

MEDICINE IN THE TWENTY-FIRST CENTURY

Prevention of autoimmune attack and disease progression in multiple sclerosis: current therapies and future prospects

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Abstract

Multiple sclerosis (MS) is an important cause of progressive neurological disability, typically commencing in early adulthood. There is a need for safe and effective therapy to prevent the progressive central nervous system (CNS) damage and resultant disability that characterize the disease course. Increasing evidence supports a chronic autoimmune basis for CNS damage in MS. In the present study, we review current concepts of autoimmune pathogenesis in MS, assess current therapies aimed at countering autoimmune attack and discuss potential therapeutic strategies. Among currently available therapies, β -interferon and glatiramer acetate have a modest effect on reducing relapses and slowing the accumulation of disability in relapsing–remitting MS. β -Interferon is of doubtful efficacy in secondary progressive MS and appears to aggravate primary progressive MS, possibly by increasing antibody-mediated CNS damage through inhibition of B-cell

apoptosis. Mitoxantrone may reduce relapses and slow disability progression in relapsing–remitting and secondary progressive MS, but its use is limited by the risk of cardiomyopathy. There are currently no effective treatments for primary progressive MS. Many therapies that are effective in the animal model, experimental autoimmune encephalomyelitis (EAE), are either ineffective in MS or – in the case of γ -interferon, lenercept and altered peptide ligands – actually make MS worse. This discrepancy may be explained by the occurrence in MS of defects in immunoregulatory mechanisms, the integrity of which is essential for the efficacy of these treatments in EAE. It is likely that the development of safe, effective therapy for MS will depend on a better understanding of immunoregulatory defects in MS. (*Intern Med J* 2002; 32: 554–563)

Key words: antibodies, autoimmunity, drug therapy, experimental autoimmune encephalomyelitis, multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that typically strikes young adults. It is characterized pathologically by multifocal areas of inflammatory

demyelination with relative preservation of axons. Increasing evidence supports an autoimmune pathogenesis, with myelin antigens among the most plausible targets. The autoimmune hypothesis for MS is based on several lines of evidence. First, susceptibility to the disease is linked to genes involved in discrimination of self from non-self, specifically to certain class II genes of the major histocompatibility complex (MHC). Second, lesions morphologically identical to those of MS occur in experimental autoimmune encephalomyelitis (EAE), an animal model of MS that is known to be autoimmune in nature. Third, increased quantities of immune cells

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and antibody are found in the CNS and cerebrospinal fluid (CSF) of patients with MS. Fourth, other autoimmune diseases occur with increased frequency in patients with MS and in their families, suggesting a common genetic predisposition.¹ Finally, it has been shown that manipulation of the immune system can modify the disease course, at least in the short term.

It is clear that there is a genetic contribution to MS. Knowledge of the specific (immuno)genetic factors predisposing to MS could assist greatly in clarifying the immunopathogenesis. Such knowledge could be particularly useful in identifying primary (as opposed to secondary) immunological abnormalities, thereby helping to determine optimal targets for specific therapeutic intervention. However, other than certain major histocompatibility complex (MHC) class II genes, the nature of the genetic factors that predispose to MS are unknown. Furthermore, factors other than the basic complement of germline genes are clearly important in disease expression, as evidenced by the discordance for MS between monozygotic twins. Such factors could include variation at the level of recombination or expression of genes, or at the level of interaction of gene products with the environment. Such variations could be determined by chance and/or by environmental factors. This observation is entirely consistent with the autoimmune hypothesis for MS, as genes encoding antigen receptors undergo random recombination events and development of the immune repertoire and immune cell activation are dependent on environmental interactions.

