

Current Concepts in Multiple Sclerosis: Autoimmunity Versus Oligodendrogliopathy

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Abstract Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that affects millions of patients worldwide. The current disease-modifying therapies (DMTs) that are widely used to treat MS only show modest effects. Because MS is a chronic disease, it is important to develop treatments that have better long-term efficacy. Recently, several new-generation DMTs have been developed, most of which target specific immune molecules based on the assumption that MS is an autoimmune disease. These DMTs are designed to inhibit inflammation that is thought to directly cause demyelination. Preliminary studies suggest that these new therapies are likely to show a greater effect in reducing relapses in early MS patients, although their long-term efficacy is still unknown. In contrast, it was recently reported that the initial course of MS does not significantly influence long-term disability and that disability increases approximately at the same rate despite variable relapse frequencies. Furthermore, new neuropathological evidence now argues against the autoimmune hypothesis and suggests that MS is a primary oligodendrogliopathy disease in which the inflammatory response may be a mere epiphenomenon. So can we be

optimistic about the unproven long-term outcomes of new DMTs or should we reconsider the pathogenesis of MS when developing more disease-specific treatments?

Keywords Multiple sclerosis · Pathogenesis · Autoimmune · Oligodendrogliopathy

Introduction

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS) and is a primary cause of neurological disability in young adults. Approximately 80–90% of MS patients initially develop the relapse–remit form (relapsing–remitting multiple sclerosis (RRMS)) in their late 20s, and some degree of spontaneous neurological recovery is commonly observed during the remittance period. Years after disease onset, many RRMS patients progress to the secondary progressive form (secondary progressive multiple sclerosis (SPMS)), in which the functional recovery virtually disappears and neurological dysfunctions increase (Fig. 1). The remaining 10–20% of patients suffer from the primary progressive form (primary progressive multiple sclerosis (PPMS)), which is characterized by no apparent spontaneous recovery from the initial phase of disease.

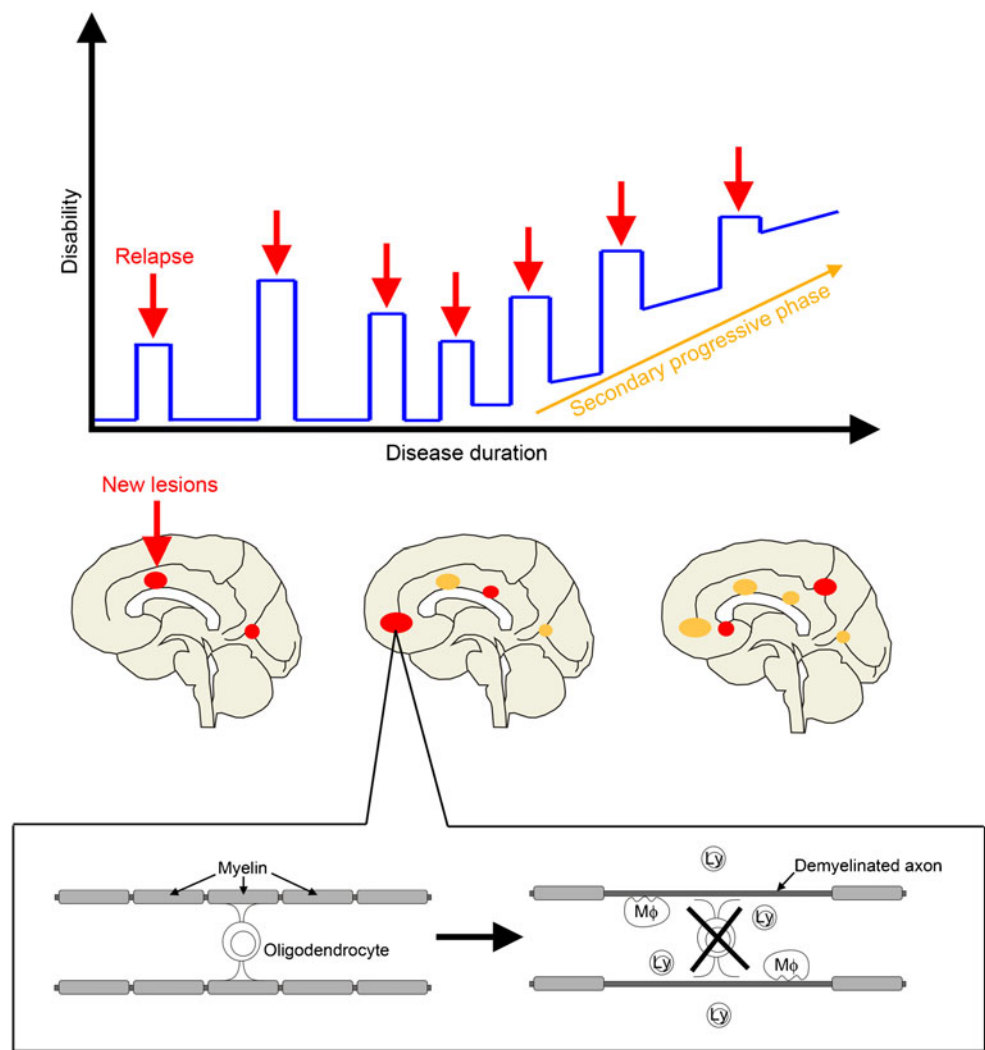
Interferon β and glatiramer acetate are currently the two major disease-modifying therapies (DMTs) that are predominantly used for RRMS patients. Although these DMTs were shown to reduce the annualized relapse rate by approximately 30% [1–3], this reduction rate is clinically unsatisfactory for many patients. Currently, several new-generation DMTs are being developed, most of which are designed to interfere with immune molecules according to the autoimmune hypothesis of MS etiology. These DMTs are likely to have higher efficacy in reducing relapses in early MS patients compared

