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# Myasthenia gravis: emerging new therapy options

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Myasthenia gravis is probably the most thoroughly understood of all human autoimmune diseases. The basic mechanism of the disease is an antibody-mediated autoimmune attack that decreases the acetylcholine receptor density at the neuromuscular junction. Current therapies aim to restore the available acetylcholine receptors, deplete the autoantibodies or suppress the immune system. Prolonged drug treatment is required, but this carries a potential risk of severe adverse effects. Therefore, the ideal treatment for myasthenia would eliminate the abnormal autoimmune response without interfering with the immune system.

## Addresses

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## Introduction

Myasthenia gravis (MG) is probably the best understood autoimmune disease. It is caused by antibodies against the acetylcholine receptor (AChR) that compromise neuromuscular transmission. This results in fluctuating skeletal muscle weakness that worsens with use, and improves with rest. Eye, facial, oropharyngeal, axial and limb muscles can all be involved in varying combinations and degrees of severity [1,2]. A proportion of patients lacking antibodies against the AChR harbors antibodies against the muscle-specific kinase, MuSK [3-5,6]. Autoantibody production in MG is a T-cell-dependent process, but how the breakdown in immune tolerance occurs is still unknown.

Once a severe and frequently fatal illness, MG can now be managed with several relatively safe and effective therapies. Nowadays, most patients do rather well. At the beginning of the 19th century, mortality from the disease was nearly 100%; however, it has declined steadily during the following decades [7,8]. Much of this impressive improvement can be attributed to the effectiveness of

general medical measures such as advances in respiratory care and the discovery of antibiotics. However, the increased understanding of MG has not been the rationale for most treatments currently used for this disease. Before the autoimmune pathogenesis of MG was elucidated in the 1970s, steroids were already being used in MG for reasons that turned out to be incorrect. Furthermore, immunosuppressive treatments for MG are largely empirical, following their use in organ transplantation and other autoimmune diseases. Thymectomy has been performed to improve non-thymomatous MG for decades; however, controlled prospective studies on the suspected benefit of this surgical procedure are still lacking [9,10].

This review summarizes the most recent advances in the treatment of MG. More specific therapies than those used today are still experimental but hopefully will soon improve the therapy of MG. Recent advances in neuroimmunology indicate several innovative new treatment options for autoimmune MG.

## Current treatment options

In general, five methods of treatment are currently used in MG [11,12,13]:

1. Enhancement of neuromuscular transmission using acetylcholinesterase (AChE) inhibitors.
2. Immunosuppression.
3. Surgical thymectomy.
4. Elimination of autoantibodies by plasma exchange.
5. Modulation of the autoimmune response by intravenous immunoglobulins.

AChE inhibitors have been used in MG since 1934, when Mary Walker as an assistant house officer at a hospital in suburban London tried physostigmine with dramatic positive results [7,8]. Even now, pyridostigmine, which was first synthesized in 1945, is still the base treatment in myasthenia. It produces a more even response with less toxicity, and is better tolerated by most MG patients, than other available anticholinesterases. Antisense technology might offer a strategy to selectively block the biosynthesis of the AChE protein [14]. The concept behind antisense therapeutics is to inhibit the expression of a specific gene at the mRNA level by using a synthetic string of a complementary oligonucleotide. This leads to specific destruction of the target mRNA, thereby selectively preventing expression of the protein encoded by this target mRNA. One Israeli company (Ester Neurosciences Ltd) is currently running a Phase IIa study of the antisense AChE compound Monarsen; results are not yet available.

It is important to note that the recent management of MG involves a graded approach. Mild and ocular MG can be treated solely with AChE inhibitors. If there is a more pronounced muscular weakness, an oral immunosuppressive medication is mandatory. These drugs have an onset of action ranging from weeks to months. Immunosuppressive treatment of patients with MG aims to induce an immunologic remission and to maintain that remission. Remission induction is usually accomplished through the use of high-dose corticosteroids. Severe weakness or significant deteriorations are treated with plasmapheresis (a process whereby antibodies are removed from the bloodstream) or intravenous immunoglobulins, the effects of which have a rapid onset but short duration. Maintenance of the remission is usually accomplished by slow tapering of the corticosteroids along with the use of 'steroid-sparing' immunosuppressive agents.

