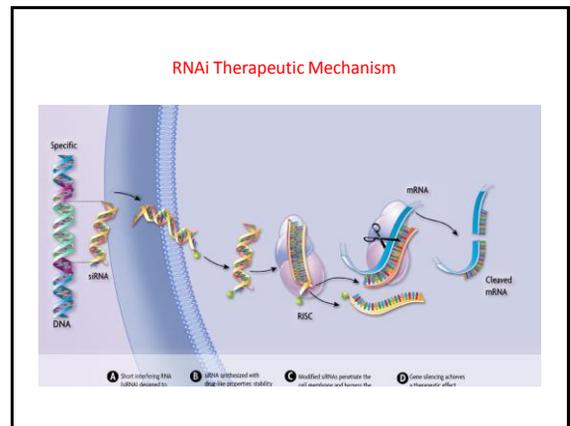
- Biosimilars (inhibitors of C5)
 - Their function is similar to eculizumab
 - RA101495 (Ra Pharma), a synthetic macrocyclic peptide that binds to C5 and prevents cleavage of to C5a and C5b and also block the binding of C5b to C6.
 - Developed for at-home subcutaneous injection. Frequency of dosing to be determined
 - ALXN1210 (Alexion), a monoclonal anti-C5, engineered for extended duration of complement inhibition
 - Given as an intravenous infusion
 - Half-life of > 30 days, with dosing intervals of 2-4 months

What's on the Horizon for Treatment of PNH

- Biosimilars (inhibitors of C5)
 - Their function is similar to eculizumab
 - Conversin (Akari Therapeutics), a recombinant small protein derived from a protein produced in the saliva of *Ornithodoros moubata* tick
 - Developed for at-home subcutaneous injection. Frequency of dosing to be determined (likely daily)
 - Biosimilars may have a less rigorous path to FDA approval given the safety and efficacy of eculizumab

What's on the Horizon for Treatment of PNH

- A Different Approach to Inhibition of C5
 - ALN-CC5 is an investigational RNA interference (RNAi) therapeutic that targets production of C5 produced in the liver
 - Being developed for subcutaneous injection
 - RNAi's are small (21-25 base pair) RNA strands that target a specific gene (in this case C5)
 - The siRNA complex binds the messenger RNA of the target gene and causes it to undergo degradation



What's on the Horizon for Treatment of PNH

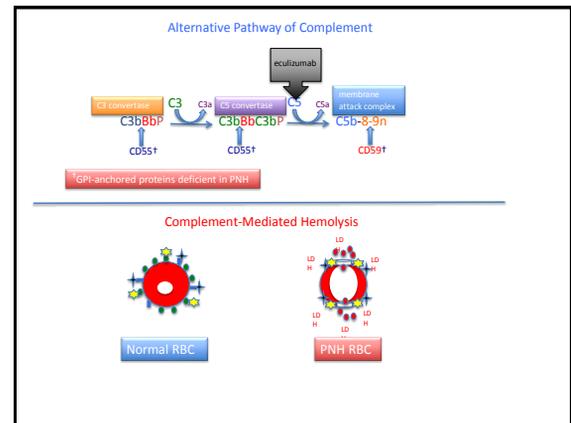
- A Different Approach to Inhibition of C5
 - ALN-CC5 is an investigational RNA interference (RNAi) therapeutic that targets production of C5 produced in the liver
 - In a phase I/II study it produced up to a 98% knockdown of C5 at day 98 after a single dose
 - In part C of the study, 6 patients with PNH were enrolled
 - Three eculizumab naïve patients were treated
 - » 37-50% reduction in LDH was achieved (LDH levels remained above the goal of <1.5 times the ULN)
 - » An exploratory data analysis suggested that treatment with ALN-CC5 may reduce the dose and frequency of eculizumab treatment for patients with PNH

What's on the Horizon for Treatment of PNH

- A Different Approach to Inhibition of C5
 - Therapeutics such as ALN-CC5 that are not eculizumab biosimilars (use different approaches to inhibition of C5 or target complement components other than C5) will likely face more rigorous proof of safety and efficacy before approval by the FDA

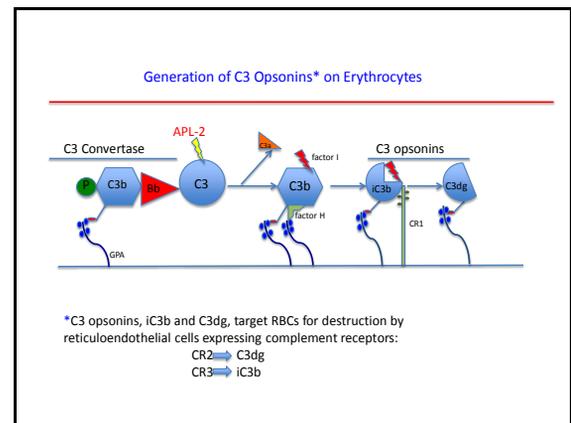
What's on the Horizon for Treatment of PNH

- Drugs that target complement components other than C5
 - These drugs have the hypothetical advantage of preventing extravascular as well as intravascular hemolysis by blocking the formation of the C3 convertase of the APC



