Toward the Development of Rational Therapies in Multiple Sclerosis: What Is on the Horizon?

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Although the cause of multiple sclerosis (MS) has remained obscure, many findings support an autoimmune pathogenesis on the background of a complex interaction between multiple genes and environmental factors. Accordingly, targeting the immune system has been a rational approach for the treatment of MS. The development of disease-modifying immunomodulatory drugs with partial efficacy, coupled with advances in understanding the pathophysiology and pathology of MS, has provided momentum to explore more specific and hopefully more effective immune-based therapeutic strategies. With increased knowledge and appreciation of the contribution of neurodegenerative processes to disease pathology, the therapeutic challenges, however, have become even more formidable. Future treatments will likely need both to target inflammation and to focus on promotion of neuroprotection and repair. In this review, we discuss the most promising therapeutic approaches for MS currently in the pipeline.

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The complexities of multiple sclerosis (MS) still pose a major challenge in translating progress in understanding disease pathology and pathogenesis into novel therapies. One of the major obstacles arises from the lack of in vitro and in vivo models that faithfully reflect the heterogeneous human disease. Although in vitro test systems involving human autoreactive T cells, antibodies, or innate immune cells may be of value to obtain some general clues on the mode of action of MS therapeutics, their value to predict activity in in vivo systems is limited. More instructive are animal models of autoimmune- or virus-induced demyelination.[1,2] The model most commonly used, experimental autoimmune encephalomyelitis (EAE), has significantly advanced our knowledge of autoimmunity in the central nervous system (CNS) but has unfortunately so far been less successful in deciphering the cause of MS. Currently, it is believed that traditional EAE models mirror quite well some of the features characteristic of MS (eg, CNS damage mediated by $CD4^+$ T cells and macrophages), whereas other features of MS are poorly replicated (eg, CNS damage mediated by $CD8^+$ T and B cells, neurodegeneration in the absence of inflammation).[1,3] The limitations of EAE may explain, in part, the discordant treatment effects observed with a number of therapeutic agents (eg, tumor necrosis factor-α [TNF-α] blockers) in EAE and MS.[4,5] Newer EAE models have been designed to replicate B-cell and $CD8^+$ T-cell–mediated demyelination and axonal damage.[3,6–9] Also, humanized mouse models have been generated that may be better suited to address the intricacies of immunological changes operative in MS.[10,11] Models of primary neurodegeneration may also be appropriate to study MS-associated axonal pathology, but these have not yet been applied in this context.

A second challenge for the development of new therapies is the likely heterogeneity of the disease, perhaps reflecting the highly variable disease course and the existence of distinctive subgroups or variants of brain pathology.[12,13] This heterogeneity not only challenges the development of appropriate animal models but also the design of clinical studies to explore new therapies.

Immune-Directed Therapies

Given the prominence of inflammatory changes in acute MS lesions, therapy of the disease has focused for the past three decades on antiinflammatory strategies (Figs 1 and 2). The development of immunological treatment started with more or less broad-based antiin-

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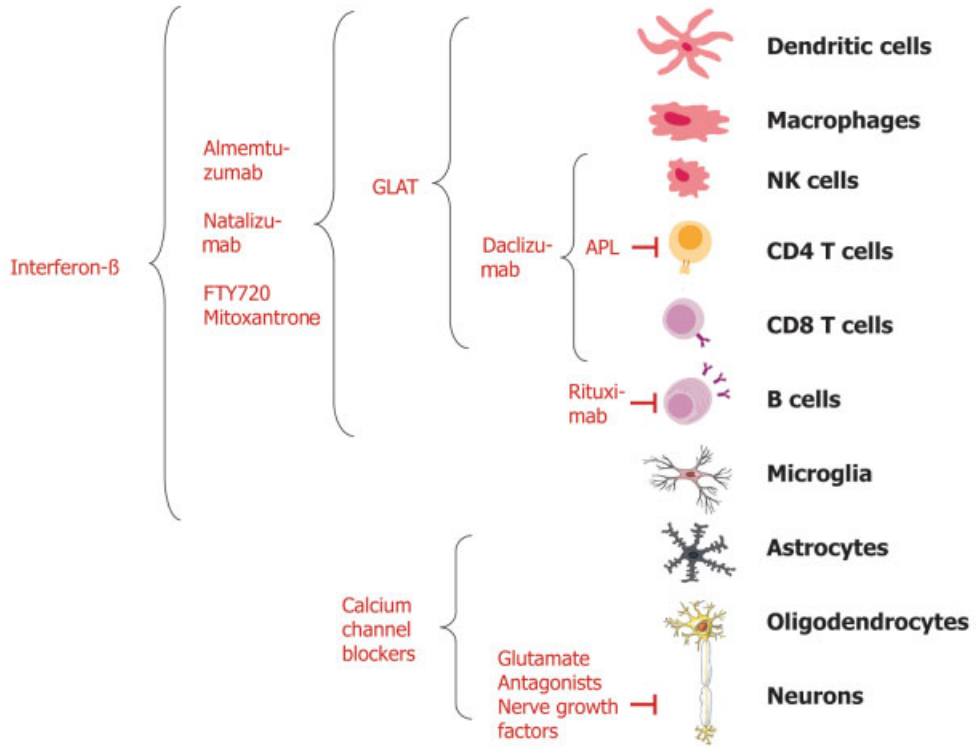

