The Challenge of Multiple Sclerosis: How Do We Cure A Chronic Heterogeneous Disease?

Howard L. Weiner, MD

Multiple sclerosis is (MS) a T-cell autoimmune disease characterized by a relapsing-remitting followed by a progressive phase. Relapses are driven by the adaptive immune system and involve waves of T helper cell 1 (Th1), Th17, and CD8 cells that infiltrate the nervous system and provoke a attack. These cells are modulated by regulatory T and B cells. Infiltration of T cells into the nervous system initiates a complex immunological cascade consisting of epitope spreading, which triggers new attacks, and activation of the innate immune system (microglia, dendritic cells, astrocytes, B cells), which leads to chronic inflammation. The secondary progressive phase is due to neurodegeneration triggered by inflammation and is driven by the innate immune system. Why a shift to the progressive stage occurs and how to prevent it is a central question in MS. Effective treatment of MS must affect multiple disease pathways: suppression of proinflammatory T cells, induction of regulatory T cells, altering traffic of cells into the nervous system, protecting axons and myelin, and controlling innate immune responses. Without biomarkers, the clinical and pathological heterogeneity of MS makes treatment difficult. Treatment is further hampered by untoward adverse effects caused by immune suppression. Nonetheless, major progress has been made in the understanding and treatment of MS. There are three definitions of cure as it applies to MS: (1) halt progression of disease, (2) reverse neurological deficits, and (3) prevent MS. Although the pathways to each of these cures are linked, each requires a unique strategy.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that primarily affects young adults. Great strides have been made in our understanding and treatment of MS, and given this progress, we must now ask what it mean to cure MS and what is needed to achieve this goal. When one examines the question, it becomes clear that there are three definitions of “cure” as it relates to MS: (1) halt progression of the disease, (2) reverse neurological deficits, and (3) develop a strategy to prevent MS. We are making progress in halting or slowing progression of MS, have approaches that may help reverse neurological deficits, and for the first time are beginning to develop strategies to prevent MS.

Clinical and Magnetic Resonance Imaging Features of Multiple Sclerosis

In most instances, MS begins as a relapsing-remitting disease that, in many patients, becomes secondary progressive. Approximately 10% of patients begin with a primary progressive form of the disease. Although primary progressive MS differs clinically and in response to treatment from relapsing MS, it is somehow related because there are families in which one member has relapsing MS and another the primary progressive form. Not all patients enter the secondary progressive stage, and there are both benign and malignant forms of MS. Early stages of MS are associated with relapses and gadolinium enhancement on magnetic resonance imaging (MRI), which decrease with time even without treatment. It is not clear why this happens, though as discussed later, it may relate to changes that occur in the adaptive and innate immune system over the course of the illness (Fig 1). The progressive forms of the disease are the most disabling and are likely similar in their pathogenic mechanisms. Epidemiological studies have raised the question whether relapses are related to or are independent from the development of progressive MS. This raises the central question: Will current therapy that is effective in reducing relapses delay or prevent the onset of progression?

From the Partners Multiple Sclerosis Center, Center for Neurologic Diseases, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Address correspondence to Dr Weiner, Partners Multiple Sclerosis Center, Center for Neurologic Diseases, 77 Avenue Louis Pasteur Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115. E-mail:lweiner@rics.bwh.harvard.edu

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What Causes Multiple Sclerosis?

CNS inflammation is the primary cause of nervous system damage in MS. The exact factors that initiate inflammation are unknown, but it is generally believed that MS is caused by environmental factors in a genetically susceptible host that trigger a T-cell autoimmune response against the CNS. Recent studies have begun to identify genes that are associated with MS, and they are related to the immune system. The major genetic factor in MS is the major histocompatibility complex, which overlaps other susceptibility genes that have been identified (eg, interleukin-7 [IL-7], IL-2). The major histocompatibility complex is most probably related to MS by affecting both the immune repertoire and immunoregulatory circuits, and the DRB1*1501 allele is linked to disease severity. Although viruses may trigger MS relapses, there is no definitive evidence that there is an MS virus or an ongoing chronic infection of the nervous system. It is possible, however, that a self-limited CNS infection in childhood could trigger MS, and epidemiological evidence suggest that Epstein–Barr virus, a ubiquitous virus, plays a key role in MS.

