Over the past 2 decades, enormous progress has been made with regard to pharmacotherapies for patients with multiple sclerosis. There is perhaps no other subspecialty in neurology in which more agents have been approved that substantially alter the clinical course of a disabling disorder. Many of the pharmaceuticals that are currently approved, in clinical trials, or in preclinical development were initially evaluated in an animal model of multiple sclerosis, experimental autoimmune encephalomyelitis. Two Food and Drug Administration–approved agents (glatiramer acetate and natalizumab) were developed using the experimental autoimmune encephalomyelitis model. This model has served clinician–scientists for many decades to enable understanding the inflammatory cascade that underlies clinical disease activity and disease surrogate markers detected in patients.

In this review, we will outline some of the pharmacological agents that have been developed and tested in the laboratory and successfully brought into clinical trials and through the regulatory approval process. Agents that are currently in development will also be discussed. We will also give examples of how clinical observations following the approval of particular drugs led to new discoveries with regard to their mechanisms of action. Finally, we will contemplate some of the challenges that lie ahead in drug development and how novel biomarkers and laboratory methods may help to overcome these challenges.

Experimental Autoimmune Encephalomyelitis

Any discussion about translational research in multiple sclerosis (MS) has to include a discussion of an animal model that has been used for 8 decades to study its underlying inflammatory and autoimmune mechanisms: experimental autoimmune encephalomyelitis (EAE).1–3 The EAE model was originally created to study neurological disease in the context of infections, not MS. It is induced either through vaccination with a central nervous system (CNS) autoantigen(s) or through adoptive transfer of CNS autoantigen-specific T lymphocytes.3 While there has been very vocal criti-
Table. Glatiramer and Natalizumab Details

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Models of EAE</th>
<th>Effects in EAE</th>
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<tr>
<td>Glatiramer acetate</td>
<td>Random copolymer of L-alanine, L-glutamate, L-lysine, and L-tyrosine</td>
<td>Tested in murine, rat, and nonhuman primate models of EAE</td>
<td>Shown to be effective in prevention and treatment models</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Humanized monoclonal antibody specific for α4 integrin subunit of VLA-4</td>
<td>Multiple classes of VLA-4 antagonists have been tested in murine, rat, and nonhuman primate models of EAE</td>
<td>Reduction in EAE severity given prior to disease onset in active and adoptive models, although exacerbation of EAE severity was noted following withdrawal of therapy in some models</td>
</tr>
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Expected observations subsequently led to preliminary clinical testing. The initial clinical study of glatiramer acetate was undertaken in patients with MS and acute disseminated encephalomyelitis. Further clinical evaluations demonstrated that glatiramer acetate was effective in reducing relapses in relapsing-remitting MS (RRMS). Based on the results of a multicenter, randomized, double-blind, 2-year phase 3 clinical trial of 251 patients with RRMS, glatiramer acetate was approved by the Food and Drug Administration in 1996 for the treatment of RRMS. In this study, glatiramer acetate at a dose of 20 mg subcutaneously per day reduced the relapse rate by 29% compared with placebo. Several long-term studies have confirmed the benefit for patients with RRMS with regard to disease relapse rate reduction and other clinical and paraclinical outcome measures. Another multicenter, randomized study was designed to determine the effect of glatiramer acetate on magnetic resonance imaging (MRI) surrogate disease markers. In 239 patients with RRMS, glatiramer acetate showed a significant reduction in the total number of gadolinium-enhancing lesions compared with placebo.

More recently, the efficacy of glatiramer acetate was also tested against placebo in a randomized, double-blind trial in 481 patients who sustained a first, unilateral, acute clinical demyelinating event of the CNS involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), brainstem, or cerebellum—a clinically isolated syndrome. At baseline, these patients also had lesions on MRI suggestive of prior subclinical inflammatory demyelinating events. Glatiramer acetate reduced the risk of experiencing a second clinical attack or of developing clinically definite MS over a 36-month period by 45% compared with placebo. These results are similar in magnitude to interferon beta-1b, the first agent that had been approved for treatment of RRMS in 1993.

FROM BENCH TO BEDSIDE: NATALIZUMAB

Natalizumab is a humanized recombinant monoclonal antibody that binds to the adhesion molecule known as...
very late activating antigen 4 (VLA-4). Natalizumab was designed to interfere physically with the binding of VLA-4 on activated leukocytes to the natural ligands of VLA-4, vascular cell adhesion molecule 1, fibronectin, and mucosal addressin cell adhesion molecule.

