The past 20 years have seen marked improvement in treatment of immune-mediated neuromuscular diseases because of (1) better understanding of the various pathogenic processes and (2) research and development of immunotherapies. This review focuses on treatable neuromuscular diseases; amyotrophic lateral sclerosis (ALS) is included because new therapies may alter its course. Table 1 outlines the various immunotherapies most commonly used for treatment of immune-mediated neuromuscular diseases today.

### Inflammatory Myopathies

The 3 major inflammatory myopathies—dermatomyositis (DM), polymyositis (PM), and inclusion body myositis—have different pathogenic mechanisms. In DM, there is a complement-dependent humoral attack on unidentified antigens on the endothelial cell. In PM, the endomysial cell infiltrate contains an abundance of cytotoxic CD8 T cells, with invasion of nonnecrotic muscle fibers by these same cells and macrophages. In inclusion body myositis, immunopathologic factors are less well understood, and it is unresponsive to immunotherapy.

Corticosteroids are the mainstay of therapy for inflammatory myopathies. Initially, prednisolone acetate or prednisone, 50 to 75 mg/d (1 mg/kg), is given. This dose can be maintained for 4 to 6 weeks, at which time improvement should be seen in strength and elevated creatine kinase levels. Attempts to discontinue medication use should be done gradually over several months to avoid the likelihood of relapse.

In 20% to 30% of patients with DM or PM there is no adequate control of the disease with corticosteroid use alone. Methotrexate (beginning at 7.5-10.0 mg/wk and increasing by 2.5 mg/wk per month to 20.0 mg/wk) or azathioprine (2-3 mg/kg per day) are commonly used second-line agents. There are no good comparative data to clarify which is better. Either can be used as “steroid-sparing” agents in patients in whom long-term high-dose corticosteroid use is likely to produce intolerable adverse effects. Their combined use with corticosteroids decreases long-term disability compared with corticosteroid use alone.

Use of other agents might be necessary in the absence of adequate response. Cyclosporine (5 mg/kg per day) therapy was found in an open study to be as effective as prednisolone and azathioprine therapy in inducing complete or partial remission. Two studies using intravenous cyclophosphamide show conflicting results. Chlorambucil (4 mg/d) therapy may be effective in resistant cases of DM.

Intravenous immunoglobulin (IVIG) therapy has shown various degrees of improvement in several studies. There are no reliable dosage guidelines, but current practice is to administer a daily dose of 400 mg/kg per day for 5 days, followed by monthly 3-day courses for 3 to 6 months. Improvement should be apparent after the first or second course. Plasmapheresis is currently not justified as treatment for DM or PM.

Unlike PM and DM, inclusion body myositis is much less responsive to immunosuppressive therapy. In a retrospective review of 25 patients with inclusion body myositis, 40% thought that they had some benefit from prednisolone use and 20% thought that there was some benefit with...
azathioprine or methotrexate therapy. Two to 6 months of oral corticosteroid use alone or in combination with a steroid-sparing agent might be a reasonable approach.1

INFLAMMATORY DEMYELINATING POLYNEUROPATHIES

Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy are acute and subacute/chronic neuropathies characterized by immune-mediated demyelination. They have different time courses of symptoms and responses to therapy. In Guillain-Barré syndrome, the goals of therapy are to reduce the inflammatory attack, early, reduce morbidity, and improve final outcome. In chronic inflammatory demyelinating polyneuropathy, the goal is to suppress the ongoing immune reaction. Corticosteroid therapy is not helpful in preventing progression of disease or expediting recovery,2 except to relieve the severe back pain that many patients experience.

North American3 and French4 trials showed the efficacy of plasmapheresis within the first 2 weeks of illness. Mechanical ventilation and median time to independent ambulation were decreased. However, in both trials,3,4 many patients had to have 1 or more plasmapheresis sessions held because of complications. Treatment with IVIG is a reasonable alternative to plasmapheresis, with published studies2 showing its effect to be similar or better. Many patients will continue to deteriorate after receiving a full course of IVIG (18%) or plasmapheresis (17%). About 10% of patients treated with IVIG or plasmapheresis might initially improve and then deteriorate. This condition should respond to a second course of the same therapy.7 Intravenous immunoglobulin or plasmapheresis is administered once the patient is nonambulatory or respiration is significantly impaired.