As the genetic factors predisposing to MS and the additional factors determining disease expression remain cryptic, specific therapeutic intervention to inhibit disease expression is not yet feasible. Rather, treatments that have been developed so far have been mainly empirical, in some cases based on efficacy in other autoimmune diseases or in EAE, and in other cases owing much to serendipity. This may explain why none of the treatments developed to date has more than modest efficacy. Effective immune manipulations in EAE frequently fail to translate into effective treatments in MS. Indeed, some therapeutic strategies, such as the administration of γ -interferon and blockade of tumour necrosis factor (TNF)- α , improve EAE but make MS worse. The discrepancy between outcomes of identical immune manipulations in MS and EAE can be understood by considering the differences between the two conditions.² MS is a spontaneously arising condition occurring in individuals who may have an inherent defect of immune regulation. EAE, however, is an

artificially induced condition in animals with intact immune regulation. Agents that rely on intact immunoregulatory mechanisms to have a beneficial effect on EAE will have no effect in MS patients with defects in these mechanisms. For interventions with dual potential for anti-inflammatory and pro-inflammatory effects, such as γ -interferon, the balance might favour anti-inflammatory effects in a setting of effective immunoregulatory mechanisms such as EAE, but pro-inflammatory effects in a setting of deficient immunoregulation such as MS.

To develop more effective treatment, it is necessary to gain a better understanding of the genetic, environmental and immunological factors involved in MS pathogenesis. This requires the development of a model that incorporates and is compatible with current knowledge of the disease, and which can then be tested and modified according to further observations.

Our current model begins with genetic predisposition to the disease. The nature of this predisposition could be twofold. First, in at least a proportion of cases, it may include a more widespread tendency to autoimmunity, given the increased occurrence of other autoimmune diseases in patients with MS and in their families. A more widespread autoimmune diathesis might be the result of a genetically determined failure of regulation of autoimmunity. Such a failure could involve, for instance, defective apoptotic elimination of activated autoreactive T cells in the target organ.² Alternatively, immune dysregulation could involve B cells or some other component of the immune system. Second, the concordance for MS (rather than just autoimmunity in general) between monozygotic twins indicates that specific genetic factors predisposing to MS *per se* must also exist. Such factors might include polymorphisms of myelin genes, genes involved in susceptibility to environmental triggers specific for MS or genes involved in protecting the CNS against autoimmune attack.

Events leading from disease predisposition to expression (or initial lesion formation) might include multiple steps, each of which represents a potential target for therapeutic intervention, including: (i) peripheral activation (such as by a virus or superantigen) of myelin-reactive T cells (which are present in both the normal and MS immune repertoire), (ii) migration of these activated cells to the CNS, (iii) traversal of the blood-brain barrier, (iv) reactivation by autoantigen presented by CNS antigen-presenting cells, (v) failure of apoptosis of

activated autoreactive T cells leading to their retention in the CNS, (vi) cellular proliferation and cytokine production, (vii) production of chemokines and upregulation of adhesion molecules, (viii) recruitment and activation of autoreactive T and B cells and non-specific immune cells and (ix) orchestration of local autoimmune attack. An important feature of autoimmune attack on the CNS in MS is that it is ongoing, presumably due to persistence of factors that maintain autoimmunity or to the absence of factors that curtail autoimmunity. Memory B and T cells have the capacity to maintain chronic autoimmunity. In acute disseminated encephalomyelitis – a monophasic autoimmune disorder of the human CNS – oligoclonal immunoglobulin G bands in the CSF may be present initially but then disappear, whereas in MS they persist. The persistence of B cells/antibodies in the CNS may be important in the maintenance of chronic autoimmunity. The immune attack on the CNS might also be maintained by epitope spreading, whereby lymphocytes become activated against additional target CNS antigens.

