

Immunomodulation in multiple sclerosis: promises and pitfalls

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Multiple sclerosis (MS) afflicts about 2.5 million people globally and poses a major personal and socioeconomic burden. The recognition of MS as an inflammatory disease, characterized by infiltration of immune cells into the central nervous system, has spurred research into the autoimmune etiology of the condition and has provided the rationale for its treatment through immunomodulation. Experience with immunotherapies in MS to date has suggested a disparity between the observed immune cell infiltration and the progressive loss of neurons. However, recent clinical efforts are providing new insights into progressive MS that once again place the immune system at center stage. This article reviews the main mechanisms of MS immunopathogenesis, and the benefits, risks and challenges of immunomodulatory treatments for the disease.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the brain and spinal cord, and is one of the top causes of serious physical disability in young adults. The condition often affects women and the average age of onset is 30 years, with approximately half of patients needing permanent wheelchair use within 25 years of their diagnosis. Although motor impairment is typical of MS, the symptomatology of the disease can be very heterogeneous. Other common clinical manifestations include visual disturbances - which are often amongst the first signs of the disease - as well as sensory problems, urinary issues, pain, fatigue and cognitive impairment [1].

The disease course of MS is also variable, but broadly discernible patterns in the development of the condition over time have led to the categorization of patients into three main types. Approximately 85% of patients have relapsing-remitting MS (RRMS) whereby an initial neurological dysfunction event is followed by bouts of remission and relapse. Relapses coincide with the presence of inflammatory, demyelinating lesions within the CNS and are detectable by magnetic resonance imaging (MRI). These lesions are a hallmark of the disorder and arise due to the infiltration of peripheral immune cells into the brain and spinal cord [2]. As disability accumulates periods of remission become less pronounced, and eventually some 80% of patients develop secondary progressive MS (SPMS), which is characterized not by immune cell infiltration but by continual, irreversible neurological decline, a reduction in brain volume and axonal loss. Approximately 10-15% of MS patients are diagnosed with a primary progressive (PPMS) form of the disease; these patients have no relapses and instead display only progressive neurological decline [1].

Given the prominent immune cell infiltration observed in the majority of MS patients, the capacity to modulate these cells to reduce inflammatory attacks in the CNS has provided a tangible therapeutic target. Clinical experience amassed from more than two decades using immunotherapies in MS has demonstrated the benefits of reducing relapse rates on patient welfare, although drug efficacy can be offset by an increased risk of serious side effects. The use of immunomodulatory treatments has also revealed substantial insight into MS pathogenesis: chiefly that reducing relapses does not halt progressive disease, which may instead require direct targeting of neurodegenerative processes occurring independently of immune attacks in later stages [3]. Intriguingly, however, the CD20⁺ B-cell depleting drug ocrelizumab has now been reported to lower rates of clinical and MRI-ascertained progression of PPMS [4••]. This result is once again changing our perception of MS etiology as it indicates that immune cells help to drive a seemingly less inflammatory form of the disease, and it suggests that continued research into the immunopathological mechanisms underlying MS provides a prospect for further improvements in healthcare provision to patients in the future.

The immunopathogenesis of MS

MS arises in individuals with a background of genetic predisposition, with environmental factors and stochastic events ultimately triggering the disease. The strongest genetic determinant is the human leukocyte antigen (*HLA*)-*DRB1**15:01 allele, which likely defines the CNS specificity of the condition, whilst the more than

100 non-HLA associated loci may function to alter immune cell activation thresholds in a non-antigen-specific fashion [5,6] - for example, by influencing immune genes involved in cytokine signaling [7-12]. Of the many potential environmental contributors to disease development, Epstein-Barr virus (EBV) infection is the one of the most robustly confirmed robustly correlated risk factors [13,14], although its putative precise role in MS initiation is still an enigma and it is unclear if correlations between MS and EBV infection [15], EBV-dependent infectious mononucleosis [16] and anti-EBV antigen antibody titers [17] are due to a causal link or demarcate an MS-prone immune system. Postulated mechanisms by which EBV might promote disease development include EBV-infected autoreactive B cells in the CNS producing autoantibodies and activating autoreactive T cells [18], possibly through molecular mimicry between EBV- and myelin protein-derived antigens [19,20], or EBV-infected cells in the periphery or the CNS causing bystander activation [21].

