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Steroids and Immunosuppressant Drugs in Myasthenia Gravis

Sivakumar Sathasivam

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Summary and Introduction

Summary

In chronic autoimmune conditions such as myasthenia gravis (MG), immunosuppression-usually long-term-is often necessary. The mechanisms of action of immunosuppressant drugs in MG fall into three main categories: inhibition of the cell cycle (azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil), immunosuppression of T cells (steroids, ciclosporin and tacrolimus), and B-cell depletion (rituximab). Data on immunosuppressant drugs in MG derive mainly from clinical experience, observational studies and expert opinion. The main drawbacks of the randomized evidence are the small size of most drug trials, variations in study design, and a lack of head-to-head studies. It is therefore difficult to determine the relative efficacy of each immunosuppressant. Oral prednisolone, usually started at a low dose on an alternate-day regimen, and gradually increased, is the recommended first-choice short-term immunosuppressant. Long-term immunosuppression regimens vary between different countries and physicians. Azathioprine is often the first-choice drug for long-term immunosuppression, and it is usually started together with steroids to allow tapering of steroids to the lowest dose possible. Methotrexate, mycophenolate mofetil or tacrolimus should be considered in patients who are intolerant of or unresponsive to azathioprine. Ciclosporin and cyclophosphamide should only be considered as a last resort, as these drugs can cause serious adverse events. Data on rituximab use in MG are sparse, but the initial results are promising.

Introduction

Myasthenia gravis (MG) is a neuromuscular disorder characterized by fluctuating, painless muscle weakness. It typically starts in the extraocular muscles and remains purely ocular in 15% of patients. In the remaining 85% of patients, MG becomes generalized, usually by descending to involve the bulbar muscles, followed by the neck, proximal limb and sometimes respiratory muscles. Severe bulbar or respiratory weakness constitutes a myasthenic crisis, which can require intubation and mechanical ventilation.

Mechanistically, MG is an autoimmune disorder of neuromuscular transmission, usually caused by antibodies to postsynaptic nicotinic acetylcholine receptors (AChRs).[1] The antibodies reduce the number of functional AChRs, thereby impairing neuromuscular transmission. Approximately 15% of patients with generalized MG do not have detectable AChR antibodies;[2] however, sera from these AChR-antibody-negative patients contain other immune factors, including IgG antibodies to muscle-specific tyrosine kinase (MuSK) in a fraction of cases (<40%).[3] Activation of B cells and T cells is important in the pathogenesis and immunoregulation of MG: a detailed explanation of the immune activation is beyond the scope of this article, and the topic has been extensively reviewed elsewhere.[4,5]

Estimates of the annual incidence of MG range from about 1 in 10,000 to 1 in 50,000 of the population.[6] The natural history is characterized by exacerbations and remissions. In untreated MG, the most disabling-

sometimes life-threatening-phase is usually in the first 5-7 years.[7] Spontaneous remissions, often temporary, occur in 10-15% of patients in the 10 years after onset.[8]

In the past 40 years, advances in treatment have greatly reduced the morbidity and mortality of MG.[7,8,9] In generalized MG, the first-line option is symptomatic therapy with cholinesterase inhibitors. Definitive therapy includes immunosuppression with steroids, azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, tacrolimus, cyclophosphamide or rituximab. Thymectomy might be useful in selected cases of generalized MG, and a trial is currently being undertaken to determine its role in this condition. Plasma exchange, immunoadsorption and intravenous immunoglobulin are useful emergency therapies in generalized MG.

In this Review, the mechanisms of action of steroids and other immunosuppressants, and randomized and nonrandomized evidence of their efficacy in generalized MG, will be examined. The evidence regarding the optimum dosing schedule of steroids and the role of each immunosuppressant in the treatment of generalized MG will be discussed.

Mechanisms of Immunosuppression

The mechanisms of immunosuppression by drugs in MG are complex and incompletely understood. Broadly speaking, there are three main mechanisms by which immunosuppressant drugs are thought to work in MG. The first is by interfering with the cell cycle, resulting in a blockade of T-cell and B-cell proliferation (Figure 1). Immunosuppressants that act by this mechanism include azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil. Azathioprine, a purine analog, functions as a purine antagonist when metabolized to 6-mercaptopurine. It is a cell-cycle-specific inhibitor, exerting its actions mainly in the resting (G_1) and DNA synthesis (S) phases of the cell cycle.[10] Mycophenolate mofetil, when converted in the liver to its active compound, mycophenolic acid, inhibits the lymphocytic purine synthesis enzyme inosine monophosphate dehydrogenase. Like azathioprine, it acts predominantly on the G_1 and S phases of the cell cycle,[10] although it has a higher specificity than azathioprine for activated lymphocytes.[10,11] Methotrexate, which also mainly affects the G_1 and S phases of the cell cycle,[11] is a folate antagonist that can inhibit *de novo* synthesis of both purines and pyrimidines. Cyclophosphamide is a DNA-alkylating drug and nonspecific cell-cycle inhibitor, with more-pronounced effects on B cells than on T cells.[11]