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Fig. 1 A typical clinical course of multiple sclerosis. Most of MS patients initially develop RRMS, and spontaneous neurological recovery is usually observed during the remittance. Later, these patients progress to SPMS, in which the functional recovery virtually disappears. Inflammatory demyelination (with lymphocytes (*Ly*) and macrophages (*Mφ*)) is the hallmark of MS lesions. Loss of mature oligodendrocytes, the myelin-forming cell, is often associated with such demyelination



with the current DMTs. However, a relapse reduction does not guarantee a superior outcome (i.e., fewer disabilities) over a long period, as demographic studies indicate that long-term disability in the natural history of MS is not significantly influenced by the frequency of relapses or by the initial disease phenotype [4]. On the other hand, novel neuropathological evidence suggests that primary oligodendroglial pathology causes demyelination [5, 6], and in such cases, the inflammatory response that appears “autoimmune-like” may be a mere epiphenomenon due to the clearance of myelin debris. If this is true, there may be better treatment options than the aforementioned DMTs that are designed to inhibit oligodendroglial pathology. In this review, we will compare the two major hypothesis that consider MS as an autoimmune disease or an oligodendroglial pathology.

The Autoimmune Hypothesis

The currently most widely accepted hypothesis regarding MS pathogenesis is the autoimmune hypothesis (Fig. 2a),

which proposes that autoimmune inflammation causes demyelination and that auto-reactive leukocytes initiate disease. According to this hypothesis, disease begins when naïve myelin antigen-specific CD4-positive T cells are primed in the peripheral lymph nodes (CNS-draining