The infiltration of the CNS with immune-competent cells is a histopathological hallmark of both MS and its animal model EAE. The extravasation of leukocytes from the blood into the brain and spinal cord involves numerous steps that occur in a defined chronological order: rolling, chemotraction, cell adhesion, and proteolytic degradation of the basal lamina and extracellular matrix. Each event in this paradigm is conditional for the ensuing step.23

Activated lymphocytes express highly adhesive molecules termed integrins.24 Following rolling, the adhesion of lymphocytes and myeloid cells to the luminal surface of venules is mediated by 1 of the 4 main integrins: αβ, LFA-1, Mac-1, and αβ (VLA-4).23 The interaction of VLA-4 on CD4+ T lymphocytes with its natural ligand fibronectin has also been shown to promote CD3-mediated T cell proliferation.25

In 1992, Yednock et al evaluated the effects of monoclonal antibodies against VLA-4 in the EAE model. The investigators demonstrated that lymphocytes and monocytes bind selectively to inflamed EAE brain vessels and that this binding was inhibited by antibodies against VLA-4.25 Furthermore, in vivo administration of anti-α4 integrin effectively prevented the development of EAE and the migration of inflammatory leukocytes into the CNS.26 To evaluate the impact of VLA-4 on EAE onset and disease perpetuation, Theien and coworkers administered monoclonal antibodies against VLA-4 before or after disease onset. These antibodies delayed the onset and reduced the incidence and severity of EAE.27 However, treatment with anti-VLA-4 antibodies at the peak of acute disease or during remission exacerbated the signs of clinical disease and amplified the accumulation of T lymphocytes in the CNS. The humanized recombinant monoclonal antibody natalizumab was also successfully tested in the EAE model of MS. Treatment initiation after disease onset resulted in a reversal of clinical disease and reduced the accumulation of T lymphocytes and monocytes in the CNS.28

In 2004, natalizumab was approved by the Food and Drug Administration and other regulatory agencies after the successful completion of 2 phase 3 trials in patients with relapsing forms of MS. The AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting MS) study evaluated the effects of natalizumab used as monotherapy in patients with RRMS.29 The SENTINEL (Safety and Efficacy of Natalizumab in Combination with Avonex [interferon beta-1a] in Patients with Relapsing-Remitting MS) study assessed the effects of natalizumab used in combination with interferon beta-1a.30 In the AFFIRM study, patients were randomized in a 2:1 ratio to receive 300 mg of intravenous natalizumab or placebo every 4 weeks for up to 116 weeks.30 At 2 years, natalizumab significantly reduced the annualized relapse rate by 68% and the risk of sustained disability progression by 42% compared with placebo.31 Furthermore, natalizumab significantly reduced the mean number of new or enlarging T2 hyperintense lesions by 83% and the mean number of gadolinium-enhancing lesions by 92% compared with placebo.20 In the SENTINEL trial, patients receiving a standard regimen of intramuscular interferon beta-1a who experienced breakthrough disease were randomized (1:1) to receive 300 mg of intravenous natalizumab or placebo once monthly for up to 116 weeks.30 After 2 years, the combination of natalizumab with interferon beta-1a reduced the annualized relapse rate by 55% and the risk of sustained disability by 24%.30

A SWITCH: FROM BEDSIDE TO BENCH

Translational research does not stop after the introduction of a pharmacological agent into clinical practice. Instead, often there continues to be a flow of information from observations made in patients back to the laboratory. The EAE model and laboratory studies in humans have also often assisted in elucidating mechanisms of action of pharmacotherapies long after these drugs successfully passed their regulatory approval. This is certainly true for the disease-modifying agents interferon beta32,33 and glatiramer acetate.34,35 With the more selective or monospecific agents, it is perhaps less likely that unexpected mechanisms of action will be discovered. However, daclizumab is an example of a drug that possesses biological effects distinct from that intended. Daclizumab is a humanized recombinant monoclonal antibody that binds to the subunit of the high-affinity interleukin 2 receptor CD25. CD25 is expressed on thymocytes, myeloid precursor cells, and activated T cells and B cells. The rationale for daclizumab use was to interfere with the activation and proliferation of potentially encephalitogenic CD4+ T cells.36 However, it was recently demonstrated that daclizumab does not reduce the activation or proliferation of T lymphocytes but results in the expansion of a regulatory subset of CD56bright natural killer cells.37

Unfortunately, unexpected adverse events are also often discovered after the approval of a drug by regulatory agencies. This is also certainly true for natalizumab. Since its initial approval in November 2004, more than 50 patients have been diagnosed with progressive multifocal leukoencephalopathy, an opportunistic infection with the human polyomavirus JC,38 while undergoing natalizumab therapy.39,40 There had been no indication from any of the clinical trials that the risk of CNS infections would be increased with natalizumab therapy. Also, the EAE model did not help to predict this particular adverse effect, since mice are not susceptible to human polyomavirus and do not develop progressive multifocal leukoencephalopathy. It was only after the announcement of the initial progressive multifocal leukoencephalopathy cases that research has been conducted on the pharmacodynamics of this agent.41-45

