Beyond Efficacy and Safety: Where We Go From Here in the Management of Multiple Sclerosis

Introduction

When selecting a disease-modifying therapy (DMT) for patients with multiple sclerosis (MS), clinicians must first consider the efficacy and safety of the agent.[1] Other considerations include initiating treatment as early as possible, adherence to current and subsequent DMTs, understanding when to switch patients from their current DMTs to other medications (and knowing when not to switch), and cost factors.[2-5]

Although the currently approved DMTs are reliable, constantly being improved, effective in treating relapses, and able to reduce long-term disability, they have only limited efficacy in treating progressive disease that is not associated with inflammatory relapses.[6] More effective DMTs are needed specifically for patients with primary progressive MS. Likewise, agents that repair or regenerate neurons, oligodendrocytes, and supporting glia are essential for effective treatment.[7]

Several new medications have entered the market in recent years and others are in late-phase clinical studies for the treatment of patients with relapsing or progressive forms of MS.[8] These agents represent a variety of mechanisms of action, providing not only lower relapse rates but also improvement in disabilities.

Importance of Early Diagnosis and Early Treatment

MS is characterized by both inflammation and progressive neuroaxonal damage.[9] Although this damage often occurs in the early stages of disease, it may be masked by compensatory mechanisms. Thus, progressive damage may go unrecognized until it is too late for intervention to be beneficial. As MS progresses, the balance between the degenerative and the reparative processes shifts, resulting in progressive neuroaxonal degeneration and increasing disability (see **Figure 1**).[9]

Because brain atrophy creates permanent damage, and correlates with physical and cognitive disability, it is important for patients with MS to be treated with DMTs as early in the disease course as possible, in order to decrease the loss of brain volume and its effects.[2] Additionally, patients with clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) who are at high risk for the development of clinically definite MS (CDMS) should also be treated with DMTs as soon as possible.

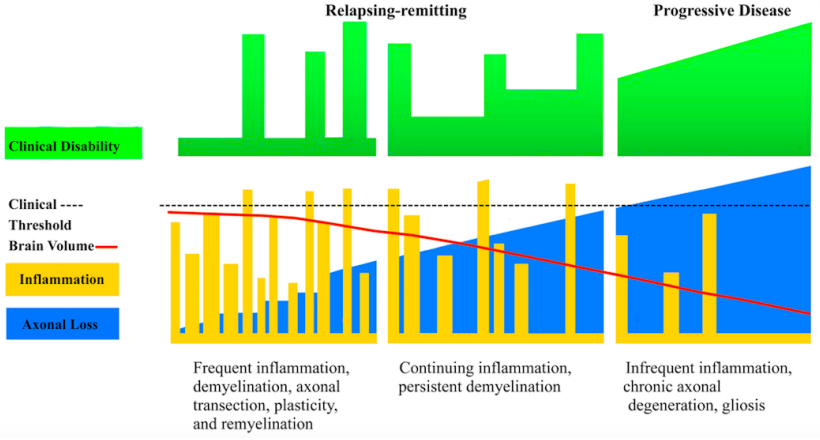
Several clinical trials have provided proof of concept for an early window of initial treatment intervention in patients with CIS.[9] Significant reductions in the risk for developing CDMS were observed with the use of interferon beta agents and glatiramer acetate when treatment was initiated early on. Physical disability and number and/or volume of brain lesions were also improved with early treatment. Similar results have been reported with some of the newer DMTs, such as teriflunomide, alemtuzumab, and fingolimod.

Adherence to Disease-Modifying Therapies

According to the World Health Organization (WHO), adherence is defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes— corresponds with agreed recommendations from a health care provider."[10,11] There are 3 distinct components of adherence: (1) acceptance, (2) persistence, and (3) compliance.[10,12] Patients must accept that they need treatment, they must persist in taking the treatment over time, and they must comply with their prescribed treatment (that is, take the right dose at the right time and with the correct frequency).

