Title: Recent Developments in Multiple Sclerosis Therapeutics

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Abstract
Multiple sclerosis, the most common neurologic disorder of young adults, is traditionally considered an inflammatory, autoimmune, demyelinating disease of the central nervous system. Based on this understanding, initial therapeutic strategies were directed at immune modulation and inflammation control. These approaches, including high dose corticosteroids for acute relapses and long term use of parenteral interferon-β, glatiramer acetate or natalizumab for disease modification, are at best moderately effective. Growing evidence supports that, while an inflammatory pathology characterizes the early relapsing stage of multiple sclerosis, a neurodegenerative pathology dominates the later progressive stage of the disease. Multiple sclerosis disease-modifying therapies currently in development attempt to specifically target the underlying pathology at each stage of the disease and while avoiding frequent self-injection. These include a variety of oral medications and monoclonal antibodies to reduce inflammation in relapsing multiple sclerosis, and agents intended to promote neuroprotection and neurorepair in progressive multiple sclerosis. Although newer therapies for relapsing MS have the potential to be more effective and easier to administer than current therapies, they also carry greater risks. Effective treatments for progressive multiple sclerosis are still being sought.

Review
Introduction
Multiple sclerosis (MS) is a chronic progressive disorder of the central nervous system (CNS). It is traditionally considered an inflammatory disorder characterized by episodic CNS demyelination but current understanding is that neurodegeneration dominates progressive stages of disease. This article summarizes the pathogenesis of MS, reviews approved MS therapies, and then discusses the proposed mechanisms, and likely benefits and risks of new MS therapeutics.

Disease pathogenesis and disease subtypes
MS presents in most people (85%) with clinical relapses characterized by fully or partially-reversible focal neurological deficits. Relapsing-remitting MS (RRMS) is dominated by inflammation, edema, and the physiologic actions of cytokines. Active inflammation of the brain and spinal cord is visualized as gadolinium enhancing white matter lesions on magnetic
resonance imaging (MRI). After 10-20 years, about half of those with RRMS gradually accumulate irreversible neurologic deficits in the absence of clinical relapses or new white matter lesions on MRI. This stage is known as secondary progressive MS (SPMS). The remaining 15%, who have progressive clinical deterioration from disease onset have primary progressive MS (PPMS). PPMS and SPMS are thought to be dominated by axonal degeneration in the absence of overt inflammation[1] likely as a result of oxidative damage and/or increased susceptibility to injury caused by loss of the myelin sheath.

**Current MS therapeutics**

Clinically significant acute MS relapses are usually treated with high-dose, short-term, intravenous corticosteroids (methylprednisolone 1g/day for 3-5 days). This shortens relapse duration but does not improve the degree of recovery or the long term course of the disease.[2],[3],[4] Disease-modifying therapies (DMT) for MS alter the disease course. They lower clinical relapse rate, extend time to next relapse, and reduce the accumulation of new lesions on MRI, all of which are intended to decrease the long term accumulation of disability. The first approved DMT for MS, subcutaneous interferon beta-1b (IFNβ-1b, marketed as Betaseron in the US and as Betaferon in Europe), was FDA approved for RRMS in 1993 based on the pivotal placebo-controlled trial in which treated subjects had significantly lower annualized relapse rates (ARR) and more subjects were relapse-free after two years.[5] IFNβ acts as an anti-inflammatory and has several mechanisms of action including reduction in the production of pro-inflammatory IFNγ and TNFα, inhibition of T-cell activation and clonal expansion, modulation of cytokine and matrix metalloproteinase production and release and inhibition of T-cell migration and entry into the CNS.[6]

