Intense immunosuppression in patients with rapidly worsening multiple sclerosis: treatment guidelines for the clinician

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Several lines of evidence link immunosuppression to inflammation in patients with multiple sclerosis (MS) and provide a rationale for the increasing use of immunosuppressive drugs in the treatment of MS. Treatment-refractory, clinically active MS can quickly lead to devastating and irreversible neurological disability and treating these patients can be a formidable challenge to the clinician. Patients with refractory MS have been treated with intense immunosuppression, such as cyclophosphamide or mitoxantrone, or with autologous haematopoietic stem cell transplants. Evidence shows that intense immunosuppression might be effective in patients who are unresponsive to immunomodulating therapy, such as interferon beta and glatiramer acetate. Natalizumab, a new addition to the armamentarium for treating MS, might also have a role in the treatment of this MS phenotype. This Review describes the use of intense immunosuppressant drugs and natalizumab in patients with rapidly worsening MS and provides clinicians with guidelines for the use of these drugs in this patient group.

Introduction

Several immunomodulatory treatments can partially alter the course of relapsing-remitting multiple sclerosis (MS).1 By contrast, the effect of immunomodulatory treatments on the course of progressive MS phenotypes is modest at best.2–4 Treating patients with rapidly worsening or fulminant MS who have frequent relapses that result in sustained clinical worsening despite immunomodulatory treatments and repeated pulses of intravenous methylprednisolone is an even greater challenge. Placebo-controlled trials in these patients are ethically tenuous because patients are likely to accumulate permanent disability without treatment, and patients whose condition rapidly worsens during clinical studies are deemed treatment failures. Intense immunosuppression might be an option for such rapidly worsening patients. In this Review, we will assess the effectiveness and safety of intense immunosuppression in patients with rapidly worsening MS, and provide clinicians with guidelines for the use of intense immunosuppression in patients with this MS phenotype.

Immunosuppressant drugs used in MS

Cyclophosphamide

Mechanism of action

Cyclophosphamide is an alkylating drug, which is related to nitrogen mustards, that binds to DNA and interferes with mitosis, cell replication, and causes suppression of cell-mediated and humoral immunity through its effects on B cells and T cells.5 Cyclophosphamide is commonly used as an antineoplastic drug to treat several autoimmune disorders, including immunomediated neuropathies and lupus nephritis.6,7 Treatment with cyclophosphamide has been shown to decrease the secretion of interferon γ and IL-12 by monocytes8 and increase secretion of IL-4 and IL-10 from peripheral blood mononuclear cells.9 Increased secretion of interferon γ and IL-12 has been reported in patients with secondary progressive MS,10 and increased concentrations of IL-12 are linked to clinical activity.11 The cyclophosphamide-induced shift from a Th1-type to a Th2-type cytokine profile might, therefore, positively affect the course of MS.12

Early studies

The results of early, open-label studies with cyclophosphamide were encouraging. In an uncontrolled, open-label trial in 1975, Hommes and co-workers showed stabilisation of the disease for 1–5 years in 69% of patients after a short course of cyclophosphamide (400 mg cyclophosphamide and 1 g prednisone per day) to 86 patients with chronic progressive MS.13 Hauser and co-workers conducted an open-label, prospective, randomised trial in 58 patients with progressive MS, and compared a short course of high-dose intravenous cyclophosphamide and ACTH (adrenocorticotropic hormone) with ACTH alone and with low-dose cyclophosphamide with ACTH and plasma exchange.14 The authors reported 80% disease stabilisation or improvement in patients in the high-dose cyclophosphamide and ACTH arm compared with 20% and 50% disease stabilisation in the ACTH alone and ACTH and low-dose cyclophosphamide groups, respectively. The authors of two large trials published in the 1990s reported contrasting results with regard to the use of cyclophosphamide in patients with MS. The Northeast Cooperative Multiple Sclerosis Treatment Group conducted a randomised trial of 256 patients with progressive MS15 who were randomly assigned to one of four arms: intravenous cyclophosphamide and ACTH given according to an established induction regimen, with or without intravenous boosters of cyclophosphamide every other month; or intravenous cyclophosphamide and ACTH given according to a modified induction regimen (600 mg intravenous cyclophosphamide per m² on days 1, 2, 4, 6, and 8), with or without intravenous boosters of cyclophosphamide every other month. Initially, the...
authors found no differences in disease stabilisation between the two induction regimens; however, the patients who received maintenance boosters of cyclophosphamide had a significant delay in reaching time-to-treatment failure—defined as a one-point increase on the Expanded Disability Status Scale (EDSS) score that lasted for 2 months—compared with the patients who did not receive boosters. Furthermore, amelioration of disease progression occurred mostly in patients of a younger age.

