Immunotherapy of Multiple Sclerosis

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Based on the assumption that multiple sclerosis is an autoimmune disease, a number of clinical trials designed to suppress the immune system or to restore immune balance in multiple sclerosis have been attempted. Depending on the disease category, the clinical goals of immunotherapy differ. Therapeutic goals include improving recovery from acute attacks, preventing or decreasing the number of relapses, and halting the disease in its progressive stage. The ultimate goal of multiple sclerosis therapy is the early treatment of patients in an attempt to halt the onset of progression. Specific strategies of immunotherapy include generation of a suppressor influence, removal of helper/inducer cells, manipulation of activated T cells, manipulation of class II major histocompatibility complex–bearing cells, alteration of lymphocyte traffic, extracorporeal removal of serum factors or cells, and manipulation of antigen-specific cells. Present treatment modalities are beginning to show some efficacy of nonspecific immunosuppression, but these treatments are limited by their toxicities. As the immunotherapy of multiple sclerosis moves to the next stage in the coming years, patients at an earlier stage of their disease will have to be treated, nontoxic forms of therapy developed, clinical trials lengthened, and a laboratory monitor of the disease developed. Given the positive effects of immunotherapy seen thus far in the disease, it is possible that appropriate immunotherapeutic intervention may provide effective treatment for the disease in the future.

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Although the cause and pathogenesis of multiple sclerosis (MS) are unknown, the most commonly held view is that it is an autoimmune disease related in some way to a viral infection [70, 110, 117]. Pathologically, there is an inflammatory response in the central nervous system (CNS) consisting predominantly of activated T lymphocytes and macrophages [95] accompanied by a local immune reaction with the secretion of interleukins, which results in the synthesis of oligoclonal immunoglobulin (IgG) by plasma cells [39]. Immune abnormalities have been described in the peripheral blood of MS patients, including loss of suppressor function [3], the presence of activated T cells [42, 49, 50], and alterations in T-cell populations [6, 58, 64, 93, 96, 118]. It has been hypothesized that the loss of suppression or "imbalance" in the immune system may play a crucial role in the disease pathophysiology [110]. The most widely studied animal model of MS, experimental allergic encephalomyelitis (EAE), is known to be a T cell–mediated autoimmune disease in which there is inflammation and, in chronic models, demyelination [4, 91]. Immune suppressor mechanisms play an important role in modulating the disease process: EAE can be treated with a variety of immunoregulatory agents, and the application of immunotherapeutic strategies to MS has often stemmed from their success in EAE, even though EAE may or may not be a true model for the disease [2, 15, 16, 18, 25, 55, 61, 92, 102, 104, 105, 111].

Given the potentially debilitating course of MS, physicians have attempted a variety of treatments to ameliorate or prevent the nervous system dysfunction that may occur. Many of these treatments are designed to alter or suppress the immune response. In the past five years, there have been increasing numbers of new and planned trials of immunotherapy, some of which are beginning to claim efficacy in the disease [19, 54, 84, 107]. These trials not only hold promise for developing an effective treatment for MS, but are raising important questions concerning pathogenic mechanisms in the disease. The present overview will (1) analyze the different clinical categories of the disease, the different goals of immunotherapy depending on the category being treated, and the unique problems associated with treatment of each of the categories; (2) describe current and planned strategies of immunotherapy; and (3) review current treatment programs in terms of how they specifically or nonspecifically affect the immune system and what information they provide concerning the pathogenesis of MS. This review assumes, as do the investigators treating patients with immunomodulatory agents, that MS is an immune-mediated disease, and focuses on cellular immune mechanisms in the disease and attempts to modify them.

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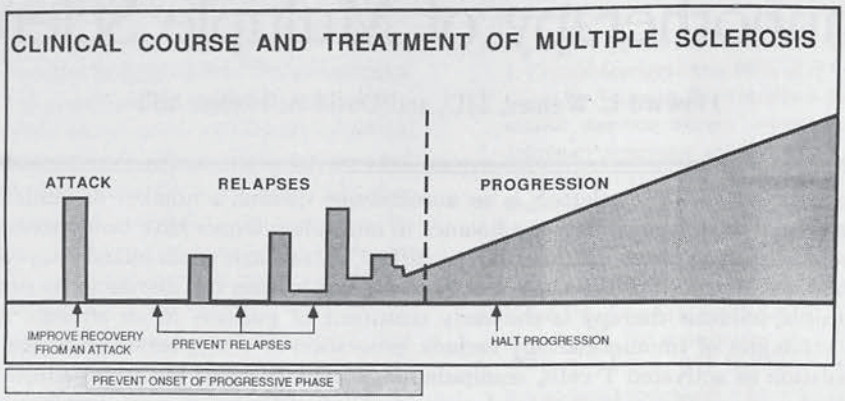

