Advances in the Treatment of Multiple Sclerosis

Carolyn Goldschmidt[1], **Marisa P. McGinley**[1]

[1]Cleveland Clinic Mellen Center, Cleveland, OH, USA

Keywords

multiple sclerosis; disease modifying treatment; remyelination therapies; neuroprotection therapies; treatment approaches

Introduction

Multiple sclerosis (MS) is an immune-mediated, inflammatory demyelinating disease of the central nervous system that leads to irreversible disability, and currently is estimated to affect 1 million in the United States and over 2 million people globally.[1,2] The most common disease type is relapsing remitting (85–90%) and most treatments target this disease subtype. Some of these relapsing remitting MS (RRMS) patients will transition to a secondary progressive course. A small proportion of patients (10%) have primary progressive MS (PPMS), which is characterized by progression from onset. Treatment options for progressive disease are currently limited.

As our understanding of the disease has evolved, treatment options and treatment approaches have also advanced. The definitions of clinical courses were revised to better reflect underlying MS pathology.[3] Importantly, disease activity was added as a temporal qualifier to the MS phenotypes because clinical and radiographic disease activity along with disability progression can occur in both relapsing and progressive disease. This balance of disease activity reflects a combination of inflammatory and neurodegenerative processes that is important to understand treatment decision-making. This review will discuss the evolution of the treatment landscape of MS, treatment approaches, and future directions.

Disease Modifying Therapies

The first disease modifying therapy (DMT) was an injectable medication approved by the FDA in 1993. Subsequently there have been a variety if injectable, oral, and infusions DMTs developed that have unique risks and benefits.

Corresponding Author: Marisa P McGinley, DO, MSc, Address: Mellen Center U-10, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, mcginlm@ccf.org, Phone: 216-636-1158.

Injectables

Interferon beta-1b was the first FDA-approved treatment for RRMS.[4] There are currently five formulations of interferon injections available for RRMS. The initial phase 3 IFNβ trials showed a reduction in relapse rates by 18%–34% in patients with relapsing MS.[5] Shortly after the interferons were approved, glatiramer acetate was approved with similar efficacy.[6] Injectable therapies were the mainstay of MS treatment for over 15 years, until the first oral medications were approved. The injectables DMTs have the most long-term safety data, and there are patients who have remained stable on them for many years with few side effects. However, in the current landscape, use of injectable therapies has diminished due to the development of alternative DMTs with improved tolerability and higher efficacy.

Orals

Fingolimod, a sphingosine 1-phosphase (S1P) receptor modulator, was the first FDA approved oral DMT in 2010, which was a major advancement because of the improved efficacy and new route of administration. Since this development there have been a variety of oral options approved changing the landscape of treatment (see Table 1). Sipomimod and ozanimod are both selective S1P receptor modulators that were recently approved. These medications, although similar to fingolimod, have unique side effects and monitoring requirements. All patients started on fingolimod require first dose observation (FDO) due to the possibility of first dose bradycardia from interaction with receptors on cardiac myocytes. Conversely, only patients with a cardiac history are suggested to undergo a FDO with siponimod and there is no FDO recommendation with ozanimod. These varying recommendations are due to the more selective S1P receptor subtypes of the newer medications. Teriflunomide, like the S1P receptor modulators, has convenient once daily dosing, but with a different mechanism of action (pyrimidine synthesis inhibition). The fumarates are another class of oral medications. The most recently approved fumarate, diroximel fumarate, has the same dosing frequency and mechanism of action and dimethyl fumarate, but was shown to have improved tolerability, specifically reduction of GI side effects.[7,8] Finally, cladribine is unique in the oral medication group because it has an induction type dosing schedule of two 5 day cycles 12 months apart.[9] Overall, the oral medications are more efficacious than the injectable therapies, except for teriflunomide which is similar in efficacy to injectables, and cladribine has the highest efficacy. They are well-tolerated, though their side effect profile vary. The risk of infections is increased compared to the injectable therapies, and some may be limited due to other risks such lymphopenia in fingolimod or dimethyl fumarate and transaminitis with teriflunomide.