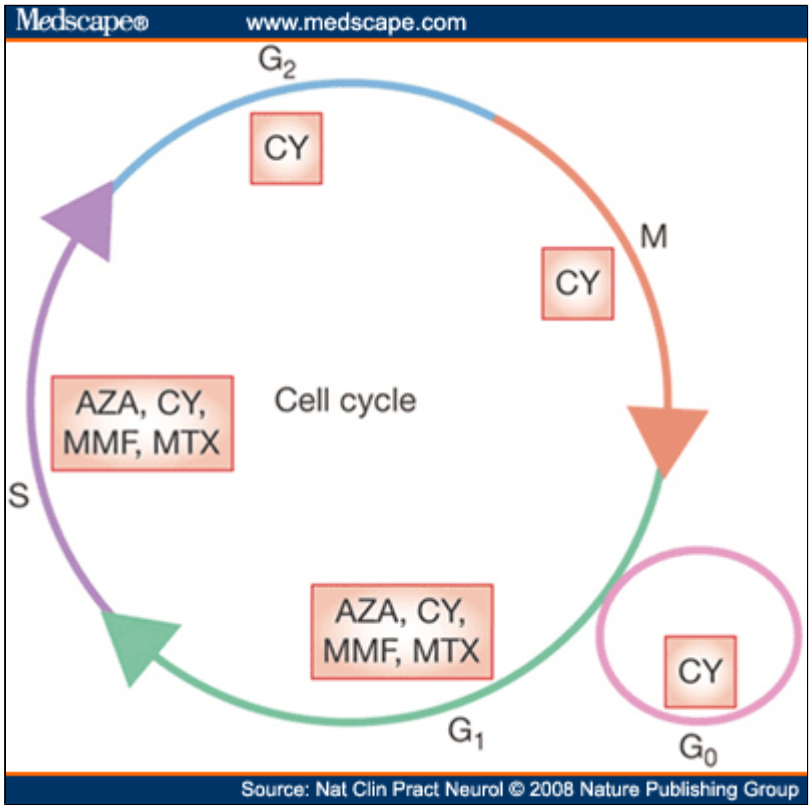

Figure 1.

Inhibition of the cell cycle by immunosuppressants. Azathioprine, mycophenolate mofetil and

methotrexate are relatively specific cell-cycle inhibitors, affecting mainly the resting and DNA synthesis phases. Cyclophosphamide is a nonspecific cell-cycle inhibitor and affects all phases. Abbreviations: AZA = azathioprine; CY = cyclophosphamide; G_0 = dormant phase; G_1 = resting phase; G_2 = premitotic phase; M = mitotic phase; MMF = mycophenolate mofetil; MTX = methotrexate; S = DNA synthesis phase.

The second main mechanism of action of immunosuppressant drugs in MG is immunosuppression of T cells (Figure 2). In the cytoplasm, ciclosporin binds to its immunophilin, cyclophilin. The ciclosporin-cyclophilin complex binds to and blocks the function of the enzyme calcineurin, eventually inhibiting T-cell activation. Tacrolimus binds to the FK506-binding protein (FKB), forming the tacrolimus-FKB complex, which also binds to and blocks calcineurin. Although ciclosporin and tacrolimus bind to different target molecules, both drugs inhibit T-cell activation in the same manner.[10,11] Steroids are thought to inhibit the activation of T cells by interfering with the activation process in the cell nucleus.[10,12] In addition, steroids impair the function of cells of the monocyte-macrophage lineage by inhibiting antigen processing and decreasing the number of circulating T cells.[10]

