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Emerging Immunopharmacological Targets in Multiple Sclerosis

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Abstract

Inflammatory demyelination of the central nervous system (CNS) is the hallmark of multiple sclerosis (MS), a chronic debilitating disease that affects more than 2.5 million individuals worldwide. It has been widely accepted, although not proven, that the major pathogenic mechanism of MS involves myelin-reactive T cell activation in the periphery and migration into the CNS, which subsequently triggers an inflammatory cascade that leads to demyelination and axonal damage. Virtually all MS medications now in use target the immune system and prevent tissue damage by modulating neuroinflammatory processes. Although current therapies such as commonly prescribed disease-modifying medications decrease the relapse rate in relapsing-remitting MS (RRMS), the prevention of long-term accumulation of deficits remains a challenge. Medications used for progressive forms of MS also have limited efficacy. The need for therapies that are effective against disease progression continues to drive the search for novel pharmacological targets. In recent years, due to a better understanding of MS immunopathogenesis, new approaches have been introduced that more specifically target autoreactive immune cells and their products, thus increasing specificity and efficacy, while reducing potential side effects such as global immunosuppression. In this review we describe several immunopharmacological targets that are currently being explored for MS therapy.

Keywords

neuroimmunology; immunotherapy; multiple sclerosis

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Declarations

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Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) that has devastating clinical outcomes in many patients. MS is a leading cause of neurological disability in young adults and in the middle-aged population (1); it imposes an incredibly high socio-economic burden on society (2), with medication making up a great share of these costs (3, 4). The majority of patients experience a relapsing-remitting (RR) clinical course, and gradual accumulation of neurological deficits can eventually cause permanent disabilities. A minority of patients suffer from a progressive clinical course characterized from the beginning by steady disease progression without remissions (primary progressive MS; PPMS), and there is no evidence that any treatment works in this type of MS or in secondary progressive MS (SPMS) (5). Even in RR-MS, which can be treated using several immunomodulatory medications, treatment outcomes have not been reported as unequivocally effective for all patients, i.e., the outcomes show wide inter-individual variations, likely due to the nonhomogenous nature of the disease course. The scientific strategy of choice for treating these types of disease is to better understand their pathophysiology.

It has been suggested that MS pathogenesis is initiated by activation of myelin antigen-specific T and B cells in the periphery (6, 7). While the origin of activation of these immune cells is not known, it has been proposed that certain autoantigens or organisms with peptide homology to these antigens might trigger this process (1, 8). These myelin-reactive cells, upon migrating into the CNS, encounter autoantigens, become reactivated, and an inflammatory cascade ensues that results in demyelination and axonal injury (9). In this scenario, T cells appear to play an important role, although B cells also contribute (10). Thus, targeting T cells, B cells and mediators involved in their activation provides major routes for therapeutic interventions in MS. Current treatment options basically target the immune system to modulate disease.

While a number of drugs for MS therapy are being developed, the longlasting neuroprotective efficacy of current drugs has not been confirmed (11). In almost all cases, immunopharmacology has been the basis for drug design and development. To date, there are several approved medications for MS, including interferon beta (IFN- β) 1a, IFN- β 1b, glatiramer acetate, mitoxantrone (12), natalizumab (13, 14), fingolimod, triflunomide, dimethyl fumarate (15) and a recently approved medication, alemtuzumab (16). These drugs, mainly through modulating or interfering with different aspects of immune responses, reduce the relapse rate or decrease the need for steroids during exacerbations. However, in many patients, the response to some drugs is suboptimal, and for other medications, safety is a concern. Moreover, there is debate on how and to what extent these medications can modify the long term course of the disease. Furthermore, the lack of curative modalities and low rate of compliance in taking medication are therapeutic issues in MS (17). The cost effectiveness of these drugs in MS is also under debate.

Current understanding of the immunopathogenesis of MS has identified novel immunological processes and molecules that could be pharmacologically modulated in order to provide more effective and less toxic drugs; new MS therapies are being investigated and

clinical trials are underway, based on the fine immunological processes underlying MS. The effectiveness of every target in MS therapy is controversial, and T cells, B cells, their crosstalk mechanisms, and a handful of inflammatory mediators and processes are being studied.