Infusions

Natalizumab was the first approved infusion DMT for RRMS in 2004. It is a monoclonal antibody against alpha-4 integrin and is a selective adhesion molecule inhibitor, given by a monthly infusion.[17] This therapy dramatically changed the landscape of treatment not only because of its route and frequency of administration, but also due to its high efficacy on relapses and MRI activity. Its use has been limited due to the serious risk of developing progressive multifocal leukoencephalopathy (PML). Risk can be stratified by JC virus status and index level, but for patients that are seropositive and on the medication for greater than 2

years the risk climbs to 3 cases per 1000. For this reason, this medication is primarily used in JCV seronegative patients and seropositive patients are not typically recommended to continue this medication beyond 2 years. There is evidence that dosing intervals can be extended, which can mitigate PML risks.[18,19]

Ritxuximab is a CD20 monoclonal antibody that historically has been used off label for treatment of MS supported by phase 2 placebo-controlled trial evidence demonstrating efficacy in RRMS. [20] This DMT was often employed in patients with highly active disease that were JCV seropositive thus limiting the use of natalizumab. In 2017 ocrelizumab, also a CD20 monoclonal antibody, was FDA-approved for the treatment of RRMS and PPMS based on the results of the OPERA I/II and ORATORIO studies respectively.[21,22] Ocrelizumab is different from rituximab because it is humanized, which has the potential to decrease infusion reactions. These medications are becoming more commonly prescribed due to their high efficacy, ease of dosing, and side effect profile.

Alemtuzumab is a humanized monoclonal antibody that targets the CD52 antigen expressed on T-cells, B cells, monocytes, and eosinophils that produces rapid, profound, and prolonged lymphocyte depletion with gradual reconstitution. It is administered for 5 consecutive days during the first cycle followed by a 3-day course one year later, with the potential for re-treatment.[23] Even after reconstitution, the cell profile and function are altered leading to continued efficacy that may not require further treatment. Monitoring is burdensome and includes malignancy screening with annual gynecologic and skin exams, pre-treatment lab work up, and monthly blood and urine testing for 4 years post-treatment. The monthly monitoring is part of a REMS program to monitor for autoimmune conditions such as thyroid disease, glomerular basement membrane disease, and thrombocytopenia.[23] Additionally, acyclovir 200mg-400mg BID is given prophylactically during the course of treatment and continues until CD4+ lymphocytes recover to at least 200 cells/μL, with a minimum duration of 2 months due to the risk of herpes virus infections and reactivations.[24]

Stem Cell Transplant

Stem cell therapy is of increasing interest in a number of neurologic conditions, including MS. Particularly, the role of immunoablation and autologous hematopoietic stem cell transplantation (AHSCT) in treatment-resistant relapsing disease is currently under investigation. Despite the variety of DMTs listed above, there is a subset of patients who have continued inflammatory disease activity or are limited by adverse events who may be candidates for AHSCT.[25] Recently, the American Society for Blood and Bone Marrow Transplantation created a task force to review the evidence and provide recommendations regarding treatment-refractory MS as an indication for AHSCT.[25] Their review of retrospective studies found an overall incidence of relapse-free survival at 5 years post-transplant of 80–87%, with many studies showing EDSS stability or improvement.[25] They also reviewed a number of single-arm clinical trials (NCT00278655, NCT01099930, NCT00288626, ACTRN 12613000339752) and two randomized controlled trials (NCT00273364, EUDRACT 2007–000064-24) that differed in inclusion criteria, conditioning regimens, primary outcomes, and comparators in the randomized trials. These trials also showed high rates of relapse-free survival, disability stability or improvement, and

improved MRI measures.[25] Mortality rates across these studies ranges from 0%–4.2%, has and have significantly improved over time. Overall, it appears that AHSCT is most effective and of most benefit in patients with active, relapsing disease despite DMT, who are younger with a relatively short disease duration, still ambulatory though accruing disability.[25] There is an ongoing randomized trial evaluating the safety, efficacy, and cost-effectiveness of AHSCT compared to best available therapy (natalizumab, CD20 monoclonal antibodies, and alemtuzumab) in treatment-refractory relapsing patients with the goal of determining the optimal use of this treatment in the current landscape (BEAT-MS, NCT04047628).

