Extended Abstract

Extended abstract: cutting edge developments and new therapeutics in myasthenia gravis

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Over the past fifteen years, there have been remarkable strides in our comprehension of myasthenia gravis and the development of therapeutic approaches. This progress has evolved from a single Phase 3 trial to an impressive array of over 25 trials encompassing various early phases and the approval of new medications by the FDA. This substantial therapeutic advancement has been propelled by a deeper understanding of the immune system, coupled with technological advancements in immune system analysis (1).

Within this context, myasthenia gravis is stratified based on several key metrics that significantly influence the choice of treatment. From an autoantibody perspective, individuals with acetylcholine receptor antibodies can be classified into early-onset and late-onset categories, with symptom onset occurring either before age 45 to 50 years or later in life. Early-onset patients, who are predominantly women and often exhibit thymic hyperplasia, tend to benefit from thymectomy (2-4). On the other hand, late-onset patients, who are more frequently men and typically associated with thymic atrophy, do not typically show improvement following thymus removal. Moreover, late-onset and early-onset patients exhibit genetic distinctions (5,6).

Approximately 10% of myasthenia gravis patients are diagnosed with a thymoma, which is more prevalent in cases with AB and B2 thymomas. Interestingly, transcription profiling has revealed variations in the mechanisms underlying myasthenia gravis induction for each thymoma subtype (7). Thymoma patients almost invariably present with acetylcholine receptor antibodies, although there have been rare reports of muscle-specific kinase antibodies. The pathogenesis of myasthenia gravis induced by acetylcholine receptor antibodies involves complement activation, receptor cross-linking, rapid muscle surface removal, and receptor function blockade. The recognition of complement-mediated injury has spurred the development of inhibitors for myasthenia gravis treatment over the course of two decades (8). Eculizumab, ravulizumab, and zilucoplan are approved treatments (9). Clinical trials of these agents have yielded positive results, albeit with some variability, underscoring the significance of other mechanisms contributing to neuromuscular junction injury.

Immunoglobulins undergo a robust recycling process in which antibodies attach to Fc receptors on endothelial cells and are subsequently internalized, with a portion undergoing proteolysis and the majority returning to circulation (10). This physiological process has been targeted by inhibitors that enhance antibody removal, resulting in a concurrent reduction in circulating antibodies. Neonatal Fc receptor (FcRn) inhibitors, such as rozanolixizumab and efgartigimod, have received approval for myasthenia gravis. Rozanolixizumab is approved for both muscle-specific kinase and acetylcholine receptor antibody myasthenia gravis, while efgartigimod is specifically indicated for acetylcholine receptor antibody myasthenia. These FcRn inhibitors, although currently approved only for myasthenia gravis, hold promise for the treatment of other antibody-mediated diseases. It is worth noting that these novel treatments come with a significant cost, ranging from $225,000 to $700,000 per year.

Despite these encouraging advancements, it is important to acknowledge that the new treatments do not directly impact the production of underlying antibodies. Rituximab, an antibody targeting CD20, has shown efficacy in muscle-specific kinase myasthenia, but its effectiveness is somewhat limited in cases of acetylcholine receptor antibody myasthenia gravis (11). This distinction suggests

that CD20-expressing short-lived plasma cells drive the pathology in muscle-specific kinase myasthenia, whereas long-lived plasma cells lacking CD20 contribute to the pathology in acetylcholine receptor myasthenia gravis (12).

Within the context of new treatment options and appreciation of biomarkers that guide therapy, conventional treatment, in particular prednisone, are highly effective and offer patients the potential for long-term remission (13-15). As a neurologist and scientist, I am excited to be living during the most exciting time in myasthenia gravis therapeutic development and I look forward to a bright future in the field.

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