The efficacy of corticosteroids in the treatment of chronic inflammatory demyelinating polyneuropathy is well established, with improvement occurring in as many as 95% of patients.8 As many as 70% of patients relapse after discontinuation of corticosteroid use.8 The usual starting dose of prednisone is 0.5 to 1.0 mg/kg, tapering to the lowest effective dose. Azathioprine (2-3 mg/kg per day) use might facilitate the tapering of prednisone therapy. Plasmapheresis and IVIG treatment have proven to be beneficial in as many as 80% of patients, without any clear advantage of one or the other modality.9 The major drawbacks of IVIG therapy and plasmapheresis are their high cost and potential for serious complications. Corticosteroids are inexpensive, but long-term adverse effects of their use are substantial.

Table 1. Immunotherapies Most Commonly Used for Immune-Mediated Neuromuscular Diseases*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Actions</th>
<th>Adverse Effects</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Broad range of effects on T and B cells</td>
<td>Hypertension, diabetes mellitus, obesity, osteoporosis, and cataracts</td>
<td>Blood pressure, diabetes, weight</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Purine analog inhibits DNA and RNA synthesis</td>
<td>Hepatotoxicity, bone marrow suppression, and possibly late malignancy</td>
<td>LFT results and CBC</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Interferes with production and release of interleukin 2; blocks early activation of T cells</td>
<td>Nephrotoxicity, hypertension, and headache</td>
<td>Blood pressure, creatinine, serum urea nitrogen, LFT, and CSA</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Modulation of cytokines and proinflammatory release inhibition of complement idiotypic anti-idiotypic interaction</td>
<td>Hemorrhagic cystitis, bone marrow suppression, and tuberculin reactivity, and late malignancy</td>
<td>CBC and cumulative dose</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>Removes antibodies and immune complexes</td>
<td>Hypertension, altered clotting factors, hypoalbuminemia and hypocalcemia, and vascular access</td>
<td>Blood pressure, fibrinogen, PT, and PTT</td>
</tr>
<tr>
<td>Neurotrophins†</td>
<td></td>
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</tbody>
</table>

*LFT indicates liver function test; CBC, complete blood cell count; CSA, cyclosporine blood levels; PT, prothrombin time; and PTT, partial thromboplastin time.
†See Table 2.

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy is characterized by asymmetrical, distal weakness. The presence of anti-GM1 antibodies is well described in this entity and might
provide the answers to the immunopathogenesis. Electrophysiologic abnormalities include conduction blocks in motor nerves, fasciculations, and myokymic discharges.

Because multifocal motor neuropathy seems to be immune mediated, several treatments directed at immune modulation have been attempted. Most studies were with small numbers of patients and without placebo control. Plasmapheresis and corticosteroid therapy seem to be ineffective, and the latter may cause rapid deterioration. Three trials with IVIG have shown transient effectiveness. Most patients studied showed no improvement in GM1 antibody titers, and only a few patients showed improved electrophysiologic results. Cyclophosphamide is an alternative therapy for patients with IVIG treatment failure or to reduce the frequency of IVIG infusions. The relatively benign course in many patients allows withholding IVIG for extended periods, until clinical deterioration warrants its use.

MOTOR NEURON DISEASES

Motor neuron diseases include progressive bulbar palsy, progressive spinal muscular atrophy, ALS, bulbo-spinal motor neuron disease (Kennedy syndrome), and primary lateral sclerosis. Therapeutic attempts largely have been directed at ALS.

There is no effective treatment for ALS. Riluzole, 50 mg twice daily, was the first drug found to alter disease course. The mechanism of action involves noncompetitive blockade of N-methyl D-aspartate receptors, inhibition of glutamate release, and inactivation of voltage-dependent sodium channels on glutaminergic nerve terminals. There was statistically significant improvement in survival in patients treated with riluzole compared with placebo, with this difference most notable in those with bulbar onset. Survival is increased by several months at best. Other drugs, including gabapentin, ascorbic acid, vitamin E, and beta carotene, are without proven benefit.

Motor neuron growth factors have profound abilities to enhance motor neuron survival in experimental animals during early development and maturity. Four classes of growth factors have been identified: neurotrophins (brain-derived growth factor, neurotrophin 3, and neurotrophin 4), cytokines (ciliary neurotrophic factor, leukemia inhibitory factor, and cardiotrophin-1), transforming growth factor (glial cell–derived neurotrophic factor and neurotulin), and insulin-like growth factors I and II (Table 2). Two placebo-controlled trials of recombinant human ciliary neurotrophic factor did not show any effect using various end points. A second motor neuron growth factor, recombinant human insulin-like growth factor, in higher doses was effective in slowing the rate of disease progression but is currently still under study.

