International Scientific Symposium on Myasthenia Gravis - Notes from Dr. Robert Ruff

Tuesday, May 10, 2022

8:15 – 9:05 **Session 1- Rationale for Therapeutics in Development Chair: Nils Erik Gilhus, MD, PhD, University of Bergen, Norway**

8:15 – 8:35 **Complement Inhibition: From Basics to RCT Data,** Saiju Jacob, MD, PhD, University of Birmingham, UK

An important observation was the recognition that complement is deposited on the damaged muscle membranes of muscle from people with MG and animals with experimental MG induced by antibodies (Abs) to AChR. Complement is a collection of chemicals that functions as the enforcer of the immune system by attacking and destroying autoimmune targets. Early studies in animals demonstrated that disrupting complement activation would prevent tissue damage in animal models of MG. The trick has been to find ways of safely inhibiting complement so that this strategy can be used to treat people with MG. Current effective strategies employ 1) using antibodies to target components of the complement system, for example eculizumab, or chemical agents that interfere with the complement activation such as zilucoplan.

8:35 – 8:55 **FcRn: Mechanism and RCT Data,** Sally Ward, MD, University of Southampton, UK

Immune modulation in disorders such as MG needs to balance tamping down the immune system without rendering the patient excessively susceptible to infections and other complications of immune suppression. Antibodies (Abs) are circulating chemicals produced by B-cell lymphocytes especially the group of B-cells called plasma cells. Abs bind to specific targets and in so doing can mark their targets for destruction. There are several classes of antibodies. The pathogenic antibodies in MG are the class IgG. Treatments that wipe out all antibodies can render an individual excessively immunosuppressed. Therapeutic strategies for MG include selectively targeting IgG. A recent strategy is to lower the concentration of IgG without eliminating IgG. This strategy is based on the observation that portions of the IgG molecules are recycled by immune cells. Disrupting the recycling of IgG will lower, but not eliminate, circulating IgG. Vyvgart is a recently FDA approved treatment for AChR+ MG that acts by compromising IgG recycling. The lifetime of IgG is short, which enables Vyvgart to have a relatively quick clinical onset. Other agents that act on IgG recycling are being evaluated.

9:10 – 9:50 **Keynote Speaker**: Angela Vincent, MBBS (Hon PHD Bergen), FRCPath, FMedSci, FRS, University of Oxford, UK

Dr. Vincent presented a meaningful historical summary of the development and evolution of research and treatment strategies for MG. The field of MG understanding and treatment exploded in the 1970's when Dr. Vincent entered the field of MG research. Her presentation had the unique prospective of coming from a person who was immersed in the field, hence she could properly weigh the contributions of different research groups and studies to the advancement of the field. Important milestones included: 1) the recognition that most commonly MG was mediated by Abs directed against constituents of neuromuscular junction, especially AChR-Abs; 2) destruction of the neuromuscular junction was mediated by complement; 3) dramatic advances in treatments of MG that targeted the immune system; 4) the recognition that early onset/congenital forms of impaired neuromuscular function were usually caused by genetic mutations involving components of the neuromuscular junction; 5) successful completion of the international thymectomy trial demonstrating the value of thymus resection and 6) large clinical trials to determine the effectiveness of strategies to treat MG.

10:30 – 12:00 Session 2: Other Therapeutics Chair: Volkan Granit, MD, University of Miami, US

10:30 – 10:50 **B Cell Depletion: Mechanisms and RCT Data,** Richard Nowak, MD, MS, Yale School of Medicine, US

Since B-cells are antibody producing immune cells, a strategy to treat MG is target the B-cells that produce MG-related antibodies. Retuximab is a manufactured Ab that targets the CD-20 class of B-cells, which are implicated in MG. Targeting CD-20 B-cells is most useful for MuSK MG where anti-complement Rx may not be effective. Rituximab is FDA approved for some autoimmune disorders, but not MG.

10:50 – 11:10 **CAR-T Therapy for AChRAb positive MG**, Volkan Granit, MD, University of Miami, US

CAR-T treatment that targets plasma cells is being studied in MG target. The treatment introduces a "target" protein into T cells to induce the T cells to attack specific classes of cells, in this case to target antibody producing plasma cells. Plasma cells are class of long-lived B-cell lymphocytes that produce large quantities of Abs. When initially implemented, the Rx had appreciable side effects. Descartes-8 was a modified technique that reduced side effects. Initial small sized patient studies using modified CAR-T therapy are encouraging, but too early and too small to draw definitive conclusions.