Fig 1. Clinical course and treatment of multiple sclerosis. The horizontal axis represents time, and the vertical axis level of disability. The vertical dotted line *represents the onset of the progressive disease phase. The progressive phase may evolve after a number of relapses or, in a subcategory of patients, may be the clinical course of the disease from the onset.*

Clinical Course and Treatment of Multiple Sclerosis

The clinical course and treatment of MS are outlined in Figure 1. Although the clinical course of MS is often unpredictable, studies of large numbers of patients suggest that clear disease patterns emerge over time and that these patterns are important in designing therapy [29, 67]. There are four clinical categories of MS, although at times they overlap. Different immune mechanisms may be operating during various stages of the disease, and different strategies of immunotherapy have been attempted, depending on the clinical stage.

Treatment of Acute Attacks

It would seem logical that some form of therapy should be administered at the time of an acute attack, that is, when the disease is active. The goal of such therapy would be to shorten the attack and/or improve the degree of recovery from the attack. Two difficulties with measuring the effect of treatment on an acute attack are that many patients recover from an attack with no treatment at all and an attack may represent not a new immunological event, but temporary worsening of an old symptom related to changes in physiology of conduction along a demyelinated axon, such as occurs with elevated body temperature. Nonetheless, careful neurological examination and history can identify most attacks. In addition, magnetic resonance imaging (MRI) may help define when new lesions occur [40, 65], and pleocytosis in the cerebrospinal fluid (CSF) may also indicate the presence of active inflammation, although acute attacks may occur without CSF pleocytosis. The most commonly used treatment for acute attacks is some form of corticosteroid preparation. There have been few clinical trials measuring the effect of treatment on acute attacks. The major study is a double-blind trial of adrenocorticotropic hormone (ACTH) versus placebo carried out almost twenty years ago [99]. Although ACTH was found to shorten the time to recovery, it did not affect the level of recovery. One fault of the study is that the follow-up period was only six weeks. A double-blind study of plasma exchange in conjunction with ACTH and oral cyclophosphamide for the treatment of acute attacks is currently in progress [114].

It is postulated that an acute attack represents the movement of cells into the brain, leading to an inflammatory response with subsequent edema and demyelination. If this is true, a major immunological question is, why does the attack stop? There is suggestive evidence that acute attacks are associated with changes in peripheral blood T-cell populations and function [6, 58, 118]. For example, in one study, acute attacks were associated with a decrease in T-cell suppressor function, whereas during recovery, increased functional immune suppression was found [58]. Because the brain and spinal cord do not normally have the large number of lymphocytes and macrophages present in the CNS of MS patients, these cells must initially migrate from the blood into the brain and spinal cord. Some of the more important questions regarding immunotherapy of MS are the following. In which, if any, compartment(s) outside the CNS does disease activity occur? Is this activity related to the stage of the disease? To what extent is inflammation in the CNS dependent on or independent of the peripheral immune compartment? The answers to these questions are crucial in devising effective immunotherapy. Furthermore, a monitor of disease activity within both the CNS and the peripheral immune compartment may ultimately be needed to monitor response to therapy.

Treatments Designed to Prevent or Decrease the Number of Relapses

Another goal of therapy is to prevent or decrease the number of relapses. Such trials generally involve continuous treatment on a daily basis, with the presumption that whatever initiates a relapse can be prevented. However, certain difficulties exist in trials that use re-

lapses as an endpoint: (1) the natural history of MS at this stage of the disease is variable, and with time, the incidence of relapses usually decreases and the disease may enter the progressive phase [29, 67]; (2) the clinical definition of a relapse can sometimes be difficult; and (3) all relapses are not clinically the same, with some causing greater disability than others. Furthermore, repeated MRI imaging of the CNS in relapsing-remitting MS indicates that new lesions can appear without clinical sequelae, suggesting that whether a clinical attack occurs depends on the location of the lesion in the CNS. A number of drugs have been tried and are currently being studied in relapsing MS. The chronic toxicities of globally immunosuppressive agents such as azathioprine and cyclophosphamide prevent the long-term prophylactic use of these agents for early, mild cases of relapsing-remitting MS.

Treatments Designed to Prevent Onset of the Progressive Phase

A number of clinical studies have demonstrated that the most debilitating and clinically predictable form of the disease is the progressive stage [29, 83]. Although some patients have progressive MS from the onset, the majority enter the progressive phase after a number of relapses. A common pattern is less and less recovery from successive relapses. In addition, increasing frequency of relapses and short intervals between relapses often herald progression [29].