Fig 1. Targets of the various established and emerging antiinflammatory therapies in multiple sclerosis. APL = altered peptide ligand; NK = natural killer; GLAT = glatiramer acetate.

flammatory and immunosuppressive drugs, and has advanced to increasingly selective and specific interventions.

Immunosuppression

The first breakthrough came with the use of steroids in the treatment of relapses, which shorten the duration of the relapse and may in addition have some long-term effects on disease activity.[14,15] Global immunosuppression with drugs effective in preventing organ transplant rejection, such as azathioprine, cyclosporin, methotrexate, and cyclophosphamide, provided additional clues that interfering with immunoinflammatory processes may modify disease activity in relapsing remitting MS (RR-MS).[16–19] Following this path, the efficacy of newer immunosuppressive drugs such as mitoxantrone was established. Mitoxantrone not only reduces relapse rates but may arguably slow disease progression in highly active MS patients.[20–23] It may interfere with antigen presentation, diminish several lymphocyte subsets, decrease proinflammatory cytokines, and attenuate migration of different immune cell subsets via inhibition of matrix metalloproteinases.[24,25] Given its potential cumulative cardiotoxicity, the duration of treatment is, however, limited.[26] The structurally related aza-anthracenedione pixantrone (BBR 2778) appears to be far less cardiotoxic, has been demonstrated to attenuate EAE, and may soon be examined in MS.[27]

New immunosuppressive drugs with fewer side effects have been developed and are currently being evaluated in clinical trials. Laquinimod (ABR-215062) is an orally bioavailable quinoline-3-carboxamide; it is an analogue of linomide (roquinimex), whose development was terminated because of severe negative side effects (endocarditis, serositis). Laquinimod has shown efficacy in EAE. In two phase II trials, involving 209 and 306 RR-MS patients, respectively, a high dose (0.3 or 0.6mg/day orally) was superior to placebo after 24 weeks in reducing the number of active magnetic resonance lesions (Table).[28–30] A larger phase III trial in RR-MS patients is under way. Similarly, the purine nucleoside analogue cladribine (Mylinax), an orally bioavailable compound with profound and long-lasting lymphocytotoxic activity, has been successfully tested in EAE and a phase II trial.[31,32] A large phase III trial is currently ongoing.

Teriflunomide belongs to the group of malononitrilamide agents that block the mitochondrial enzyme dihydro-orotate dehydrogenase and inhibit T- and B-cell proliferation.[33,34] It is closely related to leflunomide, which is an approved therapy for rheumatoid arthritis. Teriflunomide abrogated EAE, probably via suppression of the production of TNF-α and

