MYASTHENIA GRAVIS
FOUNDATION OF AMERICA, INC.

Striving for a world without MG...

2008 Scientific Session

A summary by Robert L. Ruff, MD, PhD

The annual scientific session of the Myasthenia Gravis Foundation of America (MGFA) was held on September 20, 2008, in Salt Lake City, UT, at the Grand America Hotel. The session was organized by Dr. Matthew N. Meriggioli.

The meeting included discussion of the ongoing international clinical trial on thymectomy. There were seven presentations from around the world. Many of the presentations related to clinical treatment studies. Brief reviews of the role of the immune system in MG and seronegative MG are provided to enhance understanding of the presentations.

The Role of the Immune System in MG

MG is an auto-immune disease involving the site of communication between nerve and muscle, the neuromuscular junction. In MG, the body's immune system malfunctions and attacks specific proteins at the neuromuscular junction. The most common target of the autoimmune attack is the acetylcholine receptor (AChR). Lymphocytes (one type of "white blood cells" in your blood) are a class of immune cells that are divided into two large groups: Thymus-derived lymphocytes (T-cells) and B-cell lymphocytes. T-cells are involved in cell-medicated immune responses in which cells attack immune targets. B-cells are responsible for producing antibodies that target specific parts of proteins called epitopes. Cells that process and present potential immune targets (also called antigens) to the immune system are called antigen presenting cells (APCs). T-cells can modulate the activity of B-cells. MG is T-cell dependent antibody mediated disease in which T-cells modulate the activity of B-cells that produce antibodies that are directed primarily against the AChR and secondarily against other sites (epitopes) at the neuromuscular junction. The antibodies binding to the AChR trigger a complement-mediated cellular immune attack against the neuromuscular junction. Complement is an immune-medicated chemical cascade that destroys proteins and injures or destroys cells. Cytokines are proteins produces by the body that modulate the immune system. Interleukins (IL) are a class of cytokines that are secreted by lymphocytes. IL regulate the activities of different classes of immune system cells. Interferons (IFN) are a different class of immune regulatory proteins. DAF is a recently recognized factor that can alter the immune response seen in different tissues. Tolerance refers to a process in which an immune response to a specific agent is suppressed. One mechanism of tolerance is for T-cells to become insensitive to a disease-inciting antigen.

The MG Composite

Authors: Ted M. Burns, MD, (University of Virginia), Don Sanders (Duke University), Gary Cutter (Emory University) and Mark Conaway (University of Virginia)

One needs good tools for assessing the severity of MG and the response of MG to interventions in order to perform effective clinical studies. This presentation described a 10 question evaluation tool to evaluate the severity of MG, called the MG composite. Dr. Burns and Sanders are members of the MSAB who are actively

involved in clinical trials related to MG. Drs. Burns and Sanders designed the instrument to evaluate information that was meaningful to clinicians and people with MG. They also designed the instrument to be practical to administer in a clinical setting. Drs. Cutter and Conaway are bio-statisticians who helped design the MG composite so that it provided statistically relevant information. The MG composited was developed from three existing scales: QMG, MMT and ADL. They also selected elements that changed in a manner consistent with a quality of life monitor. An important feature of the MG composite was that it needed to accurately indicate when a subject improved or worsened. Each element was weighted to reflect the importance of an element to a subject's functional state. The authors called upon a group of MG experts from the MSAB and other MG experts from outside the US to weight the items in the MG composite. The MG composite also incorporated a feature where two of the items were selected from a list by a subject based upon how importance of each element to a specific subject.

The Characteristics of Childhood Generalized Myasthenia Gravis

Authors: Yoshiko Nomura, Kei Hachimori, Yuri Nagao, Kazue Kimura, Masaya Segawa
From the Segawa Neurological Clinic for Children, Tokyo Japan

Autoimmune MG in children is rare in the United States and Europe, therefore it is necessary to collect information from around the world in order to understand this condition and obtain an impression of this condition that will enable clinicians to predict how the disease will progress and when to initiate therapy. Some observations included that steroid treatment was more effective if started within 2 years of disease onset. In addition, children responded better to thymectomy if this was done in the first two years of disease onset. Thymectomy is usually done when a child does not respond well to steroid treatment. The immune markers (HLA class II markers) were different for generalized childhood MG compared with other forms of childhood MG such as ocular MG. In Japan there is a higher incidence of MG during the first five years of life compared with the US and Europe. The authors suspect that the high incidence of childhood MG in Japan is related to differences in genetic makeup. This study emphasizes that genetic makeup greatly influences an individuals likelihood of developing MG.

pDNAs encoding AChR autoantigen decrease clinical symptoms and pathogenic autoantibodies in animal models of MG

Authors: Lucy (Ya-Ping) Lou, Ph. D., Nanette Solvason, Rui Yun, Michael Levitren, Erick Blanco, Sara Nava, Fulvio Baggi, Hideki Garren. Bayhill Therapeutics Palo Alto CA

