Immunotherapy for Multiple Sclerosis
A Review of the Clinical Experience

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Summary

Multiple sclerosis is the most common cause of non-traumatic neurological disability affecting young adults in the northern hemisphere. Recent technological advances in immunology, molecular biology and neuroimaging have accelerated our understanding of the pathogenesis of this disorder. Improvements in clinical trial methodology will soon allow researchers to test therapeutic agents in a fraction of the time traditionally required to study therapeutic claims in multiple sclerosis. The recent approval of interferon beta-1b by the US Food and Drug Administration has already had a profound effect on clinical trials in progress and on the manner in which neurologists in the US treat multiple sclerosis outside the confines of clinical trials. It will certainly be difficult to perform placebo-controlled clinical trials in the future.

In light of these recent advances, we review the clinical experience of immunosuppressive and immunomodulatory therapies that have progressed beyond the pilot stage of testing. These therapies include azathioprine, copolymer I, corticosteroids, cyclophosphamide, cyclosporin, interferon-β, plasma exchange and total lymphoid irradiation. For each therapy a discussion of the potential mechanism of action is followed by a critical review of the pertinent clinical experience. Each section concludes with a commentary regarding the potential or proven risks and benefits of each therapy.
Multiple sclerosis is the most common cause of nontraumatic disability affecting young adults. There are approximately 350,000 existing cases and nearly 10,000 new cases diagnosed annually in the USA.

The clinical course of multiple sclerosis is highly unpredictable. In its most classical form it is characterised by rapid deterioration of neurological function subserved by white matter tracts (exacerbating or relapsing disease) followed by complete or partial improvement over days to weeks (remitting disease). After a variable interval of years, patients tend to worsen slowly between exacerbations (exacerbating/progressive disease) or worsen without further distinct exacerbations (chronic progressive disease).

Approximately 10 to 15% of patients experience a progressive course from onset without ever experiencing an exacerbation. Disease in these patients is termed primary progressive. As befits the unpredictable nature of multiple sclerosis, patients frequently experience long intervals of spontaneous stabilization between exacerbations or periods of steady progression.

The pathogenesis of multiple sclerosis remains unclear. A disturbance of normal immune system function was suspected for many years because of the disease's clinical course, the presence of elevated levels of immunoglobulins of restricted heterogeneity in the cerebrospinal fluid (oligoclonal bands) and the histopathological features of a perivascular cell-mediated immune response within well-demarcated areas of demyelination (plaques).

Unfortunately, the initial animal model for multiple sclerosis, experimental allergic encephalomyelitis (EAE), presented several problems for those who held multiple sclerosis to be a disease resulting from a disturbance of immune function. Specifically, classic EAE, unlike multiple sclerosis, is a monophasic disorder. Furthermore, the pathology of the two conditions is dissimilar.

The subsequent development of chronic models of EAE with a histopathology showing significant demyelination provided more cogent support for the autoimmune hypothesis. Nevertheless, even chronic forms of EAE are an imperfect and artificial model for multiple sclerosis. For instance, EAE is characteristically produced in inbred animal species and has a consistent immunopathogenesis. In contrast, human genetics is far more complex and it has never been clear that the immunopathogenesis of multiple sclerosis is similar in all patients. As an example, primary progressive forms of multiple sclerosis appear to have distinct clinical, imaging, epidemiological and immunogenetic characteristics when compared with classical exacerbating and secondary progressive forms of multiple sclerosis.

Despite these difficulties, significant evidence has accumulated that points to an alteration of normal immune system function in the pathogenesis of multiple sclerosis. This evidence includes:

- A characteristic distribution of interleukins, interferons, tumour necrosis factor and T cell subsets within acute and chronic multiple sclerosis plaques, suggesting an immune system role in plaque formation.
- An association of disease frequency with specific HLA-DR haplotypes in several different ethnic groups, and a susceptibility locus linked to the T cell receptor β-chain complex using analysis of affected sibling pairs.
- A diminished suppressor T cell number and function and a possible correlation of these abnormalities with disease activity.
- A transient benefit seen with immunosuppressive therapy.
- A clinical worsening seen with interferon-γ (IFN-γ).

This accumulating research has been interpreted to mean that multiple sclerosis is the result of organ-specific autoimmunity initiated and perpetuated by immune dysregulation in a genetically susceptible host.

Initial efforts in the field of immunotherapy for multiple sclerosis were influenced by the observation, mentioned above, of a defect in the suppressor T cell population of the immune system. This defect might result in immune system overactiv-