What happens immunologically when the disease moves from the relapsing to the progressive stage? One possibility is that a self-perpetuating immune reaction is established within the CNS. If this were true, it would have important implications for therapy, as it would suggest that once the progressive phase began, treatment would have to be directed at the CNS compartment. However, results from clinical trials and immunological studies suggest that the peripheral immune system plays an important role in the progressive phase of the disease. Specifically, treatment of progressive MS patients with total lymphoid irradiation, a treatment directed only at peripheral immune organs, which spares the neuroaxis, has been found in a double-blind trial to affect the course of the disease favorably [30]. In addition, as mentioned previously, a large number of immunological abnormalities are found in the peripheral blood of MS patients, including the presence of activated T cells and the loss of both phenotypic and functional measures of suppression. These abnormalities are most consistently found in patients with progressive disease. Although these immunological abnormalities could be secondary to the disease process, they add to the weight of evidence that the peripheral immune compartment plays an essential role in chronic progressive MS.

There have been no studies designed with the ex- the relapsing-remitting stage of the disease to prevent the onset of the progressive phase. Ultimately, it seems logical that this must be one of the major goals of MS immunotherapy. The difficulties in carrying out such a trial are twofold: (1) finding an agent that can be administered over the length of time needed to perform such a study which does not have long-term toxicity, and (2) embarking on a large controlled trial in which a minimum of five years would be needed to reach the defined outcome.

Treatment Designed to Halt the Progressive Phase

Although most patients enter the progressive phase following a number of relapses, there is a subcategory of patients whose disease is progressive from the onset [29, 67]. It is not known whether these patients represent a subcategory of disease related to different immunological or other mechanisms or whether they might, in fact, have had subclinical attacks. The following immune mechanisms could be operating: (1) the relapsing-remitting form could involve an autoimmune response against one white-matter antigen, whereas in the progressive phase, a different autoantigen could become the target; (2) with time, a localized immune response in the CNS could be created that might not be antigen specific, that is, it could involve nonspecific activation of immunocompetent cells in the CNS by interleukins; (3) with time, a more consistent defect in immunoregulation could occur in the peripheral immune system; and (4) it is theoretically possible that changes within the nervous system itself could affect immune regulation.

Because of the disabling nature of the progressive disease, several trials have been undertaken and are currently in progress in patients with progressive MS. Although some benefit has been reported with certain agents, the long-term effects of treatment and the potential toxicities associated with these agents should engender caution in their use. Two treatment regimens that have been reported to be of benefit, cyclophosphamide [22, 43, 52, 56, 119] and total lymphoid irradiation [30], illustrate a feature important in designing treatment programs for progressive MS. In both trials, although positive results have been reported, reprogression began within one to three years following initial treatments. These results suggest that once the patient enters the progressive phase, retreatment or some form of maintenance must be added to original induction regimens to maintain clinical effects.

These treatments demonstrate that immunosuppression can indeed affect the course of progressive MS and that patients' conditions are not made worse. This helps support the role of immunopathogenic mechanisms in the disease and provides a rationale for attempting to find an immunospecific, relatively nontoxic form of therapy that can be administered over