Experimental allergic encephalomyelitis (EAE) serves as the primary animal model for MS, and from the time it was first described by Rivers in 1933, forms of the model have been developed that mimic virtually all the clinical features of MS including relapsing, relapsing-remitting, progressive, and opticospinal forms. In addition, spontaneous forms of EAE have been developed (Table 1). The majority of treatments for MS have stemmed from studies in the EAE model, further supporting the concept that autoimmune processes in the EAE model are relevant to MS.

Immune System in Multiple Sclerosis

Adaptive Immune System in Multiple Sclerosis: Pathogenic T Cells

It is generally believed that the acute MS lesion is initiated by a myelin-reactive CD4+ T cell that is stimulated in the periphery and enters the brain and spinal cord (Fig 2). These CD4+ T cells have previously been believed to be interferon-γ-secreting T helper cell 1 (Th1) cells. It is now recognized that Th17 cells play a crucial role in autoimmunity in the EAE model, and increased numbers of Th17 cells have been identified in MS as well. Both types of pathogenic cells (Th1 and Th17) most probably play a role in MS and could account for the immunological and clinical heterogeneity of the disease. Immunohistochemical examination of brain demonstrates a Th1/Th17 immune response. Th1 versus Th17 responses have been associated with different types of EAE. Transforming growth factor-β (TGF-β), which is a central cytokine in the induction of regulatory T cells (see later), induces Th17 cells when combined with IL-6, and anti–IL-6 therapy is being investigated for the treatment of autoimmunity. Although CD8 T cells have not been at the forefront of thinking in MS, CD8 T cells are found in MS lesions, and a greater frequency of CD8+ T cells reactive to myelin antigens have been reported in MS. It is likely that CD8+ T cells play a role in MS and also contribute to disease heterogeneity. Natural killer cells (NK cells) most likely also play a role in MS and may have either an inflammatory or antiinflammatory role in MS.

Table 1. Clinical Phenotypes of Experimental Allergic Encephalomyelitis Models

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<thead>
<tr>
<th>Animal</th>
<th>Induction</th>
<th>Disease Type</th>
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<tr>
<td>Lewis rat</td>
<td>MBP</td>
<td>Acute relapse ADEM</td>
</tr>
<tr>
<td>SJL</td>
<td>PLP</td>
<td>Relapsing remitting</td>
</tr>
<tr>
<td>C57Bl/6</td>
<td>MOG</td>
<td>Relapsing remitting</td>
</tr>
<tr>
<td>NOD</td>
<td>MOG</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>MOG TCRa</td>
<td>MOG</td>
<td>Optic neuritis</td>
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<tr>
<td>MOG TCRb</td>
<td>MOG</td>
<td>Devic’s disease</td>
</tr>
<tr>
<td>SJL</td>
<td>Theiler’s virus</td>
<td>Relapsing/progressive</td>
</tr>
<tr>
<td>C57Bl/6</td>
<td>Monocyte</td>
<td>Progressive</td>
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MBP = myelin basic protein; ADEM = acute disseminated encephalomyelitis; MOG = myelin oligodendrocyte glycoprotein; aMOG TCRa × MOG BCRa; bMOG TCRb × MOG BCRb.
Adaptive Immune System in Multiple Sclerosis: Regulatory T Cells

It is now clear that the adaptive immune system consists of a network of regulatory T cells (Tregs).\(^1\) Defects in regulatory T-cell function have been described in MS,\(^2\)\(^2\)\(^4\) and a major goal of MS immunotherapy is to induce regulatory cells in a physiological and non-toxic fashion (see Fig 2). Regulatory T cells can broadly be classified as natural Tregs and induced Tregs. Foxp3 is the major transcription factor for Tregs. CD25 marks natural Tregs and TGF-β/H9252 induces Tregs. Th3 cells are induced Tregs that secrete TGF-β/H9252,\(^2\) and Tr1 cells are induced Treg cells that secrete IL-10.\(^2\)\(^6\) Th2 cells may also have regulatory T-cell function, and patients with parasitic infections that induce Th2-type responses have a milder form of MS.\(^2\)\(^7\) Experimental data suggest that regulatory cells may not be effective if there is ongoing CNS inflammation.\(^2\)\(^8\) We have taken the approach of using the mucosal immune system to induce regulatory cells and have found that oral anti-CD3 monoclonal antibody\(^29\) and oral ligands that bind the aryl hydrocarbon receptor induce TGF-β-dependent regulatory T cells that suppress EAE and these approaches provide a novel avenue for treating MS.\(^3\)\(^0\)