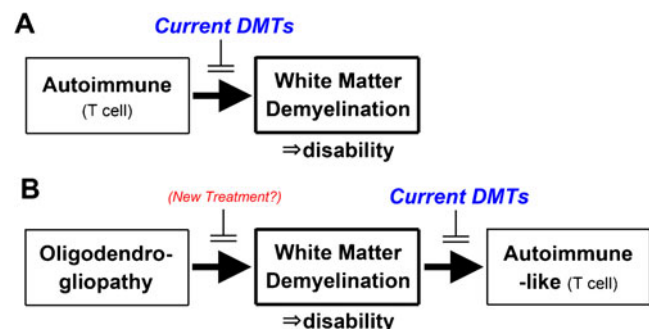


Fig. 2 The autoimmune hypothesis (a) versus the oligodendroglial pathology hypothesis (b). Current DMTs are designed to interfere with autoimmune inflammation and thus developing new treatments that halt oligodendroglial death may provide better clinical outcomes based on the latter hypothesis. See main text for details

cervical lymph nodes [7]) by dendritic cells that present myelin or myelin cross-reactive epitopes. These activated T cells are induced to differentiate into Th17 cells by interleukin (IL)-23, which seems to play a pivotal role in CNS autoimmunity [8, 9]. These Th17 cells express CC chemokine receptor 6, whereas its ligand CC chemokine ligand (CCL) 20 is expressed by choroid-plexus epithelial cells, which constitute the blood–cerebrospinal fluid (CSF) barrier. As a result, the myelin-reactive Th17 cells drain into the CSF in the subarachnoid space (SAS) for CNS-immune surveillance [10] (very recently, it has also been shown that the small intestine also expresses CCL20 and that Th17 cells are controlled there [11]). When the myelin-reactive Th17 cells reach the SAS, they are reactivated by MHC class II-expressing macrophages or dendritic cells that express myelin epitopes and subsequently infiltrate into the CNS parenchyma, resulting in inflammation and blood–brain barrier (BBB) stimulation [12]. After BBB activation, T cells in the peripheral circulation contact and migrate along activated endothelial cells and then penetrate and enter the SAS [13]. The T cells that enter the CNS parenchyma, together with activated macrophages and glial cells (i.e., activated microglia [14] and astrocytes [15]), secrete soluble factors such as tumor necrosis factor (TNF)- α and lymphotoxin (LT)- α , both of which bind to TNF receptors. TNF- α and LT- α are thought to induce demyelination via oligodendroglial TNF receptor 1 [16]. Interestingly, however, TNF- α induces remyelination and vice versa through the other TNF receptor, TNF receptor 2 [17].

Importantly, a large amount of evidence that supports the autoimmune hypothesis was obtained with the most widely used MS animal model, experimental autoimmune encephalomyelitis (EAE), rather than directly from MS patients. While some aspects of EAE and MS are similar, there are major differences between the two [18]. Then what is EAE and why is it so widely used as a model for MS?

Historically, the inflammation detected in MS lesions was thought to be an infectious immune reaction. At that time, researchers failed to fulfill Koch's postulates; they could not transmit the disease from man to animals, and this failure made them consider that inflammation may be a non-infectious, autoimmune reaction. On the other hand, in 1933, Thomas Rivers and colleagues generated a model of human acute disseminating encephalomyelitis that occasionally occurred after vaccination. Although this model was not for MS, they described a few successful cases of monkeys that developed autoimmune encephalomyelitis that was characterized by perivascular demyelination after repeated immunization with rabbit brain extracts, providing the first cases of EAE [19]. By the late 1950s, EAE was proposed to be a useful animal model of human MS based on the assumption that inflammatory demyelination in MS is autoimmune related, although this was solely based on

the aforementioned negative results and the autoimmune nature of this disease has not been rigorously proven.