The Northeast Cooperative Study results were challenged by the results of a clinical trial by the Canadian Cooperative Multiple Sclerosis group. This single-blinded, placebo-controlled, multicentre trial randomly assigned 168 patients with progressive MS to receive intravenous cyclophosphamide and oral prednisone, oral cyclophosphamide and oral prednisone on alternate days, with weekly plasma exchange, or oral placebo and sham plasma exchange. The investigators found no significant between-group differences in time-to-treatment failure—defined as a worsening of one or more points on the EDSS on two consecutive examinations that were separated by at least 6 months. As a result of the conflicting data, a prolonged debate about the use of cyclophosphamide in patients with MS ensued.

Recent studies
Since the early 1990s there have been numerous trials of cyclophosphamide in patients with rapidly worsening or treatment-refractory MS. Weinstock-Guttman reported an open-label series of 17 consecutive patients with fulminant MS—defined as a deterioration of more than one and a half points on the EDSS for more than 3 months—who were treated with cyclophosphamide; after 24 months, 69% of patients were stable or had improved. In an open-label observational study of 95 patients with progressive MS, Hobol and co-workers found that 80% of patients with secondary-progressive MS who had monthly cyclophosphamide with intravenous pulses of prednisone had stable or improved EDSS scores at 12 months. Gobbini and co-workers reported a rapid reduction in gadolinium-enhancing lesions, seen with monthly brain MRI scans, and clinical stability in five patients with rapidly deteriorating, relapsing-remitting MS who were treated with monthly cyclophosphamide for 6 months followed by cyclophosphamide on alternate months. Khan and co-workers reported an open-label study of intravenous cyclophosphamide given monthly to 14 patients with relapsing-remitting MS who were rapidly deteriorating (defined as a greater than three-point increase in EDSS score in the previous 12 months despite immunomodulating therapy and intravenous prednisone). Compared with baseline scores, the mean EDSS scores were significantly lower at follow-up (up to 18 months) and no relapses were reported. In an open-label study of 24 patients with clinically active and treatment-refractory MS, Perini and co-workers reported significant improvement in EDSS scores, relapse rate, and MRI measures in patients who were treated monthly with intravenous cyclophosphamide and intravenous prednisone for 1 year then alternate months for a second year. Zephir and co-workers did a retrospective, open-label review of 362 patients with secondary-progressive MS and 128 patients with primary-progressive MS who were given 12 monthly pulses of intravenous cyclophosphamide. Compared with baseline, the EDSS score stabilised or improved at month 12 in 78.6% of patients with secondary-progressive MS and 73.5% of patients with primary-progressive MS, and a shorter progressive disease course predicted the response to therapy. A report of a single patient with relapsing-remitting MS who, on one occasion, accidentally received a dose of 3800 mg (3.8-times the normal dose) of cyclophosphamide showed no evidence of clinical or MRI disease activity for the next 7 years. An open-label study by Gladston and co-workers of 200 mg per kg cyclophosphamide over 4 days in 15 patients with treatment-refractory MS patients showed significant stability of disease and improvement in quality of life after 15 months.

Combination studies
In a randomised, multi-centre trial of 59 patients with relapsing-remitting MS who did not respond to interferon beta, the combination of cyclophosphamide and interferon beta-1a reduced clinical disease activity and gadolinium-enhancing MRI lesions in the brain. In 10 patients who had frequent and severe attacks despite interferon beta therapy, the addition of intravenous cyclophosphamide every month led to a significant reduction in the number of relapses, EDSS score, and number of T2-weighted lesions; these benefits were maintained for 36 months after cyclophosphamide was stopped.

Conclusions
Collectively, these data from several open-label studies indicate that patients with rapidly worsening, treatment-refractory, relapsing-remitting MS might benefit from treatment with intravenous cyclophosphamide. The beneficial effect of cyclophosphamide in patients with secondary-progressive MS without superimposed relapses is unclear, as shown by the contrasting results of the Northeast Cooperative and Canadian Cooperative studies. Factors that confound assessment of the response to cyclophosphamide in patients with secondary-progressive MS include the treatment regimens, outcome measures, and the heterogeneity of disease progression. Nonetheless, despite the limitations of the open-label observations, cyclophosphamide appears to benefit appropriately selected patients with the rapidly worsening MS phenotype.