Finally, the occurrence of unexpected adverse events has led to postapproval evaluations of several pharmacological agents with regard to a more individualized therapy. This is true for mitoxantrone. Cotte and colleagues recently showed that mutations in ABC transporter genes may help physicians to identify patients who will have a good benefit-risk ratio with mitoxantrone therapy.
EXISTING TECHNOLOGIES IN TRANSLATIONAL RESEARCH IN MS—NEUROIMAGING

The complex relationship between various features of MS pathology has not been fully elucidated. Magnetic resonance imaging has been a relevant research tool in translating imaging information to our clinical and pathophysiologic understanding of this disease. One of the most difficult challenges in MS is to understand mechanisms of disease progression and consequently prevent clinical disease progression. As a noninvasive and increasingly available tool, MRI provides a unique in vivo opportunity to illustrate histopathologic aspects of MS. In this regard, destructive aspects of MS pathology have been extensively studied.47 This has led to the exploration of how chronic T1-weighted hypointense lesions (persistent black holes) evolve and how interventions may reduce accumulation of such destructive pathology. Estimation of T1-weighted injury has much better correlation with disability than T2-weighted lesion load.48 The latter is more associated with inflammatory injury of a wide-ranging pathology. In contrast, persistent black holes reflect irreversible axonal injury. Thus, considerable attention has been paid to study the effect of therapeutic intervention that may reduce the accumulation of this destructive pathology.49-51 Similarly, measures of changes in brain volume over time are among the best studied and validated measures to investigate neurodegeneration.52 Brain atrophy occurs at a faster rate in patients with MS (0.5%-1% annually) compared with healthy controls (0.1%-0.3% annually) and correlates with disability.53 However, measuring whole-brain volume lacks strong pathologic specificity since automated computerized registration techniques that quantify brain volume change can be influenced by a variety of factors that may not include actual tissue loss. In contrast to white matter, gray matter atrophy is more marked in MS and correlates with disease phenotype and disability to a greater extent.54 Currently, few studies have explored how therapy may influence gray matter atrophy. Cortical pathology has also gained importance because significant cortical lesions are missed on conventional MRI. However, advanced MRI techniques have demonstrated significant cortical pathology, usually identified on autopsy. Double-inversion recovery is exquisitely sensitive in detecting cortical lesions that are otherwise relatively invisible on T2-weighted or fluid-attenuated inversion recovery sequences.55 This has led to significant ongoing work examining the effect of immunomodulation on reducing cortical lesion accumulation and how cortical lesions evolve longitudinally.56

Nonconventional MRI techniques have made major inroads into the understanding of injury into the so-called normal-appearing brain tissue, whether in the white matter or gray matter. Proton magnetic resonance spectroscopy can quantify mitochondrial metabolite N-acetylaspartate, a putative marker of axonal injury.57 Numerous studies in the past decade have examined axonal injury with magnetic resonance spectroscopy. While therapies may stabilize N-acetylaspartate levels in the white matter,58 the effect on gray matter remains unknown. However, it is increasingly being adopted as a second-ary outcome in several multicenter studies with the objective of examining neuroprotection. Another very promising advanced MRI technique used in MS imaging is magnetization transfer ratio. This technique measures the relative amounts of free and bound water in brains with MS based on the capacity of macromolecules in tissue to exchange magnetization with surrounding water.59 Post-mortem studies have shown that magnetization transfer ratio is strongly associated with myelin content as well as residual axons.60 In an 8-year follow-up study, decline in gray matter magnetization transfer ratio in the first year was independently predictive of clinical disability.61 Further advances in magnetization transfer ratio imaging that use voxelwise analysis provide in-depth analysis of reparative potential in individual lesions. Of all the currently available techniques, magnetization transfer ratio remains the most promising to quantify myelin injury as well as remyelination. Similarly, diffusion-weighted imaging can provide substantial information regarding tissue architecture and fiber alignment.62 This also identifies injury in the normal-appearing brain tissue that correlates with disability, including neuropsychological domains.63

Recently, MRI techniques that examine iron accumulation in MS have gathered considerable attention. This is largely because of the increasing recognition of the role of iron deposition in neurodegenerative disorders.64 Studies indicate that inflammation increases local iron content due to iron-rich macrophages as well as reduces axonal clearance of iron.65 Iron is also found to be within the oligodendrocytes and myelin, presumably associated with myelinogenesis, as one explanation.66 Imaging studies using phase imaging or susceptibility-weighted imaging that are dedicated applications to detect iron-based signals generated from brain tissue have shown increased iron signal in the deep gray matter structures.67 Attempts have also been made to quantify iron content in MS lesions.68 Though preliminary, this work requires considerable investigation, including longitudinal studies, to establish if iron measurement in MS is a primary event or a consequence of tissue injury. Only after such work can one explore the utility of iron as a surrogate marker of disease pathology.