What's on the Horizon for Treatment of PNH

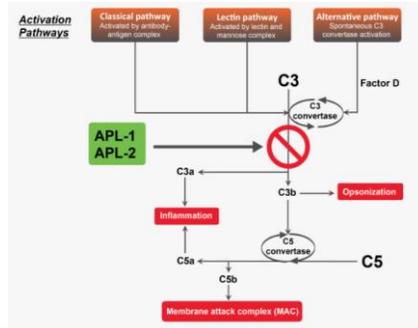
- Drugs that target complement components other than C5
 - AP-2 (Apellis), a cyclic peptide inhibitor of C3, being developed for in home subcutaneous administration
 - In the phase II stage of development
 - Concern that inhibition of APC C3 convertase formation will increase the risk for bacterial infection or autoimmune disease
 - Burden of proof of safety will likely be high



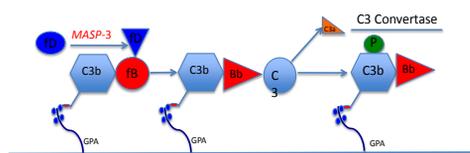
What's on the Horizon for Treatment of PNH

- Drugs that target complement components other than C5
 - APL-2 (Apellis), a cyclic peptide inhibitor of C3, being developed for in home subcutaneous administration
 - In the phase II stage of development
 - Concern that inhibition of APC C3 convertase formation will increase the risk for bacterial infection or autoimmune disease
 - Burden of proof of safety will likely be high
 - Congenital deficiency of C3 is associated with early mortality due to bacterial infection

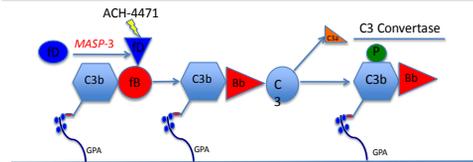
Apellis Targeting of C3



Generation of the C3 Convertase on Erythrocytes



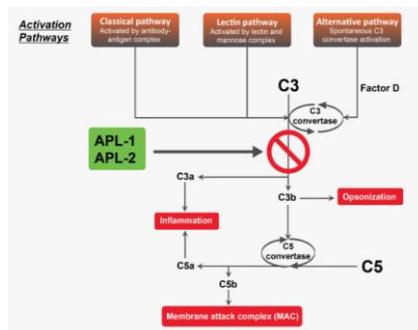
Generation of the C3 Convertase on Erythrocytes

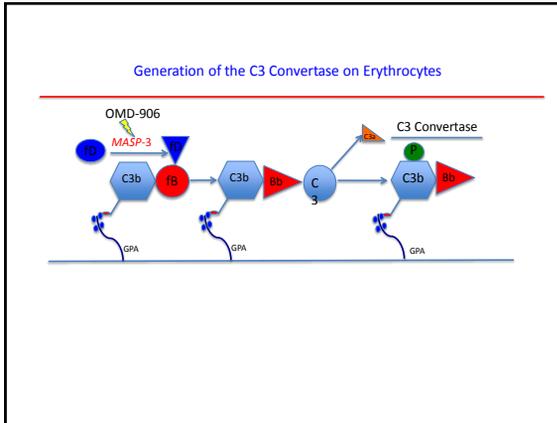


What's on the Horizon for Treatment of PNH

- Drugs that target complement components other than C5
 - ACH-4471 (Achillion), small molecule factor D inhibitor being developed for oral administration
 - Phase I study showed safety and efficacy with BID dosing with goal of formula modifications to allow QD dosing
 - As with other inhibitors of APC C3 convertase formation, there is concern for risk for bacterial infection with long-term use
 - Burden of proof of safety will likely be high
 - Congenital deficiency of factor D have a variable clinical course with some patients experiencing recurrent life-threatening infections but others (including affected family members) having few clinical consequences.
 - » Notably, factor D deficient individual are at risk for Neisseria infections (as are patients treated with eculizumab). Therefore vaccination ± prophylactic antibiotics may protect patients treated with a factor D inhibitor.

Apellis Targeting of C3





What's on the Horizon for Treatment of PNH

- Drugs that target complement components other than C5
 - OMS906 (Omeros), monoclonal anti-MASP-3 inhibitor being developed for intravenous administration
 - In pre-clinical stage of development
 - Congenital deficiency of MASP1/3 cause the 3MC syndrome characterized by facial, umbilical, coccygeal and auditory abnormalities
 - Plasma from a patient with the 3MC syndrome had normal APC activity in vitro
 - Recurrent infections is not a part of the 3MC syndrome

What's on the Horizon for Treatment of PNH

- Future Directions
 - Bone marrow transplant remains the only therapeutic approach that can cure PNH (and the bone marrow failure component of the disease).
 - Research is the key to understanding the pathophysiologic mechanisms that lead to selection of the *PIGA* mutant clone(s) and to expansion of the *PIGA* mutant clone.

Hypothetical Model for Selection and Expansion of *PIGA*-Mutant, GPI-AP Deficient Hematopoietic Stem Cells

