Delivery of Myelin Peptides through The First Line of Defense, Skin, to Counter Autoimmunity in Multiple Sclerosis

Military metaphors provide a convenient way to help understand the powerful and exciting new therapies for relapsing remitting multiple sclerosis (RRMS). In fact, military language is highly relevant for describing the immune system, our physiological defense force that when functioning normally protects us from harmful microbes and engages in surveillance against malignancies. A key first line of immune defense is our skin. In this month’s Annals, Jurynczyk and colleagues\(^1\) show how that key defense line can be used to help regulate an aberrant immune response in multiple sclerosis (MS). One of the main characteristics of MS pathology is the immune system’s “friendly fire,” which mistakenly targets self-antigens, in this case myelin.\(^2\) The transdermal delivery of myelin peptides was shown to induce immune tolerance regulation or tolerance, in order to achieve a “cease fire” in those immune responses to myelin seen in MS.

Such an approach stands in stark contrast to the types of strategies seen these days in many successful phase 2 and phase 3 trials in RRMS. Most of these trials involve administration of a molecule that inhibits a major immune function and often eliminates a wide swath of immune cells. Such strong weapons frequently make the individual with MS who is under treatment, lymphopenic, or even severely depleted in 1 or more of the major immune cell populations. Perhaps a more sensible approach is contained within the tactics employed by Jurynczyk and colleagues,\(^1\) in which the investigators attempted to induce regulatory control of autoimmunity without major impairment of the normal functions of the immune system.

Current approaches that show greatest promise for treating the inflammation associated with MS use heavy weaponry: For example, Rituximab and Alemuzumab, two monoclonal antibodies that reduce relapse rate,\(^3,4\) were first developed and approved for their activities in combating lymphoid malignancies.\(^5\) These monoclonal antibodies deplete critical components of the immune system. Rituximab, which depletes CD20 B cells,\(^3\) is approved for treatment of B cell lymphoma, while Alemuzumab depletes cells bearing CD52,\(^4\) found on T cells, B cells, and other monocyteid cells and is approved for chronic lymphocytic leukemia. Another small-molecule drug, Cladribine, a purine analog used for hairy cell leukemia\(^6\) that kills T cells and B cells, also reduces MS relapse rate\(^7\) and is being reviewed by the U.S. Food and Drug Administration (FDA) for approval. One needs T cells and B cells for normal immune function.

The metaphor of “heavy weaponry” can be applied to most of today’s experimental drugs for RRMS, as well as to an approved therapeutic. For example, Natalizumab blocks lymphocyte migration into the brain,\(^8\) while Fingolimod inhibits lymphocyte egress from regional lymph nodes.\(^9\) Both drugs exemplify a strategy to interdict the movement of immune cells to the target in the central nervous system. Natalizumab blocks lymphocyte homing to the brain via blockade of a\(_4\) integrin,\(^8\) while Fingolimod blocks lymphocyte egress from lymph nodes by targeting the sphingosine phosphate 1 receptor.\(^9\) Lymphocytes, in order to guard against infection, must have the capabilities of a mobile force, so they can patrol distant tissues like the brain. Mobility and surveillance is key for protection against dormant viruses in the brain that reside in the central nervous system. While inhibition of homing to brain may be beneficial for reducing inflammation inside the brain, there is a real risk that inhibition of surveillance will lead to opportunistic infections. Of course this has been seen most dramatically in the case of Natalizumab, in which prolonged use beyond 2 years is associated with rates of progressive multifocal leukoencephalopathy (PML) approaching 1 in 500. In contrast to these “big guns,” which aim to impair wide swaths of the immune system, the induction of antigen-specific tolerance or regulation has not received much attention for treatment of RRMS.

In this month’s Annals, Jurynczyk and colleagues\(^1\) have attempted to induce a form of regulation that would target only a small part of the immune system: those cells directed to making autoimmune responses to components of the myelin sheath. The success of this approach, whereby self-antigens are delivered transdermally to induce immune tolerance, would amount to the
use of a truly “smart weapon”—a weapon that would only regulate the pathological immune responses, while leaving the rest of the immune system intact. Such a pursuit to find a drug that targets only the pathology and leaves one’s normal physiology intact has been associated with an enchanting term, again taken from the realm of weaponry—the “magic bullet.” A therapy which achieves specific immune tolerance would truly constitute a magic bullet, a term attributed to Paul Ehrlich 150 years ago. Ironically the term magic bullet has often been applied to describe that magnificent twentieth-century invention: the monoclonal antibody. Unfortunately, although monoclonal antibodies can have bullet-like precision, current MS approaches involve monoclonal antibodies that delete large populations of essential components of the immune system, such as T cells and B cells.