This presentation was from a company that is testing a strategy that can be modified to treat a number of autoimmune diseases such as multiple sclerosis (MS), and MG. The strategy is to incorporate the gene for alpha subunit of the AChR (the subunit that binds ACh) into a plasmid (a bacterial molecular tool that once incorporated into a cell will induce the production of the DNA carries by the plasmid) to produce the AChR alpha subunit protein in muscle cells or perhaps immune cells in skeletal muscle that can serve as antigen presenting cells. The technique was tested in rodent models of MG (EAMG). In the experiments the plasmid was injected into muscle and from the muscle the plasmid distributed to the entire body. After injection, the plasmid is taken up by muscle cells and then produces the AChR alpha subunit DNA. What is proposed to happen is that the plasmid induces the muscle cells to produce AChR alpha subunit protein. The muscle cell or dendritic cells that reside in muscle cells acts as the antigen presenting cells to present the AChR to T-cells. Presumably the excessive presentation of the AChR subunit protein results in the T-cells becoming desensitized to the AChR. Once desensitized the T-cell would produce less interferon-gamma, which would attenuate the immune reaction. While the mechanism of action is still speculative, the authors observed that the plasmid treatment could attenuate EAMG if treatment was started after the EAMG was induced. In addition, the plasmid treatment would reduce the likelihood of an animal developing EAMG if the plasmid

treatment preceded EAMG induction. In rats and mice the plasmid seemed to be well tolerated without apparent tissue reaction to it. The initial results were promising. However, extreme caution must be observed before these findings are extended to patients with MG. This treatment has not undergone human testing as yet (further animal studies are needed to get FDA approval to proceed to human trials). It is not clear how this strategy will work in humans – for example if the plasmid will be tolerated and if the plasmid will trigger desensitization to attenuate MG. It was very encouraging that the MGFA via the scientific session was able to interest a company in applying a treatment strategy for autoimmune disease specifically to MG. The company is engaged in studies of MS and immune-related diabetes.

Background for presentation on Seronegative MG

Antibodies are proteins produced by the immune system that bind to and target substances for destruction by the immune system. Antibodies are designed to target foreign substances such as bacteria. In patients with MG, antibody production is disturbed and antibodies are produced against self (i.e., antibodies target normal body proteins). The most common and the major pathogenic autoantibodies in MG are directed against the AChR on skeletal muscle. Patients with antibodies against the AChR are considered to have seropositive MG. A fraction of patients with MG, about 20% of patients with MG, do not have anti-AChR antibodies. The MG in these patients is referred to as seronegative. Many people with seronegative MG have autoantibodies against other components at the neuromuscular junction. The autoantibodies cause additional problems for patients with MG. Serum from patients with seronegative MG can be injected into animals and cause a MG-like condition. Immunoglobulins from seronegative patients bind to muscle cells, but not to AChR. The most common target for antibodies in patients with seronegative MG appears to be a muscle protein called MuSK (muscle-specific receptor tyrosine kinase). MuSK is a muscle-specific protein that regulates how AChRs are incorporated into the neuromuscular junction. About 30-50% of seronegative MG patients are have antibodies directed against MuSK. The seronegative patients who have antibodies against MuSK are sometimes referred to in studies as MuSK+ or MuSK-MG. For comparison, patients with antibodies against the AChR are sometimes referred to as having AChR-MG.

Experimental Models of MuSK-MG and SNMG

Authors: Angela Vincent, Stuart Viegas, Saiju Jacob, M Isabel Leite and Leslie Jacobson
Immunoregulation of Experimental Myasthenia Gravis. Department of Clinical Neurology, Oxford England

Animal models are used to evaluate strategies for treatment and to understand how a disease develops and progresses. This presentation dealt with animal models of MG without antibodies to AChR, seronegative MG (SNMG). Some patients with SNMG have antibodies directed against a protein at the neuromuscular junction called MuSK, MuSK can be used to immunize mice to produce an MG like disease. MuSk seemed to have an effect on the nerve terminal as well as to reduce the response of the post-synaptic membrane. The unexpected finding was that antibodies to MuSK reduced ACh release from the nerve terminal. MuSK is not located on the nerve terminal so presumably some alteration in MuSK function on the postsynaptic membrane alters the communication between the pre- and postsynaptic membrane to reduce ACh release.

METHOTREXATE: Safety and Efficacy in Myasthenia Gravis

Faisal Raja MD, Mazen M Dimachkie MD, April L McVey MD, Mamatha Pasnoor MD, Richard J Barohn MD. Department of Neurology, The University of Kansas Medical Center

Methotrexate is an immuno-suppressant medication that has a long history of use for cancer treatment and some immune diseases. It is much lower in cost than newer immunosuppressant medications. Methotrexate

has been used to treat MS. This study examined the possibility of using methotrexate for people with MG. The authors studied 6 patients. Methotrexate was well tolerated, but the number of subjects was too small to compare the efficacy of methotrexate vs steroid. The possible uses of methotrexate include allowing the dose of steroid to be reduced and serving as a replacement for steroid.

Phase II Trial of Methotrexate in Myasthenia Gravis IND #101,306

Richard J. Barohn, Mamatha Pasnoor, Mazen Dimachkie, April McVey, Laura Herbelin. University of Kansas Medical Center

This is a planned study of methotrexate for MG. The study would involve 50 patients, 25 receiving methotrexate and 25 placebo. The dosing of methotrexate is increased gradually. The study will examine if using methotrexate permits a lower dosing of steroid (prednisone). The study is being evaluated for funding by the FDA.

Update on the Thymectomy Trial

Gil Wolfe, University of Texas, Southwestern Campus in Dallas.

Dr. Wolfe is one of leaders of the international research program that is evaluating the effectiveness of thymectomy. The MGFA is supporting a portion of this research program and the NIH is the main funding source. The study compares thymectomy plus prednisone treatment to prednisone alone. There are 61 centers currently involved in the study. So far more than 4900 patients have been screened only about 100 satisfied the strict eligibility criteria and of the eligible subjects and 55 agree to participate. The main reason that patients have voiced for refusing to participate is that an individual does not want to have a thymectomy. The study is continuing to work to increase the number of subjects recruited.