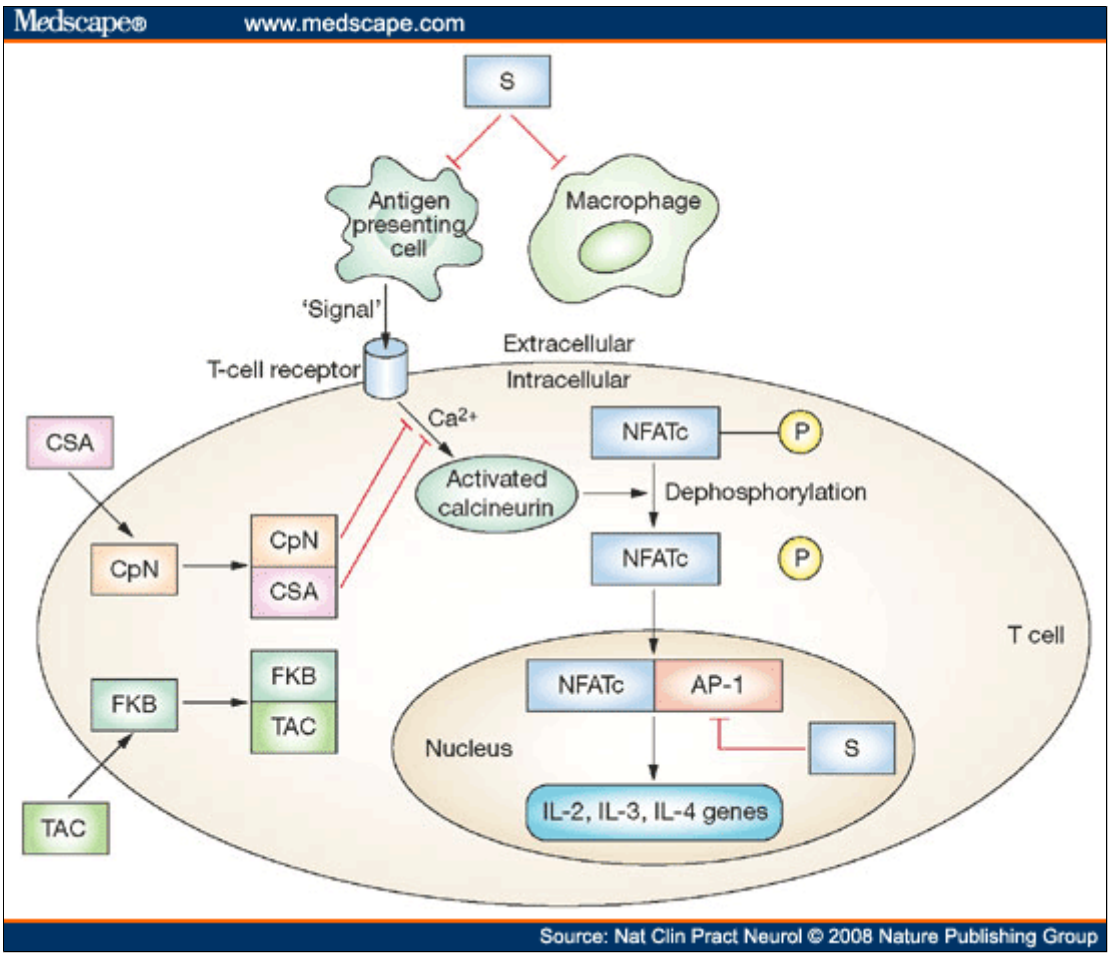

Figure 2.

Immunosuppression of T cells. Steroids, ciclosporin and tacrolimus all ultimately cause suppression of T cells. In the cytoplasm, ciclosporin binds to its immunophilin, cyclophilin, and tacrolimus binds to the FKB. The ciclosporin-cyclophilin complex and the tacrolimus-FKB complex each bind to and block the function of the enzyme calcineurin, which has serine-threonine phosphatase activity. As a result, calcineurin fails to dephosphorylate NFATc. The nuclear component of NFAT, which is made up of NFATc and AP-1, regulates expression of IL-2, IL-3 and IL-4. Steroids inhibit the activation of NFATc by blocking the activator protein-1 component. Steroids also affect the function of cells of the monocyte-macrophage lineage by blocking antigen processing and decreasing the number of circulating T cells. Abbreviations: AP-1 = activator protein-1; CpN = cyclophilin; CSA = ciclosporin; FKB = FK506-binding protein; IL = interleukin; NFATc = cytoplasmic component of nuclear factor of activated T cells; P = phosphate;

S = steroids; TAC = tacrolimus.

Rituximab, a monoclonal antibody against the B-cell surface marker CD20, has recently been used in patients who do not improve with the use of steroids or any of the immunosuppressant drugs described above, alone or in combination. The mechanism of action of rituximab is through B-cell depletion, postulated to occur via complement-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity and induction of apoptosis.[13]

Azathioprine

Nonrandomized Evidence

There have been several observational studies of azathioprine treatment in MG. In one series, azathioprine improved MG in 78% of 26 patients who had previously been unresponsive to adrenocorticotropic hormone (ACTH) or glucocorticosteroids.[14] In another study, 91% of 78 patients showed improvements when treated with azathioprine, given alone or in combination with steroids, thymectomy or both.[15] Fifteen of 18 patients (83%) improved when treated for more than 6 months with azathioprine alone.[16] In a separate study, 41 patients with MG were followed for more than 3 years and all showed improvements when azathioprine was used either as monotherapy or in combination with prednisolone.[17] In another study, 75% of 32 patients treated with azathioprine alone showed improvements, compared with 70% of 57 patients treated with azathioprine plus steroids.[18] Early 'high-dose' immunosuppression with azathioprine and prednisolone resulted in 50% of patients achieving remission after 2 years, compared with a remission rate of only 16% in those on a 'low-dose' regimen.[19]

Randomized Evidence

A randomized, unblinded trial of azathioprine plus initial prednisolone (21 patients) versus prednisolone alone (20 patients) was carried out in patients with generalized MG (Table 1). The primary endpoint was time to the first episode of clinical deterioration within the first 60 months. Among the 21 deterioration events, 9 were observed in the azathioprine group and 12 in the prednisolone group, giving a relative risk for azathioprine plus prednisolone versus prednisolone alone of 0.71 (95% CI 0.39-1.31). In addition, no differences in muscle strength measurements were observed between the two groups.[20] Therefore, there was no evidence from this trial that azathioprine was better than steroids at improving MG clinically.

A randomized double-blind trial of azathioprine plus prednisolone (15 patients) versus prednisolone plus placebo (19 patients) in generalized MG (Table 1) showed no significant differences between the two treatment groups in terms of objective or subjective muscle strength measurement scores (exact figures not given).[21] The median prednisolone dose did not differ significantly between the two treatment groups at 12 months (exact figures not given), but was significantly reduced at 36 months ($P = 0.02$) in the azathioprine plus prednisolone group compared with the prednisolone plus placebo group. There was no significant difference in the number of patients experiencing treatment failure between the two treatment groups ($P = 0.1$). Analysis of those who completed the trial showed that the duration of remission was significantly longer in the azathioprine plus prednisolone group than in the prednisolone plus placebo group ($P = 0.024$), giving a relative risk of 0.28 (95% CI 0.08-0.94). If those who withdrew or died were included as treatment failures, the duration of remission was not significantly different between the azathioprine plus prednisolone versus prednisolone plus placebo groups ($P = 0.1$), with a relative risk of 0.67 (95% CI 0.43-1.04) for azathioprine versus placebo. Therefore, although there was no clear evidence from this trial that azathioprine improved MG clinically, it seemed at least to have a steroid-sparing effect.