An important feature of MS is its tendency to progress from an episodic to a gradually progressive course. In most patients with MS, the clinical course is initially relapsing–remitting, with episodes of symptomatic deterioration followed by recovery of variable completeness. Much of the disability that occurs during this phase is thus reversible. However, irreversible disability may occur in patients with relapsing–remitting disease due to incomplete recovery from relapses, and may accumulate with recurrent such episodes. In the majority of patients, after a variable period of time (typically 8–15 years) the disease enters a clinical phase in which gradual progression of disability occurs independently of discrete episodes. This is termed secondary progressive disease. In about 10% of cases, there is gradual progression of disability from disease onset (primary progressive MS). Epitope spreading might explain the transition from a relapsing–remitting to a secondary progressive course. Autoreactivity against myelin antigens might result in a relapsing–remitting pattern, with clinical improvement due to remyelination, whereas spread of autoreactivity to axonal antigens might determine transformation to a secondary progressive course because axonal regeneration does not occur in the CNS. In cases where axonal antigens are the primary target, a primary progressive course might result.^{2,3} Alternatively, relapses might be due to predominantly T-cell-mediated autoimmune attack, whereas gradual progression might be due to predom-

inantly antibody-mediated autoimmune attack on the CNS.

The goals of disease-modifying treatment in MS are to prevent clinical relapses and, more importantly, to prevent irreversible damage and consequent disability. Although current treatments reduce relapses, they have limited efficacy in retarding the accumulation of disability, particularly during the progressive phase of MS wherein much of the disability develops.⁴

Magnetic resonance imaging (MRI) studies indicate that episodes of inflammatory attack on the CNS, represented by new gadolinium-enhancing lesions, exceed the frequency of clinical relapses by up to 10-fold.⁵ It has been demonstrated pathologically that such inflammatory lesions are accompanied by axonal damage.⁶ Cumulative axonal injury is widely regarded as a major substrate of irreversible disability.⁷ Furthermore, enhancing lesions have been linked to subsequent cerebral atrophy in patients with early relapsing MS.⁸ Although the majority of such enhancing lesions may initially be clinically silent, cumulative axonal injury and cerebral atrophy associated with repeated inflammatory episodes are unlikely to remain silent throughout the course of the illness. The association of enhancing lesions early in the disease course with cumulative damage of a presumably irreversible nature supports the notion that intervention to prevent autoimmune attack should be instituted as early as possible in the disease course, provided that it is both safe and effective. It also suggests that the goal of therapy should be to prevent autoimmune attack, rather than simply to prevent relapses.

It has been demonstrated through the use of novel MRI techniques that widespread cumulative axonopathy, not restricted to lesions visible on conventional MRI, may occur from the earliest stages of the illness.⁹ Furthermore, disease progression may continue despite marked suppression of MRI-detected inflammatory lesions.¹⁰ In primary progressive MS, progressive axonal loss and disability occur in the setting of a relative paucity of inflammatory lesions. Contrary to widely held opinion, these observations do not necessarily imply a primarily degenerative (rather than autoimmune) process. Rather, the autoimmune attack in these patients may be associated with a less focal, less intense, more diffuse pattern of inflammation (which may be missed by MRI) or may be produced by different autoimmune effector mechanisms. For example, while

acute inflammatory lesions may be due to predominantly T-helper type 1 (Th1) autoimmune attack, chronic progressive tissue damage might be due to predominantly T-helper type 2 (Th2) and B-cell/antibody-mediated autoimmune attack. This notion is consistent with the finding of ongoing disease progression, despite marked suppression of enhancing lesions, in the setting of profound T-cell depletion and enhanced B-cell activity.^{10,11} This raises the possibility that agents that are useful in preventing relapses may not be effective in combating gradual progression, and could even be harmful in the long term if they promote a shift to an altered type of immune attack that conduces to gradually progressive damage rather than episodic attacks. Alternatively, progressive axonopathy and tissue loss in relapsing–remitting or secondary progressive MS may represent Wallerian degeneration secondary to axonal injury, or possibly secondary to persistent demyelination. This would again indicate the need for early intervention to prevent autoimmune attack in order to prevent later irreversible disease progression.

Another important consideration regarding any therapy to counter autoimmune attack in MS is durable efficacy (e.g. >10 years). This is because of the long median duration of the disease course in MS (>30 years).¹² Clearly, an additional requirement is extended safety throughout such prolonged administration.