Adaptive Immune System in Multiple Sclerosis: B Cells and Antibodies

Although autoantibodies have been reported in MS, there is no evidence that there are high-affinity pathogenic antibodies in MS as in other antibody-mediated autoimmune diseases such as myasthenia gravis.\(^3\)\(^1\) Antibodies to myelin components, however, may participate in myelin loss.\(^3\)\(^2\) A classic finding in MS is increased locally produced IgG and oligoclonal bands in the cerebrospinal fluid, the pathogenic significance of which remains unknown. Treatment with rituximab, a monoclonal antibody that deletes B cells, dramatically reduces inflammatory disease activity as measured by MRI without affecting immunoglobulin levels, demonstrating a clear role for B cells in relapsing forms of MS.\(^3\)\(^3\) The almost immediate clinical response to ri-
tuximab suggests that B cells are most likely affecting T-cell function via their antigen presentation properties, though they most likely directly participate in lesion formation as well. B cells may have antiinflammatory and proinflammatory function.\textsuperscript{34,35} In this sense, B cells are part of the innate immune system (see below), affecting T cells, whereas myelin specific antibodies represent an adaptive immune response. Furthermore, B cells may also play an important role in progressive MS.\textsuperscript{36}

**Innate Immune System in Multiple Sclerosis**

The innate immune system consists of monocytes, dendritic cells, and microglia. It is becoming increasingly recognized that the innate immune system plays an important role in the immunopathogenesis of MS. Although the secondary progressive phase of MS has been believed to be related to neurodegenerative changes in the CNS, it is now clear that the peripheral innate immune system changes when patients transition from the relapsing-remitting to the progressive stage. We have observed this in our studies of IL-12, IL-18, and dendritic cells.\textsuperscript{37–40} Furthermore, chronic microglial activation occurs in MS.\textsuperscript{41} This leads to a different view of the immunopathogenesis of MS that integrates both limbs of the immune system and links them to different disease stages and processes. Thus, the adaptive immune system drives acute inflammatory events (attacks, gadolinium enhancement on MRI), whereas innate immunity drives progressive aspects of MS (Fig 3). This raises important questions regarding the pathogenesis and treatment of different stages of MS. Of note, there do not appear to be abnormalities of CD4\textsuperscript{+}CD25\textsuperscript{+} regulatory T cells in secondary progressive MS.\textsuperscript{42} It is not known the degree to which the adaptive and innate immune systems affect each other in MS. A major question is whether aggressive and early antiinflammatory treatment will prevent the secondary progressive form of the disease. There is some evidence that this is occurring; studies are beginning to show that treatment with interferons delays the onset of progressive stage.\textsuperscript{43} Of note, there is a form of EAE driven by the innate, rather than the adaptive immune system.\textsuperscript{44} There are no specific therapies designed to affect the innate immune system in MS, and scientists are only beginning to investigate the innate immune system in MS and characterize it as relates to disease stage and response to therapy. Furthermore, like the adaptive immune system, there are different classes of innate immune responses, for example, protective and tolerogenic versus pathogenic and proinflammatory. Of note, we have found increased osteopontin expression in dendritic cells in relapsing MS\textsuperscript{45} and changes in expression of IL-27 (unpublished data). Thus, in the re-

![Image](image-url)

**Fig 3.** Immune pathways and innate immunity in the progression of multiple sclerosis (MS). Inflammatory T cells that enter the central nervous system (CNS) initiate a complex immunological cascade consisting of epitope spreading, which triggers new attacks, and activation of the innate immune system (microglia, dendritic cells, astrocytes, B cells), which leads to chronic CNS inflammation. IFN = interferon; NAWM = normal-appearing white matter; NO = nitric oxide; TNF = tumor necrosis factor.
lapses stage, a pro-inflammatory milieu that combines both the innate and adaptive immune system is present, whereas in the progressive stage abnormalities of the innate immune system predominate.

