On the Cusp of Something Big?

For so long, multiple sclerosis has frustrated physicians and patients. With bold new treatments on the way, payers are thinking about tighter management. Formal treatment guidelines would help. Biomarkers could also sort out the 'right-drug, right-patient' conundrum.

BY SUSAN WORLEY

The best literature on multiple sclerosis has the unmistakable air of a suspenseful detective mystery. It tracks accumulating evidence, inserts unexpected twists and turns, and keeps the tension mounting, reflecting the more-than-century-old quest to find both the cause of the disease and its cure.

In 2010, the U.S. Food and Drug Administration approved the first oral medication for MS, fingolimod (Gilenya)[1]. The impact of this long-anticipated approval (Carroll 2010) was twofold: It brought some patients the hope of never having to face another needle, and it encouraged payers — buoyed by the anticipation of better adherence — to accept the cost in exchange for better outcomes.

The introduction of oral therapies, in concert with other scientific, economic, and political developments, has advanced the story of this disease in unanticipated ways. For example, it is now clear that adherence is far more complicated than was previously understood. Attempting to discover why a patient with MS fails to adhere to a treatment is sometimes like being in a hall of mirrors — reasons multiply and are intricately connected, often reflecting related or unsuspected problems. Oral medications alone are not the answer; the complexity of adherence calls for coordination of care among neurologists and other medical specialists, primary care physicians, pharmacists, payers, employers, and patients. "It's going to take a village," says neurologist Lily Jung Henson, MD, fellow at the American Academy of Neurology (AAN).

In the future, imaging technology may be used to suggest ideal treatments for MS, says Daniel S. Reich, MD, PhD, Translational Neuroradiology, National Institutes of Health.

Guidelines: the missing piece

Closely managing care may be the best strategy for addressing the cost of MS drugs because payers and employers have few other acceptable strategies at their disposal. The correlation between higher out-of-pocket expenses and lower rates of adherence requires that limits be placed on cost sharing. And because no formal guidelines exist for the treatment of MS, it is difficult to place drugs on a tiered system as a rational way to control costs.

"A few years ago," says Jung Henson, "AAN initiated a project whose goal was to develop a complete set of guidelines for the diagnosis and treatment of MS. But the data we reviewed were often inadequate or contradictory, it was hard to get all participants to come to agreement on particular issues, and everything in the field is moving so quickly. So we came to the conclusion that we could not make recommendations that would rise to the level of rigor necessary to be published."

Without formal treatment guidelines, payers must support clinician autonomy with regard to treatment decisions. But, as Ronald J. DeBellis, PharmD, at Albany College of Pharmacy and Health Sciences–Vermont, points out, with a disease like multiple sclerosis, "outcomes-based formulary decisions are exceedingly difficult to make." DeBellis serves as faculty for a series of continuing education programs on the management of MS. "True outcomes are difficult to assess, and they vary greatly from patient to patient," says DeBellis.

It's also about cost

Payers understand the dilemma. According to Irene Girgis, PharmD, director of pharmacy at Denver-based Colorado Access, a not-for-profit health plan, "We don't know which drug is going to be superior for any given patient. Response to treatment is quite variable, so if a drug works well for a patient, it makes sense to remove barriers."

Cheryl Larson, vice president of the Midwest Business Group on Health, tells her large self-insured members that the issue isn't cost reduction but cost containment. "We can't wait for the cost of drugs to come down," she says. "We have to

[1] In September, the second oral drug for MS, teriflunomide (Aubagio), was approved.

manage the disease so that any given treatment is as cost-effective as possible and leads to the best outcome."

Efforts to reduce cost by eliminating variations in treatment may not work with a complex disease like MS. Manifestations and trajectories of the disease, responses to treatment, and neuroradiological findings vary significantly among patients. Until more is known about the disease, a unique approach to cost and management is required. "Employers need to know that patients with MS struggle with a complex disease that must be managed closely," says Larson. "Neurologists don't have time to spend on all the details. Others need to follow up on treatment and manage expectations."