EAE has successfully served as an MS model in several aspects, especially in the development of certain DMTs, namely glatiramer acetate (Copaxone®), mitoxantrone, and an antagonistic antibody against $\alpha 4\beta 1$ integrin (natalizumab; Tysabri®) [20]. All of these drugs were developed based of their efficacy in EAE animals. On the other hand, there are many more agents that can successfully treat EAE that have failed to show any beneficial effects in MS (and in some cases ultimately exacerbated disease [19]). The two most disappointing results were therapeutics that were directed against CD4 and TNF- α , both of which are critically involved in (either in the beginning or end) the autoimmune hypothesis. According to the autoimmune hypothesis, CD4-positive T cells are critical players in pathogenesis, and indeed an anti-CD4 antibody prevented the onset of EAE or even reversed EAE in paralyzed animals [21]. Nevertheless, no beneficial clinical effect was observed in a phase II trial in RRMS and SPMS patients, despite a substantial decrease in CD4-positive cells in treated patients [22]. On the other hand, based on the autoimmune hypothesis, TNF- α is a factor that directly induces demyelination in the final course of disease, and indeed an anti-TNF- α antibody inhibited demyelination without interfering with the induction phase of EAE [23, 24]. Again, however, a randomized placebo-controlled phase II trial of an anti-TNF- α antibody in RRMS patients showed that this treatment exacerbated MS [25]. Another study indicated that even the onset of MS may be associated with inhibiting TNF- α [26]. These adverse effects of the anti-TNF- α therapy are unlikely the result of inhibiting of the role of TNF- α in remyelination [27]. After all, anti-TNF- α therapies, which are now widely used in rheumatoid arthritis, are currently contraindicated for MS. Additionally, a recent phase II study on ustekinumab, an IL-12/23 p40 neutralizing antibody that is expected to halt the Th1/17 pathways, also failed to show efficacy in MS patients [28].

EAE enabled us to study CNS-immune relationships, and EAE is a suitable animal model to test anti-autoimmune drugs targeting the CNS. Nevertheless, EAE is an incomplete model of MS, and the autoimmune hypothesis of MS pathogenesis remains unproven.

The Oligodendroglial Hypothesis

The oligodendroglial hypothesis (Fig. 2b) arose from neuropathological studies on MS, although these studies are far less reported compared with studies using EAE due to the difficulty in obtaining appropriate MS specimens.

Lucchinetti et al. defined four major patterns in MS lesions based on careful histopathological examinations,

each of them possibly reflecting a different pathogenesis [29]. Type 1 (T cell-mediated autoimmune encephalomyelitis) and type 2 (T cell plus antibody-mediated autoimmune encephalomyelitis) lesions frequently exhibited sharply demarcated active demyelination perivenously that was associated with inflammation consisting mainly of T cells and macrophages with (in type 2) or without (in type 1) pronounced antibody and complement depositions. These two types of active lesions did not show primary oligodendroglial apoptosis and the reappearance of oligodendrocytes in inactive plaques was frequently observed. Type 3 (primary oligodendroglial apoptosis) and type 4 (primary oligodendroglial dystrophy) lesions frequently exhibited either ill-defined (in type 3) or sharply demarcated (in type 4) active demyelination in no typical association with veins or venules, although these lesions were associated with T cells and macrophages. In both of these lesions, oligodendroglial death was prominent in active or inactive lesions. Oligodendroglial apoptosis was observed in type 3 lesions, whereas oligodendroglial death without apoptotic features was frequent in type 4 lesions. Lucchinetti et al. reported that type 4 lesions were exclusive to PPMS and that type 1 lesions were rather infrequent compared with the resting two types (types 2 and 3). Type 2 lesions were the most frequently observed pattern in RRMS or SPMS with various disease durations, whereas type 3 lesions were primarily observed in patients with a short disease duration. Lucchinetti et al. also reported that the lesion type was consistent across different lesions within the same patient but heterogeneous between different patients.

The above study indicated that there are at least four types of MS, one (type 4) in PPMS and three (types 1–3) in RRMS/SPMS. Although types 1 and 2 differ in respect to the involvement of humoral immunity (i.e., antibody and complement), both types may be explained by the T cell-based autoimmune hypothesis because similar pathological features were observed in EAE animals. In contrast, types 3 and 4 lesions with primary oligodendrocyte deaths have never been described in relation to the autoimmune hypothesis or in EAE animals, and thus resulted in the novel oligodendroglialopathy hypothesis for MS pathogenesis. Theoretically, MS patients with type 3 or 4 lesion may not fully respond to DMTs that are designed to inhibit autoimmune responses by targeting immune molecules.