Medication adherence is a major concern in the MS population, particularly with DMTs.[10,12,13] The WHO estimates an average adherence rate of only 50% among

Figure 1. Brain Atrophy Occurs Early in the Disease Process



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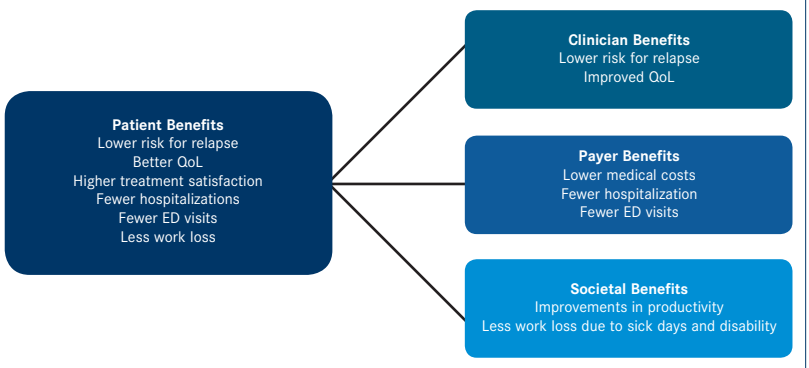
chronically ill patients in the developed world.[10,13] Although overall rates of adherence to DMTs in patients with MS is estimated to be higher than 50%,[10,12] variations among studies and medications do exist. Suboptimal adherence to DMTs has a negative impact on patient morbidity and mortality outcomes, as well as on overall costs of patient care.[1,10] Some of the major benefits associated with patient adherence to therapy are displayed in **Figure 2**.

Figure 2. The Benefits of Adherence[10]



ED indicates emergency department; QoL, quality of life.

Four recent studies have evaluated adherence rates with the first-generation, injectable DMTs (including interferon beta-1b, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, and glatiramer acetate) used in the treatment of MS.[13-16]

- In a population-based cohort study of 4830 patients, optimal adherence was observed in 76% of patients after 1 year of therapy.[13] Patients who initiated therapy in recent years were more likely to have suboptimal adherence and to discontinue their DMT within the first 12 months versus those who began treatment in earlier years.
- In a systematic review of medication adherence from 24 studies with a combined population of >2400 patients, 59.6% of patients were adherent to therapy.[14] Common barriers to adherence included patients forgetting to their take medication, perceived lack of efficacy, anxiety about injections, and adverse reactions.
- In a multicenter, observational study of 798 patients, nonadherence was reported by 36% to 39% of patients surveyed.[15] Forgetting to administer their injections, which was the most common reason cited by participants for nonadherence, was reported by 58% of those with adherence issues. Other reasons for nonadherence included injection-site reactions, effects on quality of life, and symptoms of depression.
- Of the 2648 patients evaluated in the Global Adherence Project, 75% were adherent to therapy.[16] The most common reported reasons for nonadherence included forgetting to administer the injection and other injection-related reasons.

Adherence is difficult to quantify.[10] In many cases, there can be multiple contributing factors to poor adherence versus only one factor. Clinical trial data have identified a myriad of contributing factors that lead to poor adherence, including cognitive impairment, perceived lack of efficacy from DMTs, economic/financial challenges, adverse events (AEs) associated with the agent, and fear/anxiety over using injections.[10,11] A number of different approaches might help to improve adherence among patients with MS.

- Enlist support from family members and/or caregivers.[10]
- For patients who experience cognitive impairment and those who frequently forget to take their medication, efforts should be made to simplify treatment regimens.[10] Medications that can be administered fewer versus more times per day should be suggested, and monotherapy options rather than combination therapies should be recommended.
- Establish realistic expectations about the potential benefits of treatment.[1,12] Patients should understand that DMTs do not "cure" MS, that they may not eliminate MS symptoms, and that they may not completely eradicate future disease activity.
- Evaluate the economic burden on patients associated with the use of MS medications.[10,11] Providers should have an improved understanding of formulary issues, such as the selection of agents that are available on the formulary, the formulary override process, prior authorization, initiation and ongoing approval, and adherence to Risk Evaluation and Mitigation Strategies (REMS), where needed.[5] Additionally, support from a social worker can be helpful, along with enlisting aid from the manufacturer. Medication assistance programs exist for all of the FDA-approved DMTs.

Provide injection training for injectable DMTs.[10-12] For example, patients should be trained to rotate injection sites, to use an autoinjector (which is available free of charge from manufacturers), to inject medications at room temperature, to ice the area before and after injecting medication, and to massage the area following injection (for interferon beta products only).