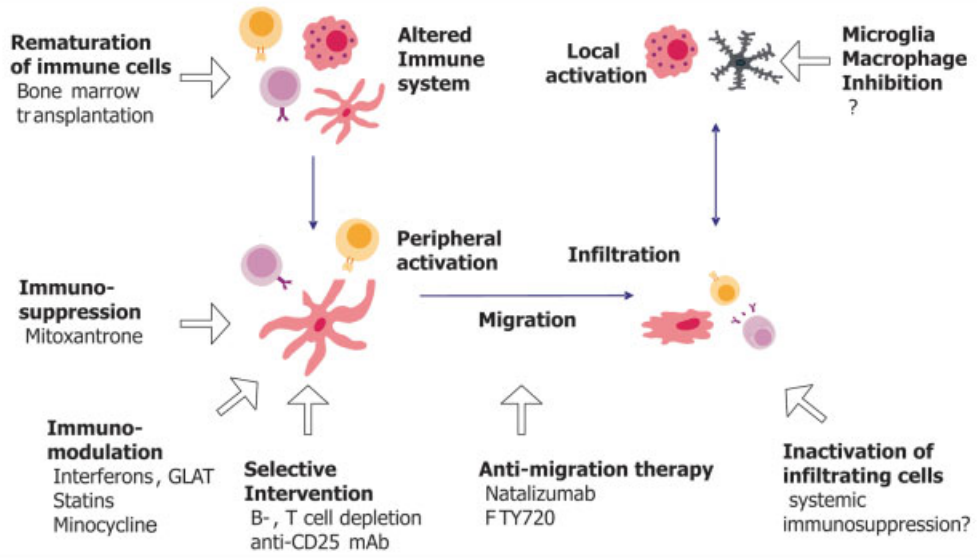

Fig 2. Therapeutic intervention in multiple sclerosis based on the hypothetical models of disease pathogenesis. mAb = monoclonal antibody.

interleukin-2 (IL-2).[35,36] The results from a clinical phase II study in 179 patients with relapsing MS and 157 patients with secondary progressive MS (SP-MS) comparing placebo with 7 and 14mg/day study drug administered over 36 weeks have recently been published (Table).[37] The primary end point of the study was met: Subjects receiving teriflunomide had significantly fewer new and active MS lesions on magnetic resonance imaging (MRI). Extended Disability Status Scale progression was also delayed with the higher dose, and a trend toward reduction in relapses was observed. Overall, teriflunomide was well tolerated, with upper respiratory tract infections and headache as the most common adverse effects. The safety and efficacy of the drug in MS are being further investigated in an ongoing phase III trial. Newer members of this class of immunosuppressants with shorter half-lives, FK778 and FK779, are being assessed in phase II trials in transplantation.

Other orally active and well-tolerated broad-based immunosuppressants (eg, mycophenolate mofetil, tacrolimus), which have been used in other autoimmune diseases, are currently being evaluated in small pilot trials in MS.[38] The macrolide temsirolimus (CCI-770), a derivative of rapamycin, like tacrolimus, belongs to the family of mammalian target of rapamycin inhibitors.[39] It inhibits T- and B-cell proliferation and has demonstrated efficacy in a phase II trial in RR-MS.[40]

Treosulfan, L-threitol-1,4-bis(methanesulfonate), is a bifunctional alkylating agent with a favorable side effect profile that is approved for the treatment of ovarian cancer. In vitro, it inhibits proliferation and induces apoptosis of mononuclear cells. It inhibits EAE, has shown promising results in a small number of patients with SP-MS, and is currently under investigation in a phase II study.[41,42]

Immunomodulation

CYTOKINES AND THEIR INHIBITORS. Based on the success of the β-interferons, many other cytokine-based therapies were studied in EAE and some in MS. The main rationale was derived from the EAE models and aimed at converting a proinflammatory Th1 or Th17 response (IL-17–producing T cells) into an ameliorating Th2 response.[43] The strategies included silencing of proinflammatory cytokines (eg, TNF-α, IL-12) or promoting Th2 cytokine responses (eg, IL-4, IL-10). In particular, silencing TNF-α was extensively studied in EAE and MS. Whereas TNF-α antibodies and TNF-receptor blockers were highly active in EAE and other human autoimmune diseases (eg, rheumatoid arthritis), TNF blockade unexpectedly increased relapse rates in MS.[4] Similarly, all other approaches involving administration of cytokines or specific blockade of their receptors failed either because of lack of efficacy or more frequently because of adverse effects.[44] Recent advances involving small molecules that bind or inactivate particular cytokines or cytokine groups may revive the field of cytokine-based therapies.[45] Future directions in this area may not exclusively focus on T-cell cytokines but are likely to also consider molecules active in the innate immune or B-cell response such as atacicept, a recombinant fusion protein containing the extracellular domain of the transmembrane activator

and CAML-interactor (TACl) receptor and the Fc portion of human IgG. (eg, BLyS/BAFF, IL-6).[46–48]