Treatment Strategies for RRMS

There are currently nine classes of DMTs that were discussed above. These medications vary in mechanism of action, efficacy, route of administration, and side effect profiles. With the increasing number of approved therapies there are a variety of treatment approaches that can be used. Treatment decisions should be tailored to each individual patient with regards to disease phenotype, risk profile, and patient preference, but there are two general approaches: escalation and early highly effective treatment.

For an escalation approach, the patient is started on a low to moderate efficacy DMT (e.g. injectable or oral DMT) and if there is breakthrough disease the patient's therapy is escalated to a highly effective choice (e.g. monoclonal antibody). This approach has been commonly used because the older medications have a well-established safety profile. While some patients will remain stable on the first DMT, some will require a change in therapy due to disease activity. Evidence of disease activity is most commonly defined as clinical relapses and/or new lesions on MRI. A stricter target that has been suggested is no evidence of disease activity (NEDA). NEDA-3 includes measures such as clinical relapses, disability progression, and MRI activity, while NEDA-4 adds brain volume loss to account for the neurodegenerative process.[26] NEDA has been suggested as a target outcome, but not currently used in clinical practice. With the advent of the newer DMTs, the threshold for escalation has lowered, but is still dependent on comfort of the practitioner and patients using the medications, access to the support needed for the therapies (i.e. infusion centers), and cost. The benefit of escalation therapy is minimizing the risk, but the concern is for the potential for undertreatment of disease activity that may lead to accumulation of disability and disease progression.[27]

The alternative approach is to start a highly effective therapy as the first treatment option. Subgroup analysis and observational studies demonstrate starting DMT earlier in the disease course, preferably after the first clinical attack, leads to a better long-term clinical outcomes. [27] A goal of the most recent 2017 McDonald criteria revisions was to facilitate earlier diagnosis, allowing for earlier treatment.[28] The DMTs that are considered highly effective include natalizumab, rituximab, ocrelizumab, and alemtuzumab,.[27] The tradeoffs to higher efficacy are increased risks such as infection, autoimmunity, and malignancy with less long term safety data for many of these medications. Currently in clinical practice the decision between treatment strategies in made based on a variety of prognostic indicators and shared decision making between the patient and provider. Several demographic and disease characteristics that may suggest a more severe course include male gender, older age at

presentation, increased severity and frequency of relapses, higher burden of spinal cord and infratentorial lesions, increased T2 lesions burden, increased contrast-enhancing lesion burden, and increased brain atrophy.[27] Although observational studies suggest that early high efficacy treatment may have long term benefits there is currently no randomized trials that have evaluated the two treatment strategies. There are two ongoing large, randomized multicenter trials in treatment naïve RRMS patients that will rigorously evaluate the two treatment approaches: Determining the Effectiveness of Early Intensive versus Escalation approaches for the Treatment of Relapsing-Remitting Multiple Sclerosis (DELIVER-MS, NCT03535298) and Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS, NCT03500328).

Progressive Disease

There have been a multitude of advances in the treatment of RRMS, but developments in progressive MS treatment have been slow. All of the currently available DMTs primarily target inflammatory disease activity, which is typically present to a lesser degree in progressive disease. Progressive patients can have evidence of disease activity such as superimposed relapses on a progressive decline or MRI activity (e.g. new or enhancing lesions). In progressive patients with evidence of disease activity all of the currently available DMTs are now approved for secondary progressive MS with evidence of disease activity. In 2019 the EXPAND phase 3 trial of siponimod demonstrated efficacy in a secondary progressive disease with activity which lead to its approval in both RRMS and SPMS with activity. Around this time the FDA also changed the approval of all DMTs to include both RRMS and active SPMS. This prescribing information change reflected the understanding that progressive disease can have inflammatory disease activity in which current DMTs may be of use. Ocrelizumab is the only approved DMT for primary progressive MS, however anti-CD20 treatments are likely more effective in younger individuals with evidence of disease activity.