Mitoxantrone
Mechanism of action
Mitoxantrone is an anthracendione drug that was developed to treat malignancies by intercalating into DNA and inhibiting topoisomerase II enzyme, thereby
delaying cell-cycle progression by preventing ligation of DNA strands. Mitoxantrone also inhibits B-cell functions, including antibody secretion, abates helper and cytotoxic T-cell activity, and decreases the secretion of Th1 cytokines, such as interferon γ, TNF, and IL-2.\(^2\)

Mitoxantrone is released slowly from tissues and has a terminal half-life of between 8-9 hours and 9 days.\(^2\) Mitoxantrone can persist in the body for up to 272 days after treatment stops,\(^2\) and it effectively suppresses experimental autoimmune encephalomyelitis.\(^3\)

**Monotherapy clinical studies**

The authors of an open-label study of 13 patients with progressive MS reported on the effects of intravenous mitoxantrone (8 mg per m\(^2\)) given every 3 weeks for a total of seven infusions.\(^3\) Although the disease did not progress in most patients, compared with untreated historical control groups there was no statistically significant difference. The first placebo-controlled trial of mitoxantrone, in which 51 patients with relapsing-remitting MS were randomly assigned to either monthly infusions of mitoxantrone (8 mg per m\(^2\)) or saline for 1 year, showed a significant reduction in the annual relapse rate and an increase in the proportion of patients who were relapse-free in the mitoxantrone group at the end of years one and two, but no mean change in EDSS score.\(^4\) There was a trend in the treatment group towards a reduction in the number of new brain MRI T2-weighted lesions. Edan and co-workers, in an unblinded, multi-centre trial of 42 patients with worsening relapsing-remitting MS and secondary-progressive MS found that monthly infusions of intravenous mitoxantrone (20 mg) and intravenous prednisone (1 g) improved the clinical and MRI indices of disease activity over 6 months, whereas no change was seen in these indices in the group on intravenous prednisone alone.\(^5\) In a double-blind trial of 49 patients with secondary-progressive MS with superimposed relapses who were randomly assigned to receive 13 infusions of either mitoxantrone (12 mg per m\(^2\)) or intravenous prednisone (1 g) over 32 months, neurological disability, relapse rate, and the number of gadolinium-enhancing lesions seen in the brain with MRI were significantly reduced in the group taking mitoxantrone.\(^6\) A phase III trial of 194 patients with worsening relapsing-remitting or secondary-progressive MS were randomly assigned to receive either placebo or intravenous mitoxantrone (12 mg per m\(^2\)) or 5 mg per m\(^2\)) every 3 months for 2 years.\(^7\) The higher dose of mitoxantrone had significantly more effect than placebo on the combined primary end point, which consisted of five clinical measures, including change from baseline EDSS score at 24 months, change from baseline ambulation index at 24 months, number of treated relapses, time to first treated relapse, and change from baseline standardised neurological status at 24 months. The results of this trial led to the regulatory approval of mitoxantrone as the first immunosuppressive chemotherapy drug for patients with MS.

Weinstock-Guttman and co-workers conducted a 2-year, prospective, open-label trial to assess the use of mitoxantrone (12 mg per m\(^2\)) and intravenous prednisone (1 g) given monthly for 6 months followed by three additional infusions every 3 months.\(^8\) Four of the five patients showed a remarkable reduction in relapse rate and the resolution of longitudinally extensive spinal cord lesions. Le Page and co-workers reported an observational study of 100 patients with aggressive relapsing-remitting MS who were induced with 20 mg intravenous mitoxantrone and 1 g intravenous prednisone every month for 6 months.\(^9\) This was followed by maintenance therapy of either mitoxantrone every 3 months, interferon beta, glatiramer acetate, azathioprine, or methotrexate in 57 patients, with a mean follow-up of 3-8 years. In the year after induction, relapse rate, EDSS score, and MRI activity were significantly decreased, and this decrease was sustained for up to 5 years.

**Combination studies**

Jeffery and co-workers did an open-label, add-on, pilot study in 10 patients with MS who had active disease despite at least 6 months of interferon beta therapy.\(^10\) With the addition of mitoxantrone (12 mg per m\(^2\) for the first month, then 5 mg per m\(^2\) every month for 2 months, then 5 mg per m\(^2\) every third month), the mean frequency and volume of gadolinium-enhancing lesions decreased by 90% and 96%, respectively, after 7 months, and the relapse rate was reduced by 64%. In an open-label study, 27 consecutive patients with clinically active relapsing-remitting MS were treated with variable dose regimens of mitoxantrone, including monthly infusions for 3–6 months followed by mitoxantrone every 3 months, in combination with glatiramer acetate.\(^11\) At a mean follow-up of 36 months (range 16–66 months) from the first dose of mitoxantrone, EDSS scores and relapse rate were significantly reduced compared with baseline.