Regardless of the exact events that trigger MS, peripheral immune cells become mobilized to enter the CNS through the leaky blood-brain barrier (BBB), the subarachnoid space or the blood-CSF barrier, and acute lesions display a high content of macrophages and CD8⁺ T cells, and to a lesser extent CD4⁺ T cells, B cells and plasma cells. Demyelination is largely localized to these focal lesions in early RRMS, such that other areas of the white matter appear normal. However, over time, T and B cell infiltration becomes more diffuse, and axonal injury is more widespread, leading to both white and grey matter atrophy [22]. As the disease progresses, invasion by peripheral immune cells wanes. Inflammatory processes are instead predominantly driven by the action of the CNS-resident innate microglia cells, and there is also some evidence that in SPMS meningeal lymphoid-like structures may form and contribute to late-stage inflammation [23].

The risk-benefit balance of immunomodulation in MS

There are currently ten-eleven drugs approved for the treatment of MS (Table 1), all of which have an immunomodulatory action and serve to keep the immune system at bay: there is little evidence that any of these drugs have a direct impact within the CNS (Figure 1). Since the early to mid 1990s, interferon (IFN)- β and glatiramer acetate (GA) have been used as first-line disease-modifying drugs for RRMS. IFN- β is thought to reduce BBB permeability and inhibit autoreactive T cells, potentially by skewing differentiation towards a CD4⁺ T helper cell type (T_H) 2 phenotype, and an antiviral effect has been postulated but remains controversial [24]. Several mechanisms of action have also been proposed for GA, including modulation of

antigen-presenting cells, the T_H1 - T_H2 axis, and regulatory T cells to inhibit effector function [25-27]. Both IFN- β and GA have relatively good safety profiles, they reduce relapses by ~30%, and their effects on patient disability are maintained and are cost-effective for at least a five-year period [28•,29]. However, both show efficacy in only a proportion of RRMS patients, potentially because of genetic or other factors [30], whilst some patients become refractory to treatment, for example due to the development of neutralizing antibodies [31].

Teriflunomide was approved as a first-line oral therapy for RRMS in 2012, and as for IFN- β and GA, it has a moderate efficacy in MS [32]. It acts to inhibit pyrimidine nucleotide synthesis thereby blocking the proliferation of activated T cells [33], but safety concerns include teratogenicity and toxicity. Cladribine, a short-course oral therapeutic that also acts by inhibiting DNA synthesis, has received marketing authorization from the European Commission in August 2017, for treating highly active relapsing MS. This drug has a high efficacy [34], and side effects noted to date include opportunistic infections, particularly with herpes viruses. Dimethyl fumarate (DMF), ~~is also~~ a first-line oral RRMS drug approved in 2013, has with a moderate to high efficacy [35], but can lead to lymphopenia. DMF likely exerts its effect by altering dendritic cell activation, T_H cell differentiation, and regulatory B cell induction, and its anti-oxidative impact may even have directly neuroprotective properties [36].

Patients are switched to second-line disease-modifying therapies if they are not responding to first-line drugs, have RRMS with two or more disabling relapses per year or have progressive disease with relapses or an active MRI scan. Second-line drugs approved for MS include mitoxantrone, natalizumab, fingolimod, alemtuzumab, and daclizumab. Mitoxantrone is the first cytotoxic immunosuppressant licensed for SPMS [37]. It functions to reduce lymphocyte numbers, but longer-term use can lead to cardiotoxicity and malignancies. Natalizumab is a blocking antibody that prevents leukocytes from crossing the BBB by binding to integrin VLA-4, and it can reduce the annualized relapse rate by almost 70% [38]. The trade-off of this high efficacy, however, was the development of progressive multifocal encephalopathy (PML): a serious opportunistic infection in which the JC virus causes acute oligodendrocyte destruction in the CNS. Up until 2005 the incidence of natalizumab-dependent PML was ~1 in 1,000 patients, but comprehensive efforts for improved risk management have led to specific drug administration guidelines that limit the duration of natalizumab treatment to prevent PML [39]. A few cases of PML have also been reported in DMF- and fingolimod-treated patients. Like natalizumab, fingolimod

prevents leukocyte entry into the CNS, but it mediates this by blocking sphingosine-1-phosphate-dependent lymphocyte egress from secondary lymphoid organs [40].

Alemtuzumab is an antibody that binds CD52 expressed on all leukocytes, and promotes the depletion of large proportions of T and B cells - including pathogenic effectors - then leading to reconstitution with cells with a different repertoire. Despite its efficacy [41], 30-40% of alemtuzumab-treated MS patients develop secondary autoimmune disorders, including autoimmune thyroid disease, immune thrombocytopenia, Goodpasture syndrome, and secondary CNS disease [42,43•,44•,45]. A more extreme reconstitution and re-setting of the immune system is achievable through autologous CD34⁺ hematopoietic stem cell transplantation (AHSCT), whereby immune cells are eliminated by chemotherapy, and re-established by the transplantation of autologous stem cells harvested prior to immunoablation [46]. In trials to date AHSCT can suppress MS for 4-5 years in over 70% patients, and primarily benefits young patients with active disease and in which irreversible CNS damage has not yet accumulated. Given the immunosuppression conferred by AHSCT, side effects include infection and viral reactivation, as well as off-target adverse reactions such as neurotoxicity, alopecia, and amenorrhea [47].