CURRENT THERAPIES

β-Interferon

The initial rationale for using interferons in MS was as antiviral agents, in the belief that the disease may be caused by a latent viral infection of the CNS.¹³ The initial trials suggesting efficacy of β-interferon in MS involved intrathecal administration. The development of recombinant β-interferon and the demonstration of efficacy when administered via the subcutaneous route paved the way for large-scale clinical application.

Nine years have passed since the first published report of the phase III trial of subcutaneous β-interferon-1b in relapsing–remitting MS. In patients treated with 8 million international units (MIU) on alternate days, the study demonstrated a reduction in annualized relapse rate after 2 years of approximately one-third, with a reduction of approximately one-half in moderate and severe relapses.¹⁴ It also demonstrated a beneficial effect on MRI measures of apparent disease progression such as progression of T2-lesion load ('MRI-detected burden

of disease') and appearance of new T2 lesions.¹⁵ The treatment was generally well tolerated, with a dropout rate due to adverse events in the 8 MIU treatment group of <10% over 4 years. This was the first convincing demonstration of an apparently safe, effective, disease-modifying treatment for MS. However, the benefits were only modest, applicable only to patients with relapsing–remitting disease, and the safety and efficacy were demonstrated only over a short period relative to the typical course of MS. Subsequently, β-interferon-1a preparations were shown to have a similar effect on relapses – along with beneficial effects on gadolinium-enhancing lesions and progression of disability – in relapsing–remitting MS, as well as a similar systemic adverse effect profile.^{16,17} Neutralizing antibodies against β-interferon develop in some patients and are associated with reduced clinical and MRI efficacy.¹⁷

Two recent studies have shown that treatment with β-interferon following an initial clinical demyelinating event delays the first relapse of MS and slows the accumulation of T2 lesions.^{18,19} However, these findings are not unexpected, given the known effects of β-interferon in reducing relapse frequency and T2 lesion accumulation in patients with relapsing–remitting MS. They do not imply any additional effects or long-term benefit.

Among the many suggested mechanisms for the beneficial effect of β-interferon on relapses and gadolinium-enhancing MRI lesions in MS, the most plausible seems to be repression of Th1 cell generation through inhibition of CD40-induced production of interleukin-12 by dendritic cells.²⁰

In 1998, a European trial found a beneficial effect of β-interferon-1b on disability progression, as well as on relapse frequency, in patients with secondary progressive MS.²¹ Two subsequent trials have failed to demonstrate benefit of β-interferon in slowing disability progression in secondary progressive disease,^{22,23} although post-hoc analyses suggested greater benefit in certain subgroups (such as women and patients with recent relapses).²³ β-Interferon has no demonstrated efficacy in primary progressive MS. In fact, one study demonstrated that it worsens spasticity in such patients.²⁴

Thus, at present, it is unknown whether β-interferon has any effect on disease progression beyond its effect on relapses.²⁵ Indeed, the absence of a relationship between relapses and progression of irreversible disability in MS suggests that agents that reduce relapses may not necessarily delay the development of

disability in the long term.⁴ It should be noted that α -interferon and β -interferon inhibit B-cell receptor-mediated apoptosis,²⁶ which is an important mechanism for controlling B-cell/antibody autoreactivity. Given the increasing evidence that antibodies against myelin and axonal antigens have a pathogenic role in MS, it should be considered whether β -interferon might aggravate antibody-mediated myelin and axonal damage.²⁷ If antibody-mediated damage contributes to progression of disability, this could explain why β -interferon has no beneficial effect on disability progression in established secondary progressive MS and causes worsening in primary progressive MS. Aggravation of B-cell-mediated autoimmunity may also explain how α -interferon and β -interferon induce or aggravate other autoimmune diseases.^{28–30} As there is accumulating evidence that MS patients are genetically predisposed to other autoimmune disorders,¹ β -interferon treatment may eventually induce or exacerbate conditions such as autoimmune thyroid disease and psoriasis in a significant number of MS patients.