Meanwhile, patients, who are generally excluded from decisions related to treatment costs, cling tenaciously to their healthcare benefits.

"Insurance is a big issue for patients," says Nicholas LaRocca, PhD, vice president for healthcare delivery and policy research at the National Multiple Sclerosis Society (NMSS). "It's such a significant part of compensation for them that it becomes an important reason to keep a job." Thus, patients invited to participate in collaborative efforts to manage their care might be highly motivated to do so. And health plans might find that patient engagement could help minimize costs.

Biomarkers needed

Better data for managing MS begins with better tools. Large databases incorporate data from patients with MS to generate clues about best treatment practices. But how meaningful are the data being captured? Consider the case of Brian Howard, editor-in-chief of *Book Business*, in Philadelphia, for whom a single episode of optic neuritis (diagnosed as clinically isolated syndrome, or CIS) was his only symptom of MS.

"I'm doing well. I haven't had any more symptoms," says Howard, who has been taking glatiramer acetate (Copaxone) for five years. "However, I am not confident that this is due to the drug, and neither is my doctor." Indeed, while characteristic abnormalities on an MRI have some predictive value for patients with CIS, many patients never develop full-blown MS. In Howard's case, the success of his treatment cannot be distinguished from a remission or a naturally benign course of the disease.

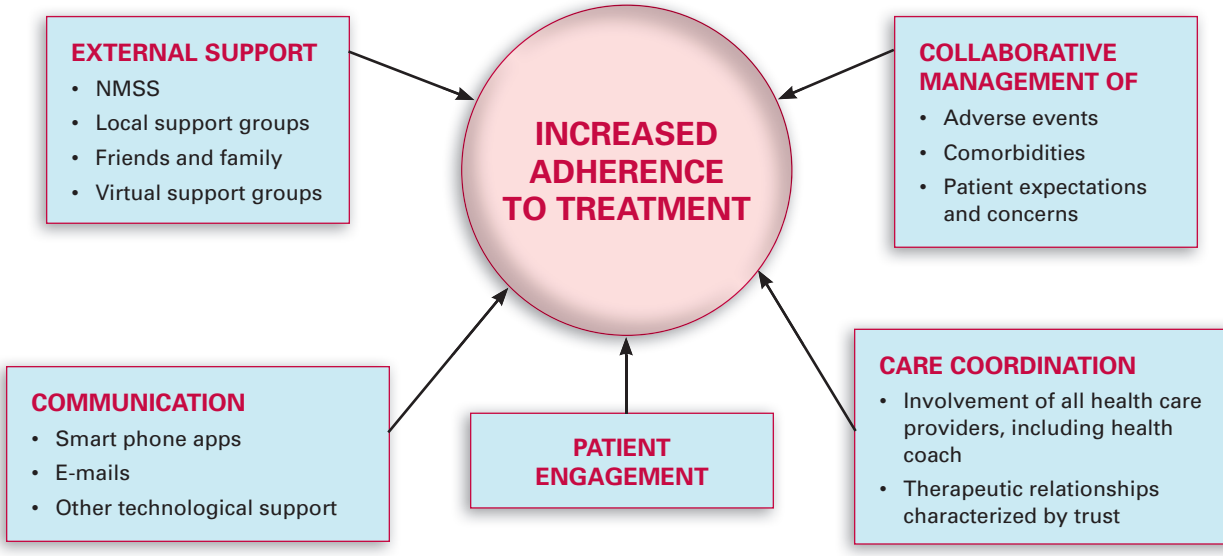
Jeff Januska, PharmD, director of pharmacy for CenCal Health, a California Medicaid plan, is familiar with CIS scenarios. "We know that a certain number of these patients will go on to develop MS," he says. "But how do we know which ones? We need a biomarker."

Richard Rudick, MD, at the Cleveland Clinic, agrees and thinks biomarkers are important for three reasons: "to predict disease severity, to predict response to treatment, and to evaluate response to treatment."

