Multiple sclerosis (MS) is a disease state that does not remit. For virtually all patients suffering with MS, ongoing damage will occur if their disease goes untreated, regardless of how they might feel. The term, “relapsing-remitting” is an outdated concept that arguably gives patients a false impression of the disease and fosters less urgency for treatment. Relapsing MS is the term that should be used.

In recent years, the field of MS research and treatment has expanded significantly, giving our patients many potential options for treatment. Despite these advances, we should never forget a strong relationship between the physician and the patient remains the most important aspect of successful interventions. This requires education about the condition and consideration of the number of factors that may impact adherence.

This article examines how physicians can harness the latest developments in MS diagnosis, imaging, and treatment toward a stronger partnership with patients to optimize therapeutic efficacy.

**DIAGNOSIS AND IMAGING**

In recent years we have come to understand the importance of early diagnosis to institute early treatment. Specifically, there may be a window of opportunity early in the disease for many patients, meaning that the sooner we begin treatment, the more we are likely to maximize therapeutic response.

However, since there is still no diagnostic biomarker, early diagnosis remains a significant challenge. We are currently using a compilation of history and examination, and while MS remains a clinical diagnosis, it would be inappropriate not to do a laboratory work-up.

An appropriate laboratory workup consists of the following:

- **Blood testing**, for the purpose of exploring any comorbid conditions and important factors that might be influential in MS, such as vitamin D and vitamin B₁₂ levels;

- **Appropriate neuroimaging**, which many are now accepting as imaging the entire central nervous system (CNS) using brain MRI (with and without contrast), as well as cervical and thoracic MRI scan at onset to look for macroscopic lesions involving the CNS;

- **Routine examination of cerebrospinal fluid**. Although there are some neurologists who will only do this in very selected cases, it is important to note that the...
The finding of positive oligoclonal bands is a very helpful diagnostic finding. It’s not unique to MS, but clearly MS is the major disorder that causes it, and you have a positivity rate even early on of greater than 80 percent.

*Accurate diagnosis is critical.* One of the fundamentals of diagnosis of MS is to create a differential diagnosis, and rule out other possibilities. Doing a thorough laboratory diagnostic work-up can make everybody feel very comfortable about having done the due diligence to rule out mimicking conditions and arrive at an accurate diagnosis of MS as early as possible.

*Standardizing MRI.* While a complete diagnostic work-up is essential, there are still roadblocks to achieving early and accurate diagnosis. Chief among these is the lack of standardized imaging protocols. Fortunately, recent efforts to address this have resulted in a revision of the recommended MRI protocol in MS for both brain and spinal chord.¹ This protocol should be presented to every neuroimaging facility that does MRI studies on MS. Additionally, several protocols have been developed for sub-areas within MS, such as, for example, a protocol for patients on natalizumab who may develop progressive multifocal leukoencephalopathy (PML).

The revision calls special attention to imaging of the spinal cord, which can be difficult to image. Currently there are some facilities that aren’t using very good protocols and are giving inferior results and potentially missing important findings. In general, the revised protocol guidelines reflect a growing need for the standardization of MRI techniques. It is important that neuroimaging facilities are held to these guidelines and doing optimized sequences and protocols to maximize the benefit of an MRI and give the reader the most information.

In addition to the standard tests that are done on our MRI currently, there are a number of very interesting non-conventional research imaging techniques that have not reached daily clinical utility yet, but may in the future. It is possible that someday we will be able to do things like automated total lesion load volumes, brain volume loss/atrophy measures, and other very interesting techniques that can actually analyze microscopic injury. We know that the best conventional MRI scans see the macroscopic lesions, but the normal-appearing brain tissue (actually 70 percent of it) is abnormal, with microscopic changes that we don’t visualize at all on our best conventional MRI scan. In the future, it may be that selected such techniques will be used routinely to analyze both macroscopic and microscopic injury in the CNS in MS.