IMMUNOMODULATORS WITH BROAD MODES OF ACTION. Besides the highly specific and potent immunologically active compounds listed earlier, a number of drugs with immunomodulatory properties and approved for treatment of other diseases have been explored for their therapeutic efficacy in EAE and potentially in MS. These include statins (eg, simvastatin),[49–53] peroxisome proliferator-activated receptor agonists (eg, pioglitazone, gemfibrozil),[40,54,55] substance P receptor blockers,[56,57] and the sex hormone estriol.[58,59] Many of these drugs not only have immunomodulatory properties but may also influence neurodegeneration and neural repair. Some of these compounds have shown promising results in pilot trials and are currently being evaluated in phase II trials in RR-MS as monotherapies or add-on therapies.[60,61]

Another immunomodulating drug is fumaric acid, which is used for the treatment of psoriasis. Because of side effects, novel fumaric acid esters (BG12, dimethyl fumarate) have been developed with better tolerability and tested in RR-MS.[62,63] Results of a phase II trial of BG12 were promising,[51] and the clinical utility of this drug is currently being studied in two large phase III trials. This agent may operate not only by promoting a shift toward Th2 cytokines, it may also have neuroprotective activity, acting on the Nfr2-ARE signaling pathway and resulting in the generation of antioxidant and detoxifying enzymes.[64,65]

ANTIGEN AND ANTIGEN-RECEPTOR–BASED THERAPIES. Expectations that more selective interventions might yield more effective and safer treatments have fueled investigations into strategies that interfere at crucial checkpoints in the activation of pathogenic T cells. Antigen-based therapies are aimed at silencing autoreactive, myelin protein–specific T cells. A number of strategies were developed in the EAE model including administration of autoantigenic peptides (via oral, nasal, or subcutaneous administration), major histocompatibility class-peptide complexes, altered peptide ligands, and DNA vaccination with myelin genes.[68–75] Based on their efficacy in EAE, some of the strategies entered clinical phase II and III trials. These include the use of autoantigenic peptides, altered peptide ligands, and oral myelin.[5,76–79] Thus far, all antigen specific therapies have failed, either because of side effects, lack of efficacy, or both. DNA vaccination with a myelin basic protein construct (BHT 3009) administered intramuscularly has been studied in 30 patients with RR-MS and SP-MS in a phase Ib/IIa trial with a crossover design and was found to be safe, well tolerated, and to generate possibly beneficial immune changes such as decreases in interferon-γ–producing T cells and myelin-reactive antibodies. It showed a trend toward beneficial effects on MRI.[74] Preliminary results of a phase IIb placebo-controlled three arm trial in patients with RR-MS have partially confirmed these results in a subgroup of patients harboring myelin basic protein antibodies.[80] Presumably, these findings will prompt a larger study. Complementary DNA vaccination may be more potent than peptide therapy, but the immune responses that are induced might also be more difficult to control. Although antigen-specific therapies may be the ideal approach for the treatment of autoimmune disease, currently too little is known about the molecular targets attacked by the immune system in MS to reasonably expect major breakthroughs in the near future. Designing such tailor-made therapies and products for individual patients may also be hampered by feasibility and economic obstacles. Finally, such precise interventions may be effective only early in MS. As the disease evolves, an initially focused autoimmune response may broaden to include a variety of targets and may then no longer be responsive to such antigen-specific therapies.[81]