In the following sections, a brief review is presented of therapies targeting immune system components, with the goal of providing novel immunopharmacological treatment options for MS.

1. Targeting T Cells in MS

T cells provide important targets for MS therapy. Different T cell types and their surface markers have been experimentally targeted based on the immunopathology of MS. In the periphery, as well as the CNS, autoreactive T cells differentiate into several subtypes of T cells including proinflammatory cytokine secreting T-helper (Th) 1 and recently discovered Th17 cells, both of which contribute to the development of autoimmune response (18). In contrast, Th2 and regulatory T cells (Tregs) are anti-inflammatory. T cell-directed therapies could be effective if stages of T cell activation at different phases of MS pathogenesis are properly targeted (Table 1).

1.1. Targeting CD4+ T Cells

It is believed that autoreactive CD4+ T cells play a central role in MS pathogenesis. Thus, CD4+ T cell targeting with anti CD4+ antibody (cM-T412) was tested as a therapeutic option, and clinical trials with this antibody were performed in RRMS patients (19, 20). In the trials, reduction of relapse rate was observed in patients treated with this antibody, and side effects were limited; however, its efficacy in reducing T2/FLAIR lesions in MRI was not shown. Based on this report, it was concluded that this strategy has no long-term clinical benefits (21). The reason for its ineffectiveness is not known, but it has been suggested that this strategy leads to depletion of all CD4+ T cells. While a proportion of CD4+ T cells are pathogenic in MS, some CD4+ T cells, such as Th2 and Tregs, have anti-inflammatory effects (18). Anti-CD4+ antibody depletes both pathogenic and protective CD4+ T cells, with the resulting net effect of therapeutic inefficacy. The failure of this clinical trial indicated the necessity of selectively targeting only pathogenic CD4+ T cells, and not the totality of these cells, as a proper approach for MS therapy.

1.2. Targeting CD52+ Immune Cells

CD52 is an orphan receptor on the surface of mature immune cells, such as lymphocytes and monocytes, whereas progenitor cells do not express CD52. Targeting CD52 with alemtuzumab, a humanized IgG1 kappa monoclonal antibody, selectively depletes mature cells while progenitor cells remain unaffected. Depletion of mature cells is rapid and induces durable lymphopenia after one course of treatment with alemtuzumab (22, 23). After depletion of mature lymphocytes, progenitor cells proliferate and a new population of T cells is formed, with regulatory T cells predominating in this newly constituted cell population. As a consequence, Alemtuzumab induces immunological reconstitution of T cell subsets, leading to modulation of the immune system by expansion of regulatory T cells (24).

Alemtuzumab has been approved for treatment of chronic B lymphocytic leukemia (25) and is a candidate medication in T cell lymphomas and prevention of rejection in organ graft and bone marrow transplantation (26, 27). To study the potential of targeting CD52 in MS therapy, Alemtuzumab has been tested therapeutically in MS patients since 1991 (28, 29). This antibody proved to be effective in reducing demyelinated plaques, as shown on MRIs, and clinically decreased relapses in the relapsing-remitting form of MS, but did not show satisfactory modification of disability in this group. However, when tested in RRMS patients who had failed to respond to other treatments, the antibody was effective in decreasing the relapse rate. Furthermore, after five years of treatment, Alemtuzumab continued to show greater efficacy than interferon beta-1a (IFN- β -1a) in reducing relapse rate and in sustained improvement in patient disability (30). This disability-modifying effect encouraged continued investigations on Alemtuzumab for treatment of RRMS. In clinical trials Alemtuzumab was reported to be superior to IFN- β -1a and, despite safety concerns about the increased risk of emerging secondary autoimmune disorders such as thyroid autoimmunity, *idiopathic thrombocytopenic purpura* (ITP), Goodpasture's disease and glomerulonephritis, a phase III clinical trial of this antibody was completed in 2012 and the drug was submitted to the FDA for new drug application approval in RRMS. After a long challenge due to lack of evidence that the benefits outweighed side effects, the drug was finally approved by the FDA in November 2014 for RRMS patients who had not responded to two disease-modifying medications (16).