**Conclusions**

During a phase III trial, mitoxantrone decreased relapse rate by 68% compared with placebo and significantly prolonged the time to confirmed progression.\(^12\) Similar to cyclophosphamide, mitoxantrone also appears to be an effective treatment to stabilise rapidly worsening, treatment-refractory MS. However, unlike cyclophosphamide, the use of mitoxantrone is limited by dose-related cardiotoxicity and treatment-related acute leukaemia.\(^13\)

**Autologous haematopoietic stem cell transplantation**

**Mechanism of action**

Intense immunosuppression followed by autologous haematopoietic stem cell transplantation has been investigated as a treatment for severe autoimmune disorders such as MS.\(^14\) This treatment requires the mobilisation and collection of haematopoietic stem cells from peripheral blood followed by ablation of the immune system with a regimen of chemotherapeutic drugs, and
then reinfusion of the stem cell graft. Autologous grafts have a lower mortality rate (3–10%) than allogenic transplants (15–35%). The aim of autologous haematopoietic stem cell transplantation for patients with MS is to ablate their aberrant immune system and reconstitute one that is more tolerant to self-antigens, thereby stabilising or possibly curing the disease altogether.

**Early studies**

Disease stabilisation in patients with MS after autologous haematopoietic stem cell transplantation was first described in several case reports of individual MS patients who were treated for concurrent malignancies. These observations and favourable results from autologous haematopoietic stem cell transplantation in the experimental autoimmune encephalomyelitis animal model have encouraged further investigation of autologous haematopoietic stem cell transplantation in patients with MS.

**Recent studies**

Fassas and colleagues treated 24 patients with chronic progressive MS with autologous haematopoietic stem cell transplantation, with a median follow-up of 40 months: 18 patients either improved or stabilised, five patients progressed, and one died of aspergillosis 65 days after transplantation. Of those who stabilised or improved, nine later developed relapses or slowly resumed progression. The probability of progression-free survival at 3 years compared with entry status was 92% for patients with secondary-progressive MS and 39% for patients with primary-progressive MS. Nash and co-workers enrolled 26 patients with MS of various phenotypes (relapsing-remitting, secondary-progressive, and primary-progressive MS) into an open-label, multi-centre study to assess the safety of high-dose immunosuppressive therapy followed by autologous haematopoietic stem cell transplantation. The Kaplan–Meier 3-year estimates for progression of one or more points on the EDSS score and survival were 27% and 91%, respectively. A pilot study was done by Saiz and co-workers to evaluate prospectively the disease course after autologous haematopoietic stem cell transplantation in 14 patients with relapsing-remitting MS or secondary-progressive MS with severe treatment-refractory disease. The 3-year probability of progression-free survival was 85.7%, and the 3-year probability of disease-free survival was 46.4%. Brain MRI gadolinium-enhancing lesions were completely resolved during the 3-year period, and T2-weighted lesion load decreased by 20%: no deaths or serious complications were reported. The European Group for Blood and Marrow Transplantation reported an overall transplant-related mortality of 5.3% in 178 patients with MS who received autologous haematopoietic stem cell transplantation before 2000.

Data on brain atrophy and the persistence of CSF oligoclonal bands after autologous haematopoietic stem cell transplantation have recently been reported. Saiz and co-workers found that five patients with MS who had autologous haematopoietic stem cell transplantation had atrophy of the corpus callosum at 1 year, with more than 50% of the reduction in volume seen in the first 3 months after autologous haematopoietic stem cell transplantation. All patients had oligoclonal bands in the CSF before autologous haematopoietic stem cell transplantation, and the four patients who were retested after 1 year all had persistent oligoclonal bands, which suggests that the B cells that secrete IgG in the CNS had survived. Chen and co-workers reported a significant decrease in brain volume compared with baseline (3.2% over a median time of 2.4 months) that was not accounted for by the resolution of oedema or a decrease in the size of T2-weighted lesions in nine patients who had immunoablation and autologous haematopoietic stem cell transplantation. Similar changes in brain volume were seen in a patient with non-CNS lymphoma who had autologous haematopoietic stem cell transplantation, which suggests a direct neurotoxic effect of this therapy.