Several uncontrolled studies have suggested that early use of steroids may prevent generalization of the disease [15–17]. Monsul *et al.* [16] reported on 56 patients whose initial symptoms were purely ocular. Significantly fewer patients who received early immunotherapy progressed to generalized myasthenia when compared with the untreated group. Prospective trials are warranted to confirm this beneficial effect of early steroid treatment on the course of MG. Recent data suggest that long-term prednisone treatment might induce P-glycoprotein overfunction, resulting in multidrug resistance [18]. P-glycoprotein antagonists might improve the current use of steroids in myasthenic patients.

The most widely used immunosuppressive drug in MG is the purine synthesis inhibitor azathioprine. Azathioprine has considerably fewer side effects than do corticosteroids. Within the first weeks of treatment, about 10% of patients will show an idiosyncratic reaction consisting of fever, anorexia, nausea, vomiting and abdominal pain [12<sup>•</sup>]. Occasionally, patients with inborn errors of metabolism, such as thiopurine methyltransferase deficiency, can develop bone marrow suppression at lower doses [19,20]. However, the main drawback of azathioprine treatment is the slowness of response, ranging from three to 12 months. Those MG patients with insufficient therapeutic effect or intolerable side effects require immunosuppressive alternatives to azathioprine. Such drugs include cyclosporine, methotrexate and cyclophosphamide. High-dose cyclophosphamide treatment is useful in patients with refractory myasthenia [21<sup>•</sup>,22,23]. Drachman *et al.* [21<sup>•</sup>] treated three patients with high-dose cyclophosphamide (50 mg/kg/d intravenously for four days) followed by granulocyte colony-stimulating factor. Such immunoablative treatment does not damage haematopoietic stem cells, permitting repopulation of the immune system without bone marrow transplant. Indeed, all three patients of Drachman tolerated the treatment well and showed marked and durable improvement in myasthenic weakness.

The spectrum of agents used for immune-therapy in MG has broadened recently. New therapeutic alternatives are emerging that could be helpful especially in those patients who do not respond to conventional immunotherapy or cannot tolerate their side effects.

#### **Mycophenolate mofetil**

Mycophenolate mofetil (MyM; CellCept) suppresses both T and B cell proliferation by selectively blocking purine synthesis. An international multicenter, double-blind, placebo-controlled study of MyM is currently ongoing. However, retrospective case studies [24–27] and a small controlled pilot study [28] indicate that MyM is an effective adjunct therapy for MG. MyM is the second-line immunosuppressive agent for patients with a need for rapid therapeutic effect. In one large retrospective review [29], the mean onset of benefit was 10 weeks (ranging from four to 40 weeks). Maximal improvement can be seen on average 27 weeks (range from eight to 104 weeks) after starting MyM. Standard doses are 2000–3000 mg/d in two divided doses. Patients are started on 500 mg twice a day and, after one week, increased to 1000 mg twice a day. MyM is well tolerated in most patients. The main adverse effects are gastrointestinal, primarily diarrhoea. The efficacy of MyM appears to be similar to that of cyclosporine but with less toxicity.

#### **Tacrolimus**

Tacrolimus (FK506; Prograf) suppresses interleukin-2 production associated with T cell activation, and inhibits differentiation and proliferation of cytotoxic T cells [30]. It is one of the cornerstones of immunosuppressant therapy in transplantation medicine. There is an increasing number of case reports and open clinical trials on the efficacy of tacrolimus treatment in MG [31–33]. Konishi *et al.* [31] reported on a 16-week open clinical trial of 3–5 mg tacrolimus daily in 19 patients with generalized MG. At the end of the trial, total MG scores (range from 0–27 points) improved by three points or more in seven of the 19 patients. Anti-AChR antibody serum titres and interleukin-2 production decreased significantly. No serious adverse effects (e.g. renal toxicity or diabetes mellitus) were observed during the treatment period. The authors concluded that tacrolimus could safely serve as an adjunct to steroid therapy for MG at low dosage. An international controlled trial on the use of tacrolimus in generalized MG is upcoming.