At this time, the most important part of caring for the patient with ALS is supportive. Dysphagia requires diet modification and later a percutaneous endoscopic gastrostomy tube. Respiratory failure is the usual cause of death.

Table 2. Motor Neuron Growth Factor Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Actions</th>
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<tbody>
<tr>
<td>Neurotrophins (NT)</td>
<td>Prevents axotomy-induced MN death and reduces atrophy after axotomy</td>
</tr>
<tr>
<td>BDGF</td>
<td>Prevents axotomy-induced MN death and prevents programmed cell death</td>
</tr>
<tr>
<td>NT-3</td>
<td>Prevents axotomy-induced MN death and prevents programmed cell death</td>
</tr>
<tr>
<td>NT-4</td>
<td>Prevents axotomy-induced MN death, prevents postaxotomy atrophy, decreases adult MN death in ventral root avulsion, and increases neurotransmitter synthesis after axotomy</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
<tr>
<td>CTNF</td>
<td>Prevents axotomy-induced MN death and prevents programmed cell death</td>
</tr>
<tr>
<td>LIF</td>
<td>Prevents axotomy-induced MN death and prevents programmed cell death</td>
</tr>
<tr>
<td>CT-1</td>
<td>Prevents axotomy-induced MN death and prevents programmed cell death</td>
</tr>
<tr>
<td>Transforming growth factors</td>
<td></td>
</tr>
<tr>
<td>GDNF</td>
<td>Prevents axotomy-induced MN death, prevents postaxotomy atrophy, decreases adult MN death in ventral root avulsion, and increases neurotransmitter synthesis after axotomy</td>
</tr>
<tr>
<td>Neuroturtin</td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factors I and II</td>
<td>Promotes MN sprouting, prevents axotomy-induced MN death, and prevents programmed cell death</td>
</tr>
</tbody>
</table>

MYASTHENIA GRAVIS

Demonstration that acetylcholine receptor antibodies are responsible for the neuromuscular transmission defect in myasthenia gravis (MG) has provided a rationale for immunosuppression. These therapies, along with better modes of ventilation and antibiotic therapy, have contributed to a major decrease in the morbidity and mortality of MG. Therapies can be divided into those that improve strength rapidly with a short duration of action vs those that improve strength slowly with a more permanent response.

Use of acetylcholinesterase inhibitors impedes the hydrolysis of acetylcholine at the neuromuscular junction, allowing more acetylcholine for interaction with the receptor. They provide symptomatic relief in most patients, sometimes dramatically, but are rarely effective in the long term. Pyridostigmine bromide (15-60 mg every 4-6 hours) and neostigmine bromide (7.5-15.0 mg every 4-6 hours) are the most commonly used acetylcholinesterase inhibitors. The most common adverse effects of their use are gastrointestinal tract hypermotility and increased oral and respiratory secretions. Atropine therapy is usually effective should these adverse effects become problematic.

Plasmapheresis provides a rapid but relatively short-term improvement. The improvement of symptoms has been correlated with a reduction of antibody titers. The usual regimen is exchanging 1 plasma volume per treatment every day or every other day for 5 or 6 treatments. The effects can be seen as early as 24 hours. The duration of benefit rarely exceeds 10 weeks without other immunosuppressive treatment. Major drawbacks include hypotension, depletion of clotting factors, difficulty in obtaining vascular access, the complications of invasive devices, and the expense of the treatment.

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Another viable option for the treatment of acute exacerbations of MG is IVIG. Indications for its use are the same as those for plasmapheresis. The standard dose of IVIG is 400 mg/kg per day for 5 consecutive days. Results of a recent study suggest that IVIG therapy is as efficacious as plasmapheresis. There are, however, reports of patients who did not respond to IVIG therapy but responded to plasmapheresis. For this reason, plasmapheresis might be the best initial choice for patients in crisis, reserving IVIG therapy for those not tolerating plasmapheresis.

Medications currently used for long-term management in patients with MG include corticosteroids, azathioprine, cyclophosphamide, and cyclosporine. Corticosteroids have been the mainstay of treatment. The response usually begins within 2 to 3 weeks in at least 70% of patients. Patients with continued symptoms who are taking cholinesterase inhibitors are candidates for corticosteroid therapy. Caution must be exercised in instituting corticosteroid therapy because there is well-documented early deterioration in strength with large doses during the initial 5 to 7 treatment days. In an attempt to avoid this transient exacerbation, one can begin with 20 to 25 mg of prednisone daily or every other day and increase the dose 5.0 to 12.5 mg every 2 to 5 days.