**Neurodegeneration in Multiple Sclerosis**

Axonal and myelin loss are prominent pathological features of MS and can be directly caused by immune cells, for example, cytotoxic CD8 cells damaging neurons or macrophages stripping myelin from the axon, or can result from release of toxic intermediates, for example, glutamate and nitric oxide. These intermediates can trigger immune cascades that further enhance inflammatory-mediated CNS damage. Thus, glutamate and nitric oxide can lead to enhanced expression of chemokine (C-C motif) ligand 2 (CCL2) on astrocytes, which, in turn, leads to infiltration of CD11b cells and additional tissue damage. \( \alpha \)-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists have been shown to have an ameliorating effect in acute EAE models, and we have found that a carbon-based fullerene linked to an NMDA receptor with antixicitotoxic properties slows progression and prevents axonal damage in the spinal cord in a model of chronic progressive EAE. Although the compound is not an immune compound, it reduces infiltration of CD11b cells into the CNS (see Fig 3). Another important component of neurodegeneration relates to changes in Na channels, and these are targets of therapy.

**Clinical and Pathological Heterogeneity of Multiple Sclerosis**

MS is a nondescript term that refers to “multiple scars” that accumulate in the brain and spinal cord. MS is more a syndrome than a single disease entity, and the MS syndrome has both clinical and pathological heterogeneity. The clinical heterogeneity is reflected in the different types and stages of the disease. An important question in MS is the relation of the progressive to relapsing forms. Devic’s disease appears to be an MS variant associated with antibodies to the aquaporin receptor. There are rare malignant forms including Marburg’s variant, tumefactive MS, and Balo’s concentric sclerosis. An unanswered question relates to why benign forms of MS exist. Although some cases of MS which are defined as benign progress with prolonged follow-up, there are clearly benign forms of the disease. By definition, patients with benign MS do not enter the progressive phase. The ability to identify benign or malignant MS early in the course of the illness is important for treatment strategies. We compared brain parenchymal fraction over a 2-year period in benign versus early relapsing-remitting MS matched for age and expanded disability status scale, and found that patients with benign MS had less decrease in brain parenchymal fraction (BPF). As it impinges on the expanded disability status scale, the majority of disability in MS relates to spinal cord dysfunction. The relation between spinal cord changes and brain MRI changes is not well known, but changes in the medulla oblongata that reflect spinal cord but can be visualized on brain MRI may correlate with entering the progressive phase. In addition, a human leukocyte antigen D–related type 2 (HLA-DR2) dose effect may be associated with a more severe form of the disease.

**Multiple Sclerosis Biomarkers**

**Magnetic Resonance Imaging**

A major tool to address the heterogeneity of MS and devise appropriate treatment strategies is to develop reliable biomarkers. MRI has served as the primary biomarker for MS, and although conventional imaging does not link strongly to clinical outcomes, every US Food and Drug Administration–approved MS drug showed positive results on MRI. Advances in MRI are beginning to better define MS and its heterogeneity. Most important, MRI and pathological studies have shown gray matter atrophy in MS, which is linked to cognitive impairment. In addition, cortical foci of demyelination, microglial activation, leptomeningeal inflammation, iron deposition, and neuronal loss occur in the gray matter. The degree to which current therapies attenuate gray matter destruction is not known. It is likely that the processes that affect the gray matter are highly clinically relevant and will ultimately provide new therapeutic targets. MRI has also shown diffuse involvement of the normal–appearing white matter including demyelination, inflammation, and axonal injury not seen by conventional imaging, but which can be visualized by magnetization transfer, diffusion-weighted imaging, and spectroscopic imaging. These changes can precede overt gadolinium-enhancing lesions by months and result from early migration of lymphocytes into the brain.

Spinal cord dysfunction is primarily responsible for gait impairment in MS, the major disabling feature of the illness, and better spinal cord imaging should improve clinical MRI correlation. Spinal cord atrophy may occur early, and the clinical heterogeneity of MS and benign forms of MS may relate to atrophy and spinal cord involvement. The factors that predict benign versus nonbenign MS are poorly understood. As discussed, we have found that the rate of atrophy progression is less in benign MS, and an MRI study using double inversion recovery imaging to detect cortical lesions suggests the importance of gray matter sparing in predicting a benign clinical course. We have developed a Magnetic Resonance Disease Severity Scale that combines multiple measures to provide an index of disease severity and progression as measured by MRI. The addition of spinal cord imaging and gray
Involvement in multiple sclerosis (MS), sulci/fissures MRI or disability to the Magnetic Resonance Disease Severity Scale should enhance its value as a biomarker.