Since the release of IFNβ-1b, five other parenteral medications have been approved for the treatment of MS: IFNβ-1a (Avonex©), IFNβ-1a (Rebif©), glatiramer acetate (GA, Copaxone©), mitoxantrone (Novantrone©), and natalizumab (Tysabri©). The IFN products are thought to all have similar mechanisms of action although they differ in route of administration, rapidity of onset of action and risk of induction of neutralizing antibodies.[7] In contrast, GA, a synthetic copolymer of glutamic acid, lysine, alanine and tyrosine is believed to activate Th2 regulatory cells in the periphery. These activated Th2 cells cross the blood brain barrier (BBB)
and enter the CNS where they shift the immune response from pro-inflammatory to anti-inflammatory by secreting cytokines that down-regulate the inflammatory response and inhibit pro-inflammatory Th1 cells. Mitoxantrone is an antineoplastic agent that inhibits DNA and RNA synthesis of B and T-cells. While approved for treatment of RRMS and SPMS, [8-11], it has only shown clear benefit for patients still experiencing relapses and developing new MRI lesions. Increasing recognition of short and long-term risks of cardiotoxicity, acute leukemia and bone marrow suppression limit its use.[12],[13],[14] Natalizumab is the first monoclonal antibody (MAB) therapy approved for the treatment of MS. Natalizumab binds to VLA-4 on the surface of leukocytes, preventing T-cells from crossing the BBB into the CNS.[15] Natalizumab was found to reduce MS relapses by 68% compared to placebo[16] but its use is limited by its association with the development of progressive multifocal leukoencephalopathy (23 patients at the time of this writing), as well as possibly melanoma and primary CNS lymphoma, all likely due to altered immune surveillance. In response, the FDA limited approval of natalizumab to patients failing other MS therapies, and requires patients to be enrolled in a safety monitoring program.

**Future directions**

DMT development for MS is an area of active research, and many potential agents are in various phases of investigation. Most of these are oral medications or MABs that target specific aspects of inflammation in RRMS. Others are designed to have neuroprotective and neurorestorative effects in PPMS and SPMS (Fig 1).

**Oral anti-inflammatory agents for RRMS** (Table 1)

**Fingolimod (FTY720)**, a small molecule derived from a fungus and chemically related to sphingosine, causes internalization of sphingosine-1-phosphate (S1P) receptors on lymphocytes thereby blocking their egress from lymph nodes and thymus. The reversible lymphocytopenia prevents activated T cells from crossing the BBB and causing inflammation.[17] Fingolimod may also have direct effects via the S1P receptors present on all CNS cells types. A phase II clinical trial in RRMS found that fingolimod significantly reduced gadolinium-enhancing lesions and relapse rate compared to placebo,[18] and a second trial demonstrated fingolimod’s superiority to IFNβ-1a.[19] A European phase III clinical trial of fingolimod for RRMS has been
completed, and a US phase III trial is underway. Frequent adverse events associated with fingolimod include nasopharyngitis, dyspnea, headache and nausea. Rare serious adverse events in the trials were skin cancers and two deaths, one each from herpes encephalitis and disseminated varicella, all suggesting inadequate immune surveillance.

The antimetabolite **cladribine**, an adenosine analogue, incorporates into DNA and causes death of rapidly proliferating inflammatory B and T cells thus resulting in selective and long-lasting lymphocyte depletion. Approved as therapy for use in hairy cell leukemia, early trials indicated that cladribine was effective for RRMS but not SPMS.[20],[21] A recent phase III trial in RRMS (CLARITY) demonstrated a significant benefit of cladribine over placebo with a reduction in annualized relapse rate of over 50% at 96 weeks.[22] Based on this trial, the manufacturers are applying for FDA registration for cladribine. Cladribine has an appealing short administration schedule and is generally well-tolerated but there were some serious adverse events in the trial including herpes zoster in 2% of subjects, 3 cancers, and 4 deaths in the cladribine groups.

There are three oral agents in phase III trials in RRMS, **laquinimod**, **teriflunomide** and **BG00012**. Laquinimode and teriflunomide are thought to work in part by shifting the T-cell balance from pro-inflammatory Th1 cells to anti-inflammatory Th 2 cells. Laquinimod is a chemically and pharmacologically distinct derivative of the drug roquinimex, which has significant pulmonary and cardiac toxicity.[23] A 24 week phase II trial of laquinimod showed benefical effects over placebo on new MRI lesions.[24] Based on these promising early results, two phase III trials are underway in patients with RRMS. Teriflunomide is the active metabolite of leflunomide, a drug used in rheumatoid arthritis. Teriflunomide also inhibits dihydro-orotate dehydrogenase, the enzyme necessary for *de novo* synthesis of pyrimidine, thus reducing activated B and T cell proliferation.[25] A promising phase II trial[26] has led to phase III placebo-controlled trials of teriflunomide RRMS and CIS. Need for pre-treatment with cholestyramine or activated charcoal and the frequent association of hypertension, alopecia and rash potentially limit its use. BG00012 probably affects MS primarily through its anti-oxidant effects. It is an oral formulation of dimethyl fumarate, a topical agent used to treat psoriasis. Promising early studies [27] led to a phase III trial now underway.
Based on the observation that there is a reduction in MS relapses during pregnancy, a condition associated with high levels of estrogen and progesterone, it is thought that estrogen or progesterone may benefit patients with MS. Estrogen and progesterone have potent anti-inflammatory effects and may also provide neuroprotective benefits by increasing oligodendrocyte precursor cell number[28] and promoting oligodendrocyte process formation.[29] Phase III trials of oral estriol in conjunction with glatiramer acetate in RRMS are ongoing.

