MYASTHENIA GRAVIS TREATMENT

Stopping the Complement Cascade in Autoimmune Disease

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The drug eculizumab, an approved therapy for paroxysmal nocturnal hemoglobinuria, has been found to prevent muscle weakness and restore strength in animal models of MG.

What is Myasthenia Gravis?

Myasthenia gravis (MG) is an autoimmune neurological disorder affecting approximately 120,000 Americans. Myasthenia gravis is caused by acetylcholine receptor antibodies that interfere with the messages sent by nerves to muscles. Unable to receive these messages, muscle movement is impaired. Myasthenia gravis primarily affects muscles in the head and causes symptoms affecting eye and eyelid movement (ocular myasthenia gravis), facial expression and swallowing.

The hallmark of myasthenia gravis is muscle weakness that increases during periods of activity and improves after periods of rest. Besides the facial and eye muscles, the muscles that control breathing and neck and limb movements may also be affected. In severe cases, MG can interfere with breathing.

Normally, nerve endings release a neurotransmitter (chemical messenger) called acetylcholine that attaches to receptors on your muscles and tells your muscles to contract. In MG, muscles are unable to receive this response.

MG Research

Researchers at the Saint Louis University School of Medicine in Missouri have discovered that severe muscle weakness in myasthenia gravis (MG) can be dramatically prevented or reversed by blocking a key step in the immune response that’s responsible for the disease process. Specifically, these researchers have found a way to block the complement cascade, a process in which a step-wise release of immune system proteins is initiated. When complement is activated and C 5 is released in MG, a complex known as membrane attack complex primarily composed of C5 and antibodies is formed. This complex injures nerve membranes and interferes with signal transmission.

Complement Activation

The complement cascade, which occurs during the immune system’s response to foreign antigens (and autoantigens in autoimmune disease), involves a series of chemical reactions that cause complement proteins to bind together and attack cells. The end result is similar to punching a hole in the cell. During these reactions, the acetylcholine receptors on the cells are damaged in persons with myasthenia gravis. Damaged, the cells
are unable to receive messages from the neurotransmitter acetylcholine. Unable to receive these messages that signal or order muscle movement, muscle movement becomes severely impaired.

**The Thymus in MG**

The thymus gland, a small organ which lies in the upper chest area beneath the breastbone, plays an important role in the development of the immune system in early life. Here, T lymphocytes develop and mature. The thymus gland is large in infants, grows gradually until puberty, and then gets smaller and is replaced by fat with age. In adults with myasthenia gravis, the thymus gland is abnormal. It contains certain clusters of immune cells indicative of lymphoid hyperplasia - a condition usually found only in the spleen and lymph nodes during an active immune response. Some individuals with myasthenia gravis develop thymomas or tumors of the thymus gland. Generally thymomas are benign, but they can become malignant.

The relationship between the thymus gland and myasthenia gravis is not yet fully understood. Scientists believe the thymus gland may give incorrect instructions to developing immune cells, ultimately resulting in autoimmunity and the production of the acetylcholine receptor antibodies, thereby setting the stage for the attack on neuromuscular transmission.

**The St. Louis Study**

In their study, which used animal models of MG, the scientists at Washington University found that they could prevent muscle weakness, and in some cases restore strength, by stopping the complement cascade at the C5 step. This inhibition prevents the production of C5. The researchers accomplished this by administering an anti-C5 agent called eculizumab (Soliris) that targets one of the proteins in the complement cascade. In doing so the process of complement activation is stopped, and the C5 complex isn’t formed.

One of the study’s lead investigators, Henry Kaminski, M.D., reports that the findings are so encouraging that human clinical trials using eculizumab are expected to begin within the next year.

To date, eculizumab is an approved therapy for paroxysmal nocturnal hemoglobinuria (PNH) and it is being studied as a treatment in Guillain-Barre syndrome. The researchers in St. Louis report that if eculizumab proves effective in human trials of MG, it could one day help them find new therapies for other autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus (SLE).

**Resources:**

Yuefang Zhou, Bendi Gong, Feng Lin, Russell P. Rother, M. Edward Medof, and Henry J. Kaminski, Anti C-5Antibody Treatment Ameliorates Symptoms of Weakness in


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