Although the siponimod and ocrelizumab trials demonstrated efficacy in progressive populations, there are still forms of progressive MS that have little inflammatory disease and more neurodegeneration. There have been a number of negative trials in progressive disease with currently available DMTs.[29–34] While these studies did not demonstrate an effect on the primary outcome of disability progression they helped confirm there is another underlying progress beyond inflammatory activity. There is still a great amount of work needed in the field to discover and develop treatments that target the non-inflammatory portion of progressive disease. Remyelination and neuroprotective therapies are two potential treatment targets that are now being explored.

Remyelination therapies

Demyelination of both white and grey matter is a key pathologic feature of MS. While remyelination does occur, the amount is variable and it decreases with age.[35] Mitochondrial dysfunction and demyelination leads to virtual hypoxia making axons prone to degeneration and irreversible disability. Oligodendrocytes are the cells that produce myelin and appear crucial for axonal health independent of myelination.[36] It is currently thought that impaired

oligodendrocyte precursor cell (OPC) differentiation is involved in remyelination failure, and subsequently that increased OPC differentiation may promote remyelination and have an impact on disability.[37] OPC recruitment into demyelinated lesions and their differentiation is decreased with age, which parallels decreased remyelination.[38] Additionally, the microenvironment around the demyelinated lesion appears to also impair OPC differentiation, adding another challenge to therapy development.

Remyelination is an important target for progressive therapies as this could theoretically halt disability accrual and potentially reverse some already accumulated disability. One compound that demonstrated potential to promote remyelination was high dose biotin. Biotin is a cofactor for carboxylases that are expressed in oligodendrocytes in addition to supporting myelin repair by enhancing fatty acid synthesis and protecting against hypoxia-driven axonal degeneration. In one phase 3 placebo-controlled trial of high dose biotin 12.6% of treated participants compared to no placebo participants met the endpoint of a decreased in EDSS or decrease in timed 25-foot walk, however the biotin-treated group had more new or enlarging MRI lesions.[39] Unfortunately, the definitive phase 3 trial had no effect on disability improvement.[40]

Another potential remyelination target that has gained interest is opicinumab. This is a humanized monoclonal antibody against the leucine-rich repeat neuronal protein 1 (LINGO-1). LINGO-1 is a cell-surface glycoprotein expressed on CNS neurons and oligodendrocytes, and inhibits oligodendrocyte differentiation, myelination, neuronal survival, and axonal regeneration.[41] In vitro and in vivo studies showed that LINGO-1 blockade facilitates axonal remyelination, however in the phase 2 study RENEW that included individuals with a first time episode of optic neuritis failed to show an improvement in the primary outcome of visual evoked potentials.[42] SYNERGY, another phase 2 trial failed to show improvement in the primary outcome of disability.[41]

A high-throughput screening approach identified several already available compounds including antihistamine that have the potential to stimulate OPC differentiation in vivo. Clemastine is a first-generation antihistamine that has been available over the counter since 1992. It readily crosses the blood-brain barrier and has been shown to promote remyelination through an effect on human OPCs.[43,44] ReBUILD is a phase 2, randomized, placebo-controlled, cross-over study that showed reduced latency in visual evoked potentials in MS patients with chronic optic neuropathy.[43] Although this study demonstrated a significant reduction in the primary outcome, it is unclear if the reduction in latency translates to a clinically meaningful improvement in individuals. The overall success of the trial demonstrates the utility of high-throughput screening approach for identifying potential therapies and introduced a new trial design for evaluating efficacy.