Jurynczyk and colleagues 1 attempted to induce immune regulation to disable only a small part of the immune system, those cells directed to making autoimmune responses to components of the myelin sheath. They applied peptides that are targets of the immune response from 3 myelin proteins—proteolipid protein (PLP), myelin basic protein (MBP), and myelin oligodendrocyte glycoprotein (MOG)—to patches for transdermal delivery. The patch was changed weekly in the first month and then monthly for the remainder of the year. The clinical trial had a placebo control group. Biopsies showed that Langerhan’s cell was activated in skin, and that granular-appearing dendritic cells appeared in the draining lymph node of patients receiving the myelin peptides on patches.

In the trial, T cells in the blood were isolated and those individuals who were exposed to the myelin peptides via the patch showed reduced proliferation to myelin peptides, as well as diminished production of gamma interferon production in these cells. Interferon gamma is associated with MS pathology; worsening of disease upon administration of this cytokine was seen in small trials over 20 years ago. 10 Administration of myelin peptides via the patch was also associated with increased production of the cytokine interleukin (IL)-10 in myelin reactive T cells. IL-10 is regarded as a cytokine imbued with regulatory properties that suppress the activity of pathogenic gamma interferon–producing T cells. Certain populations of Langerhan’s cells and dendritic cells, both potent antigen-presenting cells (APCs), are capable of promoting development of anti-inflammatory IL-10–producing and regulatory T cells (Tregs). 11 This raises the possibility that transdermally-applied myelin peptides may mediate T cell regulation via its effects through these APCs. Though the work is in the early stage, and was performed on 30 patients, the current conclusions indicate that an anti-inflammatory regulatory cell that suppresses autoimmune responses to myelin has been induced. In moving forward, it will be important to determine by magnetic resonance imaging (MRI) in clinical trials whether transdermal dermal delivery of myelin peptides also reduces clinical relapse rate and development of MS lesions. Such information will be disclosed soon, and we await those results with optimistic expectations.

Antigen-specific regulation—or tolerance, as it is often described in immunological parlance—is a goal that only a few groups are currently pursuing. Notably, a phase 3 trial in which a single MBP peptide was administered intravenously to individuals with secondary progressive MS failed to show any benefit. 12 The study here used this same peptide from MBP as well as peptides from PLP and MOG. The immune response in MS is highly diverse, with T cell and antibody responses against a wide spectrum of myelin proteins and myelin lipids, as well as proteins and lipids found on neurons. Immunological strategies must take into account the diversity of the immune attack in MS. Strategies aimed at targeting a single peptide of 1 myelin protein may be inadequate. In this regard, it is recognized that CD4+ T cells from MS patients also recognize other peptides of MBP and PLP than those that were used in this trial. In general, T cell responses to individual myelin peptides are genetically determined by expression of a variety of different human leukocyte antigen locus D (HLA-D) molecules. Thus, in future clinical studies it may be important to examine individual patients’ HLA genotypes at the time of enrollment to determine whether they express the HLA-D proteins associated with T cell recognition of the myelin peptides tested.

At least 3 other groups are pursuing antigen-specific therapy of MS. Wraith 13 and colleagues are delivering soluble peptides from 4 regions of MBP intradermally. Phase 1 studies have been completed with this product in SPMS. Turley and Miller 14 are coupling multiple peptides from different myelin proteins covalently to lymphocytes and then reinfusing them to attempt myelin-specific tolerance in individuals with RRMS. Garren and colleagues 15 reported in Annals on a different approach using a specially engineered DNA vaccine encoding full-length MBP. In a phase 2 trial, reductions in antibodies to various myelin proteins were reported in the cerebrospinal fluid (CSF) at the 0.5-mg dose, providing evidence of induction of immune tolerance to myelin.

For now, the heavy weapons targeting major components of the immune system are receiving the greatest amount of attention, based on their indications of strong efficacy. Determining whether these approaches can be used chronically is going to be a challenge. If these approaches are going to be used chronically in individuals with MS, inadequate immune surveillance over long periods of time may lead to serious opportunistic infections and cancer. We have already seen over 60 cases of PML since Natalizumab has been approved for RRMS.

A reasonable approach might be to use these heavy weapons to achieve a remission, a cease-fire, so
to speak, and then to rely on approaches involving regulation of those unwanted immune responses to myelin. The work by Jurynczyk and colleagues provides such a strategy to controlling autoimmunity in patients with MS.

**Potential Conflicts of Interest**

Nothing to report.

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**References**


DOI: 10.1002/ana.22255

November, 2010 569