1.3. Targeting CD25 (Interleukin-2 Receptor α)

CD25 (IL-2R α) is the α chain of interleukin-2 receptor (IL-2R) expressed on T and B lymphocytes (31). IL-2, a pro-inflammatory cytokine, is secreted by activated T cells and stimulates proliferation, differentiation and activation of lymphocytes. Some findings indicate a contribution of IL-2R to the immunopathogenesis of MS. Certain polymorphisms of IL-2R genes have been found to be associated with increased susceptibility to MS (32). Furthermore, up-regulation of IL-2R on activated CD4⁺ T cells might be associated with disease activity in MS (33). Daclizumab is a humanized monoclonal antibody against CD25 (IL-2R α). The drug likely acts as a pharmacological antagonist of IL-2R and decreases lymphocyte response to the trophic signals conferred by IL-2. This could inhibit IL-2-mediated proliferation of activated CD4⁺ T cells. Based on this mechanism of action, Daclizumab has been approved for treatment of some T cell-dependent disease states such as human T lymphotropic virus 1 (HTLV-1)-induced adult T cell leukemia (34) and allograft rejection prevention (35).

In contrast to its anti-CD4⁺ activity, Daclizumab stimulates the expansion of a subpopulation of natural killer cells (NK cells) called CD16–CD56 bright NK cells through an IL-2 dependent mechanism (36). These cells have an immunomodulatory function, which might be beneficial in modifying autoimmunity (37). In MS, CD56bright NK cells cross the blood-brain barrier and kill autoimmune T cells in the CNS, likely through a direct cytotoxic effect on these T cells as suggested by results in vitro (36).

In clinical trials, Daclizumab has been effective in decreasing relapses in RRMS (38), an effect that was more pronounced in patients with highly active RRMS. This greater efficacy

in highly active disease appears to be important as there are few effective treatments for this subtype of RRMS (39). Moreover, combining Daclizumab with IFN- β in a therapeutic regimen has been clinically and radiologically beneficial in patients with limited response to interferon (40–44). Although based on some reports, the safety of Daclizumab is a matter of concern (45), other reports indicate the safety of the drug after two years of administration to RRMS patients (46).

1.4. Targeting T cell Activation

1.4.1. Altered Peptide Ligands (APL)—The first step in activation of T cells is recognition of the “MHC-peptide complex” by the T cell receptor (TCR) (47). To prevent T cell activation, TCR can be blocked by altering peptides that bind to TCR but cannot activate T cells. These “altered peptide ligands (APLs” have a minor structural modification compared to immunogenic peptide ligands and compete with them in binding to TCR. By antagonizing the “MHC-peptide complex,” T cell activity will be inhibited (48, 49). It has been proposed that APL can provide a selective and specific tool for modulation of T cell response to a “known antigen” (49).

Several autoantigens are thought to contribute to MS pathogenesis, such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). Some of these antigens have been used as templates for APLs (50). A number of experimental studies with APLs carried out in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), have shown suppression of CNS inflammation and improvement of neurological deficits (51–54).

In clinical trials, however, the safety and efficacy of different APLs have not been proven (49, 55). For example, five out of six clinical trials testing an APL of MBP failed to show any benefit in MS (56). In addition, unacceptable immunological side effects have been reported (57). In a phase II study (58), an APL exacerbated disease in a few patients, and systemic hypersensitivity reactions in some patients have been reported (57). In a phase III multicenter randomized 2-year, double-blind, placebo-controlled study using an APL of MBP, its efficacy in secondary progressive MS (SPMS) patients was not proven (55). An APL of MOG35–55, recombinant TCR ligand 1000 (RTL1000), has proved effective in reversing neurological deficits in EAE (59, 60) and had a favorable toxicity profile and promising outcomes in MS clinical trials (61, 62).