Mesenchymal stem cells (MSCs) are an area of interest in progressive disease for potential remyelination due to their ability to differentiate into various types of cells. These cells can be isolated from bone marrow, adipose tissue, umbilical cord, and other sources.[45] Neural progenitor cells less frequently differentiate into mesodermal cells which makes them more attractive for transplantation in MS. While MSCs do not appear to stay in the CNS for long after intrathecal injection (IT), they may have other effects such as secretion of neurotrophic

factors inducing axonal outgrowth and increasing cell survival.[45] One study of neural progenitor MSCs transplanted intrathecally in 3 injections in MS patients showed improve median EDSS, strength, and bladder function.[46] There are currently a number of studies investigating the use of MSCs in progressive MS given intravenously, intrathecally, and in combination both from autologous and umbilical sources (Intravenous studies: NCT01377870, NCT03778333, NCT02034188, NCT00395200, NCT01745783, NCT01056471, NCT02495766; Intrathecal studies: NCT01895439, NCT01933802, NCT03355365, NCT03822858, NCT03799718, NCT03696485; comparing IV and IT: NCT02166021, NCT03069170). Although there is potential with MSC, there are a number of concerns including the risk of infection, infusion related toxicity, and theoretical risk of malignancy or ectopic tissue formation.[45] Additionally, there remain several questions regarding appropriate dosing, route of administration, cell culture protocol, and storage procedures before these therapies should be considered in clinical practice.[47]

Neuroprotective treatments

The goal of therapies aimed at neuroprotection is to prevent irreversible disability and slow progression. Studies to date have been limited and encompass medications with a variety of mechanisms of action including simvastatin, phenytoin, ibudilast, alpha-lipoeic acid (ALA), and metformin.

Simvastatin has been proposed as a potential neuroprotective agent due to evidence from animal models demonstrating its impact on multiple immunomodulatory effects. MS-STAT was a phase 2, randomized study of 80mg simvastatin versus placebo in a SPMS population with a primary outcome of whole brain atrophy. The simvastatin group had a decreased rate of whole brain atrophy compared to placebo. [48]

Ibudilast inhibits cyclic nucleotide phosphodiesterases, toll-like receptor 4, and macrophage inhibitory factor and is able to cross the blood brain barrier. SPRINT-MS was a phase 2 randomized trial of ibudilast compared to placebo with a primary outcome of rate of brain atrophy in a progressive MS population. Ibudilast had a significantly slower rate of brain atrophy compared with placebo.[49] This study also utilized five advanced imaging metrics as secondary outcomes that may help inform future clinical trials in progressive MS. Further studies of ibudilast would be needed to better understand the impact on clinical measures of disability progression.

There have been smaller studies investigating the potential neuroprotective effects of phenytoin, ALA, and metformin. Phenytoin is a voltage-gated sodium channel inhibitor, which is a mechanism that has shown to have neuroprotective properties in pre-clinical trials.[50] One randomized, placebo-controlled phase 2 trial showed that patients with acute optic neuritis who were given phenytoin within 2 weeks of onset had 30% less retinal nerve fiber layer thinning compared to placebo.[50] The clinical relevance of this is not entirely clear, and there are potential serious adverse events with phenytoin administration such as rash and interactions with other medications thus limiting its use. ALA has potential neuroprotective effects as it is a co-factor for the oxidation-reduction portion of mitochondrial reactions and with anti-inflammatory properties. A small phase 2 trial showed benefit in reducing the rate of brain atrophy with a trend towards improvement of the timed

25-foot walk compared to placebo.[51] Animal studies have suggested that metformin may exhibit neuroprotective effects by protecting against oxidative stress, inducing an anti-inflammatory profile by decreasing Th1 and Th17 cells while increasing Treg cells, and also may induce remyelination by improving OPC responsiveness.[38]

Finally, the Multiple Sclerosis Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART) was a phase 2 trial that utilized a unique multiarm, parallel group randomized trial design to investigate the neuroprotective effects of three medications: amiloride, fluoxetine, and riluzole. These three compounds were chosen via a systematic review of available evidence of oral neuroprotective drugs that were tested in clinical trials in various neurologic diseases as well as in EAE models that all have different mechanisms of action targeting axonal pathobiology. None of the medications were superior to placebo for the primary outcome of percentage brain volume change. [52]

All of the studies to date evaluating the efficacy of a neuroprotective therapy in MS have demonstrated modest or negative results. The main advances that have emerged are new techniques to identify potential components, such as high throughput screening, and novel trial designs and outcomes to better evaluate the potential neuroprotective effects.

