Researchers Expand Focus on Progressive Forms Of Multiple Sclerosis

Efforts to Pinpoint the Beginning of Disease May Yield Clues to Treatment

Susan Worley

After more than a century of impressive research, multiple sclerosis (MS)—a complex inflammatory, demyelinating neurodegenerative disorder—continues to have no known cause and no known cure. Important achievements in recent decades have included the development of more than a dozen disease-modifying treatments (Figure 1) for patients with relapsing and remitting forms of MS (RRMS). These drugs have been proven to reduce disability and likely delay progression in patients with RRMS; however, because the most effective among them pose risks for serious adverse events, the search for more tolerable agents for RRMS continues. Meanwhile, despite a lack of head-to-head clinical trials, efforts to establish a rational ordering of current treatments have led to early-stage treatment algorithms and efficacy rankings.

RRMS, which is characterized by episodic inflammatory attacks on the central nervous system (CNS) and followed by spontaneous recovery of varying degrees, represents only one of several recognized categories of the disease. It is estimated that approximately 10% of patients have a primary progressive form of MS (PPMS), characterized by a gradual, irreversible progression of clinical disability, and more than 50% of patients who present with RRMS will eventually transition to secondary progressive MS (SPMS). Drugs used to treat RRMS have so far demonstrated little efficacy in the treatment of progressive MS and are not currently approved to treat PPMS or SPMS. The absence of treatments for progressive disease has become an increasingly important focus of an international community of researchers.

“A treatment for progressive MS is unquestionably the most important unmet need today, in part because progressive disease is the most significant source of disability,” says Philip De Jager, MD, PhD, Associate Professor of Neurology at Brigham and Women’s Hospital and Harvard Medical School. “Recently MS organizations around the world have launched a collaborative effort to tackle progressive MS, which will likely lead to some breakthroughs. Genetic studies and other research have taught us that if we join together rather than compete with one another on big questions such as this one, we stand a chance of being successful. We are at the point now where small studies of progressive disease led by individual investigators are unlikely to provide us with an answer.”

Some of the current research on progressive disease involves delving deeper into its biology and pathophysiology. Homing in on the elusive beginnings of the disease, investigators believe,

Susan Worley is a freelance medical writer who resides in Pennsylvania.

Figure 1 Timeline of Approvals of Major MS Medications

This timeline shows milestones in the development of 12 available MS treatments, all of which are disease-modifying except for dalfampridine (Amphra). It begins with the first patient visit of the oldest clinical trial, provides the FDA approval date, and ends with the last patient visit of the most recently completed and published clinical trial. It includes FDA-approved compounds and completed phase 2 and 3 trials, but it excludes unapproved compounds, ongoing trials, pilot studies, and phase 4 trials.
may provide insight into causes and potential treatments for all forms of MS.

“We are basically at an inflection point in terms of understanding the onset of the disease,” Dr. De Jager says. “As with Alzheimer’s disease, MS develops over many years before symptoms appear, and so far we have not had an opportunity to observe the transition from health to MS; we’ve only observed patients already diagnosed with the disease. However, we now have detailed maps of the genes involved in the onset of MS, and we are on the road to discovering others. We also are zeroing in on environmental risk factors. As we gain a greater understanding of the biology that leads to MS, we eventually will be able to investigate primary prevention—strategies that will prevent the disease from starting in the first place.”

Genes and Environment: The Search for a Trigger

The complex pathophysiology of MS, which is not yet completely understood, begins with neural inflammation that leads to the destruction of myelin in the brain and spinal cord of patients. Inflammation of the brain endothelium compromises the blood–brain barrier, allowing the entry of immune cells into the brain. The mechanism of action for natalizumab (Tysabri, Biogen) (Figure 2), which is widely considered the most effective treatment for MS, has provided researchers with greater insight into the disease. While some experts are inclined to think of MS as an autoimmune disorder, others are willing only to recognize an autoimmune component, and they remain in search of a “triggering event” that may or may not have autoimmune features.