**Conclusions**

Autologous haematopoietic stem cell transplantation might lead to prolonged periods of stable disease in patients with treatment-refractory, rapidly deteriorating MS. Important questions with regard to patient selection, toxicity, and treatment-related brain atrophy require further investigation and long-term follow-up, which currently limit autologous haematopoietic stem cell transplantation to specialised centres in controlled study settings.

**Other immunosuppressive drugs**

Several other immunosuppressive drugs, including cladribine, mycophenolate mofetil, methotrexate, azathioprine, and cyclosporin, have been studied in patients with MS. However, there are no data on the effects of these drugs in patients with rapidly worsening MS, which precludes further discussion of them in this Review. Although these drugs might be useful as add-on therapies in patients with treatment-refractory MS or patients with breakthrough disease, recent data appear to limit this potential.

**Immunomodulation with humanised monoclonal antibodies**

Although monoclonal antibodies are not immunosuppressive agents, they are highly promising therapies that selectively bind to specific antigens on targeted cells. Humanised monoclonal antibodies, which have a limited murine component, substantially decrease immunogenicity compared with purely non-human monoclonal antibodies. Several humanised monoclonal antibodies are currently being investigated as therapies for MS but only one has been approved for use in patients with MS. A brief discussion follows to provide clinicians with the...
potential options of monoclonal antibodies in patients with rapidly worsening MS.

**Natalizumab**

Natalizumab is the most recent addition to the armamentarium of disease-modifying drugs for patients with MS. Although not a form of immunosuppression, treatment with natalizumab is increasingly considered for patients with rapidly worsening MS on the basis of the data available from clinical trials. Natalizumab is a selective adhesion-molecule-inhibitor humanised monoclonal antibody against α4 integrin that prevents adherence of activated leukocytes to the endothelium, thereby blocking an important step in the formation of MS lesions.\(^{35}\) In the phase III AFFIRM trial, monotherapy with natalizumab decreased annual relapse rate by 68%, the rate of disability progression by 42%, the number of brain T2-weighted MRI lesions by 83%, and the number of brain gadolinium-enhancing MRI lesions by 92%, compared with placebo.\(^ {36}\) In the phase III SENTINEL trial, natalizumab and intramuscular interferon beta-1a improved clinical outcome compared with intramuscular interferon beta-1a alone.\(^ {37}\)

Natalizumab was temporarily suspended, however, after two cases of progressive multifocal leukoencephalopathy were diagnosed in patients with MS who received natalizumab in combination with interferon beta-1a.\(^ {38,39}\) A third case of progressive multifocal leukoencephalopathy was later diagnosed in a patient treated with natalizumab for Crohn’s disease.\(^ {40}\) The US Food and Drug Administration subsequently reapproved natalizumab as a second-line monotherapy for patients with relapsing forms of MS who have not responded to other immunomodulating therapies. Currently, there are no data on the use of natalizumab in patients with rapidly worsening MS phenotypes, and only the phase II trial included patients with a secondary-progressive MS phenotype.\(^ {38}\) Compared with placebo, a significantly lower proportion of patients treated with natalizumab had on-study relapses and new gadolinium-enhancing brain MRI lesions. These differences were most appreciable in patients with a more active disease at study entry (more than three relapses before study entry and more than two new gadolinium-enhancing MRI lesions at month 0). On the basis of highly impressive imaging results and a reduction in relapse rate, natalizumab is gaining popularity as an alternative treatment in patients with frequent relapses or rapidly worsening MS who have failed to respond to other therapies. Recently, the UK National Institute for Health and Clinical Excellence approved natalizumab for use in patients with rapidly evolving, severe, relapsing-remitting MS—defined as two or more disabling relapses in 1 year and one or more gadolinium-enhancing lesions or a significant increase in T2-weighted lesion load seen on brain MRI—which further highlights natalizumab as a potential therapy for these patients.\(^ {41}\)

The current estimated risk of progressive multifocal leukoencephalopathy associated with natalizumab is 0·1%, and unknown complications, such as other opportunistic infections, must also be considered. As such, the current guidelines for treatment with natalizumab, which are based on expert opinion, include careful patient selection, pretreatment brain MRI, the use of natalizumab as monotherapy, and an appropriate washout period of other immunomodulators or immunosuppressants (panel);\(^ {42}\) algorithms to diagnose progressive multifocal leukoencephalopathy in patients with MS on natalizumab have been proposed.\(^ {43}\) Natalizumab should be used in strict accordance with the TOUCH programme initiated by the drug manufacturer, which registers all patients and prescribers and helps to monitor patients closely when they are on therapy.