Manage AEs accordingly.[10-12] Remind patients using interferon beta agents that flulike symptoms often improve with time, and can be relieved by premedication with nonsteroidal anti-inflammatory drugs or acetaminophen. The impact of flulike symptoms may also be reduced by administering the agent in the evening, before bed, on the weekend, or before another convenient period of time.

For patients who experience poor treatment adherence because of anxiety or fear over administering injections, consider switching to an oral therapy.[11]

Switching Therapies

Patients who do not respond well to one DMT may need to switch to another DMT.[1,3,4,17] Possible markers of nonresponse to treatment include continued, frequent relapses or magnetic resonance imaging findings suggestive of disease activity (such as gadolinium-enhancing activity or new lesion formation).[3] Switching therapies also may be necessary for patients who experience intolerable adverse events; however, switching treatments within 6 months of treatment is discouraged, because many adverse events diminish over time.[12] Switching medications might also be indicated for patients who have difficulty remaining adherent to therapy, as switching is often an effective method in which to proactively promote medication adherence.[11]

Timing is also an important consideration when it comes to switching therapy.[1,4,18] If patients are experiencing disease progression despite being treated with a DMT, switching should be considered earlier than later, because residual impairment may worsen with each new relapse. It is also important to recognize that switching DMTs may lead to breakthrough disease, particularly with longer-acting products.

Other considerations (besides risks/benefits, which have been discussed previously) when switching therapies include the following: immunogenicity; mechanism of action of prior DMTs, which can affect the efficacy and safety of subsequent therapies; risk for progressive multifocal leukoencephalopathy (PML); and immunization status.[1,4] Patients should also be evaluated for active or uncontrolled infections.

The presence of neutralizing antibodies, which is associated with several DMTs (including beta interferon medications and natalizumab), can decrease the effectiveness of an agent and thus can lead to increased disease activity.[1,7,19] It is generally not advisable to switch a patient who has developed neutralizing antibodies from one interferon beta agent to another, because he or she will likely also develop neutralizing antibodies from use of the second interferon beta agent.

A transition period between stopping a current DMT and initiating a new DMT may be necessary in some circumstances.[4] For example, the immunologic effect of alemtuzumab (which is not related to its half-life) may persist long after the cessation of treatment. This might potentially expose patients to immune-mediated risks when they are switched to other DMTs.

TABLE 1. Annual Costs Associated With the Use of Disease-Modifying Therapies[5]

Product	FDA Approval Date	Annual Cost at Market Introduction, $	2017 Annual Cost, $
Interferon beta-1b (Betaseron)	July 1993	10,920	86,421
Interferon beta-1a (Avonex)	May 1996	8261	81,731
Glatiramer acetate 20 mg (Copaxone)	December 1996	7852	86,554
Interferon beta-1a (Rebif)	March 2002	13,875	86,179
Natalizumab (Tysabri)	November 2004	23,500	78,000
Interferon beta-1b (Extavia)	August 2009	29,842	72,160
Fingolimod (Gilenya)	September 2010	48,083	86,966
Teriflunomide (Aubagio)	September 2012	45,124	76,612
Dimethyl fumarate (Tecfidera)	March 2013	54,750	82,977
Glatiramer acetate 40 mg (Copaxone)	January 2014	60,336	75,816
Peginterferon beta-1b (Plegridy)	August 2014	62,036	81,731
Alemtuzumab (Lemtrada)	November 2014	65,833	69,166
Daclizumab* (Zinbryta)	May 2016	82,000	86,838
Ocrelizumab (Ocrevus)	March 2017	65,000	65,000

TABLE 2. Drug Pipeline for Multiple Sclerosis[8,30-33,35-42]

