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Myasthenia gravis – new, improved treatment

PERSPECTIVES

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A small subgroup of patients with myasthenia gravis experience severe muscle weakness and have a risk of respiratory failure despite receiving optimal standard therapy. Although new medications, including complement inhibitors and FcRn blockers, have well-documented clinical efficacy, they have not yet been approved for reimbursement in Norway, which is concerning.

Treatment for myasthenia gravis is evolving rapidly. New medications targeting well-defined disease mechanisms, including complement inhibitors, FcRn blockers and B- and T-cell inhibitors, have been introduced in many countries. These treatments provide substantial clinical benefit for many patients who fail to achieve adequate improvement with other therapies, and their efficacy and safety are well documented.

In Norway, however, the approval process has been lengthy, and reimbursement has not yet been granted. Only a small number of patients currently receive these medications through clinical trials. Even patients with very severe myasthenia gravis currently have no access to the most effective treatment.

These medications are extremely costly, and decisions are needed on how best to incorporate them into Norwegian clinical practice, including how they should be combined with current standard treatments. Several complement inhibitors and FcRn blockers have been approved by the European Medicines Agency, the U.S. Food and Drug Administration and regulatory authorities in Japan, and are now used routinely in countries such as Germany, Italy and the United States. Their underlying therapeutic principles are also highly relevant to other autoimmune diseases.

Myasthenia gravis is an autoimmune disease in which antibodies bind to the postsynaptic membrane at the neuromuscular junction, impairing muscle function and reducing the number of acetylcholine receptors (1) (Figure 1) (2). This results in muscle weakness that fluctuates over time and worsens with sustained activity. The prevalence of myasthenia gravis is gradually increasing, and approximately 1500 people in Norway are currently living with the condition (3).

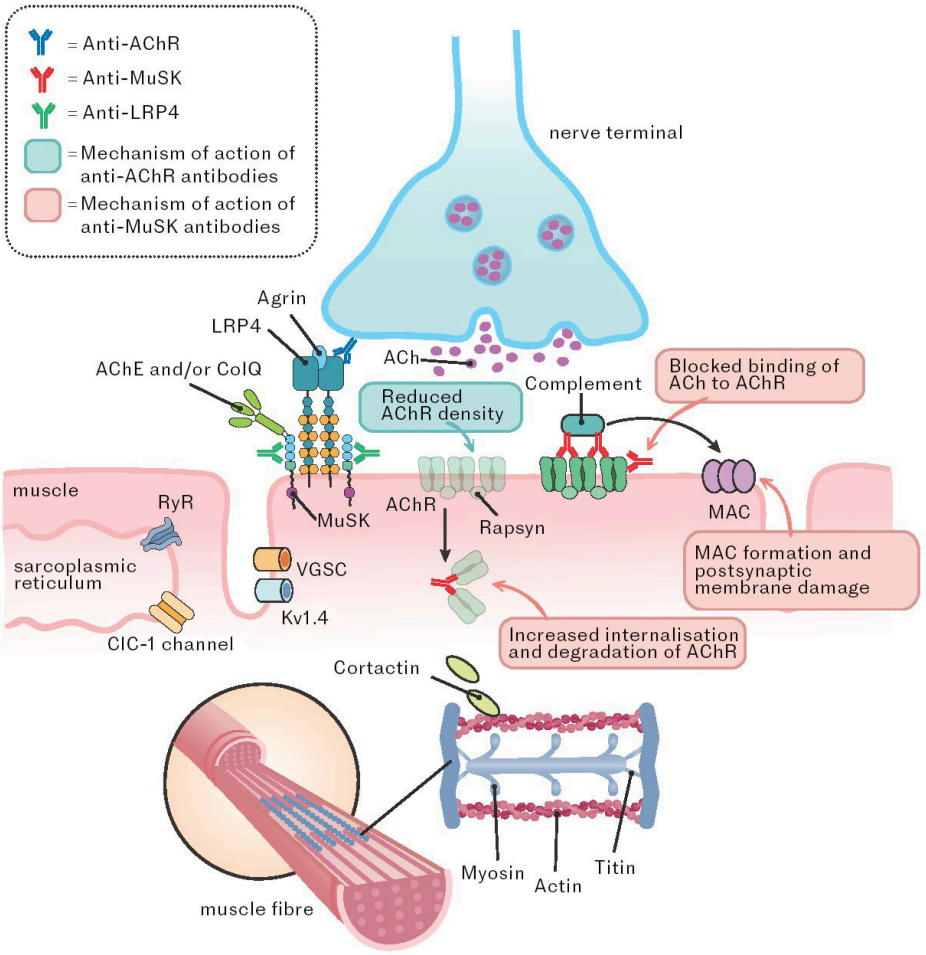

Figure 1 Neuromuscular junction showing acetylcholine receptors and relevant structures in the postsynaptic muscle membrane (2). Illustration: Jeanette Engqvist/Illumedic.