SELECTIVE DEPLETION OF IMMUNE CELL SUBSETS. The development of humanized monoclonal antibodies has permitted the targeting of specific immune cell subsets based on the expression of specific membrane proteins. Although administration of a $CD4^+$ T-helper-cell–directed antibody did not ameliorate the course of MS, alemtuzumab (Campath), a human monoclonal antibody targeting the CD52 antigen expressed by T and B cells, which produces long-term T-cell depletion, showed highly promising results in a phase II trial in RR-MS.[82,83] In a head-to-head comparison trial of alemtuzumab (24 or 12mg/day daily five times at month 0 and three times at months 12) with interferon-β1a (44μg three times weekly), alemtuzumab diminished the number of active lesions measured by MRI, and most remarkably resulted in a 75% reduction in relapse rate and disability progression after 2 years (Table).[84] Unfortunately, this highly active therapy was accompanied by significant side effects including autoimmune hyperthyroidism in more than 10% of treated patients and rarely by idiopathic thrombocytopenic purpura. Nevertheless, given the current evidence for its most impressive efficacy, a decision has been made to move forward with this monoclonal antibody in two large phase III trials.[85] Alemtuzumab may be effective only in relapsing MS because no therapeutic effect was observed in a small cohort of SP-MS patients.

Promising results were also obtained in small pilot trials with a monoclonal antibody against CD20 (rituximab), which efficiently depletes B cells from blood and cerebrospinal fluid.[86–90] Although this antibody does not eliminate plasma cells in the bone marrow, and therefore has few effects on the pre-existing pro-

tective antimicrobial antibody repertoire, it may impair antibody formation during active infection.[91] In a phase II trial in RR-MS, a significant reduction of relapses and gadolinium-enhancing T1 lesions on serial MRI scans of the brain in the rituximab-treated group compared with placebo was noted.[92] These promising results have resulted in the development of two definitive phase III trials that should begin shortly. Previously, a case series reported efficacy of rituximab in neuromyelitis optica.[87] In addition, rituximab is currently under investigation in a phase II/III trial in primary progressive MS; results are expected in 2008. Other agents that target B-cell markers (eg, CD19) or B-cell differentiation/proliferation factors (eg, BLyS/BAFF) are under development for other autoimmune diseases and may also be applied to MS in the near future.[45,46,93,94] As with other immunosuppressive therapies, the degree to which chronic B-cell depletion may impair protective immune surveillance and predispose to opportunistic CNS infections such as progressive multifocal leukoencephalopathy (PML) is a theoretical concern.[95,96]

SELECTIVE BLOCKADE OF CORECEPTORS AND COSTIMULATORY MOLECULES. Promising results were obtained with an anti-CD25 monoclonal antibody (daclizumab). This antibody directed to the α chain of the IL-2 receptor inhibits activated T cells and appears to induce regulatory CD56bright natural killer cells.[97] In RR-MS patients, a reduction in disease activity was observed in two pilot trials.[98,99] This was confirmed in a recent small phase IIa trial in nine patients with continued disease activity despite interferon-β therapy who received daclizumab for up to 27.5 months.[100] Other strategies similarly aim to promote regulatory cells.[101] One of the approaches involves oral administration of anti-CD3 monoclonal antibodies, which ameliorate EAE by inducing a subset of regulatory $CD4^+CD25^+$ T cells.[102,103]

The fusion protein CTLA-4 immunoglobulin, successfully used in psoriasis and arthritis, blocks CD28/B7 interactions during activation of naive and activated T cells.[104] It promotes passive cell death caused by growth factor withdrawal and curtails expansion of (auto)antigen reactive T cells, thereby establishing antigen-specific tolerance. Furthermore, it induces indoleamine-2,3 dioxygenase on dendritic cells, and hence indirectly abrogates activation of naive T cells. However, there is the potential danger that pathogenic T-cell activity might be enhanced after blockade of CD28/B7 interactions.[105] In addition, an early phase II trial in MS was stopped prematurely because of severe thromboembolic complications. Similarly, an anti-CD28 antibody (TGN1412), which ameliorated EAE by expanding regulatory T cells, was recently tested in a phase I trial in healthy control subjects.[106] This agent, designed for the treatment of autoimmune diseases including MS, had devastating acute and possibly chronic side effects.[107]