Although seemingly attractive, the APL approach has considerable shortcomings. For example, there is no evidence that the same autoantigen/peptide drives pathology in all MS patients. In other words “one APL for all MS patients” is not likely to be a feasible approach. It would be ideal to have a “personalized” APL approach based on the auto-antigen response of individual MS patients.

1.4.2. Targeting T cell Co-stimulatory Pathways—T cells are activated when their receptors (TCRs) recognize antigens presented by antigen-presenting cells (APCs). Binding TCR to the MHC-peptide complex is essential but not sufficient for activation of T cells after exposure to antigens. T cell activation also depends on additional costimulatory signals (63). Given that lack of co-stimulatory signals prevents T cell activation, blockade of co-

stimulatory pathways has been suggested for modulation of T cell-mediated autoimmunity (64). The role of co-stimulatory pathways in MS pathogenesis has been investigated, and blocking these pathways has been proposed as a potential pharmacological intervention (65).

CD40:CD40L (66) and CD28:B7 (67) pathways are likely to be the critical co-stimulatory axes in MS pathogenesis (65). Furthermore, CD40: CD40L interactions have been suggested to be related to B cell activation, resulting in initiating and propagating rapid and vigorous immune memory responses (68).

Targeting CD40/CD40L co-stimulatory pathway was reported to be effective in amelioration of autoimmunity in an animal model of MS (69). However, thromboembolic events occurred that caused termination of clinical trials in other diseases such as lupus (70). These safety concerns have prevented further testing of any therapy based on inhibition of this pathway.

Inhibition of the CD28:B7 co-stimulatory pathway is now thought to be a more promising approach in modulating autoimmunity (71). Expression of CD28 on T cells and of B7-1 and B7-2 on APCs is believed to be important in T cell activation (69, 72). Inhibition of the CD28-B7 co-stimulatory pathway would likely block activation of T cells. CTLA4Ig (abatacept) is a fusion protein that inhibits CD28, with subsequent interruption of the CD28-B7 co-stimulatory pathway (72, 73). CTLA4Ig appears to be safe and effective in the treatment of some autoimmune diseases (74–77). Further, based on solid data on the efficacy of CTLA4Ig in animal experiments (78), clinical trials using this medication were started in RRMS patients. CTL4Ig has been reported to be safe in phase 1 clinical trials (79), and a phase II trial to clarify the efficacy of CTLA4Ig in RRMS is ongoing (NCT01116427) (70).

2. Targeting B Cells in MS

T cells are thought to be the main immune cells playing a role in the immunopathogenesis of MS. However, oligoclonal IgG bands detected in cerebrospinal fluid (CSF) from MS patients, and B cells found in demyelinating plaques, suggest a role for B cells (7). The role of B cells in MS was substantiated after observing amelioration of disease following B cell depletion (80). B cells could contribute to MS pathogenesis in several possible ways, including antibody production (81), antigen presentation, secretion of regulatory cytokines (82, 83), and as a reservoir for the Epstein-Barr virus (EBV) (84, 85). Although there is controversy about the role of EBV in MS, epidemiologic studies suggest that EBV might play a role. In pathological studies, it has been reported that activated EBV was found in the meninges in SPMS (24) but this observation has not been confirmed by others (86). B cells can also be considered a source for non-immunoglobulin molecules, perhaps cytokines, which diffuse from the meninges into the cortical gray matter (87).

B cells have been targeted in MS with the hope of providing a treatment strategy (Table 1). Rituximab is a humanized monoclonal antibody (mAb) that binds to the CD20 antigen on B cells (except for plasma cells) and is thought to trigger B cell cytotoxicity (88). The drug has a rapid and long-term effect on lowering the number of B cells. Rituximab has been approved for treatment of non-Hodgkin's B cell lymphoma and rheumatoid arthritis (RA) by the FDA.

