Development of Complement Inhibitor Treatment for Myasthenia Gravis

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Disclosure

- Research funded by the National Institutes of Health
- Consultant for Varleigh Limited (less than $20,000)
- Consultant for Bayhill Therapeutics, GlaxoSmithKline (honoraria less than $5,000)
- National Institutes of Health R24 EY14837, R01 NS42685
Outline

- Discuss basis of complement involvement in human myasthenia gravis and experimental autoimmune myasthenia gravis (EAMG)
- Review pre-clinical initiatives targeting complement for EAMG
- Assess the status of application of complement inhibition to humans
Evidence of Complement Mechanisms in MG

- IgG Complexes and C3 at motor endplate (Engel, Lambert, Howard 1977)
- Cobra venom depletion of C prevents passive EAMG induction (Lennon et al 1978)
- C6- and C5-deficient rats are resistant to EAMG (Christadoss 2006 Chamberlain-Banoub 2006)
Intrinsic Complement Inhibitors are Protective

- Cell surface regulators (Decay Accelerating Factor, CD59, Crry)
- Uniform function to enhance/prevent membrane attack complex (MAC) formation
- Are concentrated at the neuromuscular junction
Complement Inhibitors Protect the Neuromuscular Junction from EAMG Injury

- Engineered absence of the Decay Accelerating Factor ($Daf^{-/-}$) gene in mice enhances the severity of EAMG
- DAF provides greater protection than CD59 or Crry

WT

anti-AChR McAb-3
Analyze at 24-48 hr

CD59a-/-

Protocol

Daf1-/-CD59a-/-
Hang Time anti-C9 staining

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% neuromuscular junctions with C9

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*Lower dose of anti-AChR mAb

All Dead!
Pathogenic Mechanisms of Myasthenia Gravis

(Conti-Fine B, Milani M, Kaminski HJ. J Clin Invest, 2006)
Complement regulator expression gene and protein is low in EOM and are only minimally increased by EAMG

Kaminski HJ, et al Exp Neurol, 2004
The “Complement Hypothesis” for Extraocular Muscle Susceptibility to Myasthenia Gravis

1) Intrinsic complement regulators are expressed at lower levels at EOM synapses.
2) Systemic complement inhibition does not prevent complement deposition at EOM junctions.
3) EOM demonstrates greater injury in active and passive EAMG by several measures suggesting that the lack of complement inhibition puts this muscle at risk.
Genetic Association of MG and Complement Inhibitor

- Myasthenia gravis in South Africans: Racial differences in clinical manifestations

- A functional SNP in the regulatory region of the decay-accelerating factor gene associates with extraocular muscle pareses in myasthenia gravis
  Heckman, et al. Genes and Immunity, 2010
Complement Inhibitor Therapy - Preclinical studies

- 1989. Biesecker & Gomez. Inhibition of acute passive transfer experimental autoimmune myasthenia gravis with Fab antibody to complement C6.

- 1996. Soluble complement receptor 1 (sCR1) protects against experimental autoimmune myasthenia gravis

- 2007. Antibody directed against C5

- 2009. Complement Inhibitor derived from ticks
Treatment Response to Anti-C5

- Prevents and reverses EAMG weakness
- Limits ultrastructural injury
- Decreases C9 deposition

Treatment Response to Anti-C5

Anti-C5 treatment for EAMG
C9 Deposition is Decreased and Ultrastructure Preserved

rEV576 – Inhibitor of C5

- Developed by Miles Nunn, Oxford designated OmCl (J Immun, 2005, 2084-2091)
- Recombinant form of complement inhibitor from soft tick (*Ornithodoros moubata*) saliva.
- 18.5 kDa
- Inhibits interaction with C5 convertase

P. Roversi et al. J Mol Biol. 2007 June 8; 369(3-3): 784–793
Experimental Protocol

Passive immunization:

Female Lewis Rats, 8-10 wk

Anti AChR McAb-3 + rEV576 (pre or post treatment)

48 hr

Active immunization:

Purified AChr in CFA + M.tuberculosis

Weakness at 3-4 wks

Complement inhibitor rEV576

10 days Rx

0 = forelimb can grip and lift lid of cage
1 = forelimb can grip but cannot lift lid of cage
2 = forelimb can’t grip
3 = forelimb can’t grip, hindlimb paralyzed
4 = moribund
rEV576 and EAMG

- Improves clinical scores
- Reduces complement activity
- Reduces complement deposition at the NMJ

Gains in Strength are Retained

Courtesy of Linda Kusner
We can now target complement inhibition to the junction
And demonstrate a therapeutic effect.

- **scFv-35-Daf** reduces EAMG severity in rats and mice with severe deficiency of intrinsic complement inhibitors.
Human trials of complement inhibition for myasthenia gravis
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Multi-Center Study of Eculizumab in Patients With Generalized Myasthenia Gravis (gMG) Who Have Moderate to Severe Muscle Weakness Despite Treatment With Immunosuppressants

Estimated Enrollment: 24
Study Start Date: October 2008
Estimated Primary Completion Date: July 2010 (Final data collection date for primary outcome measure)

*Alexion Pharmaceuticals, Inc*
1984
PNH shown to be caused by somatic mutations in the GPI-anchoring gene, PIGA.

1990
Case study of a C9-deficient PNH patient suggests terminal complement blockade may reduce hemolysis in PNH.

1995
Anti-C5 mAb isolated that effectively blocks the generation of the proinflammatory and cell lytic mediators C5a and C5b-9.

1997
Terminal complement inhibitor function shown to be missing from PNH RBCs.

1997
Phase 1 safety study of eculizumab in rheumatoid arthritis.

May 2002
First PNH patient dosed in an open-label phase 2 pilot study in the UK.

February 2004
Phase 2 pilot study published in NEJM.

April 2006
Open-label multinational phase 3 SHEPHERD study data interim analysis.

February 2007
Soliris registered for treatment of patients with PNH to reduce hemolysis.

March 2007
Soliris approved by EU Commission.

June 2007
Soliris approved by EU Commission.

April 2007
Soliris receives positive opinion from EMEA.

January 2006
Placebo-controlled multinational phase 3 TRIUMPH study unblinded.

September 2008
Phase 3 TRIUMPH study published in NEJM.

BLA and MAA submitted to FDA and EMEA, respectively; receive accelerated assessment.
Linda Kusner, PhD
Namita Satija, PhD
Michael Richards