Migration Modifying Therapies

ADHESION MOLECULES. The initial contact between leukocytes destined to enter the CNS and endothelial cells of the blood–brain barrier activated by cytokines is mediated, in part, by α4-integrins. Very Late Antigen-4 (VLA-4) on T cells is made up of α4/β1 integrins and binds to vascular cell adhesion molecule-1 on endothelium.[108] This knowledge was exploited to design a therapy that by disrupting this interaction would prevent egress of T cells from the blood into the brain. Seven years after demonstrating the feasibility of such an approach utilizing a monoclonal antibody to α4 integrin in EAE, the first positive results in MS were achieved with a humanized antibody to this molecule. Positive results in the largest ever conducted phase III trial in RR-MS led to approval of this drug, natalizumab, in the United States in 2004 and in Europe in 2006. Natalizumab reduced relapse rates by more than two thirds and slowed disease progression during a 2-year observation period.[109–112] Inhibition of immune cell migration to the CNS, however, had rare but serious side effects.[90] In 0.1% of patients, PML occurred, leading to the death of two patients and severe incapacity in a third. As of July 2007, with more than 17,000 patients receiving natalizumab therapy, no further cases of PML have been identified. Of the three known cases of PML, two patients with MS had received combination therapy with interferon-β, and the third with Crohn's disease had been pretreated with other immunomodulators and immunosuppressants. It is therefore tempting to speculate that effective global suppression of immune reactions may compromise immune surveillance of the CNS toward potentially noxious agents such as JC virus.[95] However, a more specific action of natalizumab mobilizing from the bone marrow JC virus–infected B cells, which carry the virus to the CNS, has also been proposed.

Currently, natalizumab appears to be the most effective treatment for RR-MS. Unanswered questions remain concerning the long-term adverse effects in patients receiving natalizumab.[113,114] A number of nonantibody prototypes of this class are small molecule antagonists, which are particularly attractive given their oral bioavailability.[103] Some are now undergoing phase II trials in RR-MS.

SPHINGOSINE 1-PHOSPHATE RECEPTOR AGONISTS. A second antimigratory strategy capitalizing on a different pathway has been pursued with a sphingosine 1-phosphate receptor 1 agonist, fingolimod (FTY720;

fingolimod), which showed highly promising results in EAE and in a phase II trial in MS.[115,116] After in vivo phosphorylation, FTY720 forms FTY720P, a high-affinity nonselective lipophilic mimetic of the sphingosine 1-phosphate receptor 1, necessary for lymphocyte egress from lymphoid tissues.[117,118] After engagement through the agonist, the sphingosine 1-phosphate receptor 1 is internalized and can no longer bind to its natural circulating ligand, sphingosine 1-P. As a consequence, the agent entraps $CD4^+$ and $CD8^+$ T cells and B cells in secondary lymphatic organs, preventing them from being recruited to possible sites of inflammation.[119] This entrapment of lymphocytes appears to depend largely on the expression of different chemokines.[120] Furthermore, recent studies imply also a direct impact of FTY720 on dendritic cells.[121] Because of its mechanism of action, FTY720 induces a marked lymphopenia in peripheral blood counts but does not provoke general immunosuppression, because neither the activation of T cells nor memory T- and B-cell responses are impaired. It crosses the blood-brain-barrier and can bind to the SP-1 receptors on oligodendrocyte precursor cells. Receptor engagement eventually results in process extension and enhanced survival implicating a potential remyelinating effect of FTY720. Two large phase III trials of this agent comparing 1.25 mg and 0.5 mg versus placebo are in progress.[122]

CHEMOKINES AND THEIR ANTAGONISTS. This group of low-molecular-weight cytokines are intimately involved in leukocyte trafficking.[123] Together with their cognate receptors, they are upregulated in inflammatory diseases and hence represent attractive targets for therapeutic intervention, in particular because chemokines act on G-protein–coupled receptors. Such an approach might involve the use of small molecule antagonists available in oral formulations. The multiplicity of chemokines, their overlapping functions, and their promiscuous binding pattern to numerous receptors displayed on many immune and inflammatory cells, however, represent significant obstacles to successful drug development.[123,124] The redundancy of this system makes it unlikely that blockade of one single receptor may have a major impact on the underlying disease process.

The first attempt to intervene at the level of chemokines was undertaken with a CCR1 receptor antagonist that had shown promise in the animal model of EAE. Unfortunately, no significant effect was seen in a phase II trial.[119] Several further phase I/II studies assessing the potential utility of other chemokine receptor antagonists (eg, directed against CCR2 and CCR5) are currently under way.