In MS, rituximab has been effective in decreasing relapse rates and MRI parameters of disease activity (89). Trials are continuing to show the safety and efficacy of rituximab in RRMS patients (90). According to reports on phase II studies, relapse rate and MRI lesions were decreased in RRMS patients receiving rituximab (91). Moreover, in a multicenter trial for PPMS patients, rituximab reduced disease progression in patients younger than 51 years old, and particularly those with inflammatory lesions shown by MRI scan (92). Considering the acceptable toxicity profile and relatively good efficacy of Rituximab, continuation of the trials on RR and progressive MS is warranted. Other antibodies against CD20 on B cells (Ocrelizumab and Ofatumumab) are being also studied in the treatment of MS (93, 94).

Although B cell depletion in MS therapy is somewhat promising, there are doubts regarding the results (95). Some B cell-targeted therapies failed to show efficacy. Blocking receptors for B cell stimulatory factor (BAFF) was not successful (96). This study indicates that B cells play complex roles in MS and that B cell-based therapies need more investigation (97).

3. Targeting Cytokines in MS

The cytokine network shapes a crosstalk system for immune cells involved in the immunopathogenesis of MS. The classification of cytokines as “pro-inflammatory” and “antiinflammatory” can provide a rationale for cytokine-based MS therapy (98) (Table 2). However, there are no reports supporting the targeting of cytokines to treat MS. Interleukin-12 (IL-12) and tumor necrosis factor (TNF) are two examples of unsuccessful efforts. Both cytokines have been reported to be upregulated in MS (99–101). A high serum level of both cytokines has been associated with exacerbation and development of active MRI lesions in progressive and RRMS patients (102–104), findings that led to attempts to target these cytokines in MS (99). Clinically, however, anti-IL-12/23 antibodies have not been reported to be effective in MS (105). Incidence of adverse events was not significantly different across treatment groups, although a numerically greater percentage of serious adverse events was reported for anti-IL-12 antibody-treated groups (105). TNF is a proinflammatory cytokine which has been studied in EAE and MS. TNF has two biologically active forms, soluble and transmembrane (106). Clinical trials using either the non-selective TNF antagonist (lenercept) or anti-TNF antibody (infliximab) reported worsening of clinical symptoms and MRI parameters of disease activity in MS patients (107, 108). However, more recently it has been shown that selective inhibition of soluble TNF significantly suppressed ongoing EAE (109), and it might therefore be effective in MS therapy.

Importantly, recent studies in animal models of MS have shown that granulocyte-macrophage colony-stimulating factor (GM-CSF) is necessary for development of CNS inflammation, and that T cells are its relevant source, indicating that GM-CSF may play a critical pathogenic role in MS (110–111). Indeed, Phase I clinical trials testing the effect of GM-CSF blockade on MS are ongoing and reported to be generally safe (112).

4. Vaccination in MS

Vaccination against T cells, TCR vaccines and DNA vaccines are three investigational approaches to treat MS (Table 3).

T cell vaccination (TCV) is an immunization against pathogenic T cells. It is expected that TCV could modulate the pathogenesis of MS. To develop vaccines, myelin-reactive T cells from the blood or cerebrospinal fluid (CSF) of MS patients are collected, expanded and re-infused to the patients. In response to TCV, regulatory T cells that recognize activation markers on the vaccine cells are expanded (113) and can suppress myelin-reactive T cells (114, 115). It has also been proposed that TCV can stimulate anti-inflammatory cytokine secretion by Th2 cells; this secretion of anti-inflammatory cytokines is independent of the antigen specificity of activated T cells and might be an immunomodulatory consequence of TCV (116).

TCV has been reported to provide resistance to EAE induction and reduction of relapse rate in EAE-induced animals (113, 117, 118). In clinical trials, a modest reduction in relapse rate was reported in vaccinated individuals with RRMS (119–121). In RRMS patients who did not respond to first-line medications, TCV was claimed to be effective (122). In a study of 4 SPMS patients, TCV has been reported effective in depleting myelin-reactive T cells, with no obvious clinical improvement (i.e., two patients were stable, one with reduced EDSS, and another one with advanced EDSS) (123). More recently, the first controlled, double-blind trial with TCV in relapsing progressive MS has been performed by Karussis et al. TCV significantly improved the walking capacity of patients, with the relapsing rate reduced by 89.6% vs. 42.9% in placebo treatment, while no significant changes were observed in MRI parameters. Importantly, the feasibility and safety of this treatment have also been demonstrated (124).