Right now, however, the first priority of physicians and imaging facilities should be to ensure that they are following the standardized protocols for how MRIs should be done in MS. This is an achievable goal; we simply need to decide to do it and insist on it. If we can do that, we increase the likelihood of adding non-conventional techniques in the future.

### TREATMENT AND ADHERENCE

After a diagnosis is made, it’s very important from the absolute beginning of the process to inform patients about the importance of a personalized wellness, health maintenance, and vascular risk factor program to improve and preserve CNS and brain reserve, to maximize basic health, and to combat a neurological condition like MS. Really close follow-up and communication with patients is a very important concept which I will address later.

In terms of treatment, we currently have multiple disease modifying therapy (DMT) options, all for relapsing forms of MS, which is quite exciting. Moreover, vehicles and mechanisms of action of these agents differ tremendously. Injectable therapies include peginterferon beta-1a

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**PRACTICAL POINTERS**

- To increase the likelihood of early diagnosis, physicians and imaging facilities should ensure that they are following the standardized protocols for how MRIs should be done in MS.
- Physicians should consider a variety of drug, disease, and patient factors when selecting a treatment to which the patient will be most likely to adhere.
- One important element of building that partnership is ensuring that patients have a completely realistic expectation of what the drug is going to do.

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**QUICK TIP...**

Regular blood testing can help bring MS comorbidities into focus while allowing you to monitor vitamin D and vitamin $B_{12}$ levels.
(Plegridy), interferon beta-1a (Rebif), interferon beta 1b (Betaseron, Extavia), and glatiramer acetate (Copaxone), while oral agents include dimethyl fumarate (Tecfidera), fingolimod (Gilenya), and teriflunomide (Aubagio). There are also several second-line intravenous therapies that have high efficacy but slightly more potential risk, such as natalizumab (Tysabri) and alemtuzumab (Lemtrada). The multi-option choice allows physicians to try to fit each individual patient to their optimum DMT. If a patient is not doing well on a particular agent, physicians then have several options to make an appropriate switch.

Importantly, there are many gaps in the therapeutic landscape. For instance, we currently have no DMT that is approved for progressive forms of MS. We also have no approved agents to date that repair fixed deficits. Rather, all of our current DMTs for relapsing MS are aimed at minimizing or stopping future disease activity, but not really reversing what's happened. However, it is worth mentioning that several new agents are being developed with a greater emphasis on progressive forms of MS, as well as repair treatments for MS that will have implications for other major nervous system disorders as well.

When selecting an agent, there are three categories of factors to consider: patient factors, drug factors, and disease factors.

**Disease Factors.** One of the key features of MS is variability: No two patients are alike. The disease may be very mild, very severe, and anything in between. From the standpoint of the disease itself, it is important to consider the degree of disease activity based on clinical and MRI characteristics. If you have patient with very active disease, drug efficacy becomes a very important factor, whereas for someone who doesn’t have very active MS maybe that's not as important. Also, what is the prognostic profile of the patient? Do they have many bad prognostic indicators, or do they have very few bad ones? That gives you a sense of a picture of the MS disease process.

**Drug Factors.** Given the variety of agents available, it is important to account for the many drug variables when selecting the best one for a patient. Things like efficacy, tolerability, adverse events, monitoring, delivery system, and pregnancy issues may all play into the consideration and come into a dialogue with the patient and will help to discard some options but raise up others.

**Patient Factors.** In concert with disease factors and drug factors, our therapeutic decision-making should be heavily guided by patient factors, as well. Shared decision-making is key for achieving the best outcome, which is why a partnership with patients can play such an important role. With multiple options available, you want to make sure the patient is going to take the medication and therefore you need buy-in.

One important element of building that partnership is ensuring that patients have a completely realistic expectation of what the drug is going to do. I often explain to patients that MS is not like a bad headache, in which the right medication can take away the pain. MS therapy is instead a kind of invisible therapy. In other words, patients are not going on an agent to feel better but instead to prevent or minimize damage to the CNS and future events that they haven’t experienced or known yet.