11:10 – 11:30 **Hinge-Deleted IgG4 Blocker Therapy for AChR MG**, Mario Losen, PhD, Maastricht University, Netherlands

As pointed out by Dr. Vincent, IG type 1 (AChR MG) activates complement and IG type 4 (MuSK MG) does not. Hinge deleted IgG4 are modified Abs that bind to AChR without activating complement. Additionally, hinge deleted IgG4 are partial Abs that do not inhibit AChR function and prevent other Abs from binding to and connecting AChR molecules to each other (cross-linking). Hinge deleted IgG4 by blocking other Ab binding also prevent complement activation. Initial animal studies are promising. This strategy may be advanced to clinical trials.

11:30 – 11:50 **MuSK CAAR-T**, Aimee Payne, MD, PhD, Penn Medicine, US

This presentation addressed a treatment strategy that is being developed for an autoimmune disorder affecting the skin and mucus mebranes, Pemphigus Vulgaris. CD-19 class B cells are involved in Pemphigus. This presentation addressed a modified CAR-T treatment in which T cells are motivated not to attack all CD-19 B cells, but a subset such as those causing Pemphigus Vulgaris. The connection to MG is that when the CAAR-T strategy is applied to MuSK MG – researchers found that they can target B cells specifically producing antibodies to MuSK. The new treatment is referred to as MuSK-CAART. MuSK-CAART is being evaluated in animal studies for possible future clinical trials.

13:30 – 15:00 Session 3: Update in MG Immunopathogenesis Chair: Kevin O'Connor, PhD, Yale School of Medicine, US

13:30 – 13:50 **Complement and Autoimmune Disease,** Jeffrey Bennett, MD, PhD, UCHealth Sue Anschutz-Rodgers Eye Center, US

This talk discussed the role of complement in causing damage to tissue such as the neuromuscular junction. The talk focused on an autoimmune disorder of the CNS. A point relevant to MG is complement activation is enhanced when the target proteins are grouped together or clustered as is the case with AChR at the neuromuscular junction.

13:50 – 14:10 **MuSK B Cells (MGNet),** Kevin O'Connor, PhD, Yale School of Medicine, US

B-cell depletion treatments will lower MuSK Abs, but not AChR Abs. This may be why B-cell depletion has been more effective In MuSK MG, than in AChR-MG. Plasmablasts (immature plasma cells) are the source of pathogenic Abs in MuSK MG. When relapses occur, the Abs are

produced by plasmablasts that are induced by memory B-cells. This information may be useful in devising future treatment strategies for AChR and MuSK forms of MG.

14:10 – 14:30 **Single-cell Profiling in Myasthenia Gravis**, Bettina Schreiner, MD, PhD, University of Zurich, Switzerland

This presentation addressed the link between B-cells and the thymus in MG. Cells of MG patients associated with produce of induce pro-inflammatory agents, chemicals that enhance inflammatory responses. B-cells associated with MG seem to concentrate or "hide" in the thymus. There are also specific groups of T-cells in the Thymus that may contribute to MG development and severity. The observation that both B- and T-lymphocytes involved in MG tend to "hide out" in the thymus may be a reason that removing the thymus can improve the course of MG.

14:30 – 14:50 **Targeting IL-23 ameliorates thymic and Neuromuscular Defects in MG**, Nadine Dragin, PhD, Sorbonne Université, France

IL-23 is a pro-inflammatory interleukin (circulating protein). MG from people with MG have an imbalance of T-cells with excess activity of helper (Th) vs. suppressor T-cells. IL-23 leads to excess of pathogenic Th17 cells. The observation that IL-23 appears to enhance or promote inflammation in MG is leading to studies that evaluate whether suppressing IL-23 is a useful strategy to treat MG.

15:30 – 16:40 Session 4: Autoantibodies Chair, Maartje Huijbers, PhD, Leiden University Medical Centre, Netherlands

15:30 – 15:50 **The Pathophysiology of MuSK Myasthenia Gravis,** Maartje Huijbers**,** PhD, Leiden University Medical Centre, Netherlands

A very important observation is that the MuSK IgG type4 (the predominant pathogenic Ab in MuSK-MG) can induce weakness in animals without complement. It appears that the pathogenic IgG type4 acts by binding to MuSK and inhibiting the role that MuSK has of stabilizing clusters of AChR at the neuromuscular junction. Thus the MuSK IgG4 Abs cause a lower concentration of AChR on the muscle endplate thereby compromising the ability of ACh released by the nerve terminal to elicit a strong enough electrical response at the endplate to trigger muscle contraction.