Monoclonal antibodies for RRMS (Table 2)

**Alemtuzumab** targets the CD52 antigen present on T cells, B cells, monocytes, macrophages and eosinophils, but not stem cells, and causes reversible leukocyte depletion. Alemtuzumab is approved for chronic lymphocytic leukemia and showed promise in early trials for RRMS[30] but not SPMS[31]. Patients with RRMS treated with alemtuzumab compared to IFNβ-1a had significantly lower risk for relapse (75%) and reduction in sustained disability (65%) over 2 years.[30] Safety concerns included 3 cases of immune thrombocytopenic purpura with one fatality, Grave’s disease, autoimmune anemias and neutropenias, and Guillain-Barre syndrome. Phase III trials are ongoing. **Daclizumab** depletes leukocytes by binding to the α-chain of the IL-2 receptor (CD25) required for T cell proliferation and activation. Daclizumab, approved for treatment of renal transplant rejection, appears to stabilize disease in RRMS patients who have failed IFN therapy[32],[33] and is in Phase II clinical trials for RRMS. Adverse events associated with daclizumab include thromboses, lymphoproliferative disorders, and infections. **Rituximab**, a MAB that depletes CD20+ B cells, is an approved therapy for hematological malignancies, rheumatoid arthritis, and thrombocytopenic purpura. B-cell dependent mechanisms such as antigen presentation, antibody secretion and demyelination, are increasingly implicated in the pathogenesis of MS.[34],[35] A phase II trial[36] and case reports[37] show promise for its use in RRMS.[38] Adverse effects of rituximab include progressive multifocal leukoencephalopathy, pancytopenias, Stevens-Johnson syndrome, and rare infections.

**Neuroprotective and neurorestorative agents for PPMS and SPMS**

Thus far, all of the anti-inflammatory therapies that are effective in RRMS have had minimal or no effect in controlling progressive MS. There is a growing belief that SPMS and PPMS will not
respond to anti-inflammatory therapies and that neuroprotective and neurorestorative therapies that affect neuronal integrity will be required for progressive MS. A variety of existing and novel approaches are under investigation as neuroprotective and neurorestorative therapies in progressive as well as relapsing MS (Table 3). Therapeutic strategies include protecting demyelinated axons as well as oligodendrocytes (the CNS myelin-producing cells) from oxidative injury, promoting neuronal remyelination, and restoring neuronal growth and function with neurotrophic factors.[39] **Lipoic acid**, a fatty acid present in certain foods and available as an oral supplement, may protect oligodendrocytes by antioxidant mechanisms and effects on microglia. Lipoic acid is well tolerated [40] and phase II trials of this compound in RRMS and SPMS are being planned. Drugs that block glutamate receptors present on demyelinated axons may prevent oxidative injury.[41] **Riluzole**, an oral glutamate NMDA receptor antagonist approved for use in amyotrophic lateral sclerosis,[42] is being evaluated in conjunction with IFNβ-1a in a phase II trial for early MS. Another strategy for neuroprotection in MS is selective sodium channel blockade with antiepileptic medications including **phenytoin**, **topiramate**, and **lamotrigine**.[43] [44] A recent phase II trial of lamotrigine in SPMS, however, failed to meet its primary endpoint of reducing the rate of central cerebral volume loss.[45]

Trials of **stem cell transplantation**, a with the goal of repopulating oligodendrocytes, are underway in people with MS. Remyelination may also be promoted by blocking LINGO-1, a protein on the surface of neurons that inhibits differentiation of precursor oligodendrocytes into mature cells. **Antibody blockade of LINGO-1** has shown promise in an animal model of MS.[46] **Neurotrophins** are protein factors produced by CNS cells that support neuronal growth, survival and differentiation.[47] In MS, secretion of the neurotrophin brain-derived neurotrophic factor (BDNF) is low and dysregulated [48] and BDNF is therefore also being considered as a therapeutic target.