**Alemtuzumab**

Alemtuzumab is a humanised monoclonal antibody against the CD52 antigen on T lymphocytes and B lymphocytes\(^ {44}\) that produces rapid and sustained lymphocyte depletion and is an approved therapy for B-cell chronic lymphocytic leukaemia. Coles and co-workers conducted a rater-blinded phase II trial to compare two doses of alemtuzumab given once a year with interferon beta-1a (44 µg subcutaneously, three times a week) in treatment-naïve patients with relapsing-remitting MS.\(^ {45}\) The 2-year interim results showed superiority of alemtuzumab over interferon beta-1a for EDSS score, multiple sclerosis functional composite, relapse rate, time to first relapse, and MRI outcomes.

Two large phase III trials are underway to establish the efficacy and safety of alemtuzumab in treatment-naïve patients and patients with relapsing-remitting MS with breakthrough disease. Alemtuzumab might be a highly effective therapy in patients with MS; however, at this time, the use of alemtuzumab is restricted to clinical trials. Off-label use of alemtuzumab in clinical practice should be avoided until ongoing problems related to the incidence of autoimmune thrombocytopenia and thyroiditis are clarified\(^ {46,47}\) and phase III trials are completed.

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**Panel: Proposed recommendations for the prescription of natalizumab**

**Patient selection**

- Confirmed diagnosis of relapsing form of MS
- Active disease course despite the use of immunomodulating therapy
- Patient understands the risks of opportunistic infections
- No history of haematological malignancy or HIV

**Pretreatment tests**

- MRI of brain within 6 months before the first infusion
- Full blood count in all patients, and CD4:CD8 in selected patients

**Washout period**

- Use natalizumab as monotherapy
- Discontinue immunomodulating therapy 1 month before natalizumab
- Discontinue immunosuppressants at least 6 months before natalizumab

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Rituximab

Rituximab is a humanised monoclonal antibody against the CD20 antigen on B cells that has shown a significant reduction in inflammation in several autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis. In a randomised, double-blind, placebo-controlled phase II trial of 104 patients with relapsing-remitting MS, rituximab given once every 6 months led to a significant reduction in gadolinium-enhancing lesions. Phase III trials in patients with relapsing-remitting MS are underway. The current use of rituximab is largely restricted to clinical trials; however, it is anticipated that rituximab might be a highly effective and unique therapy that is directed against B-cell-driven effector mechanisms.

Daclizumab

Daclizumab is a humanized monoclonal antibody against the CD25 antigen that has proven effectiveness in preventing the rejection of several different solid organ transplants. In a randomised, double-blind, placebo-controlled, phase II trial of the addition of subcutaneous weekly or alternate week daclizumab to interferon beta therapy in 230 patients with relapsing-remitting MS, the combination therapy was associated with a significant reduction in gadolinium-enhancing lesions. Phase III trials are needed to establish the efficacy and safety of daclizumab as monotherapy and combination therapy in patients with MS.

Conclusions

Humanised monoclonal antibodies have promise as powerful additions to the therapeutic armamentarium for the treatment of patients with MS. Natalizumab has already shown impressive results in phase III clinical and MRI outcomes that have led to its approval in several countries. Currently, the use of alemtuzumab, rituximab, and daclizumab in patients with MS is limited to clinical trials, and the outcomes of definitive phase III trials are eagerly anticipated. Moreover, the role of monoclonal antibodies in patients with rapidly worsening MS will need careful investigation.

Clinical guidelines for the treatment of rapidly worsening MS

Identification of appropriate patients

The factors that might predict the response to intense immunosuppression with cyclophosphamide or mitoxantrone are given (table, figure). In summary, younger ambulatory patients with active progression and frequent relapses are good candidates for intervention with intense immunomodulating therapy or natalizumab.

When to initiate therapy

The identification of the window of opportunity when treatment with intense immunosuppression is most effective is as important as the determination of a good recipient. Delays in treatment might result in a suboptimal response. Treatment-refractory patients, who are defined as those with frequent attacks with accumulating deficits over 6–12 months despite immunomodulating therapy and pulsed steroids,
should be considered for intense immunosuppression. Patients with fulminant MS from the onset, which is highly uncommon, can be treated with intense immunosuppression as a first-line therapy. However, there is a lack of published data on intense immunosuppression as an initial therapy, and further studies are needed.