I was not able to hear the remaining talks on Tuesday because of a medical appointment.

Wednesday May 11, 2022

I was unable to attend Sessions 1 and 2 due to medical appointments. The first session I was able to attend on Wednesday was Session 3 in the afternoon. This session dealt with Congenital MG (CMG) AKA Congenital Myasthenic Syndromes and Congenital disorders of Neuromuscular Transmission. The session also addressed pediatric autoimmune MG.

13:30 – 15:10 **Session 3: Congenital MG/Pediatric MG** Chair: David Beeson, MA, PhD, Nuffield Department of Clinical Neurosciences, UK

13:30 – 13:50 **Updates on CMS**, Ricardo Maselli, MD, University of California, Davis, US

Dr. Maselli discussed the wide diversity of forms of CMG. CMG includes a large number of rare disorders that are usually caused by genetic mutations that alter the function of a specific key component of the neuromuscular junction. CMG encompasses disorders of: 1) formation, storage and release of ACh from the nerve terminal; 2) processing of ACh in the space between the nerve terminal and endplate – including disorders of acethylcholine esterase (the enzyme that breaks down ACh – where pyridostigmine (Mestinon) acts); 3) density of AChR at

the endplate; 4) operation/behavior of AChRs and 5) structural stability of the end plate membrane. It is important to understand nature of defect at the neuromuscular junction in order to select appropriate Rx. Fortunately, the knowledge of diverse class of disorders that comprise CMG has improved including the recognition of specific strategies that work for different types of CMG.

13:50 – 14:10 **Mechanism of Disease and Therapeutic Rescue of DOK7 in CMS**, Steven Burden, PhD, NYU Langone Health, US

DOK-7 is a structural protein on the endplate that helps to increase the lifetime of endplate AChRs. DOK-7 binds to MuSK and stabilizes the phosphorylated form of MuSK (MuSK-P), which is critical for stabilizing endplate AChRs. A fortuitous observation is that the function of faulty DOK-7 can be replaced by synthetic MuSK Abs that are able to crosslink MuSK molecules. Synthetic MuSk Abs are able to compensate for impaired DOK-7 can restore normal endplate structure and improve synapse function. This strategy of employing engineered MuSK Abs may be useful in other forms of MG.

14:10 – 14:30 **Pediatric MG**, Emmanuelle Tiongson, MD, Children's Hospital of Los Angeles, US

This was an amazing talk. In the distant past when I was a medical student, pediatric MG did not exist in textbooks because it was dramatically under appreciated. Pediatric MG IS OFTEN autimmune. Early diagnosis and effective treatment is critical as it can limit long-term disability. Onset can be as early as one year of age or less. Onset can be as a crisis or slowly progressive and subtle. Eye movement disorders and eyelid droop (ptosis) are frequent early features. Symptoms clear with sleep and are worst with heat. Careful evaluation is needed to exclude CMG and other disorders. Treatment often starts with Pyridostigmine +/- low dose glucocorticoid (start 5mg max 15-20mg). For children with generalized MG Dr. Tiongson advocated thymectomy. IVIG is useful for providing short term improvement and is well tolerated. Steroid-sparing treatments such as azathioprine or mycophenolate mofetil can be used with caution in younger children. Over 18yo, patients can be treated as adults. A positive feature of pediatric MG is that there is a high chance of remission or achieving a condition of minimal manifestations.

14:30 – 14:50 **B-adrenergic Treatment**, David Beeson, MA, PhD, Nuffield Department of Clinical Neurosciences, UK

This session discussed treatment of people with CMG. The most common forms of CMG encountered in Oxford, UK are syndomes with deficiency of AChRs, deficiency of DOK-7, and syndromes associated with altered functioning of the AChRs (exs: slow and fast channel syndromes). Beta-2 agonists (such as atenolol or salbutamol) are most frequently used clinically to treat asthma. However, beta-2 agonists can have a beneficial effect on neuromuscular transmission. Beta-2 agonists appear to stabilize AChRs at the endplate to increase AChR lifetime. The benefit of beta-2 agonists is most evident in disorders associated with deficiency of AChRs as can occur with mutations of AChRs or DOK-7. Treatment with beta-2 agonists can improve weakness over a period of months. Dr. Beeson also found that beta-2 agonists can improve strength in people with MG who had been taking Mestinon for many years.