Glatiramer acetate

Glatiramer acetate was initially synthesized under the name copolymer 1 as a potential encephalitogen for the induction of EAE. In fact, copolymer 1 was found to have the opposite effect, inhibiting the induction of EAE in guinea pigs.³¹ It was later shown to be capable of suppressing or ameliorating EAE in a number of species, which led to trials in MS. The phase III trial in relapsing–remitting MS, published in 1995, showed that glatiramer acetate had a similar efficacy to that of β -interferon in terms of reducing the relapse rate in relapsing–remitting MS.³² In addition, there was evidence for a beneficial effect on disability progression in relapsing–remitting patients. In both the initial phase III trial³² and the extension study,³³ there was a beneficial effect on expanded disability status scale (EDSS) change between baseline and final assessment by categorical analysis (worsened, unchanged or improved by ≥ 1 EDSS steps). However, neither study was able to demonstrate a significant benefit on sustained disability progression – only a weak positive trend.^{32,33} An open-label, single-arm continuation study purported to show sustained efficacy of glatiramer acetate in slowing accumulation of disability, as well as reducing relapses, during continuous treatment for ≥ 5 years.³⁴ Although the results of any open-label study should be interpreted with caution, a favourable effect of glatiramer acetate on disease progression is supported by the finding of a beneficial effect on decline in brain

parenchymal volume as determined by quantitative MRI assessment.³⁵ There have been no phase III studies of the efficacy of glatiramer acetate on disease progression in patients with secondary progressive or primary progressive MS.

Currently, the favoured mechanism of action of glatiramer acetate involves the generation of cross-reactive Th2 cells which, it is proposed, are activated by glatiramer acetate and cross the blood–brain barrier to be reactivated by myelin antigens. This leads to local CNS production of immunomodulatory Th2 cytokines.³⁶ However, such a mechanism of action would be expected to increase antibody-mediated CNS damage, as discussed above for β -interferon.

Mitoxantrone

Mitoxantrone is an anthracenedione cytotoxic and immunosuppressive agent that is administered intravenously. Its main mechanisms of action are deoxyribonucleic acid (DNA) intercalation and inhibition of DNA topoisomerase II. Its immunosuppressive effects include reduction of B-cell numbers and inhibition of T-helper cell function. In a 2-year, randomized, multicentre, placebo-controlled, observer-blinded study involving 51 patients with relapsing–remitting MS, it has been shown to have a significant beneficial effect on disability progression, relapses and new T2 lesions.³⁷ A subsequent 2-year, observer-blinded, placebo-controlled trial including patients with either secondary progressive or ‘relapsing–progressive’ disease, randomized to receive placebo, mitoxantrone 5 mg/m² or mitoxantrone 12 mg/m² every 3 months, showed beneficial effects on sustained disability progression and progression of T₂-weighted lesion load, as well as on gadolinium-enhancing lesions and relapses, all favouring the higher dose.^{38,39} The results of the latter study have resulted in this agent receiving indications in the USA for the treatment of secondary progressive, progressive relapsing and worsening relapsing–remitting MS. However, the efficacy of mitoxantrone in secondary progressive disease per se is unclear. More importantly, the usefulness of this treatment is limited by the risk of serious cardiotoxicity in the form of irreversible cardiomyopathy, which restricts its use to a maximum total lifetime dose of 140 mg/m² (less than 3 years at a dose of 12 mg/m² every 3 months). Although duration of clinical efficacy might extend beyond the actual period of administration, it is still likely to fall far short of a desirable period of usefulness in a disease with a median duration in excess of 30 years. Furthermore, based on experience in Hodgkin’s disease, even doses within the recommended

therapeutic range will result in impaired left ventricular function in more than one-third of patients 7 years after completion of mitoxantrone treatment.⁴⁰ The effect of mitoxantrone in primary progressive MS is unknown.