A randomized double-blind trial comparing azathioprine with ciclosporin lacked key data on trial methodology-in particular, what immunosuppression patients had been given previously, and whether there was a wash out period before randomization. It was, therefore, unclear which drug was actually being evaluated.[22] Another small, randomized, crossover trial of prednisolone versus azathioprine was hampered by major violations of the trial protocol, making meaningful evaluation of the results impossible.[23]

Recommendations

Azathioprine has been associated with relatively few treatment failures and a steroid-sparing effect in two randomized controlled trials (class I evidence).[20,21] In many countries it is the first-choice long-term immunosuppressant drug, and is started together with steroids to allow tapering of steroids to the lowest dose

possible. Common adverse events of azathioprine include hepatotoxicity, nausea, vomiting, rash, cytopenia and pancreatitis. In the long-term, malignancy is a potential complication, although the absolute risk is difficult to evaluate because it is difficult to separate the effects of the drug from age-related increases in the background incidence of cancer.

Cyclophosphamide

Nonrandomized Evidence

Stable remissions were reported in 42 patients who were given cyclophosphamide for 2-37 months. Thirty-three of these participants received concomitant steroid therapy, and five underwent thymectomy.[24]

Randomized Evidence

In a randomized double-blind trial of cyclophosphamide plus prednisolone (12 patients) versus prednisolone plus placebo (11 patients) in generalized MG (Table 1), cyclophosphamide significantly improved muscle strength (Quantitative MG Score for Disease Severity [QMG score]) at 12 months, but not at 6 months. Data from individual patients were, however, unavailable from the study. The cyclophosphamide-treated patients were on significantly lower doses of prednisolone at 6 months ($P < 0.05$) and 12 months ($P < 0.03$) than at the start of the trial. There was no significant difference in treatment failures between the two groups ($P = 0.217$).[25] There is limited evidence, therefore, that cyclophosphamide is clinically effective in generalized MG, and that it has a steroid-sparing effect.

Recommendations

A relatively small randomized double-blind trial provided limited evidence that cyclophosphamide is effective in MG (class II evidence).[25] In view of the fact that cyclophosphamide is associated with relatively high risks of severe toxicity, including bone marrow suppression, opportunistic infections, bladder toxicity, infertility and malignancy, it should probably only be considered in patients who are intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil, tacrolimus or ciclosporin. Other common adverse effects of cyclophosphamide include nausea, vomiting, abdominal pain and diarrhea.

Methotrexate

Good-quality, published studies of methotrexate in MG are lacking. Despite the lack of direct evidence, however, it is recommended that methotrexate should be considered as second-line treatment in patients with generalized MG who are intolerant of or unresponsive to azathioprine. There are three reasons for making this assertion. First, data extrapolated from research in other autoimmune disorders indicate that it should be effective in MG.[26] Second, guidelines from expert panels support its use as second-line treatment in generalized MG.[26] Last, many physicians have extensive personal experience of the successful use of methotrexate in MG.

The adverse events of methotrexate are usually mild (e.g. mucositis, alopecia, gastrointestinal intolerance, mild elevation of liver enzymes), although severe adverse events such as hematopoietic suppression, hepatotoxicity and pneumonitis can sometimes occur.

Mycophenolate Mofetil

Nonrandomized Evidence

Three open-label trials of mycophenolate mofetil in MG have been conducted to date. In the first trial, 15 of 22 patients (68%) treated for between 2 and 18 months showed marked improvements. Improvement occurred in three of five patients on monotherapy, four of seven patients who were previously unresponsive to azathioprine, and seven of ten patients who were given combination therapy with steroids.[27] In the second trial, 12 patients who had not responded to steroids, azathioprine, ciclosporin, thymectomy, or all three, were recruited. Eight (67%) showed marked improvements after 6 months of treatment.[28] In the third trial, it is unclear how many of the 32 patients had undergone thymectomy or were unresponsive to steroids, azathioprine, ciclosporin, methotrexate, or all three. Nineteen (59%) showed marked improvements after an average of 11 months of treatment.[29] A retrospective analysis of mycophenolate mofetil in 85 patients, 48 of whom had undergone thymectomy, and 66 of whom were on various combinations of steroids, ciclosporin, azathioprine and

methotrexate, suggested improvement in 73% of patients.[30]

Randomized Evidence

A randomized double-blind trial of mycophenolate mofetil plus either ciclosporin or prednisolone or no immunosuppressants (seven patients) versus placebo plus either ciclosporin or prednisolone or no immunosuppressants (seven patients) ran for only 5 months (Table 1). One patient in each group showed improvement in muscle strength. The short duration of the study and small number of patients make it difficult to draw any meaningful conclusions from the study.[31]

Two randomized double-blind trials of mycophenolate mofetil plus steroids versus steroids plus placebo for generalized MG have recently been completed and are expected to be published imminently. Initial reports from Aspreva Pharmaceuticals Corporation[32] have, however, suggested that the trials failed to demonstrate efficacy for mycophenolate mofetil.