**Selection of the most appropriate therapy**

The drugs available to treat patients with rapidly worsening MS are cyclophosphamide, mitoxantrone, or natalizumab. However, the decision whether to use natalizumab or intense immunosuppression (cyclophosphamide or mitoxantrone) is difficult because of the lack of evidence to support the use of natalizumab in patients with rapidly worsening MS. Limited information can be obtained from the phase II trial of natalizumab and from patients from the AFFIRM trial who had frequent relapses. Furthermore, there are no head-to-head trials of natalizumab and intense immunosuppression or controlled trials to determine their efficacy in this patient population.

Despite these major limitations, it is reasonable to consider either natalizumab or intense immunosuppression for patients with MS who rapidly accumulate disabilities despite treatment with intravenous prednisone and immunomodulating therapy; however, the risks and benefits of each option must be assessed. So-called induction with intense immunosuppression has the flexibility of concomitant use with immunomodulating therapy, whereas natalizumab can be used only as monotherapy. Infertility and transient cytopenia, with a risk of infection, are risks associated with intense immunosuppression. Treatment with natalizumab carries the risk of opportunistic infections, such as progressive multifocal leukoencephalopathy; as more data emerge, our understanding of the risk of opportunistic infections for patients on natalizumab monotherapy might change.

### Characteristics of patients who are likely to respond to intense immunosuppression or natalizumab

- active progression during the past several months or frequent and severe relapses
- aged younger than 40 years
- aged older than 50 years
- longer, stable disability
- profound or only cerebellar symptoms due to disability
- fixed, long-standing motor deficits
- substantial spinal cord atrophy
- long-standing lack of mobility

### Characteristics of patients who are unlikely to respond to intense immunosuppression or natalizumab

- aged older than 50 years
- long-standing, stable disability
- recovery from relapses is incomplete
- fixed, long-standing motor deficits
- substantial spinal cord atrophy
- long-standing lack of mobility

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[Figure: Algorithm to identify appropriate patients with rapidly worsening MS who are suitable for intense immunosuppression or natalizumab]

*Limited data available from the phase II and AFFIRM trials for the use of natalizumab. †Suggested recommendations. ‡See panel for further uses of natalizumab.
and lead to natalizumab as the preferred first-line therapy over intense immunosuppression. For now, however, the risks of intense immunosuppression and natalizumab must be considered on an individual basis.

There are no large-scale, head-to-head studies that compare cyclophosphamide with mitoxantrone. Caon and co-workers reported a 2-year, open label, observational study that compared monthly intravenous cyclophosphamide and intravenous mitoxantrone every 3 months in 51 patients with relapsing-remitting MS. All patients had at least a one-point increase in EDSS score despite at least 1 year of treatment with immunomodulating therapy and at least two courses of intravenous prednisone. The demographics of the patients and their baseline EDSS scores were similar in both groups (cyclophosphamide 5-3 vs mitoxantrone 5-4). Mean EDSS scores after 24 months were statistically lower in the cyclophosphamide group compared with the mitoxantrone group (cyclophosphamide 4-3 vs mitoxantrone 5-3, p=0.02). Perini and co-workers compared intravenous cyclophosphamide with intravenous prednisone (1 g), given monthly for 1 year and then every other month for a second year, with intravenous mitoxantrone (8 mg per m²) plus intravenous prednisone (1 g) given every 2 months for 2 years to 50 patients with secondary-progressive MS who had recent sustained progression and relapses. Both regimens reduced the relapse rate, EDSS score, and MRI activity, with no significant between-group differences, including in the safety data, at 2 years. Larger trials are needed to confirm these findings.

Cyclophosphamide might have advantages over mitoxantrone, including no risk of cardiotoxicity, no lifetime maximum dose, and no therapy-related acute haemorrhagic cystitis and might have a lower risk of late cancers.

Cyclophosphamide

Several cyclophosphamide regimens for patients with MS have been published, however, there are no data that compare the efficacies of these regimens. One of the most commonly used outpatient cyclophosphamide regimens for patients with MS is monthly intravenous infusions: patients initially receive intravenous cyclophosphamide at a dose of 1 g per m², and a 2-week post-infusion white blood cell count nadir of 2000–2500 cells per mm³ (or decreased absolute lymphocyte count) is a reasonable outcome. Subsequent doses can be increased or decreased by 100–200 mg per m², accordingly. The adverse reactions and complications of treatment with cyclophosphamide are given (table).