15:40 – 16:20 Session 4: Tolerance Induction Chair: Amelia Evoli, MD, Università Cattolica Del Sacro Cuore, Italy

15:40 – 16:00 **Preclinical Study of an Antigen-Specific Therapy for the Treatment of MG**, Konstantinos Lazaridis, PhD, Hellenic Pasteur Institute, Greece. A technical talk about animal model for a potential new strategy for treating MG.

16:00 – 16:20 **Oral Tolerance of MuSK EAMG,** Debby Reuveni, PhD, Weizmann Institute of Science, Israel

There are several differences in the clinical presentations of AChR- and MuSK-MG. Oro-pharyngeal muscle involvement is more frequently seen in MuSK-MG. Thymus pathology is uncommon in MuSK-MG. MuSK Abs appear to act by impairing linkage of MuSK to LRP4. Complement deficient mice are very susceptible to develop MG symptoms with MuSK sensitization. Decreased number of Tregulator cells (cells that tend to reduce inflammation) in MuSK injected mice. Tried to induce oral tolerance to MuSK to combat MuSK-Abs. Oral tolerance trials in mice reduced susceptibility to develop EAMG, but was not able to suppress established EAMG. Treating mice before induction of MuSK MG successful when initiated before MuSK MG was induced.

Thursday, May12, 2022

I missed the early presentations of Session 1 due to a medical appointment.

10:30 – 12:00 **Session 2: Hot Topics I** Chair: James Howard Jr., MD, University of North Carolina, Chapel Hill, US

10:30 – 10:50 **PROMISE MG**, Pushpa Narayanaswami, MD, FAAN, Harvard School of Medicine, US

Promise MG is a program to evaluate the effectiveness of agents that are no longer under copyright protection, hence agents that are not objects of interest to companies focusing on new treatments. An initial program focused on the effectiveness of frequently used steroid sparing agents azathioprine (AZT) and mycophenolate mofetil (MMF). Studies so far indicate that both AZT and MMF are beneficial in reducing steroid doses and improving symptoms. This is an extremely important program to determine how effective currently used treatments are.

10:50 – 11:10 **Drug Pricing**, A.Gordon Smith, MD, Virginia Commonwealth University, US

Points to consider – 1) Even though individual rare diseases are uncommon, there are a large number of "rare" diseases. Therefore, collectively rare diseases are common. 2) Drug pricing has escalated dramatically in part because drug-pricing does not follow "free market" economics. 3) Orphan drugs correspond to between 10-20% of drug sales. 4) Orphan drug act made it easier to market orphan drugs. FDA fee at onset is waived. Several schemes available to "game" the orphan drug act to advantage of drug makers – one being to get an old established drug labeled as orphan, control the source and jack up the price. Rationing is politically toxic, but occurs functionally due to high cost. US does not intervene to negotiate drug costs – my opinion is that Pharma influence on politicians via contributions, which, after the Supreme Court Citizen's United decision, are not declared. In my opinion the leverage that Pharma has is basically "your money or your life." Drug companies lure physicians to prescribe expensive Rx.

11:10 – 11:30 **ICER - Health Economic Assessment of New Drugs for MG**, Foluso Agboola, MBBS, MPH, Inst. Clinical and Economic Review, US

The Institute for Clinical and Economic Review looks at economic and social inequities. Pricing should consider the improvement seen with the agent – if done Eculizumab and Vvygart would have lower pricing.

Question and Answer

Main question was why not enable ICER to work with Medicare to set pricing guidelines? While this question was logical and fair – there has been tremendous push back from Congress against allowing the Federal Government and from State Legislatures for Federal (Medicare) or State (Medicaid) agencies to negotiate medication pricing, which is done by almost every other democratic nation in the World. My opinion is that Pharma has undue ability to influence legislation due to Pharma payment/inducements to legislators. ICER currently does have a way to factor

in medication side effects. One questioner noted that the time for a treatment to improve a patient's clinical improve is usually not evaluated in drug studies.

I missed the subsequent presentations on Thursday due to medical appointments.