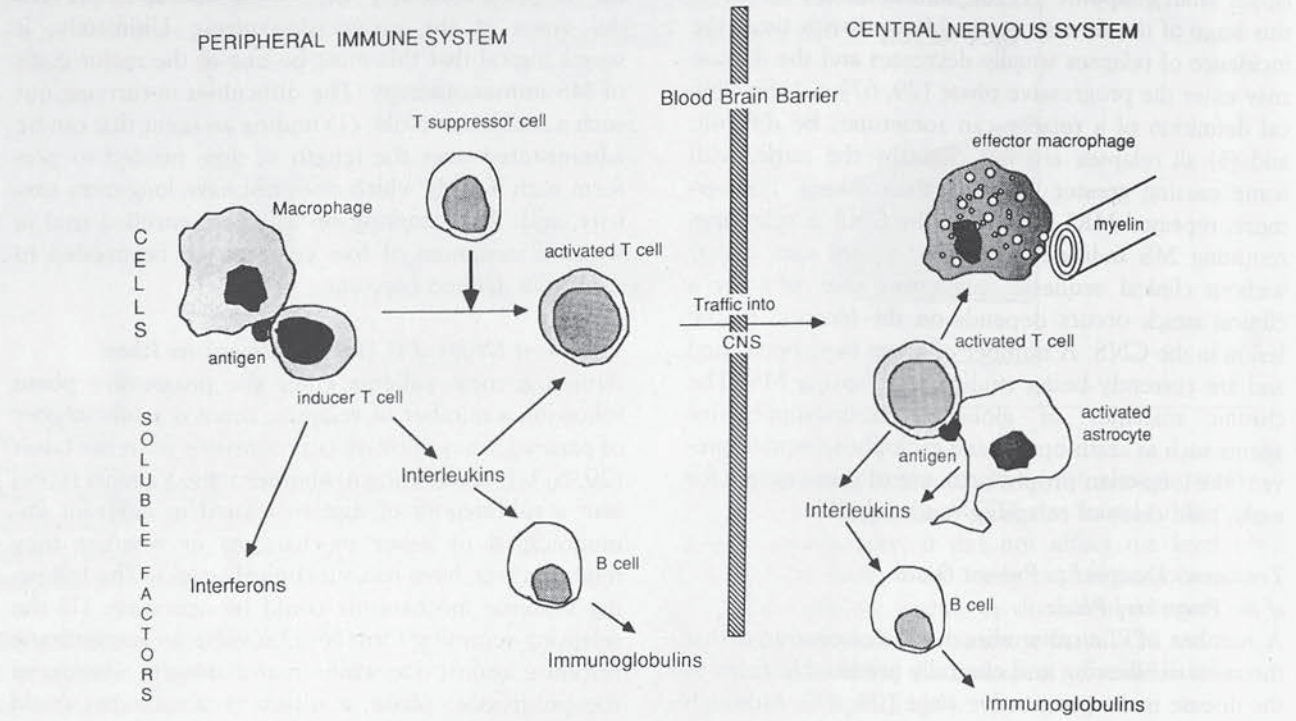

Fig 2. The immune response is initiated in the peripheral immune compartment when antigen is processed and presented to an inducer cell by a macrophage or antigen-presenting cell. The inducer cell becomes activated and releases a number of soluble factors, including interleukins and interferons, which act on both B cells and T cells to augment the immune response. T suppressor cells act to dampen the immune response. Activated T cells traffic into the central nervous system (CNS), where they again release factors, presumably after having antigen presented to them. In this regard, astrocytes are capable of presenting antigens to T cells. Other cellular elements also enter the CNS (macrophages, B cells), where the potential for a local immune response occurs. B cells are known to produce immunoglobulin locally within the CNS, and macrophages function within the CNS to phagocytose myelin, in addition to their antigen-presentation properties.

Treatment of Stable Multiple Sclerosis

The term *stable MS* raises the question of the ability to define when the disease is indeed immunologically quiescent, an ability that we do not currently have. In many instances, it is probable that subclinical disease activity occurs, especially as demonstrated on MRI studies. Patients with stable MS would be candidates for treatment with immunotherapy that could affect the disease process prophylactically, perhaps by adding a specific or nonspecific suppressive influence. More important, a central goal of devising immunotherapy for MS is the ability to identify immunological stability, which first requires an understanding of immune alterations in the disease.

The Normal Immune Response and Strategies of Immunotherapy

The normal immune response [reviewed in 85] consists of a cascade of events, and strategies of immunotherapy are designed to intervene at a number of places in the circuit (Fig 2). The immune response is generated when an antigen is presented to a T cell, or thymus-derived lymphocyte, by an antigen-presenting cell, or macrophage. T cells can only recognize antigen when the antigen is presented to the T cell in the context of particular self proteins that are part of the major histocompatibility complex (MHC) on antigen-presenting cells. T inducer cells (T4+ or CD4+ T cells) recognize antigen only in the context of class II MHC molecules, whereas other T cells (T8+ or CD8+ T cells) are class I restricted. Substances that augment class II MHC expression (such as gamma interferon) augment the immune response. T cells mediate cell-mediated immune responses such as graft rejection and delayed-type hypersensitivity reactions (e.g., sensitivity to poison ivy, tuberculin reactions). In addition, they are the major immunoregulatory cells of the immune system. T inducer (CD4+) cells induce B lymphocytes to produce antibody, as well as inducing other T cells to perform their function. T suppressor cells (CD8+) down-regulate the immune system by suppressing other T cells, although their mechanism(s) of action is unknown. It has recently been shown that the T inducer (CD4+) cells can be separated into inducers of help (CD4+4B4+) and inducers of suppression (CD4+2H4+). The suppressor-inducer (CD4+2H4+) T cell then induces the suppressor CD8+ cell to carry out suppressor function, and it has been reported that the suppressor-inducer cell is reduced in MS [24, 77, 100]. T cytotoxic cells have the ability to lyse other cells. In addition to cellular ele-

ments, there are soluble factors that play a role in the generation of the immune response. These include interleukins, such as IL-1 and IL-2, interferons, and B cell–stimulating factors, which are important in activating cells of the immune system.