**Immune Biomarkers**

We and others have shown immune measures that are associated with disease activity and MRI activity,\(^{67-69}\) and RNA profiling is beginning to identify gene expression patterns associated to different forms of MS and disease progression.\(^{70,71}\) Building on Robinson’s\(^ {72,73}\) approach, we performed antigen microarray analysis to characterize patterns of low-affinity antibody reactivity in MS serum against a panel of CNS protein and lipid autoantigens and heat shock proteins. Using informatic analysis for validation, we found unique autoantibody signatures that distinguished relapsing-remitting, secondary progressive, and primary progressive MS patients from healthy controls and other neurological or autoimmune diseases.\(^ {74}\) Relapsing-remitting MS was characterized by autoantibodies to heat shock proteins that were not observed in primary progressive or secondary progressive MS. In addition, relapsing-remitting, secondary progressive, and primary progressive MS were characterized by unique patterns of reactivity to CNS antigens (Fig 5). We also examined sera from patients with different immunopathological patterns of MS as determined by brain biopsy,\(^ {75}\) and we identified unique antibody patterns to lipids and CNS-derived peptides that were linked to type I and II patterns. This led us to identify classes of oxysterols that are differentially increased in the serum of relapsing-remitting vs. pregressive MS (unpublished). The demonstration of unique serum immune signatures linked to different stages and pathological processes in MS provides a new avenue to understand disease heterogeneity, to monitor MS, and

**Fig 4.** Magnetic resonance imaging (MRI)–defined gray matter involvement in multiple sclerosis (MS). (A, B) Fluid-attenuated inversion recovery (FLAIR) axial images of a 40-year-old woman with relapsing-remitting multiple sclerosis (RRMS) of 2 years’ duration and mild disability demonstrate cortical lesions (arrows, note hyperintensities). (C) Fast spin-echo, T2-weighted axial images of a 43-year-old man with RRMS of 4 years’ duration and mild-to-moderate disability demonstrates bilateral hypointensity in the thalamus and basal ganglia (arrows) most likely representing excessive iron deposition and diffuse brain atrophy indicated by widening of the cortical sulci/lines and ventricles (D) of an age-matched healthy control subject. (E) Spoiled gradient recalled echo coronal images of a 54-year-old man with secondary progressive MS of 29 years’ duration with moderate-to-severe disability demonstrate widespread gray matter atrophy of the cortical mantle and the deep gray nuclei, such as the thalamus in the patient with MS. (F) Age-matched healthy control subject. (A, B, E, F: Courtesy Dr Mohit Neema and Rohit Bakshi; C, D: Adapted from Stankiewicz and colleagues.)

**Fig 5.** Autoantibody immune signatures of multiple sclerosis (MS) in the peripheral blood as demonstrated by antigen arrays. (A) Schematic depiction of immune signatures associated with relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). (B) Heatmap depicting antibody reactivities against myelin antigens and heat shock proteins (HSP) in SPMS vs RRMS. CNS = central nervous system.
to characterize immunopathogenic mechanisms and therapeutic targets in the disease.

Curing Multiple Sclerosis

ImmunoTherapy to Halt Disease Activity and Progression

One could argue that a cure is a treatment that eradicates MS. This may be true for an infection or tumor but not for MS in which there is an inherent defect of the immune system and chronic inflammation of the brain. If, however, one treated MS at the clinical onset and prevented disease progression for the remainder of the patient’s life, it would be considered a cure. There may be patients who are being “cured” with current therapy, though they may have less severe forms of the disease. Interferons and glatiramer acetate are only partially effective in MS, with stronger effects observed with natalizumab and alemtuzumab. This raises a central question: Will aggressive and early immunotherapy prevent the secondary progressive form of the disease? With the strong antiinflammatory effects of a drug such as alemtuzumab, this question could be addressed in the future, though widespread testing may be prohibited by adverse effects. Other approaches of aggressive immunotherapy at disease onset to test this hypothesis include bone marrow transplantation, nonablative chemotherapy utilizing cyclophosphamide, or induction with a drug such as cyclophosphamide or mitoxantrone followed by maintenance immunomodulation. We found that a short course of cyclophosphamide was very effective in shutting down disease activity in early aggressive MS, but less effective in older patients who had entered the later progressive stages. This phenomenon was also observed in trials of beta interferon in progressive MS and with other anti-inflammatory drugs such as alemtuzumab and rituximab. Patients most likely to respond to drugs with anti-inflammatory actions are those with active disease progression and adaptive immune activity as evidence by continued relapse activity.