> ***«Even patients with very severe myasthenia gravis currently have no access to the most effective treatment»***

Effective treatment requires a precise assessment of each patient, including evaluation of disease subgroup, comorbidities and individual patient preferences (4–6). Around 80 % of patients have antibodies against the acetylcholine receptor, a small proportion have antibodies against muscle-specific kinase (MuSK) or lipoprotein-related protein 4 (LRP4), while no muscle antibodies are detectable in the remainder. Most patients require both symptomatic and immunosuppressive pharmacological treatment, and early thymectomy is often recommended. Additionally, personalised exercise programmes, general support and guidance are important elements of ongoing care. Intravenous immunoglobulin or plasma exchange is indicated for acute exacerbations.

Complement inhibition

Among the new therapies, complement inhibitors are particularly well documented. Controlled trials have shown a clear and rapid clinical benefit in patients with myasthenia gravis who have acetylcholine receptor antibodies. This includes

eculizumab (7), ravulizumab (8) and zilucoplan (9), all of which target complement factor C5 (Figure 2). Several new agents targeting other components of the complement cascade are currently under investigation. Open-label studies and long-term follow-up have confirmed sustained efficacy over several years in a large proportion of patients. Onset of effect is rapid, often within 1–2 weeks of treatment, making these therapies particularly suitable for acute and severe exacerbations. Benefit is also observed in patients with long-term, chronic weakness, with some experiencing substantial improvement.

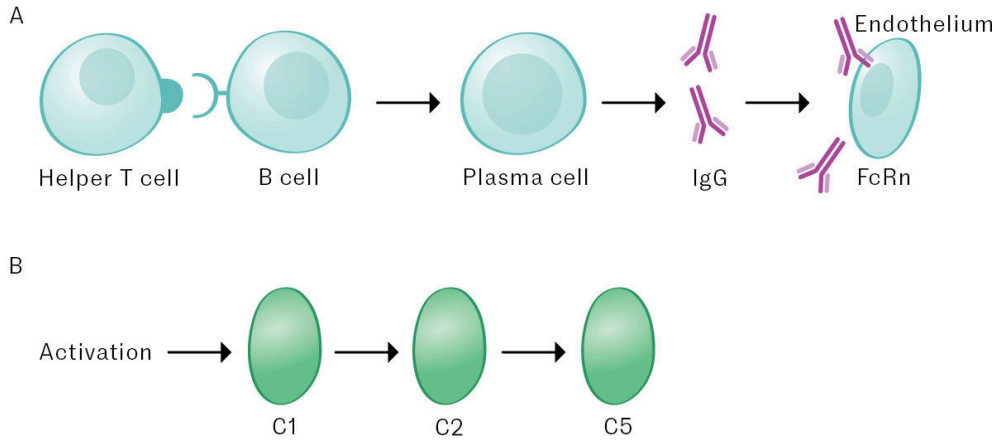

Figure 2 a) Production of IgG antibodies in myasthenia gravis and their degradation in endothelial cells, where FcRn receptors mediate IgG recycling. b) Complement activation when autoantibodies against acetylcholine receptors bind to muscle. Illustration: Jeanette Engqvist/Illumedic.

The mechanism of action is well established. Antibodies targeting acetylcholine receptors are primarily of the IgG1 subclass. Binding to receptors in the muscle membrane activates complement, resulting in destruction of the postsynaptic membrane and the acetylcholine receptors. In contrast, MuSK-associated myasthenia gravis is characterised by IgG4 antibodies, which do not activate complement.

FcRn inhibition

Blocking neonatal Fc receptors (FcRn) has shown rapid and pronounced clinical benefit in most patients with myasthenia gravis in controlled trials. This includes efgartigimod (10), rozanolixizumab (11), nipocalimab (12) and batoclimab (13). Effects are evident within 1–2 weeks, are sustained over time, and many patients with chronic, long-term disease experience significant improvement. These medications are also suitable for acute and severe exacerbations.