TCR Vaccines (TCRV): TCRs are essential for antigen recognition and subsequent activation of T cells. Certain variable regions (V-region) of TCRs are over-expressed on pathogenic T cells in MS patients, and V-regions have been used in the development of TCRV (125–126). TCRV has been reported to be safe and effective in decreasing the relapse rate in MS patients. Clinical improvement after TCRV has been attributed to enhanced function of regulatory T cells that recognize TCR determinants (127–129).

DNA Vaccines are induced by injection of pieces of DNA, constructed by genetic engineering. DNA vaccines contain "antigen coding genes" (130). It has been hypothesized that these DNA pieces are integrated into the genome and cause cells to produce antigens of a specific type. Hypothetically, production of autoantigens induces tolerance. Based on these assumptions, different types of DNA vaccines encoding myelin antigens have been tested in EAE. Some reports support protective effects of DNA vaccines in EAE, but this is controversial (131–143). Studies on human vaccines are limited. A DNA vaccine encoding the full-length MBP molecule (BHT-3009) was reported to be safe during a phase I/ II clinical trial (144). In a phase II trial, BHT-3009 was claimed to reduce lesions in MRI (145). However, neither improvement in clinical outcomes, nor neuroprotective effects have been documented (146, 147).

Overall, T cell vaccination and T cell receptor vaccination studies have been limited and not particularly impressive. Further studies are required to advocate vaccination in MS therapy.

5. Induction of Tolerance in MS

Immunologic tolerance is a condition in which the immune system cannot respond to a specific antigen as a consequence of previous exposure. This process can prevent or decrease the immune response to self-antigens. Central tolerance occurs in the thymus, and peripheral tolerance develops in the blood; both processes include deletion and functional unresponsiveness of auto-reactive lymphocytes (148). Expansion of regulatory T cells is also seen during development of tolerance. By eliminating these harmful cells through tolerance, autoimmunity could be prevented (148). Some T cells, however, may escape elimination and remain in the repertoire (149). If these T cells are reactivated by triggering factors, they could likely contribute to the pathogenesis of autoimmune diseases including MS (150). Indeed, myelin-reactive T cell lines have been established from healthy subjects, indicating failure for central tolerance for myelin antigen reactive T cells (151). Induction and amplification of peripheral tolerance to eliminate or modify self-reactive T cells is believed to be a potential treatment strategy for autoimmune states (18). To induce tolerance, tolerogenic antigens can be administered by different routes (intravenous, intranasal or oral) (152).

Induction of tolerance has been examined in numerous EAE/MS studies. In EAE animals, intravenous tolerance induction resulted in clonal deletion (153) of myelin-specific T cells and expansion of regulatory T cells (154–156). In addition, reduced disease severity in chronic EAE was seen. However, no further prevention of disease progress has been documented (157, 158). Furthermore, therapeutic treatment of EAE animals with antigens appears to be less effective than prophylactic antigen infusion before EAE induction (154, 159).

One route of antigen-specific tolerance induction is via oral mucosa. The oral administration route has specific characteristics in tolerance induction. The mucosa of the gut is equipped with a vast immune system that can process orally ingested antigens (160). Sustained interface of an antigen with the gut immune system might provide a “mucosal tolerance” against the antigen. Oral administration of tolerogenic antigens has been found to modulate the course of EAE in animals (161, 162). Clonal deletion of “antigen-specific autoreactive T cells” and induction of regulatory T cells (163, 164) have been suggested as mechanisms of action.

Earlier clinical trials in MS patients reported that oral tolerance was effective in disease modulation (165). Unfortunately during a larger trial, those favorable results (163) were not confirmed. This discrepancy may be due to the diverse doses of antigens tested (166). In a randomized, placebo-controlled phase 1/2 trial, it was found that induction of antigen-specific tolerance in MS with DNA encoding MBP (BHT-3009) effectively reduced antigen-specific immune responses both in the peripheral immune system and the CNS, with good safety and tolerability (167). Studies for the long-term clinical efficacy of antigen-specific tolerance induction in MS patients are required.