The above study by Lucchinetti et al., however, was inconclusive in regard to when the trigger that leads to demyelination is eventually recruited into each lesion. Thus, the possibility remained that the four different pathological pictures may only reflect differences in the timing of the biopsy or autopsy, rather than true differences in the pathogenesis of demyelinated lesions.

Later, Barnett and Prineas analyzed several early MS lesions, with the earliest autopsied case being only 17 h

after the onset of symptoms [5]. This 17-hour fatal lesion exhibited extensive oligodendrocyte apoptosis but no inflammatory cells (e.g., T cells and macrophages), except for increased microglia showing signs of very early phase of activation. Barnett and Prineas also analyzed several early MS lesions with a known episode duration of between 60 h to 42 days and suggested that the formation of a new MS lesion occurs along the following time-line. (1) Within hours, oligodendrocytes become apoptotic (no T cells or macrophages are observed within the lesion). (2) Within 1–2 days, oligodendrocytes disappear and myelin becomes degenerated. (3) After that, myelin phagocytosis occurs in association with T cells and macrophages while oligodendrocyte precursor cells begin to appear. (4) Within 1–2 weeks, differentiated oligodendrocytes reappear, possibly for remyelination.

According to their observations, inflammation is not the cause of disease but a mere result of oligodendrocyte apoptosis and myelin degeneration. Inflammation may be secondary to demyelination and function to clean myelin debris. The lesion formation observed by Barnett and Prineas and type 3 lesion (frequently observed in MS patients with short disease durations) in the Lucchinetti study together suggest that demyelination in MS is a consequence of oligodendroglialopathy, rather than autoimmunity.

Based on a thorough analysis of oligodendroglial apoptosis and inflammatory cell distribution in various early MS lesions, Henderson et al. provided further evidence that oligodendroglial death and microglial activation are the initial event in MS lesion formation, followed by immune responses to scavenge dead myelin. Importantly, they showed that the accumulation of inflammatory cells occurred simultaneously with the reappearance of differentiated oligodendrocytes, suggesting that these immune responses are not toxic but permissive for oligodendroglial regeneration and remyelination [30]. These results are consistent with findings in experimentally demyelinated animals in which lasting myelin debris impaired remyelination [31]. Some natural autoantibodies [32] or myelin-specific T cells [33] were also reported to be beneficial for remyelination, which also reasonably explains the necessity of inflammation after demyelination.

If oligodendroglialopathy was the true cause of MS pathogenesis, then what causes oligodendroglialopathy? It has been proposed that oxidative damage, glutamate toxicity, cytokines, mitochondrial injury, or certain autoantibodies potentially cause oligodendroglial death [34], although there is no evidence from human MS studies supporting this hypothesis. It was recently reported that the TIP30 protein, a proapoptotic protein, is abnormally overexpressed in oligodendroglial cells in chronic MS lesions [35], although its involvement in early MS lesion formation remains to be proven. Based on the oligodendroglialopathy

hypothesis, such elucidation of the cause of oligodendrocyte apoptosis may lead to a novel therapeutic strategy for MS patients.

MS: Diagnosis, Natural History and Novel Implications

Because the oligodendroglial hypothesis arose directly from MS neuropathological studies, this hypothesis may eventually override the autoimmune hypothesis that relies heavily on EAE studies, although it is possible that MS may be a group of heterogeneous diseases including some autoimmune disorders and oligodendroglial pathology. Considering this possibility, it is important to understand how MS is diagnosed.

In 1868, Jean Martin Charcot, a French neurologist, first described patients with intermittent neurological dysfunctions who had multiple perivascular accumulations of inflammatory cells in the white matter of the brain and spinal cord [36]. He named the disease “sclérose en plaques disséminées,” and we now call this disease MS. Although more than a century has been passed since Charcot’s first description, the exact cause of MS is still unknown and an etiology-based definite diagnostic test for MS is not available. MS is more characteristic of a syndrome than a disease with a simple clinical entity: CNS demyelination disseminating in time and space. Therefore, it is important to be aware that it is possible that this disease entity includes heterogeneous diseases with a different pathogenesis and that “autoimmune MS” and “oligodendroglial pathology MS” may coexist.