Recommendations

Mycophenolate mofetil has been reported not to be efficacious in randomized controlled trials in generalized MG (although two of the largest studies are still pending publication). This might be because it has a slow onset of action and its effectiveness was not captured by the relatively short trials. It is, however, well tolerated, with a relatively good adverse-effect profile. It could, therefore, be considered as third-line treatment in patients who are intolerant or unresponsive to azathioprine, methotrexate or tacrolimus. In studies on patients with MG, the adverse effects of mycophenolate mofetil were usually mild (e.g. headache, nausea or diarrhea); however, serious adverse effects such as infections and hematopoietic suppression can sometimes occur.

Ciclosporin

Nonrandomized Evidence

Three uncontrolled trials of ciclosporin in patients with severe MG have been published. In the first trial, the patients recruited were unresponsive either to anticholinesterase drugs alone or to the combination of thymectomy plus steroids or azathioprine. Eight out of ten patients (80%) showed marked improvements after 12 months of treatment.[33] In the second trial, the patients recruited had failed to respond to thymectomy, steroids, azathioprine or all three. Seven out of nine patients (78%) showed marked improvements after a mean of 2 years of treatment.[34] In the third trial, the patients recruited had not responded to thymectomy, steroids and azathioprine. Out of 52 patients, 44 (85%) showed marked improvements after an average follow-up period of 30 months on treatment.[35]

Randomized Evidence

A randomized double-blind trial of ciclosporin monotherapy (10 patients) versus placebo (10 patients) in generalized MG (Table 1) showed that at 6 months, the ciclosporin group demonstrated a significantly greater increase in muscle strength (measured by a change in the QMG score) than the placebo group (P = 0.0444). The mean difference in QMG score between the ciclosporin and placebo groups was -0.46 (95% CI -0.83 to -0.09). At 12 months, the ciclosporin group once again demonstrated a significantly greater increase in muscle strength than the placebo group (P = 0.0232), with a mean difference in QMG score of -0.72 (95% CI -1.10 to -0.34). Six patients in the ciclosporin group and five patients in the placebo group experienced treatment failure, giving a relative risk of 1.20 (95% CI 0.54-2.67).[36]

Another randomized double-blind trial of ciclosporin plus prednisolone (20 patients) versus prednisolone plus placebo (19 patients) in generalized MG (Table 1) showed that at 6 months, the ciclosporin group had a significantly greater increase in muscle strength than the placebo group (P = 0.004), with a mean difference in QMG score of -0.31 (95% CI -0.51 to -0.11). There was, however, no significant difference in the percentage change of steroid dose between the two groups at the end of 6 months (P = 0.12).[37] This outcome is surprising, because if ciclosporin is effective in MG, it might be expected to have a steroid-sparing action.

A meta-analysis of the two ciclosporin trials showed that at 6 months, the mean difference in QMG score between the ciclosporin and placebo groups was -0.34 (95% CI -0.52 to -0.17), with no evidence of heterogeneity between the studies.[38] However, the validity of this meta-analysis is unclear. The ciclosporin trials had different designs-ciclosporin versus placebo,[36] and ciclosporin plus prednisolone versus prednisolone

plus placebo.[37] It is possible that steroids influenced the outcomes of the latter trial, thereby confounding the meta-analysis and diluting evidence of the absolute efficacy of ciclosporin as a monotherapy.

Recommendations

Two relatively small randomized controlled trials have shown that ciclosporin is clinically effective in generalized MG (class I evidence).[36,37] However, because it is associated with serious adverse effects, including nephrotoxicity, hypertension and malignancy, it should probably only be considered in patients who are intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil or tacrolimus. Other common side effects include hypertrichosis, gingival hyperplasia, myalgia and 'flu-like' symptoms.

Tacrolimus

Nonrandomized Evidence

In a 16-week open-label trial, 19 patients with generalized MG, all of whom had previously undergone thymectomy and all but one of whom were on steroid therapy, were treated with low-dose tacrolimus. Seven patients (37%) showed clinical improvement at the end of the study.[39] Thereafter, 12 patients continued with tacrolimus for up to 2 years and the other 7 stopped treatment: in 3 of these patients the treatment did not show efficacy, and another 4 patients had procedural difficulties. Eight of the 12 patients who continued treatment (67%) showed clinical improvement.[40] In another open-label trial of low-dose tacrolimus in thymectomized and steroid-dependent patients, 12 of the 17 treated patients (71%) had clinical improvement after a mean follow-up of 19.2 months.[41] In an open-label study of tacrolimus in severe MG, in which all patients had undergone thymectomy and were on prednisolone and ciclosporin, 69 (87.3%) of 79 patients achieved pharmacological remission after a mean follow-up of 2.5 years.[42]

In a large retrospective trial, 212 patients with MG were treated with low-dose tacrolimus. The trial cohort consisted of 110 patients who had undergone thymectomy and were ciclosporin-dependent and steroid-dependent, 68 thymectomized patients who started tacrolimus early after surgery, and 34 patients with non-thymomatous generalized MG who were over 60 years old or had contraindications for thymectomy. In the patients included in this study, muscle strength improved by 23% on average after 1 month of treatment, and by 29% on average at the end of a mean follow-up of 49.3 months.[43]