In summary, measurement of tissue-destructive processes and neuroprotection is feasible in MS. A combination of the currently available techniques provides the best strategy to measure tissue damage, including the neuroprotective potential of new agents in MS. With the increasing availability of high-field strength MRI, new technical challenges will require extensive refinement. At the same time, these advances in MRI technology provide a unique opportunity for a better correlation between clinical and MRI findings. Imaging of the spinal cord is on the brink of extensive investigation in the coming decade. Advanced MRI techniques, coils, and postprocessing methods developed by focusing on the brain have reached a point that they may be reliably applied to the spinal cord.69 Consequently, this may facilitate the development of the next generation of therapeutics that target neuroprotection in MS with the ultimate goal of preventing disability.
The absence of a reliable biomarker that allows the rapid and early detection of CNS demyelination, degeneration, and neurorepair is perhaps the greatest challenge in testing therapeutic interventions. Clinical and paraclinical outcome measures that are currently used in clinical trials have made it necessary to conduct lengthy and very expensive clinical trials. For pharmaceutical companies, testing novel compounds has become an increasingly risky enterprise, because even the successful completion of phase 2 and phase 3 clinical studies does not preclude the risk of significant adverse events later on. Consequently, unless disease progression can be diagnosed more reliably and early, and mechanisms and adverse effects of potential therapeutic agents better understood, many promising pharmacological and nonpharmacological agents may not advance into clinical studies.

To truly model a pathological process in MS, it is critical to detect specific deficits that result from within a defined anatomical localization with measurable and reproducible physiologic changes. Optic neuritis is perhaps the ideal clinical syndrome to systematically study: it occurs frequently in patients with MS, it is easily recognizable by health care providers, and it has a very stereotypical appearance characterized by retro-orbital pain, reduction in high- and low-contrast letter acuity and sensitivity, color desaturation, visual field loss, and afferent pupillary defects. In addition, inflammation in the optic nerve can be detected by MRI when assessed at the time of the acute syndrome.

The optic nerve is composed of ganglion cell axons that originate from within the eye at the retinal nerve fiber layer and become myelinated in the retro-orbital region. Thus, the retinal nerve fiber layer itself lacks myelin and represents an anatomical structure to detect and longitudinally study neurodegenerative effects within the retina. It was recently shown that retinal nerve fiber layer striations begin to disappear within 1 month after injury to the optic nerve and that cell layer atrophy becomes stable by 2 months.

Optical coherence tomography (OCT) is a method that allows rapid assessment of retinal nerve fiber layer thickness and volumetric analyses of the macula. Optical coherence tomography uses light to create images based on different optical reflectivities of the ocular tissues. In the earliest stages of drug development, OCT studies in the EAE model may prove to be a useful tool to assess CNS neurodegeneration. Axonal loss has been described in some EAE models, and more specifically, axonal loss within the optic nerve was demonstrated by numerous investigators. Furthermore, OCT has successfully been used in rats and in mice to image retinal structures. Importantly, measures of retinal thickness performed by OCT were found to correlate with axonal thickness determined by histological analysis. Other studies demonstrated that a decrease of retinal axonal fibers is associated with decreased neuronal function measured by electroretinogram. While in most animal OCT studies, custom-designed instruments were used, there is no reason to believe that commercially available units would not also be feasible.

While preliminary investigations of OCT in patients with MS were performed a decade ago, larger-scale studies that test the impact of acute optic neuritis on retinal nerve fiber layer thickness, macular thickness, and volume in patients with MS and neuromyelitis optica are only now being conducted. Ultimately, OCT techniques will have to be tested in clinical trials of more heterogeneous MS cohorts.