Nasal mucosa is another route for delivery of antigens to develop tolerance (168, 169). Intranasal administration of antigens to EAE-induced animals has been reported to modulate disease course (170); however, studies in human MS are still lacking.

Another approach to induce tolerance is attachment of antigens to splenocytes or blood cells and infusing those cells. This “cell-bound tolerogenic peptide method” can be used for tolerization against several antigens, thereby extending tolerogenicity to a more general array of antigens involved in the pathogenesis of MS. By using this method in animals, inhibition of induction and modulation of relapses in EAE has been achieved (171–173).

6. Stem cell-based therapies in MS

Bone marrow-derived mesenchymal stem cells transplantation has had both neuro-regenerative and immunomodulatory effects in MS. These cells as well as hematopoietic stem cells are easily obtained from adults; their therapeutic application is believed to be safe and to have the potential of playing a pivotal role in MS therapy (174–176). As regards immunomodulation and neuroprotection exerted by stem cells, this method could have potential as a therapeutic approach for MS.

Conclusion

While great progress in MS therapy has been made in the last two decades, current therapies are still largely ineffective, with potential side effects such as serious toxicities or global immunosuppression. Due to a better understanding of MS immunopathogenesis in recent years, new candidates have been introduced as therapeutic targets, including specific molecules on the surface of pathogenic CD4⁺ T and B cells, as well as the soluble products of these cells, e.g., proinflammatory cytokines. Further, promising findings have been obtained in the induction of myelin autoantigen-specific tolerance without disturbing the global immune system; these novel approaches will increase specificity and efficacy and reduce potential side effects such as global immunosuppression in future MS therapy. Nevertheless, their validation as practical MS therapies is dependent on the final favorable results. Further, although these immunomodulatory therapies are beneficial in preventing future CNS tissue damage, neuroregenerative approaches to reconstitute already damaged CNS tissues, e.g., demyelination, axonal loss and neuronal loss, will be of great importance in maximizing recovery of neurological functions.

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Table 1

Targeting T and B cells in MS

TARGETING T AND B CELLS IN MULTIPLE SCLEROSIS			
Targeting Markers on T Cells			
Pharmacological Target	Experimental Results if Available	Clinical Outcomes	References
<i>CD4+ T Cells</i>	Effective in EAE	No long-term benefits	(21,177)
<i>CD52+ Cells</i>	Effective in EAE	FDA-approved drug (Alemtuzumab)	(16, 178)
<i>CD25 (IL-2R)</i>	Effective in EAE	Drug under study (daclizumab)	(39, 179)
Targeting T Cell Activation in MS			
Altered Peptide Ligands			
<i>MBP</i>	Effective in EAE	No evidence of clinical benefit to date	(51, 54)
<i>MOG</i>	Effective in EAE	No evidence of clinical benefit to date	(59, 61)
Targeting T cell Co-stimulatory Pathways			
<i>CD40/CD40L</i>	Effective in EAE	Studies discouraged due to suspected risks of adverse effects	(69–70)
<i>CD28:B7</i>	Effective in EAE	Reported safe in phase I trials	(78–79)
Targeting Markers on B Cells			
CD20	Effective in EAE	Clinical trials ongoing On Rituximab	(91, 180)

Table 2

Targeting cytokines in MS

Pharmacological Target	Clinical Outcomes	References
<i>IL-12/IL-23 (p40)</i>	Not effective in MS	(105)
<i>TNF</i>	Not effective in MS Neither TNF antagonist nor Anti-TNF antibody	(107–108)
<i>GM-CSF</i>	Phase I clinical trial ongoing	112

Table 3

Vaccination in MS

Pharmacological Target	Clinical Outcomes	References
<i>TC Vaccine</i>	Promising in some clinical aspects, but not MRI measures	(124)
<i>TCR Vaccine</i>	Some effectiveness reported	(128)
<i>DNA Vaccine</i>	Few human trials, some promising results	(145)