MATRIX METALLOPROTEASES. There is accumulating evidence that different members of the matrix metalloprotease (MMP) family mediate fundamental steps in the development of inflammatory demyelinating disorders, such as cell migration, blood–brain barrier disruption, demyelination, and cytokine activation.[125,126] Secreted by activated T cells, MMPs enzymatically digest nonfibrillar collagen in the extracellular matrix of the blood–brain barrier, promoting penetration of inflammatory cells into the CNS. MMP inhibitors prevented or ameliorated inflammatory CNS demyelination in EAE, and these data generated hope that MMPs may serve as suitable targets for the treatment of MS. Unfortunately, early available MMP blockers had unacceptable side effects. More recently, based on their chelating properties, tetracyclines and chemically modified tetracyclines were identified to be capable of blocking MMP activity independent of their antimicrobial activity.[127] The tetracycline minocycline has attracted increasing interest as a therapeutic agent for the treatment of various neurological diseases. Its effects in EAE are controversial. In a small, open-label trial in which 10 patients with RR-MS were treated with minocycline, there was a suggestion of a possible effect on MRI activity.[128–130] Controlled follow-up studies are currently under way. It should be noted that additional properties of minocycline may be relevant to its actions in MS such as deactivation of microglial cells and prevention of neuronal apoptosis.[125]

Neuroprotection and Neurorepair

Neuroprotective Agents

A number of therapeutic approaches, mainly derived from studies of animal models of primary degenerative disorders, have been applied to MS. Glutamate antagonists (eg, riluzole), sodium channel blockers (eg, flecainide, phenytoin, lamotrigine), calcium and potassium channel blockers, cannabinoid receptor antagonists, and erythropoietin have produced salutary effects in the EAE model.[131–142] Although these drugs may exert neuroprotective effects, their impact on the immune system may not always be beneficial, as recently demonstrated for sodium channel blockers in EAE.[143] Although some of these substances have been brought to clinic in pilot trials,[144,145] a current limitation is the lack of robust clinical and surrogate markers of the neurodegenerative process in MS.

Promoting Repair: Neurotrophic Factors and Cell Therapies

Besides protecting axons and glia from inflammatory damage, facilitating repair is another promising future direction for MS therapy. Theoretically, two strategies have been advanced, which involve boosting of endogenous repair mechanisms and cell replacement therapies.[146] Although premyelinating oligodendrocytes are present even in chronic lesions, they appear to be

Table. **Selected Promising Therapeutic Strategies for Multiple Sclerosis in Clinical Development (Phase II and Beyond)**

Drug (Reference)	Phase	Indication	N	Design	Duration (wk)	Results	Status
Alemtuzumab (77)	II	RR-MS	334	RB, MC, PC, RD IFN-β-1a 3 × 44μg vs 12mg daily vs 24mg daily intravenously 5 infusions alemtuzumab	104–156	Relapse-rate reduction, slowed disease progression Positive impact on all secondary MRI outcomes	Phase II completed Phase III studies (PC and active comparator/IFN-β-1a subcutaneously)
Fingolimod/ FTY720 (10)	II	RR-MS	281	DB, MC, PC, RD; 1.25mg, 5mg vs placebo (three-arm)	24	Significant effect on the total number of Gd^+ lesions on MRI (primary end point) Reduction of relapses (secondary end point)	Two phase III studies (placebo controlled and active comparator/IFN-β-1a intramuscularly)
Fumaric acid/ BG12 (59)	II	RR-MS	257	DB, MC, PC, RD; 120mg, 360mg, 720mg vs placebo (four-arm)	24	Significant effect on the total number of Gd^+ lesions on MRI (primary end point) Reduction of relapses (secondary end point)	Two phase III studies (placebo controlled and active comparator/glatiramer acetate subcutaneously)
Laquinimod (164)	II	RR-MS	180	DB, MC, PC, RD; 0.3mg vs placebo (two-arm)	24	Significant effect on mean cumulative number of active MRI lesions Reduction of relapses (secondary end point)	Phase III
MBP8298 (73)	II	Progressive MS	32	DB, SC, PC, RD; 500mg vs placebo (two-arm)	104	No overall significant difference in disease progression; however, statistical significance in HLA-defined subgroups (DR2 and/or DR4)	Phase II
Rituximab (85)	II	RR-MS	104	DB, MC, PC, RD; 2 × 1gm rituximab vs placebo (two-arm)	24-48	Significant effect on total number of Gd^+ lesions on MRI (primary end point); Reduction of relapses (secondary end point)	Phase II in PP-MS ongoing Phase III in RR-MS to be initiated
Teriflunomide (34)	II	RR-MS	179	DB, MC, PC, RD; 7mg, 14mg vs Placebo (3-arm)	36	Significant effect on the number of active lesions and new lesions on MRI Reduction of relapses (secondary end point)	Phase III