Agent	Description	Clinical Development Program
Laquinimod	• Orally administered immunomodulator being studied for the treatment of RRMS and PPMS • Although its exact MOA is unknown, laquinimod appears to influence the TH1 to TH2 cytokine shift	• Mixed efficacy results have been observed in phase 3 trials o In the ALLERGO trial, ARR, disability progression, and number of Gd-enhancing lesions all were improved significantly with laquinimod versus placebo o In the BRAVO trial, ARR was not significantly reduced with laquinimod versus placebo • In the ALLERGO and BRAVO trials, the most commonly reported AEs with laquinimod included elevated LFTs, abdominal pain, back pain, and cough • Phase 3 CONCERTO trial in RRMS has not reported results • Phase 2 ARPEGGIO trial in PPMS has not reported results
Masitinib	• Orally administered tyrosine kinase inhibitor that targets mast cells and inhibits several biochemical processes • Being studied in PPMS and SPMS	• In a pilot study, masitinib appeared to have a positive effect on MS-related impairment in patients with PPMS and relapse-free SPMS. The most commonly reported AEs included asthenia, rash, nausea, edema, and diarrhea • Phase 3 trial in patients with PPMS or relapse-free SPMS has been halted
Ofatumumab	• Depletes B cells via antibody-dependent, cell-mediated toxicity and complement-dependent cytotoxicity • Administered intravenously or subcutaneously	• In a phase 2 trial, significantly fewer T1 Gd-enhancing lesions, total number of T1 Gd-enhancing lesions, and new or enlarging T2 lesions were observed with ofatumumab versus placebo. No unexpected safety signals emerged. Infusion-related reactions were common on infusion day 1 but were not observed on infusion day 2 • Phase 2 MIRROR trial has not reported results • Phase 3 ASCLEPIOS I trial has not reported results
Ozanimod	• Orally administered, selective S1P receptor modulator being studied in RRMS • Penetrates BBB, and binds S1P1R and S1P5R • Safety profile appears to be superior to that of other S1P agents • Receptor selectivity, PK properties, and use of dose escalation potentially differentiate the cardiac profile of ozanimod from that of other S1P agents	• In the phase 2 RADIANCE trial, mean cumulative number of Gd-enhancing lesions (weeks 12-24), number of Gd-enhancing lesions (week 24), and new/enlarging T2 lesions (weeks 12-24) were decreased significantly with both doses of ozanimod (0.5 mg and 1 mg) versus placebo. The most commonly reported AEs with ozanimod included nasopharyngitis, headache, and urinary tract infection. ECGs and 24-hour Holter monitoring demonstrated no increased incidence of atrioventricular block or sinus pause with ozanimod • Phase 3 SUNBEAM trial has not reported results
Ponesimod	• Orally administered, selective S1P1 receptor modulator being studied in RRMS • Penetrates BBB and binds S1P1R	• In a phase 2b trial, mean cumulative number of new T1 Gd-enhancing lesions (weeks 12-24) was significantly lower with all ponesimod doses (10 mg, 20 mg, and 40 mg) versus placebo. Additionally, mean ARRs were lower with ponesimod 40 mg versus placebo. The most commonly reported AEs with ponesimod included anxiety, dizziness, dyspnea, increased alanine aminotransferase, influenza, insomnia, and peripheral edema • Phase 3 OPTIMUM trial has not reported results
Siponimod	• Orally administered, selective S1P receptor modulator being studied in RRMS and SPMS • Penetrates BBB, and binds S1P1R and S1P5R	• In a phase 2 trial in RRMS, a dose-response relation was observed (P = .0001) across the 5 doses of siponimod, with reductions in combined unique active lesions at 3 months compared with placebo. Common AEs included headache, bradycardia, dizziness, and infections of the nose and throat • In a phase 3 trial in SPMS, siponimod significantly reduced confirmed disability progression by 21% versus placebo (P = .013). Common AEs included headache, nasopharyngitis, urinary tract infection, falls, and hypertension

AE indicates adverse event; ARR, annualized relapse rate; BBB, blood–brain barrier; ECG, electrocardiogram; Gd, gadolinium; LFT, liver function tests; MOA, mechanism of action; MS, multiple sclerosis; PK, pharmacokinetics; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; S1P, sphingosine-1-phosphate; S1P1R, S1P receptor 1; S1P5R, S1P receptor 5; SPMS, secondary progressive MS.

The relationship between the mechanism of action of prior DMTs and subsequent therapies should be evaluated.[4] In some cases, previous DMTs could potentially nullify or attenuate the mode of action of future therapies. The T-cell– and B-cell–depleting actions of alemtuzumab and ocrelizumab, respectively, occur immediately following the use of fingolimod if lymphocytes have not yet exited from secondary lymphoid tissue.

The development of PML has been associated with the use of several DMTs.[4] The risk differs according to DMT. Natalizumab is associated with the highest risk for PML (incidence, 1/100 to 1/1000), followed by fingolimod (incidence, 1/18,000) and dimethyl fumarate (incidence, approximately 1/50,000).[4] The risk for PML with other DMTs is either very low or unclear. It is currently not known whether or how the sequencing of DMTs might affect overall PML risks.