#### **Rituximab**

CD20 is a 33–37 kDa non-glycosylated phosphoprotein expressed on the surface of almost all normal and malignant B cells and is the target for rituximab (MabThera, Rituxan) [34]. Rituximab has been given to over 300 000 lymphoma patients and is now being explored for use in autoimmune disorders. However, there are only scattered case reports on the successful treatment of refractory MG

using rituximab [35–37]. Zaja *et al.* [36] reported a marked improvement in a single case of MG (developed after bone marrow transplant) on treatment with rituximab. Rituximab induced a marked B lymphocyte depletion with a substantial reduction in the production of anti-AChR autoantibodies. We have observed a similar positive effect of rituximab in a man who developed anti-MuSK-positive MG after bone marrow transplantation [37].

### Etanercept

Tumor necrosis factor (TNF) $\alpha$  is a proinflammatory cytokine implicated in the pathogenesis of several autoimmune diseases, including MG [38]. The soluble recombinant TNF receptor Fc protein etanercept (Enbrel) blocks the action of TNF $\alpha$ . This drug is already on the market to treat rheumatoid arthritis and ankylosing spondylitis. Additionally, it is useful in psoriasis. In established experimental autoimmune MG, blocking the functional interaction of TNF with its receptors improved weakness when compared with placebo-treated mice [39].

Most recently, Rowin *et al.* [40] conducted a pilot open-label clinical trial of 25 mg etanercept twice weekly in a group of corticosteroid-dependent MG patients. Unfortunately, only six of 11 MG patients enrolled in this study improved after six-month treatment with etanercept. One patient had a severe acute clinical worsening probably related to an etanercept-induced pronounced rise in circulating TNF $\alpha$ . This suggests that, in certain patients, etanercept may upregulate the cytokine response and, as some of these proinflammatory cytokines are crucial for the pathogenesis of MG, these patients could worsen during treatment.

### Leflunomide

This isoxazole derivative is a prodrug that is rapidly and almost completely metabolized after enteral absorption to its active metabolite. Leflunomide has several mechanisms of action including inhibition of *de novo* pyrimidine synthesis and anti-inflammatory actions. It is currently used as a disease-modifying drug in rheumatoid arthritis. Clinical trials have recently evaluated the use of leflunomide in patients with systemic lupus erythematosus, Wegener's granulomatosis, Crohn's disease and solid tumours. Vidic-Dunkovic *et al.* [41] found that rats immunized with AChR protein but which did not receive leflunomide developed experimental MG between day seven and 11 post-immunization, and about 79% of these animals expressed clinical signs of disease. Treatment of AChR-protein-immunized rats with leflunomide from the day of disease induction completely suppressed the development of experimental MG. However, there have been no clinical reports indicating that this drug could be beneficial in combating MG in humans.

## Experimental approaches

Our understanding of the cellular and molecular events that lead to the autoimmune response in MG has improved dramatically in recent years. Accordingly, it should now be possible to design rational, immune-based therapies. Ideally, treatment of MG should eliminate the specific pathogenic autoimmune response to AChR, without otherwise suppressing the immune system or producing other adverse side effects. Experimental strategies can be divided into T-cell-directed or antigen-specific immunotherapies. Examples for novel experimental therapeutic strategies include:

1. Adoptive cellular gene therapy to provide long-term expression of immune-modulating molecules *in vivo* that can antagonize the chronic inflammatory process in autoimmune diseases [42].
2. Gene transfer to convert antigen-presenting cells to 'guided missiles' that target AChR-specific T cells and that induce apoptosis and elimination of those T cells [43].
3. Suppression of MG by mucosally administered recombinant AChR fragments [44–46].
4. Autologous dendritic cells that have been exposed *in vitro* to anti-inflammatory cytokines to induce tolerogenicity [47].
5. Production of the extracellular domains of human AChR subunits in eukaryotic systems, in native-like conformation, for their use as potent immunoadsorbents [48].
6. Prevention of experimental MG by an *in vitro* selected RNA aptamer [49].

## Conclusions

MG is probably the most thoroughly understood of all autoimmune diseases. The diagnosis and therapeutic management are well defined and in most patients successful, and a spectrum of specific and semi-specific interventions are available for the treatment of patients with MG. However, prolonged drug treatment is required, which carries the risk of severe adverse effects. It is hoped that one of the emerging new therapeutic options will lead us closer to the ideal of curing MG.

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