

Select Myasthenia Gravis Rx on Case-by-Case Basis

Prednisone is the most commonly used agent and most patients will require long-term, low-dose Tx.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MIAMI BEACH — The off-label use of immunosuppressive agents for myasthenia gravis can significantly decrease the need for steroids, while improving symptoms.

However, compared with prednisone, other immunosuppressants are much more expensive and carry their own risks of adverse events, so their use should be carefully evaluated on a case-by-case basis, Gil Wolfe, M.D., said at the annual meeting of the American Academy of Neurology.

Since acetylcholinesterase inhibitor monotherapy controls the symptoms of no more than 40% of myasthenia gravis (MG) patients, most patients will end up taking prednisone or other immunosuppressive agents, either alone or in combination, said Dr. Wolfe, a neurologist and codirector of the Muscular Dystrophy Association clinic at the University of Texas Southwestern Medical Center in Dallas.

► **Prednisone**—started low and slowly titrated, and tapered down very slowly after symptom improvement—is the most commonly used regimen. But few patients will be able to taper off prednisone

completely; the rest will require long-term, low-dose therapy. Other immunosuppressants may be added to prednisone to act as steroid-sparing agents and to assist in successful prednisone discontinuation, Dr. Wolfe said.

► **Azathioprine** is used as a steroid-sparing agent for patients who relapse during a prednisone taper and for those who have adverse events during long-term steroid use. “Up to 90% of patients respond well to [azathioprine], if they can tolerate it,” he said. “In those who can, it can reduce steroid consumption by up to 80% by 2 years.” One small study concluded that 63% of those who took azathioprine for 36 months had completely tapered off prednisone, compared with 20% of those who took prednisone alone.

The major cause for discontinuation is a flulike reaction, seen in 10%-20% of patients. The drug also has a long onset of action—maximum benefit may not be seen for up to 2 years.

► **Cyclosporine** works more rapidly, with maximum benefit seen by 3 months. Patients who are refractory to other agents may respond to cyclosporine; this drug is as effective as azathioprine in symptom improvement, judging from the findings

of a recent study. However, cyclosporine is less well tolerated than azathioprine, and some studies suggest that about half of patients discontinue the medication because of adverse events.

“It’s important not to mix different cyclosporine preparations, because the different brands are not bioequivalent,” Dr. Wolfe added.

► **Mycophenolate mofetil** has shown promise as the newest immunosuppressive agent commonly used for MG, he said. A recent open-label study showed that 73% of patients achieved pharmacologic remission, minimal manifestation status, or symptom improvement with mycophenolate. The drug has a rapid onset of action, with improvement seen in 9-11 weeks and maximum effect by 6 months. “You may be able to decrease steroids by up to 50% in most patients with this drug,” Dr. Wolfe said.

Mycophenolate is well tolerated. Its main adverse events are diarrhea, vomiting, increased risk of infection, and rarely, leukopenia; only about 6% of patients discontinue the drug because of an adverse event. Switching to dosing three times daily may decrease the incidence of diarrhea.

► **Cyclophosphamide** is used mainly for refractory MG patients. “This drug has a lot of potential for adverse events,” Dr. Wolfe said. “But IV pulse therapy looks like it could be safer than daily oral ther-

apy, because there is a lower cumulative dose.” However, cyclophosphamide should be considered a third-line therapy.

► **Intravenous gamma globulin** is employed as a lower-risk alternative to plasma exchange. An analysis of eight retrospective studies indicated that 73% of patients responded well to intravenous gamma globulin, and did so very quickly—in about 4-5 days. The beneficial effects can last up to several months. “IV gamma globulin is a particularly attractive alternative to plasma exchange for patients with poor venous access, hemodynamic instability, or other contraindications to plasmapheresis,” he said.

► **Investigational agents** include tacrolimus, rituximab, and monarsen. Tacrolimus has demonstrated efficacy as a monotherapy or in combination with corticosteroids, in a few recent open trials. It has a similar mechanism of action to cyclosporine but appears less nephrotoxic. However, hyperglycemia may occur. Rituximab has been reported in just a few MG cases and was associated with substantial clinical improvement at 4 weeks and with no complications or adverse events. Monarsen is being investigated in preliminary MG studies. In an open trial of 16 patients, 15 who discontinued the antiacetylcholinesterase pyridostigmine demonstrated improvement while using monarsen. ■

On the Horizon: Designer Glucocorticoids Providing Benefits Without Side Effects

BY NANCY WALSH
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BIRMINGHAM, ENGLAND — Increased understanding of the molecular mechanisms of glucocorticoids may eventually lead to the development of new agents that provide the clinical benefits without the attendant side effects that currently hamper the use of these drugs in rheumatic diseases.