Currently, MS is clinically diagnosed based on diagnostic criteria proposed by a panel of MS specialists. The first criteria were proposed in 1961 (The Schumacher criteria [37]) and were subsequently updated in 1982 (The Poser criteria [38]) and more recently in 2001 (The McDonald criteria [39]; 2010 revised McDonald criteria are now available [40]). These criteria were updated in order to more readily (i.e., without delay) and objectively (e.g., with magnetic resonance imaging (MRI)) demonstrate CNS demyelination that was “disseminated in time and space.” Thus, the exact cause of demyelination, whether the result of autoimmune, oligodendroglial pathology, or other causes, is not questioned in the diagnosis.

As mentioned above, most MS patients (approximately 80–90%) are diagnosed with RRMS in their late 20s. Once diagnosed, these patients typically suffer from new clinical relapses every 0.5–2 years. RRMS patients convert to SPMS at a relatively constant rate of approximately 2.5%/year with a median time span of 19 years after the onset of RRMS [41]. A few patients develop PPMS, although the age at disease onset is usually later than that of RRMS, typically when the patients are in their late 30s or 40s. Regardless of how MS

begins, whether RRMS or PPMS, a demographic study indicated that most patients suffer from irreversible disability with an expanded disability status scale (EDSS) of 4 (limited walking without aid) by 44 years of age, EDSS of 6 (walking with aid) by 55 years, and EDSS of 7 (wheelchair) by 63 years of age [42]. In addition, the ages at which each EDSS landmark is reached are not significantly influenced by the disease course (i.e., RRMS–SPMS or PPMS) nor by the frequency of relapses [4]. A meta-analysis of several MS registries also suggested that once EDSS 4 is reached, the subsequent progression rate is not influenced by the type of MS at disease onset [43]. These results raise the possibility that similar “accelerated aging-related mechanisms” may operate once MS has developed, regardless of its course or type [4]. The life span of MS patients is typically 10–12 years shorter than that of the age-matched control population [44].

MS patients are usually followed by repeated MRI studies to evaluate the degree of focal white matter demyelination, which is easily accessed by a T2-weighted image (T2WI). Despite its sensitivity, however, the T2WI-high lesion load either in the brain or spinal cord only weakly correlates with EDSS [45, 46]. In contrast, there is increasing evidence that the degree of gray matter pathology (i.e., demyelinating cortical lesions occasionally with axonal damage and neuronal loss) best correlates with the disability in MS [46–49]. The introduction of a novel sequence, the double inversion recovery sequence, enabled cortical lesions to be detected with 1.5 Tesla MRI, and such lesions are reported to be observed very early even in RRMS [50, 51]. It has also been reported that diffuse white matter injury in “normal-appearing white matter” occurs concordantly with cortical lesions [52]. Of great importance is that cortical lesions may not be a consequence of focal white matter lesions that are located beneath or near cortical lesions [52]. Therefore, it is possible that the pathogenesis of focal white matter lesions and cortical lesions may differ.

Indeed there are key differences in microscopic pathologies between focal white matter lesions and cortical lesions. Unlike in focal white matter lesions, inflammation is very limited in cortical lesions, and cortical lesions contain 13-fold fewer CD3-positive T lymphocytes and 6-fold fewer CD68-positive macrophages compared with focal white matter lesions [53, 54]. In addition, BBB function in cortical lesions appears to be undisrupted, and it is unlikely that plasma proteins leak into the brain parenchyma [55]. Therefore, focal inflammation is not likely to cause cortical lesions in MS.