Methotrexate

Methotrexate inhibits dihydrofolate reductase, which is involved in both DNA and ribonucleic acid (RNA) synthesis. It has both immunosuppressive and anti-inflammatory effects. A randomized, double-blind, placebo-controlled phase II trial of the effect of low-dose methotrexate (7.5 mg orally once weekly) on disability progression in 60 patients with chronic progressive MS (42 with secondary progressive and 18 with primary progressive disease) was reported in 1995.⁴¹ Sustained disability progression was defined as sustained deterioration according to any one of several criteria. A significant benefit for methotrexate on the rate of sustained disability progression was demonstrated for the patients with secondary progressive disease but not for those with primary progressive MS. Moreover, no statistically significant benefit was demonstrable in terms of EDSS progression, indicating that the composite measure was a 'softer' end-point. This raises questions about the clinical importance of any beneficial effect of this dose of methotrexate. It is possible that a higher dose would be more effective, as considerably higher weekly doses (12.5 mg) are regularly used in patients with rheumatoid arthritis. However, further studies are needed to determine this. Although low-dose methotrexate is generally well tolerated, the drug does have the potential for serious adverse effects in the form of pulmonary, hepatic and bone marrow toxicity.

Azathioprine

Azathioprine is an oral immunosuppressive agent with effects on both T and B cells. It has a long history of use in MS, which predates current demands for proof of drug efficacy through large, rigorously conducted double-blind, randomized, placebo-controlled trials. The trials that have been performed have generally been small and have included a mixture of MS types, making confirmation of efficacy difficult. Because of this, a meta-analysis of randomized, controlled, double- or single-blind trials of azathioprine in MS was carried out, the results of which were published in 1991.⁴² This demonstrated a significant increase in the likelihood of remaining relapse free at 1, 2 and 3 years, but no benefit on disability at 1 year and a small, non-significant benefit on disability at 2 and 3 years. This led the authors to

question whether the small clinical benefits of azathioprine were sufficient to outweigh its toxicity.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with powerful cytotoxic and immunosuppressive effects. Although two randomized, single-blind, placebo-controlled trials of cyclophosphamide in chronic progressive MS failed to demonstrate any beneficial effect on disease progression,^{43,44} a subsequent 2-year, randomized, observer-blinded trial comparing induction therapy followed by pulse intravenous cyclophosphamide every 2 months with induction therapy alone did suggest a beneficial effect on disease progression, which was restricted to patients aged ≤ 40 years.⁴⁵ Whereas the efficacy of cyclophosphamide is unclear, its toxicity is well documented.

Pulse high-dose methylprednisolone

Corticosteroids have a diverse range of actions, including: (i) immunosuppressive and anti-inflammatory effects, (ii) stabilization of the blood-brain barrier, (iii) acceleration of oedema resolution and (iv) promotion of T-cell apoptosis. High-dose intravenous methylprednisolone accelerates recovery from attacks of relapsing-remitting MS.⁴⁶ A randomized, controlled, 2-year, phase II trial of high-dose intravenous methylprednisolone administered every 2 months to patients with secondary progressive MS, using a low-dose treatment arm as a control group, suggested a possible clinical benefit for high-dose therapy, using a composite end-point comprising sustained worsening, by any of several measures, or at least three relapses requiring unscheduled treatment in a 12-month period.⁴⁷ A significant effect in favour of the high-dose treatment arm was demonstrated in terms of survival analysis, suggesting a delaying effect on time to reach the end-point. However, no significant benefit was demonstrated in terms of the proportion of subjects in each treatment arm reaching the end-point at 2 years. Any sustained disease-modifying effect is yet to be demonstrated and long-term high-dose corticosteroid therapy carries a risk of adverse effects, including osteoporosis.

Intravenous immunoglobulin

Intravenous immunoglobulin has multiple immunoregulatory effects, including effects on both B and T cells. The Austrian Immunoglobulin in MS study of 148 patients with relapsing-remitting MS randomized to receive monthly intravenous immunoglobulin (IVIg) or placebo over a 2-year period showed a significant beneficial effect for IVIg on

change in EDSS score between baseline and conclusion, in addition to a reduction in relapses of approximately 50%.^{48,49} Further studies are required to determine whether there is any beneficial effect of IVIg on sustained disability progression in patients with relapsing–remitting disease and whether there is any benefit in primary or secondary progressive MS. In view of problems with availability, cost, potential adverse effects⁵⁰ and route of administration, it is unclear what role IVIg might play as a disease-modifying agent in MS.

Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation should be regarded as the second part of a two-stage treatment. First, intense immunotoxic therapy is used to eliminate, as far as possible, potentially harmful cells. Second, the patient's immune system is reconstituted using haematopoietic precursor cells derived either from a human leucocyte antigen-matched donor (allogeneic transplant) or from the patient following mobilization (autologous transplant). The high mortality of allogeneic transplantation precludes its use in a disease with low mortality, such as MS. Autologous haematopoietic stem cell transplantation carries a lower mortality but also a higher likelihood of persistent contamination of the patient's immune system with autoaggressive cells, resulting in ongoing autoimmune disease. The principle behind the use of haematopoietic stem cell transplantation in MS is that factors other than genetic ones are involved in the malfunction of the immune system that causes MS. Thus, reconstitution of the immune system from precursor cells may not necessarily result in the same malfunction. Furthermore, as there is a delay between formation of the immune system and development of MS, there may at least be a latent period between the reconstitution of the immune system and the resumption of autoimmune attack. However, success in preventing ongoing autoimmunity and disease progression is dependent on elimination of cells responsible for autoimmune disease, both from the transplanted cell population (by *in vivo* or *in vitro* methods) and from the patient prior to transplantation. In essence, the theoretical aim is to return the immune system to something resembling a naïve state. However, it seems unlikely that autologous stem cell transplantation can achieve this objective.

Various protocols have been used in the limited number of trials of autologous stem cell transplantation in MS reported to date. Variables include the conditioning regimen used prior to transplantation and the additional negative selection techniques

aimed at selectively depleting potentially autoaggressive cells from the transplanted cell population. It is yet to be determined whether any protocol can produce efficacy of sufficient frequency and durability to justify the considerable inherent morbidity and mortality risks. This is likely to depend on the patients selected for treatment, as much as on the technical aspects of the treatment. The selected patients would need to have a reliably poor prognosis in order to justify the risks involved in such aggressive treatment, yet disease that is not so far advanced as to limit potential benefit. The evidence from the largest trial reported to date suggests that autologous transplantation may delay, rather than prevent, disease progression. This is probably because its effects are due to the intense immunosuppression permitted by stem cell rescue, rather than to complete elimination of autoaggressive cells.⁵¹ This trial also bears out concerns regarding the mortality and morbidity risks, particularly in relation to patients with MS.

POTENTIAL THERAPEUTIC STRATEGIES

Downregulation of T cells in the periphery

Altered peptide ligands are peptides that are designed to resemble the epitopes that are targeted by pathogenic T cells, but incorporate minor amino acid substitutions at the site of interaction with the T-cell receptor. In MS, the aim of altered peptide ligand therapy is to downregulate or modulate pathogenic T-cell responses to the relevant target peptide. Problems with this approach include: (i) the multitude of potential target myelin epitopes and (ii) the phenomenon of epitope spreading, which results in additional targets. Two phase II trials have also raised questions about the safety of this approach, with one altered peptide showing encephalitogenicity⁵² and the other inducing hypersensitivity reactions.⁵³

T-cell vaccination, which involves immunization of patients with irradiated myelin-reactive T cells derived from their peripheral blood, is aimed at selectively downregulating potentially pathogenic T cells. An alternative strategy involves vaccination with T-cell receptor peptides. A recent pilot study of T-cell vaccination in four patients with secondary progressive MS demonstrated short-term reduction in the frequencies of circulating T cells specific for various myelin antigens.⁵⁴ Larger, randomized, double-blind, controlled trials will be necessary to determine whether a significant clinical effect can be demonstrated. The effectiveness of the T-cell vaccination approach may again be limited by the diversity of

antigenic targets and pathogenic T cells, and by defects in the immunoregulatory mechanisms that allow this approach to be beneficial in EAE.