Randomized Evidence

Nagane *et al*. conducted a randomized, unblinded, non-placebo-controlled trial of tacrolimus plus steroids with or without plasmapheresis (18 patients) versus no tacrolimus plus steroids with or without plasmapheresis (16 patients) for generalized MG (Table 1).[44] They showed that the number of treatments with plasmapheresis plus high-dose intravenous methylprednisolone was significantly lower in patients treated with tacrolimus during early-phase treatment than in patients who were not given tacrolimus ($P < 0.05$), with a mean difference of -1.80 (95% CI -3.12 to -0.48). The period of early-phase treatment was significantly shorter in the group treated with tacrolimus ($P < 0.05$), with a mean difference of -2.10 weeks (95% CI -3.63 to -0.57). In the follow-up phase, the number of treatments with plasmapheresis plus high-dose intravenous methylprednisolone was significantly lower for patients treated with tacrolimus ($P < 0.05$), with a mean difference of -0.90 (95% CI -1.72 to -0.08). In addition, the number of treatments with high-dose intravenous methylprednisolone alone was significantly lower for the patients treated with tacrolimus ($P < 0.05$), with a mean difference of -1.40 (95% CI -2.79 to -0.01). At 1 year into treatment, the oral prednisolone dose was significantly lower for patients treated with tacrolimus ($P < 0.05$), with a mean difference of -3.50 mg (95% CI -5.78 to -1.22). The finding that tacrolimus reduces the need for other immunotherapy indicates that this drug is effective in generalized MG.

Recommendations

One randomized, unblinded, non-placebo-controlled trial has shown that tacrolimus reduces the need for other immunotherapy in generalized MG (class I evidence).[44] Tacrolimus seemed to be relatively safe at the doses used in MG, so it should be recommended as third-line treatment for patients who are intolerant of or unresponsive to azathioprine, methotrexate or mycophenolate mofetil. Common side effects of the drug include hypertension, mild elevation of serum creatinine, headache, eye pain, increased hemoglobin A_{1c}, and raised neutrophil and decreased lymphocyte counts. Tacrolimus might also increase the incidence of malignancy.

Steroids

Nonrandomized Evidence

ACTH was first observed to have a beneficial effect in MG in 1935.[45] In a study of more than 100 patients with 'severe, refractory' MG who were given ACTH, 'good improvement' was reported.[46] In another study, nine patients with severe generalized MG were treated with multiple short courses of methylprednisolone followed by prolonged maintenance doses of oral prednisolone. Improvement in muscle strength was seen at some point in all patients.[47] In a third report, short courses of high-dose intravenous methylprednisolone followed by maintenance doses of oral prednisolone were shown to be effective in producing good muscle strength and functional improvement in 12 of 15 patients with generalized MG.[48]

Four large retrospective studies of generalized MG with different follow-up durations have reported good efficacy of steroids used at various doses. Of a total of 422 patients, 311 (73.7%) achieved good overall improvement of muscle strength (either marked improvement [39.1% of patients] or remission [34.6% of patients]; Table 2).[49,50,51,52] A prospective study of 600 patients with MG (151 generalized, 449 pure ocular) treated with moderate doses of oral steroids followed by low-dose maintenance reported an overall improvement in 94.6% of cases.[53] No clear breakdown between the generalized and ocular cases was given, and it is also unclear how the authors defined different categories of improvement.

Randomized Evidence

A randomized, double-blind trial of prednisolone (six patients) versus placebo (seven patients) for generalized MG (Table 1) showed no significant difference in improvement of muscle strength at 6 months: three patients in each group showed improvements.[54] In all the 'improved' patients, anticholinesterase therapy was able to be reduced by at least a third.

In another randomized, double-blind trial of intravenous methylprednisolone (10 patients) versus placebo (9 patients) for generalized MG (Table 1), the steroid group showed a 7.2-times greater improvement in muscle strength than the placebo group after 2 weeks of treatment (95% CI 1.11-46.89), indicating significant short-term benefit from steroids ($P = 0.006$).[55] Eight patients in the steroid group showed improvements, compared with only one patient in the placebo group.

An open-label, randomized trial of high-dose intravenous methylprednisolone versus low-dose oral prednisolone was carried out in 39 patients with juvenile MG (8 generalized, 31 ocular; Table 1). The high-dose group consisted of 19 patients (5 generalized, 14 ocular) and the low-dose group consisted of 20 patients (three generalized, 17 ocular). No significant difference in improvement was reported between the two groups ($P > 0.05$), although the exact time of measurement, and the breakdown between generalized and ocular MG patients who showed improvements, were unclear from the paper. In the high-dose group, however, the time taken to achieve sustained improvement was significantly shorter ($P < 0.05$), and the maximal level of improvement that persisted was significantly longer ($P < 0.05$), than in the low-dose group.[56]

Recommendations

Steroids are useful as short-term immunosuppressants, and there is limited evidence for their efficacy in MG from small randomized trials (class II evidence).[54,55] Steroids are usually used as an interim measure while titrating up the doses of other immunosuppressants and waiting for those immunosuppressants to take effect. Long-term use of steroids is associated with many adverse events, including cushingoid features, infections, hypertension, diabetes, osteoporosis, psychiatric disorders, insomnia, and elevations in white blood cell count.