Azathioprine, 2 to 3 mg/kg per day, is a steroid-sparing agent that allows for more rapid tapering of corticosteroid use and is useful in patients who respond inadequately to corticosteroid therapy and thymectomy or in those who are poor candidates for these interventions. Adverse effects are mild and consist of elevation of liver function test results and bone marrow suppression requiring monitoring at regular intervals. An average of 6 months is usual before clinical response is seen, with maximal benefit seen in 12 to 36 months. Teratogenicity limits azathioprine use in women desiring to have children.

Cyclosporine has been used in patients refractory to other modes of therapy. The usual dose (3-6 mg/kg per day given twice daily) will attain blood trough levels of 100 to 150 μg/L. Onset of improvement begins at 2 weeks, with a mean time to maximal improvement of 3 to 4 months. The advantage over azathioprine treatment is the shorter time to clinical effect. Significant adverse effects of cyclosporine therapy include headache, nephrotoxic effects, and hypertension. Cyclosporine is one of the most expensive immunosuppressant agents.

Cyclophosphamide therapy is another effective alternative, with onset of clinical response within 1 month. An oral dose of 3 to 5 mg/kg per day is the usual dose, and it may be preceded by an initial intravenous dose of 200 mg/d for 5 days. The association between thymoma and thymic hyperplasia in patients with MG has led to the use of thymectomy in the treatment of MG, and patients may achieve significant improvement or complete remission after thymectomy. The best surgical approach is transternal, with complete resection of thymus tissue.

The treatment approach to patients with MG should be individualized according to patient complaints, degree of weakness, age, and other comorbid conditions. In general, patients with purely ocular myasthenia should start taking cholinesterase inhibitors, with many patients improving. If symptoms persist, immunosuppression might be necessary using corticosteroids, azathioprine, or both. Patients with generalized MG may get some benefit from using cholinesterase inhibitors, but progression of symptoms or crisis may occur if immunosuppression is not instituted. Thymectomy is considered in all patients with generalized MG, the best candidates being young, healthy, and recently diagnosed (<2 years). Generally, patients are also started on prednisone therapy (60-80 mg/d). The addition of azathioprine allows for early corticosteroid weaning. Patients with borderline respiratory function should initiate corticosteroid use in the inpatient setting, with strong consideration for precorticosteroid plasmapheresis or IVIG therapy.

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome is usually associated with oat cell carcinoma or autoimmune disorders with antibodies directed at voltage-gated calcium channels. Therapy must be individualized for each patient according to severity of symptoms, life expectancy, and other comorbid problems. Once the diagnosis is confirmed electrophysiologically, an exhaustive search for an underlying malignancy must be undertaken. If no cancer is found initially, another workup in 3 to 6 months is warranted. Initial management should be directed at treatment of the underlying malignancy because weakness frequently improves with effective cancer therapy.

Use of cholinesterase inhibitors, in the same doses as in MG, may produce some improvement in Lambert-Eaton myasthenic syndrome, although not as dramatic as those in MG. 3,4-Diaminopyridine therapy enhances acetylcholine release and can significantly improve symptoms in doses of 5 to 25 mg 3 to 4 times daily. The therapeutic effect of 3,4-diaminopyridine is augmented by the concurrent administration of pyridostigmine. Adverse effects of this are minor and include acral and perioral paresthesias, epigastric distress, and insomnia. A few patients have had seizures, which can be managed by dose reduction or anticonvulsant agent use.

In patients with significant weakness, prednisone (60-80 mg/d) and azathioprine (2-3 mg/kg per day) are the most frequently used immunosuppressant agents, given alone or together. Cyclosporine (5-6 mg/kg per day divided twice daily) can be used in patients who do not respond to azathioprine treatment, with frequent monitoring of blood levels (aiming for 100-150 mg/L) and serum urea nitrogen and creatinine levels.

Plasmapheresis and IVIG therapy have also been reported to improve symptoms, but the effects are short-lived unless immunosuppressant agents are used, and additional courses are often needed to maintain benefit. Improvement can last for longer and longer periods after each treatment.

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Corresponding author: Ludwig Gutmann, MD, Department of Neurology, Robert C. Byrd Health Sciences Center of West Virginia University, G-103 Health Sciences North, PO Box 9180, Morgantown, WV 26506.
REFERENCES