Problems associated with the diversity of pathogenic T cells in MS may be avoided by a more generalized depletion of T cells, although this may predispose to infection. Treatment of 27 patients with secondary progressive MS with the lymphocyte-depleting anti-CD52 monoclonal antibody Campath-1H resulted in reduction of peripheral blood lymphocyte counts which, in the case of T cells, was prolonged.¹¹ B-cell numbers, however, recovered within 3 months, and a subsequent reactive increase in B-cell activity was associated with autoimmune hyperthyroidism in one-third of the patients. This treatment resulted in a marked reduction in inflammatory MRI brain lesions throughout the 18-month study.¹⁰ Nevertheless, many of the patients continued to develop brain and spinal cord atrophy, T1 hypointense lesions and worsening disability. This study highlighted a dissociation between: (i) suppression of T cells and of inflammatory lesions and (ii) progressive CNS tissue loss and disability, at least in patients with secondary progressive MS. This indicates that non-specific T-cell downregulation alone at this stage of disease may be ineffective. It also raises the possibility that, by increasing B-cell activity, Campath-1H treatment led to increased antibody-mediated CNS damage with resultant progression of disability.

Inhibition of T-cell entry into the CNS

Agents that block the interaction of activated T cells with vascular adhesion molecules impede the migration of these cells across the blood-brain barrier and inhibit EAE. A short-term randomized, placebo-controlled, double-blind trial of one such agent, anti- α 4 integrin antibody (natalizumab), demonstrated reduction in MRI-lesion activity in the first 12 weeks after treatment.⁵⁵ There was no significant effect on the frequency of relapses in the first 12 weeks but a considerable increase in this frequency in the second 12 weeks in the treated group. This suggests a rebound increase in disease activity after reversal of the α 4-integrin blockade. Further studies are needed to determine the efficacy and safety of longer-term therapy.

Elimination of T cells from the CNS

Apoptosis of encephalitogenic T cells in the CNS plays an important role in the spontaneous resolution of EAE.^{56,57} The induction of apoptosis of encephalitogenic T cells in the CNS by the activation of proapoptotic molecules or blockade of anti-apoptotic molecules (for example, by targeting antisense bcl-2

oligonucleotides to T cells within the CNS) is a potential new approach to preventing autoimmune attack and disease progression in MS.²

Inhibition of pro-inflammatory cytokines in the CNS

Because blockade of the pro-inflammatory cytokine TNF- α inhibits EAE, it was hoped that inhibition of TNF- α might be beneficial in MS. A trial of lenercept (a TNF- α receptor-immunoglobulin fusion protein that captures TNF- α) in patients with relapsing-remitting MS found that lenercept did not have a beneficial clinical or MRI effect but that it did induce earlier and more frequent relapses.⁵⁸ The deleterious effect of lenercept in MS, in contrast to its beneficial effect in EAE, may be explained by predominance of the anti-inflammatory effect over the pro-inflammatory effect of TNF- α in MS.

Downregulation of B-cell/antibody responses

Given the increasing evidence that B cells and antibodies have a pathogenic role in at least a large proportion of MS cases,⁵⁹ therapies targeting B cells and/or antibody might be useful in preventing autoimmune attack and disease progression in MS. One potential therapeutic approach is the elimination of B cells from the CNS by the induction of B-cell apoptosis, as occurs during spontaneous recovery from EAE.⁶⁰

CONCLUSION

There is no treatment currently available that is capable of preventing relapses or disease progression in MS. All of the therapies that are currently used in an attempt to modify the disease course have limited efficacy and, in many cases, appreciable side-effects. A few of the many conceivable strategies for more effectively (and more specifically) inhibiting the autoimmune process that underlies the disease course have been outlined in the present paper. It is unclear what strategy (or combination of strategies) will ultimately prove effective.

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