

Suppressing immunity in advancing MS

Too much too late, or too late for much?

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Although no direct evidence exists that the immune system per se initiates the attack on myelin in patients with multiple sclerosis (MS), several observations strongly support this theory. Immune infiltrates are present at the sites of greatest damage; animal models (e.g., experimental autoimmune encephalomyelitis) prove that T cells alone can transfer disease from affected to unaffected animals; and therapies that are aimed at either modulating or suppressing the immune system can reduce disease activity. Pathologically, the destructive process includes not only demyelination, but also the early loss of axons and neurons. It is not known how inflammation leads to loss of neuronal elements but once this loss begins, it becomes a neurodegenerative condition—and may be the ultimate cause of clinical impairment and disability in MS. The effectiveness of a treatment may be dependent on which of the intertwined pathologic processes of immune-mediated inflammation and neurodegeneration predominates in the patient. In some patients, the destructive process ultimately leading to irreversible neurodegeneration arises early, becoming extensive and disabling. More powerful immunosuppression may be warranted in this select group of patients; however, because of the toxicity of these agents, they are often reserved until more advanced disabilities are present, a time when destruction may already be irreversible. It is not yet known whether complete abrogation of the early inflammatory phase of disease will prevent the degeneration of axons and neurons, but this is the rationale often given for early aggressive treatment. In this issue of *Neurology*, Saiz et al. report on their experience with one form of aggressive immunotherapy—high-dose chemotherapy followed by autologous stem cell transplantation.¹

Immunosuppression (e.g., mitoxantrone) has been somewhat effective at slowing down some measures of disease activity (i.e., relapses and MRI), but disabilities continue to accumulate, albeit at a slower rate, perhaps due to the persistence of disease-causing immune

cells. Ridding the body of the disease-causing immune system or immunoablation could in theory prevent the resurgence of disease. Immunoablative therapy followed by syngeneic stem cell transplantation stops relapses in animal models of MS.² Several case reports have described patients with autoimmune diseases going into prolonged periods of remission following bone marrow transplantation for hematologic illnesses, including one patient with chronic myelogenous leukemia and MS.³ These observations led to a number of clinical trials assessing the effects of immunoablation with autologous peripheral blood stem cell support in patients with MS.

Immunoablation followed by stem cell transplantation is a complex therapy involving cytotoxic drugs, biologic agents, and cellular therapy. They are used together to eliminate the disease-causing immune system and reconstitute a naïve and self-tolerant one. Key variables in the success of this treatment include the type and intensity of immunoablative therapy and the nature of the stem cell graft product. The dose and type of cytotoxic drug influence both the success of the immunoablation and the toxicity of the procedure. Clinical experience in transplantation has shown that more aggressive treatments result in greater immunoablation but with a concomitant increase in morbidity and mortality. Even if the immunoablation is complete, immune cells involved in the pathogenesis of MS could be reintroduced through the autologous stem cell graft. Hematopoietic stem cells are collected in a complex mixture of myeloid and lymphoid cells, serving as the seeds of the reconstituted blood and immune systems. The source of the stem cells, the manner of their mobilization, and the method used to remove the immune cells from the graft are critical in determining the success of the therapy. Corporal immunoablation and stem cell grafts free of residual mature immune cells must both be achieved before the success of this therapeutic strategy can be evaluated.

See also page 282

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A number of groups have attempted this combination of high dose chemotherapy with or without radiation for the treatment of MS.⁴⁻⁶ These treated patients were relatively old, with moderately advanced disease (high Expanded Disability Status Scale [EDSS] score), and either continued to progress or were prone to serious infections and complications. These early studies have demonstrated the importance of selecting patients at a stage of their disease most apt to respond to this form of therapy. Equally important is the ability of selected patients to tolerate the rigors of the treatment with minimal complications.

In this issue of *Neurology*, Saiz et al. report on their experience giving high-dose chemotherapy with a T-cell depleted bone marrow-derived autologous graft to 14 patients who were much younger and had less advanced disease (EDSS < 6.5) when compared to the previous reports. They monitored patients neurologically using clinical and MRI measures for 19 to 55 months (median 36). Nearly 86% of the patients were free of progression and 46% were free of any measurable disease activity. However, 4 of 14 (29%) patients continued to have clinical attacks, 3 out of 4 with multiple events. It is unclear whether treatment failures were the result of inadequate dosing of immunoablative drugs or the persistence of disease-causing immune cells in the stem cell graft. Given the evidence for both continued clinical and MRI activity typically associated with inflammation in the patients described here, it may well be that Saiz et al. did not go far enough in terms of immunoablation.

The rationale for examining immunoablative therapy for early aggressive MS is still strong. Ideally, a significant change in inflammatory activity (i.e., clinical relapses, enhancing MRI lesions) and in the rate of neurodegeneration (progressive neurologic impairment) would have to be demonstrated given the sub-

stantial toxicity associated with aggressive immunoablation. Can the complete interruption of the inflammatory process with immunoablation be expected to completely halt the progressive accumulation of neurologic impairment or simply slow it down? Will eliminating inflammation stop further deterioration when it is due to inflammation-induced neurodegeneration? The intricacies of patient and treatment variables preclude definitive answers to these questions at the present time. Progress toward selecting the best patients, the best method of immunoablation, the best transplant technology, and the optimal timing of this intervention in the course of MS will come from carefully documenting the clinical, radiologic, and immunologic changes in well-characterized patients enrolled in phase II trials. Only when these variables are optimized will it be possible to truly test the effectiveness of immunoablation in altering the course of MS.

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