Because the immune damage to myelin and axons initiates secondary pathways of CNS damage, nonimmune-based therapy may be required to control disease progression. The presence of glutamate and nitric oxide leads to axonal injury and demyelination, which in itself can set up an inflammatory response on astrocytes that express CCL2 and lead to infiltration of CD11B cells.

Thus, a complex disease such as MS will require treatment(s) that has an effect on multiple pathways including (Table 2) suppressing Th1/Th17 responses, inducting Tregs, altering traffic of cells into the CNS, protecting axons and myelin from degeneration initiated by inflammation and affecting the innate immune system. If multiple drugs are required to achieve this effect, one must be certain that one treatment does not interfere with the other. It has been reported that statins may interfere with the action of interferons. It may also be that one must first suppress Th1 and Th17 responses before inducing Tregs. Antigen specific therapies that do not disrupt immune pathways are the ultimate goal. Because of disease heterogeneity, there will be responders and nonresponders to each “effective” therapy and, the earlier treatment is initiated, the more likely it is to be effective. Finally, biomarkers are required to provide immunologic staging of MS. These immune markers would establish how far along the immunologic pathway a patient has progressed and based on this, which therapy or combination therapy is best for an individual patient.

Inherent in the concept of curing MS by halting progression is the ability to demonstrate that progression has been halted in a group of patients and to identify those factors associated with preventing the onset of progressive disease. We have initiated the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s (CLIMB) natural history study in which 1,000 patients with new-onset MS will be monitored over a 20-year period with clinical evaluation, MRI, and immune and genetic markers to identify which factors are associated with disease progression and response to therapy.

Repairing a Damaged Nervous System

There is evidence of repair in the CNS of those with MS, though the mechanisms involved are not well understood. Furthermore, it has been shown in animal models that reducing inflammation promotes repair even with nonspecific immunosuppressants such as cyclophosphamide. Blocking molecules that inhibit axonal (Nogo) or myelin (Lingo-1) growth may promote repair and treatment of animal models with anti-Lingo-1, anti-Nogo, or antibodies reacting with oligodendrocytes and have shown positive effects. Furthermore, treatments that affect sodium channels may not only affect nerve conduction but may have effects on microglial activation. Nonetheless, it must be emphasized that when severe neuronal and oligodendro-

<table>
<thead>
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<th>Table 2. Therapeutic Pathways for the Treatment of Multiple Sclerosis</th>
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<tr>
<td>Decrease Th1/Th17 cells</td>
</tr>
<tr>
<td>Induce Treg cells</td>
</tr>
<tr>
<td>Prevent lymphocyte trafficking</td>
</tr>
<tr>
<td>Deplete B cells</td>
</tr>
<tr>
<td>Affect innate immunity</td>
</tr>
<tr>
<td>Provide neuroprotection (eg, glutamate toxicity)</td>
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<tr>
<td>Promote remyelination</td>
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Th = T helper cell; Treg = regulatory T cell.
cyte loss occurs, it is unlikely that one would be able to significantly reverse neurological deficits. Of note, stem-cell therapy may be inhibited by CNS inflammation. 89

Preventing Multiple Sclerosis
If MS is triggered in the environment in susceptible individuals, it may be possible to prevent MS, though one must first be able to identify those at risk. Autoantibody signatures in the serum have the potential to identify those at risk. 74 Some believe vaccination against Epstein–Barr virus or treating children at high risk for development of MS with vitamin D may be initial approaches. It is often stated that we “cured” polio, when in actuality, we “prevented” polio by vaccinating against the virus. This would be the ultimate cure for MS and would require treatment that modulated the immune system in children so they did not develop MS. Such a vaccine could initially be given to higher risk individuals such as children whose parents have MS and where there is a strong family history.

References