Pupillometry is another potentially promising technique that will allow the detection and monitoring of CNS demyelination and neurodegeneration. Pupillometry has long been used to determine the pupil diameter and its dynamic changes in response to light in humans. Demyelination, neurodegeneration, and defects in synaptic transmission can be detected and quantified in the peripheral or central pupillary reflex pathways. This technique is most widely used in the diagnosis and paraclinical monitoring of autonomic nervous system disorders that involve the CNS. In addition, this technique has also been successfully applied diagnostically and experimentally in the assessment of pharmacological agents that are neurologically active in sleep disorders, in fatigue, and in pain medicine. In EAE and MS, pupillometry has thus far been underused and is only now being evaluated. As mentioned earlier, the clinical evaluation of animals is currently the only metric routinely used to longitudinally assess experimental animals. This clinical assessment is limited to the motor function and unlikely to detect subtle neurological deficits. Histopathological assessments of CNS inflammation, demyelination, and neurodegeneration can only be assessed post mortem in a cross-sectional manner. Pupillometry, as may also be true for OCT, is intriguing as it allows the assessment of demyelinating and neurodegenerative events affecting the optic nerve and upper brainstem of rodents, which may be correlated with disease activity outside of the pupillary reflex pathway.

Recently, the safety and feasibility of this method was tested and normal reference values for pupillary reflex metrics in different mouse strains established. The investigators showed that this technique is feasible in mouse strains that are frequently used to conduct EAE experiments. A role for pupillometry as sensitive, easy-to-use, and inexpensive detection assays can also be envisioned in clinical trials for MS.

In the past 10 years, it has increasingly been recognized that MS is not only a neuroinflammatory disorder but that neurodegenerative events also play a critical role in its pathogenesis. In the early relapsing stages of MS, the demise of healthy neurons and axons may be partially offset by regenerative mechanisms, whereas in the later progressive stages, this ability to repair damaged neuronal tissue may be diminished and eventually lost. Thus, while all current therapeutic interventions have anti-inflammatory properties and clearly benefit many patients during the relapsing stages of MS, a more complete...
treatment approach will have to include neuroprotective agents and drugs that promote neurorepair.

Basic and clinician-scientists are faced with numerous challenges when confronting these aspects of MS. The EAE model appears somewhat limited in studying neuroprotective pharmacological agents because the anatomical distribution and the kinetics of neuronal loss do not closely reflect that of the human disease. To our knowledge, no animal models of spontaneous CNS neurodegeneration are currently in existence. Even in patients with MS, it is more challenging to monitor disease progression in the absence of clinical relapses and reliable surrogate disease metrics on MRI or other biomarkers. Considering all of these hindrances, MS may in fact not be the ideal disorder for the development of neuroprotective strategies. An alternative approach may be to initially test pharmacotherapies in animal models of neurodegenerative disorders that predominantly affect defined cell populations in the CNS, including models of amyotrophic lateral sclerosis and idiopathic Parkinson disease, followed by testing as monotherapy or combined with anti-inflammatory agents in chronic EAE models (or better models to be developed). In fact, agents that are thought to be neuroprotective and that have already been approved for the treatment of other neurodegenerative diseases have also shown efficacy in EAE or animal models of primary degenerative disorders. These agents have included glutamate antagonists (riluzole) and several ion channel blockers (eg, flecainide acetate, phenytoin, and lamotrigine). Some select agents have undergone clinical testing.

Promoting neural repair is a strategy that may be even more relevant than neuroprotection, as neuronal loss is often detected very late when considerable tissue loss has already occurred. One major focus is the role of the myelin sheath in providing structural and trophic support for the CNS axon. One potentially critical cell population, oligodendrocyte precursor cells, is present in chronic lesions intuitively, therapeutic strategies should either enhance the ability of these cells to myelinate or antagonize factors that interfere with myelination. Several molecules that are thought to amplify oligodendrocyte precursor cell migration and differentiation have been assessed in EAE models with variable results, including nerve growth factor and transforming growth factor β. Transforming growth factor β has thus far been the only substance in this category that was evaluated in patients with MS in the context of a clinical trial but was found to be ineffective and associated with nephrotoxic effects. The clinical evaluation of some of the other agents listed earlier is complex because their bioavailability in the CNS is not optimal and neoplastic growth was promoted in experimental settings. These perhaps discouraging results illustrate that the development of neuroprotective and neurorepairative strategies in the laboratory, their testing in animal models, and their evaluation in clinical trials are extremely challenging and potentially fraught with often unexpected hurdles. However, without overcoming these challenges, comprehensive therapy of patients with MS, and particularly of patients with progressive forms of MS, will likely remain elusive.

CONCLUSIONS

In the past 17 years, several pharmacological agents have been approved for the treatment of MS. Many more drugs are expected to become available in the coming years. This tremendous progress is the result of translational research. A critical component of this research has been the EAE animal model of MS, which continues to play an important role in evaluating therapies. Other animal models and technologies may soon be used to measure non-inflammatory aspects of MS. It is expected that observations made in these models will also be translated into clinical research and will ultimately benefit patients.

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