It is generally recommended that live vaccinations be avoided in patients with MS.[1,4] The prescribing information for teriflunomide, fingolimod, daclizumab*, and alemtuzumab advise against the use of live attenuated vaccines during and for prespecified time periods after discontinuing therapy.[20-23]

Aside from glatiramer acetate and the interferon beta agents, all of other DMTs have been associated with a risk for infection, including both community-acquired infections and opportunistic infections.[24] Patients should therefore be screened for latent viruses and other conditions (such as hepatitis B infections) prior to initiating therapy.

The High Cost of DMTs

MS is a disabling, chronic disease that imposes a substantial economic burden on both patients and on the US healthcare system.[5] The single largest driver of MS-associated healthcare expenditures are prescription drugs, which account for more than half of all direct medical costs. In particular, the costs of DMTs have risen dramatically over the last 10 years.[5] The price of some of these medications has increased nearly 10-fold (see **Table 1**). Acquisition costs for nearly all DMTs currently exceed $70,000 per year.[5] This does not include costs incurred from the care of patients receiving these agents (such as laboratory monitoring, first-dose observation period, and physician visits), only the cost of the actual DMT itself.

It is important to note that patients with MS often require many medications in addition to DMTs. Use of these medications is responsible for additional costs in the healthcare system.

Generic formulations are available for both the glatiramer acetate 20 mg and 40 mg formulations.[25,26] Fingolimod will lose exclusivity in 2019; it is anticipated that generic competition will occur soon thereafter.

The high cost of DMTs has a cascade of negative consequences for patients, ranging from excessive cost-sharing or deductible amounts to restrictive insurance barriers, which can negatively affect patient care.[5]

Unmet Needs

Although the currently approved DMTs are reliable, constantly being improved, effective in treating relapses, and capable of decreasing long-term disability, they have only limited efficacy for the treatment of progressive disease without the occurrence of additional inflammatory relapses.[6] In fact, of all the currently approved DMTs, only 1 agent—ocrelizumab—has been approved for the treatment of patients with primary progressive MS.[27]

Because the neuroarchitectural damage that occurs during relapses accumulates over time and is associated with increasing patient disability, neuroprotective and regenerative therapies are needed.[6] Specifically, agents that repair or regenerate neurons, oligodendrocytes, and supporting glia are critical components of the MS treatment armamentarium.[7]

Limiting disability among patients with MS will inevitably require a multidimensional approach that targets both the peripheral and the central nervous systems, focusing on specific immune components, as well as on those pathways that are thought to contribute significantly to neurodegenerative processes.[28]

The MS Pipeline

As noted earlier, several new medications are being investigated in late-phase clinical studies for the treatment of patients with relapsing or progressive forms of MS.[8] These agents represent a variety of mechanisms of action, and are associated with lower relapse rates and improvements in disabilities. Several of these pipeline agents are selective sphingosine-1-phosphate (S1P) receptor immunomodulators, including laquinimod, ozanimod, ponesimod, and siponimod. These agents have similar efficacy to the currently approved S1P immunomodulator fingolimod, whereas ozanimod appears to have an improved safety profile compared with other drugs in its class.[8] Ofatumumab is a CD20-positive B-cell–targeting monoclonal antibody, and masitinib is a mast-cell inhibitor.[8] Phase 3 trials for some of these agents will conclude within the next 12 months, and their manufacturers are expected to apply for FDA approval soon thereafter. **Table 2** describes a variety of agents in the MS pipeline.

Conclusions

In addition to efficacy and safety concerns, clinicians must also consider the optimal time to initiate MS therapy, adherence factors, switching strategies, and cost issues when prescribing DMTs to patients.[2-5] These considerations are a reflection of the many unmet needs of the MS care spectrum. With more agents in the pipeline offering the potential

to lower relapse rates and improve disabilities, however, the treatment landscape is poised for continued growth, giving clinicians increased opportunities to possibly improve treatment outcomes as well as quality of life.

*** In March 2018, Biogen withdrew daclizumab (Zinbryta) worldwide following reports of inflammatory encephalitis and meningoencephalitis.**

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