It is now known that the anti-inflammatory and immunosuppressive effects of glucocorticoids primarily function via a process of negative regulation of gene expression, or transrepression, Frank Buttgerit, M.D., said at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

“Glucocorticoids are very lipophilic molecules and are able to penetrate the cell membrane and bind to the cytosolic glucocorticoid receptor complex, which becomes activated and moves into the nucleus where it binds to specific DNA sites,” he explained. The result is upregulation of anti-inflammatory proteins and downregulation of inflammatory molecules such as interleukin (IL)-1 and tumor necrosis factor (TNF)- α , he said.

An example of glucocorticoid transrepression is the effect on bone metabolism. “We currently think that

TNF- α and IL-1 are able to induce osteoclasts and T cells to produce RANK ligand, which binds to the RANK receptor on osteoclast precursor cells and to the RANK receptor of the osteoclast,” he said. This results in an induced maturation of precursor cells into mature, very aggressive osteoclasts responsible for bone erosion and progression of osteoporosis. Downregulation of the TNF- α and IL-1 through transrepression retards these effects, he said.

While the benefits of these drugs stem from the genomic effects of transrepression, many of the unwanted cardiovascular, endocrine, and metabolic effects are mediated by a separate genomic process known as transactivation, said Dr. Buttgerit of the department of rheumatology and clinical immunology, University Hospital of Humboldt University, Berlin. Certain enzymes involved in the development of diabetes, for example, are activated at the genomic level by glucocorticoids, and an ongoing research effort is intended to create designer glucocorticoids that preferentially induce transrepression

and have little or no transactivating activity—obtaining the benefit without the adverse effects.

These agents, several of which have been developed, are known as selective glucocorticoid receptor agonists (SEGRAs). One of these compounds,

Nitrosteroids not only bind to the glucocorticoid receptor, but also slowly release nitric oxide, resulting in synergistic anti-inflammatory effects.

AK 216348, has been shown in animal studies to have anti-inflammatory effects equivalent to those of prednisone but with fewer transactivating effects, Dr. Buttgerit said.

Drugs of a second type of compound that has been developed are known as nitric oxide glucocorticoids or nitrosteroids. These not only bind to the glucocorticoid receptor but also slowly release nitric oxide, resulting in synergistic anti-inflammatory effects. In vitro studies of a prototype nitrosteroid, NCX-1015, have suggested that, unlike prednisone, it does not activate unwanted osteoclast activity (Rheum. Dis. Clin. North. Am. 2005;31:1-17).

Further preclinical work and then clinical trials will be needed to determine if these preliminary findings hold up, Dr. Buttgerit said. ■

Ras Signal Defect in SLE May Offer Target

CHICAGO — An apparent defect in Ras signaling in lupus patients’ T cells contributes to sustained expression of CD40 ligand and may provide a target to suppress disease activity, Dilrukshie Cooray, M.D., reported at the combined annual meeting of the Central Society for Clinical Research and the Midwestern section of the American Federation for Medical Research.

Previous evidence suggested that a defect in the downregulation of the Ras pathway in lupus T cells led to the failure to develop anergy and to an abnormally prolonged expression of CD40 ligand (CD40L) (Arthritis Rheum. 2001;44:397-407).

Working on that hypothesis, Dr. Cooray and colleagues performed immunocytochemistry to test freshly isolated lymphocytes from patients with SLE and healthy controls before and after inactivation of Ras with the Ras inhibitor S-farnesylthiosalicylic acid.

They found that Ras inactivation markedly decreased the level of CD40L in T cells obtained from patients with lupus but not from healthy subjects.

“Our preliminary results support the hypothesis that there is an intrinsic defect in Ras signaling in lupus patients’ T cells that contributes to sustained expression of CD40L,” reported Dr. Cooray of the rheumatology department at Loma Linda (Calif.) University. “By suppressing levels of CD40L, we think we are able to suppress disease activity.”

Because the researchers tested only six patients, it’s not clear what level of CD40L is necessary for suppression of disease activity.

—Kathleen Loudon