A recent study suggested that meningeal inflammation was associated with the development of cortical lesions [56], but this association was not confirmed in another study [57], or in Alzheimer’s disease in which meningeal inflammation, although to a lesser degree, is observed

without cortical demyelination [58]. These results suggest that the causal relationship between meningeal inflammation and cortical lesions remains controversial. Another recent neuropathological study further showed that B cell follicle-like structures in inflamed meninges are associated with cortical pathology and such pathology included not only oligodendrocyte loss (demyelination), but also neuronal and astrocyte loss [59]. Patients with such cortical lesions tend to have a more accelerated course of disease [60]. The causal relationship between B cell follicle-like structures and the formation of cortical lesions, whether it is the cause (the autoimmune hypothesis (Fig. 3a), although B cell mediated) or a mere epiphenomenon (the oligodendrogliopathy hypothesis (Fig. 3b), although also with neuronal and astrocytic loss), again remains to be proven.

New-Generation DMTs and Their Implications

As mentioned above, MS may be a heterogeneous disease, in which some cases are autoimmune related while others are the result of oligodendrogliopathy. Because the latter

hypothesis arose in 2000, the currently used and newly developed DMTs are predominantly based on the autoimmune hypothesis. This raises the question as to whether these drugs are beneficial for patients who potentially have oligodendrogliopathy. It is important to mention that it is possible that secondary inflammation upon oligodendrogliopathy may also have adverse effects that contribute to clinical symptoms (i.e., EDSS for motor symptoms), and in such cases, certain DMTs may still be beneficial to MS patients with oligodendrogliopathy.

So far, the only DMT that was reported to improve EDSS is alemtuzumab. Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on all mature lymphocytes, and this antibody depletes both T cells and B cells, including auto-reactive lymphocytes. A 3-year phase II study of alemtuzumab in 334 early MS patients (average baseline EDSS of 1.9) showed slightly improved EDSS scores (average score of 0.32) after treatment, although the improvement was most obvious during the first 6 months after alemtuzumab therapy was initiated [61].

Several DMTs, namely rituximab, fingolimod, cladribine, and teriflunomide, were reported to be associated with stabilized EDSS. Rituximab is a murine/human chimeric monoclonal antibody against CD20 that is expressed on pre-B and mature B cells, and this antibody results in the lysis of circulating B cells but spares mature plasma cells. A phase II study of rituximab as an add-on therapy in 30 MS patients (average baseline EDSS of 4.7) spanning over 4 years resulted in the stabilization of EDSS in 70% of patients (improved in 23% and worsened in 7%) [62]. Fingolimod is a sphingosine-1-phosphate-receptor modulator that prevents the egress of T cells from the lymph nodes. A 2-year randomized, double-blind, placebo-controlled trial of fingolimod in 1,033 MS patients (average baseline EDSS of 2.4) showed that EDSS stabilized in the fingolimod-treated groups but worsened by 0.13 in the placebo-treated groups [63]. Cladribine is a lymphotoxic purine nucleoside analog that mimics the immune-deficient state of adenosine deaminase deficiency. A 2-year phase III trial of cladribine in 1,326 MS patients (average baseline EDSS of 2.9) showed that the time to EDSS progression was significantly longer in the cladribine-treated group than in the placebo-treated groups [64]. Teriflunomide is a novel immunosuppressant, and although the exact mechanism of action is not fully elucidated, it is expected to inhibit lymphocyte expansion and differentiation. A 9-month phase II study of teriflunomide in 179 MS patients (average baseline EDSS of 2.5) showed that the proportion of patients with increased EDSS was lower in the teriflunomide-treated group than in the placebo-treated group [65].

However, some DMTs have so far failed to show beneficial effects on EDSS. Natalizumab is a humanized monoclonal antibody against $\alpha 4$ -integrin, which is expressed on lympho-