Especially sought after are nonimaging biomarkers, or biological characteristics that can be objectively measured and used to indicate and evaluate both normal and pathological processes. Because the molecular mechanisms underlying the pathophysiology of MS involve a

FIGURE

Strategies for improving patient management and adherence to disease-modifying therapies



Source: Created for Biotechnology Healthcare by Glen Stream, MD, American Academy of Family Physicians, and Lily Jung Henson, MD, American Academy of Neurology. Adapted from Brandes DW, et al. *Curr Med Res Opin.* 2009;25:77–92.

wide range of biological phenomena, many complex "omics" technologies are enlisted in the search for viable candidates. An ideal biomarker for MS would be linked to an MS-related pathophysiological process or clinically relevant outcome and would be easy to access in biological samples, such as blood and urine (Rajasekharan 2012). But progress in this area has been slow.

The process of validating biomarkers for MS is challenging in part because brain tissue is not easily accessible. But a new project called BioScreen, led by Stephen Hauser, MD, at University of California–San Francisco, may speed up the process. The goal is to develop a secure portal that integrates patient-specific information about disease progression, treatment, environmental exposure, imaging, and genomic data to help validate biomarkers. The project received funding this year from the Patient-Centered Outcomes Research Institute.

The imaging biomarker

For now, MRI remains indispensable for diagnosing and monitoring MS. It also shows potential with regard to patient stratification — a recent study showed that development of new T2 hyperintense lesions during treatment with interferon beta was the best predictor of poor long-term response to therapy (Prosperini 2009). Yet imaging with greater sensitivity and specificity is needed to validate treatment efficacy in pivotal trials. Currently, only clinical findings (reduction in relapses and disability) are acceptable primary endpoints in phase 3 research.

Ironically, in clinical practice greater weight is often placed on MRI findings — a constant source of frustration for patients, who despite feeling fine may be disappointed to discover that a recent MRI shows disease progression. When clinicians confront such a disparity, they are

"Improving the rational selection of treatments for MS has been a goal that I have shared with Biogen Idec for a long time," says the company's chief medical officer, Alfred Sandrock, MD, PhD.

usually compelled to "treat" the MRI. Robert Fox, MD, at the Cleveland Clinic, uses a vivid analogy to explain: "If a patient with lung cancer tells his cancer specialist he feels fine but the specialist sees the tumor enlarging on an x-ray," says Fox, "the specialist will follow the scan more than the patient."

A deeper understanding of the imperfect correlation between MRI findings and clinical findings is just one goal of current neuroimaging research, which is moving at a breathtaking pace. Daniel S. Reich, MD, PhD, chief of the Translational Neuroradiology Unit at the National Institutes of Health, is detecting in the galaxies of gray and white matter revealed by MRI meaningful patterns of lesions that may eventually yield implications for treatment. In one of his many projects, Reich is trying to pinpoint the earliest pathogenic mechanisms associated with MS, and he has great faith in the future of imaging technology. Can he envision a future in which sophisticated imaging might go beyond basic stratification of patients and perhaps even suggest ideal treatments? "Yes," says Reich, without hesitation. "We're not there yet, but it is certainly conceivable."

Early patient stratification

Biogen Idec has emerged as the leader to improve the rational selection of treatments for MS. The company's Stratify JCV Antibody ELISA test assists clinicians in determining a patient's risk for developing progressive multifocal leukoencephalopathy during treatment with natalizumab (Tysabri). Natalizumab, generally recommended only after other treatments have failed, is an effective treatment option for some patients who test negative for the John Cunningham virus. "This represents a significant first step in the direction of personalized medicine," says Tim Coetzee, PhD, chief research officer at the NMSS.

"Patients must weigh the risks and benefits of every treatment," says Alfred Sandrock, MD, PhD, chief medical officer at Biogen Idec. "For patients who might benefit by taking Tysabri, this is an important effort to reduce risks up front."