Whenever anybody starts any medication, they may have a few bumps in the road with regards to side effects. But it is important to frame this discussion within the context of how the disease may affect the patient in the future if it is not treated appropriately. Putting these explanations in terms patients and their families can understand is especially important. Encouraging patients to bring family members can be helpful as well, as not everything said may penetrate when you are giving the patient information. Distributing handouts, and encouraging patients and families to read up on MS as much as possible, is also part of the process of building an effective partnership.

**QUICK TIP...**

Rendering MS in understandable terms for patients is essential to care. For example, the concept of MS therapy as an “invisible treatment” is particularly effective.

When it comes to solidifying that relationship with the patient, it is important that they feel that their preferences, expectations, and lifestyle matter. Knowing these things can also help determine the best agent for each patient. For example, physicians should learn the patient’s willingness to take risk. They may be in a position where they feel they can take high risk or they may not want to take any risk whatsoever.

These variables not only make patients feel like they are part of the process, but could also impact adherence. In MS, adherence is critically important. The injury process is largely a silent one. Moreover, patients may not have any visible change objectively on their neurological exam or even a noticeable change on their MRI scan (since the injury may
be microscopic). For these reasons, patients may be tempted not to take their medication as directed, and thus be at greater risk for relapse. In fact, there is evidence to suggest that greater adherence translates to improved outcomes. In a study published last year on which I served as co-author, we documented an association between patients not taking their DMT as directed and a higher clinical attack rate. This study offers objective evidence-based data for just how important adherence to the medication is.

Thus, as part of our partnership with patients, education is an integral component. Put simply, patients need to hear that if they don’t take the medication there may be ongoing damage that may not be apparent until years later. This underscores the importance of matching the patient to a DMT to which they can be adherent, and having a dialogue that allows the physician greater insight into a patient’s preferences.

Physicians should be aware of the warning signs that there may be adherence issue. These include:

- Patients who are depressed or have cognitive difficulties;
- Patients who lack a support system;
- Patients don’t seem to be really aware or show understanding about the disease process;
- Patients who view DMTs as unnatural or toxic, or believe in the benefits of a more natural approach.

As physicians, it is our job to have very candid educational dialogues with patients like this, as they present an alert to adherence issues.

Of course, while forming a strong partnership with patients can improve adherence and outcomes and result in more successful interventions, it bears mentioning that physicians often lack sufficient time to forge these relationships. What we’re seeing with regard to the retrenchment of reimbursement is that physicians are seeing more patients but spending less time with them, which can place a burden on physicians who prioritize education and counseling for patients, an activity that is not well reimbursed. While academic centers are sheltered to a certain extent from this problem, in the community it’s becoming more difficult. Thus, physicians under significant time constraints should inform their patients about a number of good resources and educational materials (in addition to having them at the practice).

Support services such as local MS chapters, the National MS Society, the Consortium of MS Centers, the MS Association of America, and the MS Foundation can also be helpful in bolstering education, as well.

CONCLUSION

The spectrum of MS treatment is rightfully considered one of the biggest success stories in neurology. With an increasing number of available modalities, as well as many other investigational agents in the pipeline, it’s a very exciting time for MS care. As continued advances expand and deepen the treatment field, physicians in private practice should partner with an MS center for getting quick referrals for recommendations or opinions. These resources are continuing to develop regionally and should help physicians interface with centers and experts to allow for better, more efficient care.

As the future of MS therapy continues to unfold rapidly, early diagnosis is critically important. That means performing thorough laboratory work-ups and initiating treatment in a timely fashion, ideally within three months of the first attack. And when it comes to making the selection of a DMT that not only accounts for various drug and disease factors but also represents the agent to which patients will most likely adhere, physicians should be seeking to partner with patients and engage with them in shared decision-making. With patients playing a more active role in the process, the future of MS therapy is all the brighter.

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