“It does appear that, at least what we call relapsing–remitting disease, can be highly attenuated by inhibiting the entry of the immune system into the brain,” says Lawrence Steinman, MD, Professor of Neurology at Stanford University. “The success of natalizumab has attested to a major role of the immune system; whether this represents ‘autoimmunity’ or ‘immunity to an infectious agent’ or both remains an enigma. We need to remain humble until we understand what causes the disease, and until we can cure it.”

To arrive at a better characterization of the disease and identify opportunities for earlier treatment, more MS researchers are engaging in or proposing prospective studies that allow a closer examination of disease trajectories over time. One such study, led by Dr. De Jager and colleagues at Brigham and Women’s Hospital and the National Institute of Neurological Disorders and Stroke (NINDS), including Dr. Daniel Reich (see Frontiers of MS Imaging later in this article), is designed to examine the transition from health to MS by following a unique cohort of first-degree relatives of individuals with MS. The Genes and the Environment in MS (GEMS) study, which was launched in 2011, has enrolled nearly 3,000 individuals who have provided detailed family and medical histories and saliva samples for extraction of DNA. Participants commit to completing periodic questionnaires—and, in some cases, undergoing imaging and other testing—over a period of 20 years.

Building on the work of previously conducted genome-wide association studies and published studies of environmental risk factors, Dr. De Jager and colleagues developed a risk algorithm that is used to generate a weighted Genetic and Environment Risk Score (GERS) for each subject. The study’s risk algorithm can be updated to incorporate new risk factors and significant relationships among risk factors as these are confirmed. Selected patients with high risk scores undergo imaging and other testing, generating data that eventually should enable investigators to map the intricate sequence of events that leads to MS.

“First-degree relatives of people with MS are an impor-
Researchers Expand Focus on Progressive Forms of Multiple Sclerosis

Darin T. Okuda, MD

Important population because their risk for developing the disease is approximately 30 times greater than that of the general population,” Dr. De Jager says. “However, the absolute risk for each of these individuals is still rather small—only 2% to 3% will develop MS over their lifetime. By examining not only genetic risk factors but also environmental risk factors, such as a history of smoking or mononucleosis, our risk score seeks to identify the members of this population who are at greatest risk for developing the disease. We also expect to discover critical relationships among risk factors over time.”

According to Dr. De Jager, plans are under way to expand the study to sites in more countries with the intention of making GEMS an international resource and eventually a platform for clinical trials that focus on primary prevention. As the study continues, members of the International Multiple Sclerosis Genetics Consortium and other researchers continue to identify new gene variants that may play a role in MS.7 A deeper exploration of environmental factors, including immune responses to the Epstein–Barr virus (EBV)8 and the influence of gender,9,10 also continue to yield valuable information about the disease.

RIS: The Value of Incidental Findings

Among individuals already diagnosed with MS, it has been estimated that approximately 80% initially showed symptoms after the disease had already been present for a decade or longer.4 This estimate has long posed an intriguing question to researchers in the field—among them, the lead investigator of another unique prospective study of patients with MS.

“Figures representing the estimated incidence of MS and the estimated number of patients who are diagnosed each year have remained relatively stable during the past few years,” says Darin T. Okuda, MD, Associate Professor of Neurology at the University of Texas Southwestern. “So an important question is: How many people do we think are unknowingly in some early stage of the disease? Unless we screen the general population, which is not currently feasible, or until we discover novel methods of identifying these individuals, we don’t really know the prevalence of undiagnosed disease. However, we can learn a great deal from MRI anomalies that are suggestive of MS, and that are found incidentally during evaluations for symptoms unrelated to demyelinating disease.”

In 2009, Dr. Okuda and colleagues published findings from a study of 44 asymptomatic patients with abnormalities on MRI (magnetic resonance imaging) that were discovered incidentally when these patients underwent MRI evaluation for conditions such as head injury or migraine.11 The paper introduced the term radiologically isolated syndrome (RIS), a presymptomatic category of MS, and presented formal criteria to improve diagnostic specificity and ensure accurate classification.