In addition to funding an extensive investigation of biomarkers suitable for predicting response to treatment with interferon beta-1a (Avonex) and daclizumab, Biogen Idec has entered into collaboration with Regulus Therapeutics, in LaJolla, Calif., to explore potential microRNA biomarkers that can be detected in blood samples of MS patients.

New MS business models

Efforts to address unmet needs, such as a treatment for progressive disease, are also triggering innovative business models.

"Taking the kind of risks you have to take to find a blockbuster drug for MS is getting harder," says Gail Maderis, chief executive officer at BayBio, a not-for-profit organization that supports the life science industry in Northern California. "We think the Holy Grail would be an agent that actually repairs the myelin sheath and addresses progressive

disease. We found a not-for-profit organization with a tremendous business model that's trying to do exactly that."

The Myelin Repair Foundation, a Silicon Valley-based group that focuses on developing myelin repair therapeutics, has attracted prominent members of industry and academia. Jay Tung, PhD, vice president of drug discovery, says the foundation has a three-pronged strategy for identifying agents that have the potential to repair myelin.

"Our short-term strategy involves the repositioning of currently marketed drugs. Our mid-term strategy involves the recycling of chemical matter developed for other disease indications, and our long-term strategy involves the development of new targets that have never been described or interrogated in the scientific literature for myelin repair."

The foundation has two phase 1 clinical trials underway. In one, headed by Robert Miller, PhD, of Case Western Reserve University, mesenchymal stem cells and the body's own process of repair are being harnessed to address progressive disease. Miller cautions, however, that everyone "wants a simple cure, but myelin repair may not mean a one-size-fits-all treatment. Different patients may require different treatments and they may have to be taken repeatedly."

Although the hope is that discovering the cause of MS could lead to a cure, Rudick, at the Cleveland Clinic, says, "It's possible that we may find a cure without ever learning the cause."

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TABLE
Emerging treatments for multiple sclerosis[a,b]

Agent	Manufacturer/ sponsor	Description/ mechanism of action	Route of administration	Status
Dimethyl fumarate	Biogen Idec	Modulates oxidative pathways and decreases autoimmunity	Oral	NDA filed
Alemtuzumab (Lemtrada)	Sanofi	Antibody binds CD52 to cause destruction of circulating immune cells	IV infusion	BLA to be resubmitted
Daclizumab	Biogen Idec	Monoclonal anti-CD25 antibody that blocks the IL-2 receptor	Subcutaneous injection	Phase 3
Ocrelizumab	Hoffman-LaRoche	Antibody targets CD20 and mediates destruction of B cells	IV infusion	Phase 3[c]
Masitinib	AB Science	Inhibits survival, migration, and activity of mast cells	Oral	Phase 3[c]
Abatacept	Sponsor: NIAID/Bristol-Myers Squibb	Antibody blocks an early step in immune cell activation	IV infusion	Phase 2
Estriol (Trimestra)	Sponsor: UCLA/Adeona Pharmaceuticals	Pregnancy hormone; decreases inflammatory immune response	Oral	Phase 2
Tcelna	Opexa Therapeutics	Personalized T-cell therapy	Subcutaneous injections (5 per year)	Phase 2[c]
Mesenchymal stem cells	Sponsor: Myelin Repair Foundation	Mesenchymal stem-cell signals stimulate protection and repair of myelin	Autologous mesenchymal stem cell transplantation	Phase 1[c]
Helminth-induced immunomodulation therapy	Sponsors: NMSS and University of Wisconsin	Harmless parasitic worms stimulate protective immune response	Oral (liquid)	Phase 1

BLA=biologics license application, IV=intravenous, NDA-new drug application, NIAID=National Institute of Allergy and Infectious Diseases, NMSS=National Multiple Sclerosis Society, UCLA=University of California–Los Angeles.

[a]Adapted from content provided courtesy of the National Multiple Sclerosis Society. [b]Several approved treatments, including fingolimod (Gilenya) and natalizumab (Tysabri), are under investigation for treatment of progressive disease. [c]Progressive disease indication.