Daclizumab is an antibody against the high affinity chain of the interleukin-2 (IL-2) receptor, CD25, which is present on proliferating and regulatory T cells. By blocking CD25, daclizumab prevents IL-2 binding thereby increasing its availability to CD56⁺⁺ natural killer cells that express the intermediate affinity IL-2 receptor and which then likely expand and exert their regulatory effect on pathogenic T cells [48-50•]. As this drug does not deplete immune cells, and NK cells have antiviral activity, its long-term adverse effects may not include severe infections or PML, but colon inflammation, lymphadenopathy, and hepatic and skin reactions have been observed.

The most recently [US Food and Drug Administration](#)-approved drug for RRMS therapy is the CD20⁺ B-cell-depleting antibody ocrelizumab [51•], and this drug is also the first treatment to ever be approved for PPMS [4••]. B cell depletion - by rituximab which also targets CD20 and is used off-label - has been shown to reduce pathogenic immune cells in MS patients [52], and it has been speculated that removing the reservoir of EBV-infected B cells might help drive CNS-directed autoimmunity. The observed efficacy of ocrelizumab in PPMS clinical trials may relate to the inclusion of younger patients with active MRI scans, such that there may be a window of opportunity during which inflammation driven by B cells can still be

targeted. Open questions are whether this beneficial effect is due to a more prominent involvement of B cells as opposed to other immune cells in PPMS, and what effect B-cell depletion will have on longer-term disease progression. Side effects of ocrelizumab include herpes reactivation and malignancy.

Conclusion

The results of the ocrelizumab trial in PPMS, as well as the experience accrued with the other immunomodulatory drugs and AHSCT to date, suggest that patient stratification by disease activity and early treatment will provide the most benefit [4,47,53•], although complete prevention of disease progression is unlikely for the great majority of therapeutic strategies. Concomitant efforts to develop drugs that directly target neurodegenerative processes and that have neuroprotective or neuroregenerative properties are hence a fundamental necessity to help treat patients with later-stage progressive disease [2].

The many and varied adverse effects associated with currently approved MS drugs also present a particular challenge, requiring vigilant patient monitoring. Given that these drugs have a relatively broad spectrum of action, side effects related to immunosuppression are not unanticipated, and thus the more specific targeting of particular immune cell subtypes or pathways could provide a solution. However, with the exception of daclizumab, prior trials of drugs blocking specific cytokines, such as tumor necrosis factor (TNF), IL-12/23 and BAFF/APRIL have shown no effect or have even worsened the disease [54,55], despite being efficacious for the treatment of other autoimmune conditions. In the case of TNF, genetic and functional analyses suggest that this may be due to intrinsic differences in the role of this molecule in MS compared to other diseases [10]. For the other cytokines it is unclear if this lack of drug efficacy is similarly due to a differential action or relative importance of these pathways in MS or if it reflects inadequate drug entry into the CNS to target the site of pathology. Therefore, continued research into CNS immunosurveillance and neuronflammation and its regulation, may help to further unravel the complexities of MS development and treatment, to identify improved approaches for specifically keeping CNS-directed autoreactive cells in check without fundamentally compromising the immune system.

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Table 1. Approved drugs for the immunomodulatory treatment of MS

Figure 1. The anatomy of MS therapeutic immunomodulation

Currently approved immunomodulatory drugs for the treatment of MS predominantly function to keep the immune system at bay by impairing and depleting immune cells (mitoxantrone, teriflunomide, alemtuzumab, ocrelizumab, cladribine), modifying their activity (IFN- β , GA, DMF, daclizumab), and preventing their trafficking into the CNS (fingolimod, natalizumab). Few of these drugs are thought to have direct effects in the CNS, and there is a need for the development of therapeutics that directly impact neuroaxonal degeneration and repair. APC, antigen-presenting cell; B, B lymphocyte; DC, dendritic cell; DMF, dimethyl fumarate; GA, glatiramer acetate; IFN β , type I interferon beta; IL-10, interleukin-10; NK, natural killer lymphocyte; ODC, oligodendrocyte; PC, plasma cell; T, T lymphocyte; Th1, T helper lymphocyte type 1; Th2, T helper lymphocyte type 2; Th17, T helper lymphocyte type 17; S1PR, sphingosine-1-phosphate receptor; and VCAM1, vascular cell adhesion molecule 1.