“RIS only applies to structural radiologic anomalies that are highly typical for demyelinating plaques,” Dr. Okuda says. “These lesions on imaging are not only of a specific size, containing key morphological characteristics, but also are located in specific areas within the central nervous system. These are distinctly different from the nonspecific white-matter changes or bright spots that are seen in the majority of cases by neurologists, which are not consistent with MS.”

More recently, Dr. Okuda and colleagues reported on data from 451 individuals in five countries who were retrospectively identified as having MRI anomalies suggestive of demyelinating disease.12 After following these individuals for five years, the authors identified risk factors—such as age (younger than 37 years), male gender, spinal cord involvement, and combinations of these—that were the most meaningful predictors of eventual symptom onset.

Data from this study also identified a presymptomatic phase in individuals who went on to fulfill criteria for PPMS. An examination of clinical outcomes enabled investigators to identify characteristics that separated individuals who developed RRMS from those who developed progressive disease. Characteristics of the group with PPMS included a more advanced age range, a tendency to have an abnormal cerebral spinal fluid profile, a longer period of time to first clinical event, and a much higher lesion load within the spinal cord. To date, Dr. Okuda and colleagues have collected data on more than 14 individuals with RIS who went on to develop progressive disease.

“One of our goals is to determine whether we can use imaging early on in the disease course, prior to the emergence of symptoms, to forecast what clinical subtype of MS an individual will ultimately have. Although we currently do not have any approved therapies for progressive disease, we hope to determine whether we can intervene in some way to prevent disability in patients on a progressive trajectory,” Dr. Okuda says.

Dr. Okuda, members of the Radiologically Isolated Syndrome Consortium (RISC), and colleagues at the University of Texas Southwestern have formed a strategic research alliance with Biogen to investigate, in a separate study, whether treatment has the potential to delay the emergence of symptoms in individuals with RIS. This year, the alliance will launch ARISE, the first randomized, placebo-controlled trial in the U.S. to examine the efficacy of dimethyl fumarate (Tecfidera, Biogen) in extending the time to a first neurological symptom associated with CNS demyelination.13 According to Dr. Okuda, the trial, which will involve approximately 200 subjects who fulfill RIS criteria at more than 20 sites in the U.S., is not seeking a new indication for the drug but rather the answer to scientific questions.

Dimethyl fumarate received FDA approval in 2013 for the treatment of patients with RRMS. In April 2015, noteworthy post-hoc analyses supporting its efficacy in specific types of patients were presented at the annual meeting of the American Academy of Neurology (AAN).14,15

Frontiers of MS Imaging

MRI is an indispensable tool for monitoring MS, which until now has largely been involved tracking the presence of focal, demyelinated white-matter lesions—widely recognized pathological hallmarks of the disease. However, experts have long been aware that current imaging techniques relay only a partial
Researchers Expand Focus on Progressive Forms of Multiple Sclerosis

story: The number and volume of white-matter lesions do not correlate strongly with clinical manifestations of MS. An MRI series may, for example, suggest extensive disease activity in a patient who reports relatively mild symptoms. This imperfect correlation, known in the field as the clinical/radiological paradox, is a persistent source of frustration for clinicians and patients.

The degree to which MRI can track the efficacy of treatments is also limited, in part because it is often impossible to distinguish between the efficacy of a drug and the spontaneous remission of disease.

As a result, a major goal in imaging is to identify previously uncaptured or poorly captured processes in new regions of the brain and spinal cord that may provide relevant information about disease activity. In 2014, progress toward this goal was reflected in published reports of significant relationships between gray-matter abnormalities and disability in RRMS and SPMS. More recently, researchers reported success in using a novel technique to capture leptomeningeal inflammation in individuals with MS, a process previously detected during autopsies and biopsies but never before captured in vivo. Now on the road to being validated as a new, noninvasive marker of inflammation, imaging of this pathology may eventually be used to test treatments designed to reduce this inflammation and may point to a new avenue of investigation for progressive MS.