Oral prednisolone is the recommended first-choice drug when immunosuppressants are necessary in MG.[26] Some patients have a temporary worsening of MG if steroids are started at high dose.[46,47,48,49,52] This 'steroid dip' usually occurs after 4-10 days and can precipitate a MG crisis. To overcome the problem with the steroid dip, treatment on alternate days has been tried, and was shown to be effective.[57] Treatment should therefore be started at a low dose of 10-25 mg on alternate days, gradually increasing (10 mg per dose) to 60-80 mg on alternate days. If the patient is critically ill, high-dose daily steroids should be started, and additional short-term treatments such as plasma exchange or intravenous immunoglobulin should be used to overcome any temporary worsening. Owing to the potential adverse effects with prolonged use of steroids, when remission occurs the dose should be slowly reduced to the minimum effective dose, given on alternate days.[26] There is no clear evidence, however, regarding the best time to reduce steroids, how quickly the steroids can be safely reduced, or the length of time that patients should be kept on steroids.

Rituximab

There are several promising case reports of improvement of refractory MG with rituximab.[58,59] However, this drug needs to be evaluated more extensively against the current immunosuppressants before it can be recommended. In addition, the current prohibitive cost of this drug is a major drawback.

Common infusion-related side effects of rituximab are fever, chills, nausea, vomiting, flushing and bronchospasm. Other more-serious side effects include neutropenia and increased risk of infections.

Conclusions

There are huge gaps in our knowledge regarding immunosuppressant use in generalized MG. A large amount of the evidence that we use in determining the choice of immunosuppressant drug derives from clinical experience, observational studies and expert opinion (see Table 3 for a summary of recommendations). Treatment regimes vary among physicians from different parts of the world and even among different physicians from the same country, probably because treatment decisions are made on the basis of experience and familiarity with a particular treatment regime. In addition, patients with specific personal circumstances (e.g. pregnancy), disease characteristics and treatment responses warrant individualization of treatment regimes.

There are many challenges to be overcome in carrying out treatment trials in generalized MG. One of the main problems is the difficulty of recruiting patients in the case of a rare disorder like MG.[38] In addition, it is difficult to design an immunosuppressant drug trial in generalized MG. For reasons that are unclear, the long-term immunosuppressant drugs in MG seem to take at least 6 months-and often longer-to show an effect on the disease. Consequently, it can sometimes be difficult to predict when these immunosuppressant drugs have reached their maximum effectiveness. This might be one of the reasons why results from observational, open-label or retrospective studies in generalized MG are often not replicated in randomized controlled trials.

The fluctuating course of generalized MG, the differences in clinical phenotypes between AChR-antibody-positive, MuSK-antibody-positive and seronegative patients with MG, and the confounding effects of other interventions such as thymectomy, make it difficult to know the suitable inclusion and exclusion criteria and best endpoints to choose for treatment trials.

In treatment trials of generalized MG, there is the ethical problem of the placebo arm, given that it is well known from observational studies and clinical experience that steroids are effective in generalized MG, and that symptomatic treatments such as cholinesterase inhibitors are used widely in generalized MG. It is therefore likely that any future trials will have to include steroids in the placebo arm of the study, and the use of cholinesterase inhibitors will have to be factored into the studies.

There is a lack of head-to-head studies of immunosuppressant drugs in generalized MG, and the trials that have been conducted have different study designs. These factors make it difficult to quantify the relative efficacies of different immunosuppressants in generalized MG. In view of the fact that azathioprine is cheap, effective, readily available and already widely used in generalized MG worldwide, this treatment should be considered the gold standard against which other newer immunosuppressants should be compared in future treatment trials.

In the future, it will be vital to perform better-designed randomized controlled treatment trials to help us to establish more-definitive best-practice guidelines in generalized MG.

Table 1. Design of Key Randomized Trials of Immunosuppressant Drugs in Generalized Myasthenia Gravis

Study	Interventions	
	Group 1	Group 2
Myasthenia Gravis	Azathioprine plus initial prednisolone (azathioprine 3 mg/kg daily for 1 year,	Prednisolone (1 mg/kg daily for 1 month, reduced to 0.5 mg/kg daily