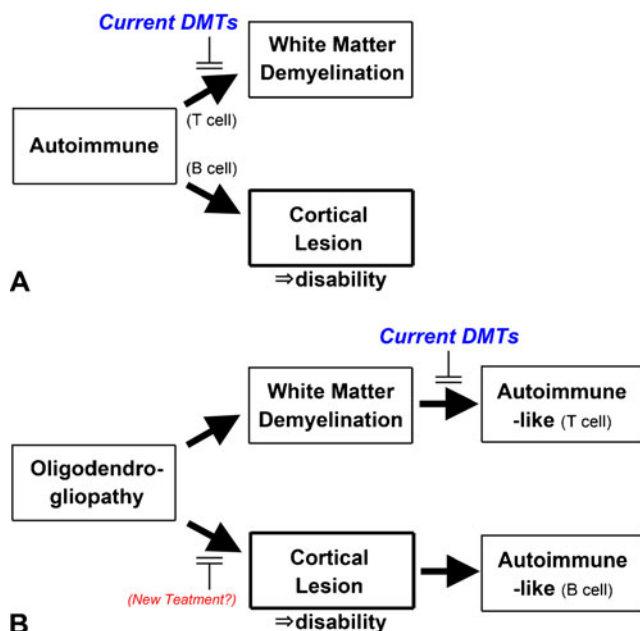


Fig. 3 The two hypothesis and cortical lesions. Recent neuropathological studies indicate that cortical lesions better correlate with MS disability than white matter lesions. In contrast to white matter lesions, cortical lesions are characterized by less inflammatory infiltrates and B cell follicle-like structures in the surrounding meninges. When these observations were combined with the two hypothesis, the autoimmune hypothesis (a) and the oligodendrogliopathy hypothesis (b), pathogenetic schema could be drawn as shown. Current DMTs are designed to primarily target T cells (except for rituximab) and therefore novel DMTs directed against B cells may be required to treat cortical lesions. Additionally, the development of new treatments that inhibit oligodendrogliopathy may result in a better clinical outcome based on the latter hypothesis. See main text for details

cytes. $\alpha 4$ -integrin is involved in the migration of lymphocytes from the circulation into the brain parenchyma via the penetration of endothelial cells (BBB), and natalizumab prevents this transmigration. A randomized double-blind placebo-controlled trial of natalizumab in 180 MS patients with acute relapses (average baseline EDSS of 4.5) that spanned over 1 year showed no differences in EDSS over time between the natalizumab-treated and the placebo-treated groups [66]. Daclizumab is a humanized monoclonal antibody against CD25, which is weakly expressed on resting T cells and strongly expressed on activated T cells. Daclizumab decreases T cell activation in vitro, whereas it may inhibit T cells by contributing to the expansion of regulatory natural killer cells in vivo. A 6-month phase II study of daclizumab as an add-on therapy in 230 MS patients (average baseline EDSS of 3.0) showed no difference in EDSS between the daclizumab-treated and the placebo-treated groups [67]. Laquinimod is a novel immunomodulatory agent that is likely to show anti-inflammatory effects via a Th1–Th2 shift, although the exact mode of action has not been fully elucidated. A 9-month phase IIb study of laquinimod in 306 MS patients (average base line EDSS of 2.4) showed that the change in EDSS during the study period was not significantly different between the laquinimod- and the placebo-treated groups [68].

The above results suggest that some immunomodulatory DMTs may be beneficial even for MS patients with oligodendroglial pathology, although additional studies are required to assess the long-term effects of these potential therapies.

Conclusions

We have briefly reviewed the two major hypotheses on MS pathogenesis: the autoimmune hypothesis and the oligodendroglial pathology hypothesis. The former lacks rigorous proof from human MS patients, whereas recent neuropathological evidence favors the latter hypothesis, although further studies are required to draw a uniform theory to explain the entire disease course of MS. Even if the oligodendroglial pathology hypothesis is true, immunomodulatory DMTs may still be partially beneficial in MS patients, as excessive inflammation may be harmful to CNS function. The long-term outcomes of such DMTs will require further investigation. However, the oligodendroglial pathology hypothesis indicates that a different strategy to halt the oligodendroglial death may result in a better treatment outcome. Ultimately, we must be cautious when diagnosing MS based on a simple clinical picture—CNS demyelination disseminating in time and space—and be cognizant that clinical MS may be heterogeneous diseases with different pathogenetic natures.

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