The FcRn receptor regulates immunoglobulin degradation by recycling IgG antibodies via FcRn, which is expressed on endothelial cells and other sites (Figure 2). This recycling prolongs IgG half-life. When FcRn is blocked, IgG is degraded more rapidly, resulting in a substantial reduction in both pathogenic and other IgG antibodies, while other immunoglobulin classes remain unaffected. FcRn blockers also prevent maternal–fetal IgG transfer via the placenta, which can in theory mitigate potential adverse effects of maternal muscle antibodies on the fetus (14).

B-cell inhibition

Several new therapies target B cells and plasma cells. This strategy is rational, as autoantibodies in myasthenia gravis are directly pathogenic and disrupt signal transmission at the neuromuscular junction. Rituximab, an anti-CD20 monoclonal antibody that depletes B lymphocytes but spares plasma cells, has shown efficacy in non-randomised trials (15). In a controlled trial of patients with long-term disease, the effect was not significant (16), but a study from the Karolinska Institute in patients with shorter disease duration demonstrated clear improvement (17). Rituximab is an effective and cost-efficient treatment option, although the combination of corticosteroids and azathioprine remains the most commonly used immunosuppressive regimen in myasthenia gravis. Rituximab is particularly effective in MuSK-associated disease.

Inebilizumab, an anti-CD19 monoclonal antibody targeting both antibody-producing plasma cells and B lymphocytes, has shown significant improvements in muscle strength and daily functioning in a recent controlled trial (18). The effect developed gradually over six months and was comparable in magnitude to that observed with complement inhibitors and FcRn blockers.

Cladribine affects both B and T cells and is currently under evaluation in controlled trials for myasthenia gravis (19).

T-cell inhibition

Among T-cell–targeted therapies, the development of CAR-T and CAAR-T cell approaches – where a patient's own T lymphocytes are engineered with chimeric antigen receptors – is of particular interest. CAR-T cells can be directed against B lymphocytes or plasma cells, for example targeting the CD20 antigen, while CAAR-T cells specifically attack B cells that produce pathogenic autoantibodies. CAR-T cell therapy is well established in oncology, and the approach shows promise for autoimmune diseases, including myasthenia gravis (20). CAAR-T therapy is especially appealing in theory, as it is disease-specific. At present, the treatment is technically demanding, extremely costly and insufficiently documented, and is unlikely to be available for Norwegian patients with myasthenia gravis in the near future. Traditional and effective immunosuppressive treatments for myasthenia gravis, including thymectomy, have a substantial effect on T lymphocytes.

Symptom-targeted therapy

Inhibition of the postsynaptic chloride channel ClC-1 in skeletal muscle is a novel therapeutic strategy currently under investigation (21). Acetylcholinesterase inhibition with pyridostigmine increases synaptic acetylcholine levels and is the standard first-line treatment. Beta-2 adrenergic agonists, such as terbutaline, may provide additional

benefit, whereas 3,4-diaminopyridine, which enhances presynaptic acetylcholine release, is more effective in Lambert–Eaton myasthenic syndrome (LEMS) than in myasthenia gravis.

> ***«Patients with severe, and in some cases life-threatening, myasthenia gravis should have access to treatments with proven efficacy»***

What now Norway?

Most patients with myasthenia gravis experience mild symptoms or are in remission with available therapies. The disease fluctuates, and particularly costly medications intended for lifelong use are unlikely to be suitable. Variations in recommended treatment duration, route of administration, dosage and dosing intervals allow new therapies to be tailored to individual needs.

Patients with severe, and in some cases life-threatening, myasthenia gravis should have access to treatments with proven efficacy. Urgent joint action is needed from health authorities, hospital trusts, clinicians, patient representatives and policymakers to make this possible. Clear and well-defined criteria for initiation and discontinuation of therapy will ensure rational use of expensive medications. The availability of new treatments is expected to reduce the need for intravenous immunoglobulin, plasma exchange and intensive care interventions.

The high cost of these new therapies makes it difficult to assess their cost-effectiveness using conventional frameworks (22). Myasthenia gravis has been cited as an example of the need for innovative funding models to ensure access to extremely costly treatments for a small patient population. It is difficult to understand why effective and safe therapies, which are available in most of Europe and North America, are effectively inaccessible to a small, well-defined group of patients in Norway with a substantial clinical need for such medications.

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