“This marker likely can be made more sensitive,” says Daniel Reich, MD, PhD, Chief of the Translational Neuroradiology Unit at NINDS and lead investigator of this study. “And further investigation may help us discover other similar and perhaps more useful markers. Once we find these, we can ask questions about the disease such as: When does meningeal inflammation start? How does it accumulate over time? Does it respond to current therapies or potential new therapies, and if so, can that help us better understand the clinical course of the disease? Perhaps most significantly, answers to these questions may eventually improve our understanding of progressive MS.”

Another critical goal in imaging is the establishment of clear and widely agreed-upon definitions of response to treatment. Even for well-established treatments, such as interferon therapy, experts continue to explore better methods for separating responders from nonresponders during clinical trials. For newer categories of drugs, including tissue-protective and putative remyelinating agents, there has been an absence of sensitive markers for documenting efficacy. A further complication is that most of these newer agents will be tested in patients concurrently receiving approved immunomodulatory therapies; however, Dr. Reich and colleagues reported this year on a unique measure of lesion recovery that addresses this problem. The documentation of changes to individual lesions over time, these researchers demonstrated, can be used as a powerful outcome measure in proof-of-concept trials for agents that are expected to accelerate lesion recovery. In 2015, this method of assessing treatment efficacy will be used for the first time in early-stage testing of guanabenz (see Research Highlights below).

“If successful, our new trial design will allow the early testing of agents that might protect brain tissue, or promote its repair, to be conducted more quickly and with fewer patients, compared with current paradigms,” Dr. Reich says. “This should allow the early testing of more agents at a lower cost, hopefully hastening the day when such treatments will reach our patients.”

Current Clinical Challenges

Despite a wide range of treatment options for patients with RRMS, clinicians face significant challenges in their efforts to tailor use of these therapies to individuals. While experts agree that early identification of the most effective drug for each patient with MS is critical, pharmacogenetic information that might help guide treatment selection is lacking. Utilization management programs used by some insurers and the need to observe risk-management strategies for many medications also can complicate the decision-making process.

Lily Jung Henson, MD, a fellow of the American Academy of Neurology and Chief of Neurology for the Piedmont Health System in Atlanta, says that although natalizumab is widely regarded as the most effective treatment for MS, it is not commonly used as first-line therapy for a variety of reasons.

“Natalizumab tends to be used as first-line therapy primarily in patients with very aggressive disease, in situations where neurologists believe that if we don’t slow down the disease quickly, the patient may end up having a lot of damage,” Dr. Jung Henson says. “For most newly diagnosed patients, we tend to recommend either injectables or the orals. The injectables make sense for patients who are more conservative in terms of their willingness to tolerate risks of adverse events. Patients can be reluctant to begin taking some of the oral drugs initially because they are relatively new, and we are still gathering information about their side effects. However, if a patient is very needle-phobic, an oral medication may be a more reasonable choice.”

While Dr. Jung Henson and many of her U.S. colleagues generally support an efficacy ranking of current treatments published this year by Ransohoff and colleagues, utilization management or “step therapy” programs developed by insurers frequently lead to delays in effective treatment. To address this problem, the American Academy of Neurology published a position statement in February 2015 that urges appropriate access to treatment.

“Not long ago,” Dr. Jung Henson says, “I wanted to prescribe natalizumab for a patient with very aggressive disease; however, her insurer insisted that we try an injectable and an oral agent first. I wasted about three months watching her go downhill while she failed therapy. Although I predicted that she would indeed
fail, we had no choice but to follow this path. These situations are frustrating and wrong—particularly when we know that they may lead to irreversible damage. We can’t take a cookie-cutter approach to treating patients, because disease activity and severity and response to treatment often vary considerably.”

Dr. Jung Henson adds that clinicians also must consider patient lifestyles, dosing preferences, and tolerance for risk when making treatment decisions. Indeed, these important factors have prompted considerable research geared toward improving patient convenience and safety for currently approved treatments.

