

Advances in Multiple Sclerosis

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There are an increasing number of new drugs in the treatment of multiple sclerosis (MS). These new treatments along with the use of the older disease modifying drugs provide the neurologist with an increasing number of options in treatment of MS patients. These treatments have also contributed to the better understanding of the underlying immunopathology of the disease.

Keywords

Multiple sclerosis, treatment, immunopathology

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Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system (CNS), mainly affecting young people. An increasing number of disease modifying treatments (DMTs) is currently available, aiming to control the disease activity, i.e., the inflammatory demyelinating attacks in the CNS parenchyma clinically expressed as relapses and the ongoing disability progression. Thanks to the progress that has been made in MS treatment, from the first immunomodulatory agents to the use of various monoclonal antibodies, much of the underlying immunopathology that would otherwise not be identified has been unmasked.¹

Most importantly, it has become clear that MS is a chronic multicellular disease where the role of a number cells has been identified. In particular, antigen presenting, Th1, Th17, T, B and regulatory cells may participate in the ongoing immunopathology leading to axonal injury and nerve cell death.¹ Moreover, CNS microglia and astrocytes have also a crucial role in the ongoing demyelination and axonal injury.^{2,3} In addition, CNS neural precursor cells (NPCs) are able to migrate and differentiate toward glial cells thus contributing to the remyelination process. However, these cells are no more able to differentiate particularly during the chronic stages of the disease.⁴ Thus, efforts to increase the function of the endogenous NPCs may be of benefit for the protection of axons.

The vast majority of DMTs target the activation of adaptive immunity, particularly the T cells and concomitant T cell-related immune reactions. However, there is increasing evidence that B cells are also important players in the underlying immunopathology of the disease, as indicated by the presence of plasma cells, myelin-specific antibodies and, to a lesser extent, B cells in both chronic MS plaques and acute MS lesions. In addition, the presence of immunoglobulin in MS CNS tissues, lymphoid-like tissues in MS CNS, B cells and plasma cells in MS cerebrospinal fluid (CSF), immunoglobulin in CSF and autoantibodies targeting myelin proteins in of MS patients highlight B-cell involvement in MS immunopathology.⁵ It has long ago been shown that the presence of B cells characterises the subtype II MS lesions, which benefit from plasmapheresis. B cells can contribute to the pathogenesis of MS through cytokine production, antigen presentation and formation of autoantibodies. T and B cells do not function independently. B cells can activate autoreactive T cells; in return, T cells signal to B cells to enable maturation to plasma cells, which produce highly specific antibodies.⁶

These findings indicate the importance of targeting B cells in order to control the disease activity. Interestingly enough, there is some evidence that even currently available DMTs have some effect on B cells, thus resulting in a shift in circulating B cell immunophenotypes, thus increasing the relative frequency of immature and naive B cells, decreasing the proportion of memory B cells, increased B cell production of interleukin-10 (IL-10) with concurrent suppression of proinflammatory cytokine secretion. B cells from DMT-treated patients are generally less able to support a proinflammatory T cell response.⁷

There is also increasing recent evidence that DMTs targeting exclusively CD-20 on B cells are able to control MS relapses and ongoing disability progression, even in progressive forms of the disease.⁸ Evidently, despite the enrichment of our armamentarium to control MS, there is much concern in which cases should the anti-B cell treatment be used and what the biomarkers indicating the predominant activity in an individual case might be. Most importantly, long-term

safety data are still missing, thus indicating a careful use of these drugs, whenever available in everyday clinical practice.⁹

Despite the use of sophisticated DMTs targeting the immune components of the underlying disease immunopathology, an effective control of the ongoing neurodegeneration and therefore disability progression is still missing. The vast majority of the relapsing remitting MS (RRMS) patients will finally enter the progressive phase of the disease, the so-called secondary progressive (SPMS) phase. Currently used DMTs may delay, though not halt, the progression of disability.¹⁰ However, it should be emphasised that even if only the major treatment target of DMTs, i.e., activation of adaptive immunity and the concomitant relapses, is considered, the use of DMTs is invaluable, particularly taking into account the impact each single relapse may have on the patient's quality of life.¹¹

A crucial issue for the treatment of MS is the early initiation of treatment as soon as the diagnosis is established,¹² and presumably the early escalation of treatment whenever the patient is not responding to the administered DMT. The choice of induction, rather than an escalation treatment at the time of diagnosis is under debate. However, induction therapy may be a first choice of treatment when a very active, fulminant MS case is considered.¹³ Currently used criteria to evaluate the response to treatment include the annual relapse rate (ARR), magnetic resonance imaging (MRI) activity¹⁴ and Expanded Disability Status Scale (EDSS)¹⁵ at a certain time point under an individual DMT. The absence of specific biomarkers for longitudinal assessment of disease progression has led to the introduction of "no evidence of disease activity" (NEDA) by

evaluating the ARR, EDSS progression and MRI scan activity (NEDA-3) whereas the brain volume loss measurement has also been recently suggested as a prognostic factor (NEDA-4).¹⁶ However, there is some criticism of the value these measurements may have either due to practical reasons during the every day clinical practice, the absence of cognitive dysfunction as an indicator of disability or the fact that NEDA as a treatment goal may be reached by less than half of all patients and is not sustained over time.¹⁷ Evidently, newer assessments even on top the traditional ones, are needed.¹⁸

Interestingly enough, the concept of "confirmed disability improvement" (CDI) has recently been introduced as an outcome measure in the long-term. CDI describes an improvement in a patient's preexisting EDSS score, maintained over a specified period of time.¹⁹ CDI is not a commonly used endpoint in MS clinical trials, but has been reported from some recent studies.²⁰ By requiring confirmation of EDSS change, CDI is resistant to the transient fluctuations that may affect single-time-point analyses and captures an improvement in disability of sufficient magnitude and persistence to qualify as a meaningful change.²¹

It is quite evident that we are entering a very interesting era, with many new drugs in the treatment of MS and new knowledge on the immunopathology of the disease. The challenge for doctors is the appropriate use of all the drugs available on an individual basis, aiming to provide our patients with a better quality of life. To achieve this goal, clinical evaluation and close monitoring of both the efficacy and safety of currently available DMTs and those to come must remain the gold standard in MS management and treatment. □

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