**Conclusions**

Current MS therapeutics are moderately effective for modifying disease during its relapsing-remitting phase. There are a number of oral and parenteral agents that target inflammation in development, and several are likely to be approved for treatment of RRMS within the next few years. These therapies will likely more effectively control RRMS, but will also carry greater
known and as yet unknown safety risks. These risks and benefits will have to be weighed carefully against the efficacy and proven safety of the IFNs and GA. Furthermore, none of the anti-inflammatory therapies currently in late stage of development are likely to benefit patients with SPMS and PPMS. Development of effective neuroprotective and neurorestorative therapies will be needed to benefit patients with progressive MS.
Competing interests
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Authors’ contributions
All authors were involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript and have given final approval of the version to be published.

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References


**Figure 1.** Disease-modifying therapies in development target the pathology underlying the phase of multiple sclerosis (MS). Anti-inflammatory therapies are useful in relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) when relapses are still present. Neuroprotective therapies are likely to be more useful during the neurodegenerative stages of disease (SPMS without relapses) and primary progressive MS (PPMS).
<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed mechanisms of action</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod (FTY 720)</td>
<td>Binds sphingosine-1-phosphate on T cells preventing circulation and CNS entry</td>
<td>Phase III for RRMS</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Selectively depletes B and T cells by causing DNA damage</td>
<td>Phase III for RRMS and CIS</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory); Blocks pyrimidine and reproduction of rapidly dividing B and T cells</td>
<td>Phase III for RRMS and CIS</td>
</tr>
<tr>
<td>BG00012 (dimethyl fumarate)</td>
<td>Antioxidant</td>
<td>Phase III</td>
</tr>
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CIS, clinically isolated syndrome; CNS, central nervous system; RRMS, relapsing remitting multiple sclerosis
<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed mechanisms of action</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzamab</td>
<td>Leukocyte depletion; Depletes CD52 B and T cell populations, monocytes, macrophages and eosinophils</td>
<td>Phase III for RRMS</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Leukocyte depletion; Binds cell-surface receptor IL2; reduces T cell proliferation and activation</td>
<td>Phase II for RRMS</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B cell-directed therapy; Depletes CD20 B cell population</td>
<td>Phase III for RRMS</td>
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RRMS, relapsing remitting multiple sclerosis
Table 3. Oral (italics) and parenteral neuroprotective and neurorestorative agents for PPMS and SPMS

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Drug class</th>
<th>Agents</th>
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<tbody>
<tr>
<td>Protection of oligodendrocytes/axons from oxidative injury</td>
<td>Antioxidants</td>
<td><em>Lipoic acid</em></td>
</tr>
<tr>
<td>Protection of demyelinated axons from injury</td>
<td>Glutamate receptor</td>
<td>NMDA: <em>Riluzole</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMPA/Kainate: NBQX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GYKI52466</td>
</tr>
<tr>
<td></td>
<td>Sodium channel blockers</td>
<td><em>Phenytoin</em></td>
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<td></td>
<td></td>
<td><em>Topiramate</em></td>
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<td></td>
<td></td>
<td><em>Lamotrigine</em></td>
</tr>
<tr>
<td>Promotion of remyelination</td>
<td>Stem cells</td>
<td>Embryonic, autologous</td>
</tr>
<tr>
<td></td>
<td>LINGO-1</td>
<td>Anti-LINGO-1 antibodies</td>
</tr>
<tr>
<td></td>
<td>Pregnancy hormones</td>
<td><em>Estriol</em></td>
</tr>
<tr>
<td>Neurotrophic factors to help restore neuronal function</td>
<td>Neurotrophic factors</td>
<td>Glial-derived: GDNF, IGF, CNTF, neurturin, artemin, persephin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuron-derived: NGF, BDNF, NT3/4</td>
</tr>
</tbody>
</table>

GDNF, glial cell line-derived neurotrophic factor; IGF, insulin-like growth factor; CNTF, ciliary neurotrophic factor; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT3/4, neurotrophin 3 and 4