Prospects for T Cell Vaccination in Multiple Sclerosis

Robert Medaer, Piet Stinissen, Jingwu Zhang and Jef Raus
Dr L Willems-Instituut and Limburgs Universitair Centrum, Diepenbeek, Belgium

Summary

Accumulating evidence indicates that multiple sclerosis, a chronic inflammatory disease of the central nervous system, has an autoimmune origin. Since T cells reactive to myelin basic protein (MBP) are thought to play an important role in the pathogenesis of this disease, it was assumed that inactivation or depletion of this pathogenic T cell subset may have therapeutic effects in multiple sclerosis. We have recently reported that T cell vaccination, i.e. immunisation with attenuated autologous MBP-reactive T cell clones, leads to the depletion of the MBP-reactive T cells. Furthermore, this approach induced favourable clinical effects in the treated patients, encouraging further studies of T cell vaccination in multiple sclerosis.

Recent advances in immunology and molecular biology have contributed to the increased effectiveness of vaccines for various classical infectious disease targets. In addition, these technologies are currently applied to design vaccination strategies for the treatment of cancer and autoimmune disorders. In these applications, vaccination makes use of the patient’s immune system to target tumour cells or autoreactive lymphocytes, respectively. Vaccination with autoreactive T cells was proven to be an effective treatment in several experimental autoimmune diseases, including animal models of rheumatoid arthritis, multiple sclerosis and insulin-dependent diabetes mellitus. Since no effective cure is currently available for these disorders, the results of the preliminary human trials are subject to intense interest. In this article, we will overview the data from our pilot study with T cell vaccination in multiple sclerosis and discuss the relevance of this trial for future studies of T cell vaccination.

1. Pathogenesis of Inflammatory Demyelination

Multiple sclerosis is a prototype of an inflammatory demyelinating disease of the central nervous system (CNS). Multiple sclerosis is thought to result from aberrant immune responses to myelin, and possibly non-myelin, self-antigens. Accumulating evidence suggests that multiple sclerosis is a predominantly T cell–mediated autoimmune disorder. Autoreactive T cells specific for a number of CNS antigens have been observed in multiple sclerosis patients. T cells with specificity for myelin basic protein (MBP) are clonally expanded and activated in multiple sclerosis. Based on the current data, multiple sclerosis is considered to result from the peripheral activation of myelin-reactive T cells by viral crossreactive epitopes or superantigens. Upon activation, these autoreactive T cells may migrate to the CNS, where they could trigger an inflammatory cascade, ultimately leading to demyelination.

2. The T Cell Receptor as a Target for Vaccination

Although the pathogenesis of multiple sclerosis is not well understood, autoreactive T cell responses to candidate myelin antigens, such as
MBP, are thought to play an important role in the initiation of autoimmune processes. Perhaps the best evidence in support of this includes: (i) the high frequency of activated MBP- and proteolipid protein (PLP)-reactive T cells in multiple sclerosis patients compared with healthy controls; (ii) the accumulation of these myelin-reactive T cells in the cerebrospinal fluid of multiple sclerosis patients; and (iii) their clonal expansion pattern, both in the periphery and in the CNS of multiple sclerosis patients (reviewed by Stinissen et al.[11]). These lines of evidence suggest, but do not prove, the pathological relevance of myelin-autoreactive T cells in the pathogenesis of multiple sclerosis.

Based on these data, several therapeutic strategies were designed to inactivate or deplete these autoreactive T cells.[7] One of these approaches is T cell vaccination.

The concept of T cell vaccination comes from studies in the animal model of multiple sclerosis. Experimental allergic encephalomyelitis (EAE) shares many clinical and histopathological features with multiple sclerosis, and is experimentally induced by immunisation with myelin or myelin fragments. Furthermore, the disease can be transferred to naïve animals by activated myelin-reactive T cells, which indicates that CD4+ T cells are the inducers of EAE (reviewed by Zamvil & Steinman[8]). Interestingly, when these animals are immunised with attenuated activated MBP-reactive T cells, they are protected against subsequent disease induction.[9] This method was termed T cell vaccination, by analogy with traditional microbial vaccinations.

Further experiments showed that EAE can also be treated by T cell vaccination. Resistance to the disease following T cell vaccination was found to be transferable by T cells induced in the vaccinated recipients. This indicated that T cell vaccination activates T cells in the recipient capable of regulating the autoimmune T cells that cause the disease. T cell vaccination is probably directed to the T cell receptors of the T cells that are present in the vaccine.[10] This theory was strengthened by the observation that peptides from the T cell receptors of MBP-specific T cells could induce resistance to EAE.[11] Anti-idiotypic T cell clones were isolated following T cell vaccination and anti-idiotypic T cells were found to mediate resistance to EAE.[10,12]

3. Trial of T Cell Vaccination in Patients with Multiple Sclerosis

Based on the potential pathogenic role of MBP-reactive T cells in multiple sclerosis, and on the successful application of T cell vaccination in the EAE model, we initiated a pilot trial of T cell vaccination in multiple sclerosis. Eight patients with multiple sclerosis (relapsing-remitting and chronic progressive) were vaccinated with irradiated autologous MBP-reactive T cell clones that had been generated from their own blood. Selected MBP-reactive T cell clones were activated in vitro and irradiated to render them incapable of proliferation. Each recipient received a total of three subcutaneous injections of 2 to 4 clones (15 × 10⁶ cells for each clone) at intervals of 2 to 4 months. The protocol of our vaccination trial was shown to be acceptable and technically feasible.[13]

Subcutaneous inoculations of autologous vaccine clones are well tolerated and cause no adverse effects. Administration of the vaccines induced substantial anticonalotypic T cell responses specifically to the vaccine clones, which were accompanied by a specific depletion of circulating MBP-reactive T cells in all recipients.[13] These responses were characterised by a boosting effect after each vaccination. The in vivo depletion of MBP-reactive T cells appears to be the direct effect of anti-clonotypic T cells, since CD8+ anticonalotypic T cell lines isolated from the vaccinated patients specifically lyse the autologous vaccine clones in an MHC class I restricted fashion. This study confirmed for the first time in a clinical setting that T cell vaccination can be used to boost clonotypic regulatory T cells leading to the specific depletion of pathologically relevant autoreactive T cells.

We have recently demonstrated that significant anticonalotypic T cell responses to the vaccine cells are still present 1 to 3 years after vaccination.[14]