In MS, it is assumed that an activated inducer or effector T cell migrates into the nervous system to initiate the disease process. Why this occurs is unknown. Nonetheless, experimental data suggest that for a T cell to migrate into the nervous system it must be activated [121]. The capacity for a localized immune response exists within the nervous system compartment of MS patients, where there are T cells infiltrating lesions and macrophages mediating demyelination, and astrocytes may express class II MHC, thus having the capacity to function as antigen-presenting cells [37]. In addition, it has been known for many years that there is local production of immunoglobulin within the CNS by B cells [39]. Given this cascade of immune reactivity, the following strategies of immunotherapy have been attempted in MS patients or are being planned.

Nonspecific Immunosuppression

Most of the immunosuppressive agents that have been tried in MS patients nonspecifically suppress the immune response [33, 71, 72, 84, 97]. These include drugs such as cyclophosphamide, azathioprine, anti–lymphocyte globulin, and treatments such as plasma exchange, lymphocytapheresis, thoracic duct drainage, and total lymphoid irradiation. Although these drugs and treatments may affect one limb of the immune response over another, they remain relatively nonspecific in their actions.

Generation of a Suppressor Influence

Many investigators feel that the immune system functions on a delicate balance of suppression and help. In MS, there is evidence that there are losses of suppressor influences, both functionally and phenotypically [3, 77, 110]. Thus, the generation of increased functional suppression is an attractive approach for treatment of the disease, although at the present time there are no specific suppressor factors or cellular elements that can be administered to patients. The immunological effects of total lymphoid irradiation result in an increase in functional suppression both by decreasing the number and function of helper T cells and by stimulating the appearance of antigen-nonspecific suppressor cells [106]. Suppressor cells have been shown to play a crucial role in down-regulating EAE [4, 91].

Removing Helper/Inducer Cells

Inducer T cells trigger the immune response and they can be specifically down-regulated using monoclonal antibodies. Monoclonal antibodies against inducer (CD4+) T cells have proven effective in both acute and chronic animal models of EAE [18, 104, 111]. Monoclonal antibodies directed against inducer cells have also been administered in phase one clinical trials in MS patients and have shown suppressive effects [116]. Further trials with anti-CD4 monoclonal antibodies in MS patients are planned.

Manipulation of Activated T Cells

Experimental data suggest that activated T cells traffic to the CNS more efficiently than nonactivated T cells [121], and rapid traffic of T cells to the CNS has been observed in progressive MS [51]. Furthermore, increased numbers of activated cells have been described both in the periphery and in the CNS of MS patients [42, 49, 50, 82]. One strategy of immunotherapy in MS is the elimination of activated T cells. Such therapy would not require knowledge of the specific antigen in MS, if indeed there is one antigen, but would allow the relatively specific removal of activated T cells. Treatment of EAE with monoclonal antibodies directed against activated T cells has been successful [102].

Manipulation of Cells Bearing Class II MHC Molecules

As discussed previously, class II MHC molecules play a crucial role in the generation of immune responses, since antigen is presented to T cells in the context of class II MHC antigens. Increased class II MHC expression results in increased immune responsiveness, with the converse also being true. In fact, a recent trial of gamma interferon, which is known to increase class II MHC expression, resulted in clinical worsening of MS patients [90]. Thus, it would appear that treatments to decrease class II MHC expression might be beneficial in MS. Of note is that corticosteroids, which have been used extensively in the treatment of MS, cause a down-regulation of class II MHC expression [10]. Another experimental approach that has been used successfully in animal models of autoimmunity is the administration of monoclonal antibodies directed against class II MHC antigens, which may have a positive effect by increasing immune suppression [105].

Altering Lymphocyte Traffic

If the progression of MS is linked to the continued trafficking or movement of cells into the CNS, treatments that prevent such traffic might be effective in altering disease progression. Molecules on the surface of immunocompetent cells that are specific for the traffic of cells have been described [60, 80]. Whether unique recognition structures and pathways of traffic into the nervous system exist is not known. However, such an approach could protect the CNS from the influx of the immunocompetent cells without requiring identification of the antigen specificity of the cells. Prazosin, an α_1-adrenergic receptor antagonist, may suppress EAE by altering permeability of CNS vasculature to cells [16]. Heparin has been shown to alter

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