Clinical Study Group (1993)[20]	followed by 2 mg/kg daily; prednisolone 1 mg/kg daily for 1 month, then gradually tapered and discontinued by the end of month 4)	by month 5, and to 0.25 mg/kg daily by month 10)
Palace *et al*. (1998)[21]	Azathioprine plus prednisolone (azathioprine 2.5 mg/kg daily; prednisolone 1.5 mg/kg or 100 mg on alternate days, maintained until remission, then tapered to minimum necessary to maintain remission)	Prednisolone plus placebo (prednisolone 1.5 mg/kg or 100 mg on alternate days, maintained until remission, then tapered to minimum necessary to maintain remission)
De Feo *et al*. (2002)[25]	Cyclophosphamide plus prednisolone (intravenous cyclophosphamide pulses given at an initial dose of 500 mg/m^2 of body surface then titrated according to response or side effects. Treatment pulses given monthly for first 6 months, then every other month; prednisolone tapered off by 10 mg/month if initially receiving more than 50 mg/day, 5 mg/month if receiving 20-50 mg/day, and 2 mg/month if receiving 20 mg/day or less. Increments of 1 mg/kg of prednisolone if there was deterioration of clinical condition)	Prednisolone plus placebo (prednisolone tapered off by 10 mg/month if initially receiving more than 50 mg/day, 5 mg/month if receiving 20-50 mg/day, and 2 mg/month if receiving 20 mg/day or less. Increments of 1 mg/kg if there was deterioration of clinical condition)
Meriggioli *et al*. (2003)[31]	Mycophenolate mofetil plus ciclosporin, prednisolone or no other immunosuppressants (mycophenolate mofetil 1 g twice daily)	Placebo plus ciclosporin, prednisolone or no immunosuppressants
Tindall *et al*. (1987)[36]	Ciclosporin (6 mg/kg daily, then adjusted on the basis of blood drug levels, renal function, clinical response and adverse events)	Placebo
Tindall *et al*. (1993)[37]	Ciclosporin plus prednisolone (ciclosporin started at 5 mg/kg daily, then adjusted on the basis of blood drug levels, renal function and adverse reactions; steroid withdrawal begun at month 2 with a reduction of 10 mg if the dose was 60 mg on alternate days or lower, or of 20 mg if the dose was 80-100 mg, then, from months 3-6, the dose was reduced by 10 mg/month. If weakness increased following reduction, the dose was increased)	Prednisolone plus placebo (steroid withdrawal begun at month 2 with a reduction of 10 mg if the dose was 60 mg on alternate days or lower, or of 20 mg if the dose was 80-100 mg, then, from months 3-6, the dose was reduced by 10 mg/month. If weakness increased following reduction, the dose was increased)
Nagane *et al*. (2005)[44]	Tacrolimus plus steroids with or without plasmapheresis (tacrolimus dose 3 mg/day; steroids and plasmapheresis were given as necessary to maintain normal quality of life)	No tacrolimus. Steroids with or without plasmapheresis (steroids and plasmapheresis were given as necessary to maintain normal quality of life)
Howard *et al*. (1976)[54]	Oral prednisolone (100 mg on alternate days)	Placebo
Lindberg *et al*. (1998)[55]	Intravenous methylprednisolone (2 g on 2 consecutive days)	Placebo
Zhang *et al*. (1998)[56]	Intravenous methylprednisolone (20 mg/kg for 3 days, 2 mg/kg daily until month 2, 1 mg/kg on alternate days until month 5, 0.5 mg/kg on alternate days for 1 month, 0.25 mg/kg on alternate days for months 6-10 [or 12 if possible], then adapted to clinical condition)	Oral prednisolone (1 mg/kg for 2 months, 0.5 mg/kg on alternate days until month 5, 0.25 mg/kg until month 10 [or month 12 if possible], then adapted to clinical condition)

Table 2. Retrospective Studies of Steroids in Generalized Myasthenia Gravis

Study	Number of patients	Patients with good overall improvement	
		Marked improvement	Remission
Pascuzzi *et al*. (1984)[49]	116	61 (52.6%)	32 (27.6%)
Sghirlanzoni *et al*. (1984)[50]	60	18 (30.0%)	25 (41.7%)
Cosi *et al*. (1991)[51]	142	42 (29.6%)	48 (33.8%)
Evoli *et al*. (1992)[52]	104	44 (42.3%)	41 (39.4%)

Table 3. Recommendations for Use of Immunosuppressants in Generalized Myasthenia Gravis

Drug	Evidence class[a]	Recommendation
Steroids	Class II	First-line therapy but only for short-term use
Azathioprine	Class I	First-line therapy for long-term use
Ciclosporin	Class I	To be considered in patients who are intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil or tacrolimus
Cyclophosphamide	Class II	To be considered in patients who are intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil, tacrolimus or ciclosporin
Methotrexate	None	Second-line therapy for long-term use in patients who are intolerant of or unresponsive to azathioprine
Mycophenolate mofetil	None	Third-line therapy for long-term use in patients who are intolerant of or unresponsive to azathioprine, methotrexate or tacrolimus
Tacrolimus	Class I	Third-line therapy for long-term use in patients who are intolerant of or unresponsive to azathioprine, methotrexate or mycophenolate mofetil

[a]Evidence class I, randomized controlled trials available; class II, controlled trial without randomization or randomized trial with small patient number; class III, uncontrolled trials; class IV, case series.

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Sidebar: Key Points

- Immunosuppressant regimes in generalized myasthenia gravis vary between different countries and physicians, owing to a lack of good randomized evidence
- Oral prednisolone is the recommended first-choice short-term immunosuppressant; it is usually started at a low dose on an alternate-day regime, and the dose is gradually increased
- Azathioprine is often the first-choice drug for long-term immunosuppression
- Methotrexate, mycophenolate mofetil or tacrolimus should be considered in patients who are intolerant of or unresponsive to azathioprine
- Ciclosporin and cyclophosphamide should only be considered if other immunosuppressants fail, as these drugs can cause serious adverse events

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Reprint Address

Sivakumar Sathasiv, The Walton Centre for Neurology & Neurosurgery, Lower Lane, Liverpool L9 7LJ, UK. E-mail: sivakumar.sathasivam@thewaltoncentre.nhs.uk

Sivakumar Sathasivam is a Consultant in Neurology at the Walton Centre for Neurology & Neurosurgery, Liverpool, UK. He has a special interest in neuromuscular disorders and was one of the authors on the Cochrane review 'Immunosuppressive agents for myasthenia gravis'.

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