RR-MS = relapsing remitting multiple sclerosis; RB = rater blind; MC = multicenter; PC = placebo-controlled; RD = randomized; IFN = interferon; MRI = magnetic resonance imaging; DB = double blind; Gd^+ = gadolinium enhancing; MBP = myeline basic protein; SC = single center; HLA = human leukocyte antigen; PP-MS = primary progressive multiple sclerosis.

largely incapable of promoting remyelination. Despite the limited knowledge about the factors involved in remyelination, a number of substances that enhance oligodendrocyte precursor cell migration and differentiation (eg, insulin-like growth factor, nerve growth factor, transforming growth factor-β) have been assessed in EAE models with variable results.[147] Transforming growth factor-β was the only substance tested in a pilot trial in MS, but the trial was stopped because of negative side effects.[148] These agents are not only difficult to deliver to the CNS but can have serious side effects, possibly including enhancement of tumor growth. It may be nonetheless worthwhile to assess the potential utility of a range of gliotrophic and neurotrophic factors to stimulate remyelination and to promote survival of axons under immunological attack and facilitate their regrowth.[149,150] Another approach would be to neutralize inhibitors of remyelination or axonal sprouting, such as LINGO, a component of the NgR1/p75/LINGO-1 and NgR1/TAJ(TROY)/LINGO-1 signaling pathway, by utilizing a monoclonal antibody against LINGO modified to lack injurious effector functions.[151,154]

The potential for stem cell transplantation has attracted much interest.[155,156] Trials in EAE models have shown that injected neural precursor cells can home to the CNS and locally differentiate into astroglial and oligodendroglial precursor cells, obviating the need to transplant them invasively. These injected cells may protect against further inflammatory attacks by inducing apoptosis of infiltrating encephalitogenic T cells.[157–160] Indeed, evidence is accumulating that neural stem cells may not primarily act to replace myelin-generating cells, but rather serve as vehicles for the release in situ of immunomodulatory molecules.[161–163]

Alternatively, replacement therapies may be based on embryonic or on adult stem cells generated from autologous Schwann cells, bone marrow, skin, sperm, olfactory bulb or cord blood.[164,165] Although these strategies are innovative and may impact on both immune attack and repair processes, numerous ethical and technical problems have to be resolved before stem cell transplantation can enter clinical trials in MS. Autologous hematopoietic stem cell transplantation involves mobilization of autologous hematopoietic stem cells, myeloablative immunosuppression, and reinfusion of hematopoietic stem cells. Autologous hematopoietic stem cell transplantation has been tried in MS, and several reports suggest benefit in patients with aggressive inflammatory disease, but this remains controversial.[166–169] The jury is still out on which stage of MS this invasive and potentially dangerous procedure may be effective. Autologous hematopoietic stem cell transplantation could conceivably work by inducing long-term suppression or eradication of an autoaggressive immune response allowing the reestablishment of tolerance to self-antigens.[170] Unfortunately, clinical, MRI, and recent neuropathological evidence suggests that although this procedure is effective against inflammation, unfortunately, demyelination, neurodegeneration, and atrophy appear to inexorably continue.[171–174]

Conclusions

During the past decade, significant progress has been made in the treatment of MS. Natalizumab represents the first highly targeted therapy whose development was made possible by advances in the field of antimigratory strategies. Other clinical checkpoints in MS pathogenesis can now be targeted. It is likely that the results of these clinical trials will continue to fuel our understanding of the basic biology of MS. Neuroprotection and neural repair are new strategies on their way to entering clinical trials, although appropriate clinical outcome measurements still need to be fully developed.[175] Further refinements and progress in MRI technology, proteomics, pharmacogenomics, metabolomics, and transcriptomics may eventually aid in the design and applicability of personalized medicine. On balance, available evidence justifies a highly optimistic view into the future of MS therapy.

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