Ascertaining a patient’s tolerance for risk is particularly important because the most effective treatments for RRMS tend to have less favorable risk–benefit ratios. For example, natalizumab25 (and, in a handful of recent cases, two other MS drugs26,27) have been associated with a risk for developing progressive multifocal leukoencephalopathy, a rare but serious brain infection. Other drugs associated with potentially serious adverse events that require patient enrollment in risk evaluation and mitigation strategy (REMS) programs include fingolimod (Gilena, Novartis), which poses cardiovascular and other risks;28 and alemtuzumab (Lemtrada, Genzyme), which poses a range of risks associated with prolonged immunosuppression.29 As efforts to develop more tolerable agents for RRMS continue, risk-management strategies for currently approved drugs are expected to undergo further refinement.30

Research Highlights: New Uses for Old Drugs

A growing number of agents currently under investigation for the treatment of MS (Table 1)—particularly for progressive forms of the disease—are drugs that have already been approved for use in other therapeutic areas. In the past, new indications for older drugs were frequently discovered by chance, but researchers are now taking a more systematic approach to repurposing drugs and to leveraging their wealth of safety profile and post-marketing data.

Simvastatin, a well-known, relatively safe, and well-tolerated cholesterol-lowering drug, for example, showed promise in a phase 2 clinical trial for slowing the progression of MS.31

Researchers Expand Focus on Progressive Forms of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Table 1 Emerging Treatments for Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Zinbryta (daclizumab high-yield process)</td>
</tr>
<tr>
<td>Ocrelizumab</td>
</tr>
<tr>
<td>Siponimod (BAF312)</td>
</tr>
<tr>
<td>Masitinib</td>
</tr>
<tr>
<td>Anti-LINGO-1</td>
</tr>
<tr>
<td>Simvastatin</td>
</tr>
<tr>
<td>RPC1063</td>
</tr>
<tr>
<td>Laquinimod</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Guanabenz acetate</td>
</tr>
</tbody>
</table>

BLA = biologics license application; IV = intravenous; MRF = Myelin Repair Foundation; MSS = Multiple Sclerosis Society of Great Britain and Northern Ireland; NMSS = National Multiple Sclerosis Society; PPMS = primary progressive multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis

Additional information available at ClinicalTrials.gov
undergoing testing as a neuroprotective drug and may be useful in treating acute optic neuritis; results of a phase 2 randomized controlled trial were presented at the AAN annual meeting in April 2015.32

More recently the Myelin Repair Foundation (MRF), in collaboration with NINDS and researchers at the University of Chicago, announced the launch of a phase 1 study of guanabenz, an FDA-approved drug used to treat high blood pressure. Researchers funded by the MRF (which has since announced its shutdown, although this is not expected to affect the ongoing study) reported in March 2015 that guanabenz prevents the loss of myelin and reduces symptoms of MS in animal models.33 Phase 1 clinical studies are assessing the safety and tolerability of the drug at doses used to treat MS.

As will likely be the case in trials of other new neuroprotective agents, patients participating in the phase 1 clinical trial of guanabenz will also be receiving an FDA-approved anti-inflammatory treatment for RMS. Since many experts believe that treatment of progressive MS ultimately will require a mix of anti-inflammatory, regenerative, and neuroprotective strategies,34 such trials may be seen as harbingers of a new era of combination treatment.

“Combination therapies already are standard in the treatment of disorders such as cancer and HIV/AIDS,” says Tassie Collins, PhD, Vice President of Translational Medicine at the MRF, “but a combination treatment approach to MS has not been possible until now. Ideally, this new generation of MS drugs, which are designed to protect tissue or to restore damaged tissue, will be coupled with approved drugs that target the autoimmune response. Combination therapy makes sense—it’s important not only to halt further damage, but also to help damaged tissue heal.”

REFERENCES


27. Food and Drug Administration. Gilenya (fingolimod): drug safety—FDA warns about cases of new brain infection. continued on page 605
continued from page 589