No study has assessed the optimum duration of treatment with cyclophosphamide in patients with MS; however, an initial course of six monthly infusions with close monitoring might be reasonable. If the 6-month assessment indicates disease stabilisation (a decrease in relapse frequency or stable or improved EDSS score), cyclophosphamide can be discontinued and immunomodulating therapy resumed. If the disease has not stabilised, cyclophosphamide pulses should be continued, either monthly or bi-monthly, for a further 6 months. Factors such as the patient’s age, neurological disability, and ability to tolerate cyclophosphamide must all be considered when deciding to extend the duration of treatment. Brain MRI scans that show stable disease (no new or enlarging T2-weighted lesions and no gadolinium-enhancing lesions) might also be useful to determine the response to therapy.

Mitoxantrone

Several mitoxantrone regimens have been used in patients with MS. The dose approved by the US Food and Drug Administration is 12 mg per m², given every 3 months. Unlike cyclophosphamide, the dose of mitoxantrone is fixed, and white blood cell counts are primarily used to monitor myelosuppression.

An alternative mitoxantrone regimen used in patients with MS that rapidly progresses comprises six monthly infusions of 20 mg. For patients who receive monthly mitoxantrone, blood counts are monitored, similar to patients who have monthly infusions of cyclophosphamide. The adverse reactions and complications of treatment with mitoxantrone are given (table).

The duration of treatment with mitoxantrone is largely determined by two factors: the lifetime maximum dose, and the type of dose regimen. In general, most patients will receive mitoxantrone therapy for 1–2 years before they reach the lifetime maximum of 140 mg per m². Current recommendations to monitor left ventricular ejection fraction include a MUGA (multiple gated acquisition) scan or echocardiogram at baseline and before each infusion.

An echocardiogram might be preferable with monthly cycles of mitoxantrone because monthly MUGA scans lead to excessive exposure to radiation. Therapy with mitoxantrone should be started only in patients with a baseline left ventricular ejection fraction of 50% or more and no cardiac disease. Mitoxantrone therapy should be discontinued if the left ventricle ejection fraction decreases by 10% or more at any time, if clinical signs of cardiac failure develop, or if the left ventricular ejection fraction is below 50%.

Resumption of immunomodulating therapy after immunosuppression

Clinical stability can be sustained for prolonged periods after intense immunosuppression is stopped. That effect, however, is unlikely to continue indefinitely; in a study by Carter and co-workers, 69% of patients treated with cyclophosphamide and ACTH reprogressed at a mean interval of 17-6 months after intense immunosuppression was stopped, which suggests that maintenance therapy is required. Therefore immunomodulating therapy can be reasonably reinstituted after...
intense immunosuppression, and several reports indicate that patients respond well to immunomodulating therapy after intense immunosuppression.\cite{11,12,13,14} In many series, patients restarted the same immunomodulating therapy that was deemed a failure before intense immunosuppression.

Conclusions
There is no class I evidence that unequivocally supports the use of intense immunosuppression in patients with rapidly worsening MS. This might be partly because of the difficulty in designing rigorously controlled studies in these patients. Despite the limitations of open-label and uncontrolled observations, intense immunosuppression appears to be effective for improving and stabilising patients with rapidly worsening MS. Considerable data suggest that younger patients with demonstrable inflammatory disease activity respond best to intense immunosuppression and natalizumab. Irreversible deficits in patients with MS are due to the axonal loss that typically occurs in an inflammatory milieu; to avoid this, timely intervention with intense immunosuppression or natalizumab, which is crucial to the success of this approach, is needed. Important questions with regard to the optimum regimen of intense immunosuppression early in the disease course as part of induction or combination therapy warrant further study. Questions also remain with regard to the role of natalizumab, which seems promising but has yet to be tested in this MS phenotype. With encouraging preliminary data, intense immunosuppression might eventually become the standard treatment for patients with rapidly worsening MS and other treatment-refractory autoimmunological disorders. Selective adhesion-molecule inhibitors, such as natalizumab, might also become first-line therapy for treatment-naive and treatment-refractory patients with relapsing MS. Further investigations, including head-to-head trials, are needed.

Search strategy and selection criteria
References for this Review were identified through searches of PubMed from 1950 to June 2007, with the term “multiple sclerosis” in combination with “fulminant”, “rapidly worsening”, “rapidly progressive”, “immunossuppression”, and “immunomodulation”. Articles were also identified through searches of the references of articles and the authors’ own files. Only papers in English were reviewed. Case reports were included if they contained outstanding new data that are otherwise not available. Abstracts and reports from meetings were included only if they presented new relevant information.

Confl icts of interest
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