Discussion

Multiple sclerosis treatments have greatly advanced since the first DMT approval in 1993. The majority of treatments continue to target inflammatory disease activity, but there remains a dearth of options for progressive disease with predominantly neurodegenerative pathology. The multitude of treatment options has changed the landscape of MS management, but ongoing research will help optimize our treatment approaches to maximize the benefit and minimize the risks for individuals with MS. Finally, the field is developing new methods of identifying and assessing a medication's potential for remyelination and neuroprotection which will lead to continued advancements.

Acknowledgments

References

1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology. 2014;83(11):1022–1024. [PubMed: 25200713]

2. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019;92(10):e1029–e1040. [PubMed: 30770430]

3. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278–286. [PubMed: 24871874]

4. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):655–661. [PubMed: 8469318]

5. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet. 1998;352(9139):1491–1497. [PubMed: 9820296]

6. La Mantia L, Di Pietrantonj C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;11:CD009333.

7. Naismith RT, Wundes A, Ziemssen T, et al. Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study. CNS Drugs. 2020;34(2):185–196. [PubMed: 31953790]

8. Naismith RT, Wolinsky JS, Wundes A, et al. Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: Interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study. Mult Scler. 2019:1352458519881761.

9. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416–426. [PubMed: 20089960]

10. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401. [PubMed: 20089952]

11. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018;391(10127):1263–1273. [PubMed: 29576505]

12. Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019;18(11):1021–1033. [PubMed: 31492652]

13. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019;18(11):1009–1020. [PubMed: 31492651]

14. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. New England Journal of Medicine. 2012;367(12):1098–1107. [PubMed: 22992073]

15. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. New England Journal of Medicine. 2012;367(12):1087–1097. [PubMed: 22992072]

16. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology. 2014;13(3):247–256. [PubMed: 24461574]

17. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003;348(1):15–23. [PubMed: 12510038]

18. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology. 2019;93(15):e1452–e1462. [PubMed: 31515290]

19. Yamout BI, Sahraian MA, Ayoubi NE, et al. Efficacy and safety of natalizumab extended interval dosing. Mult Scler Relat Disord. 2018;24:113–116. [PubMed: 29982107]

20. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–688. [PubMed: 18272891]

21. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. New England Journal of Medicine. 2017;376(3):221–234. [PubMed: 28002679]

22. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376(3):209–220. [PubMed: 28002688]

23. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819–1828. [PubMed: 23122652]

24. Epstein DJ, Dunn J, Deresinski S. Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management. Open forum infect. 2018;5(8):ofy174.

25. Cohen JA, Baldassari LE, Atkins HL, et al. Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019;25(5):845–854. [PubMed: 30794930]

26. Parks NE, Flanagan EP, Lucchinetti CF, Wingerchuk DM. NEDA treatment target? No evident disease activity as an actionable outcome in practice. Journal of the Neurological Sciences. 2017;383:31–34. [PubMed: 29246616]

27. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. Lancet Neurology. 2019;18(10):973–980. [PubMed: 31375366]

28. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–173. [PubMed: 29275977]

29. Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2004;75(5):706–710. [PubMed: 15090564]

30. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MSSG. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: Clinical results. Neurology. 2001;56(11):1496–1504. [PubMed: 11402106]

31. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology. 2003;60(1):44–51. [PubMed: 12525716]

32. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007;61(1):14–24. [PubMed: 17262850]

33. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387(10023):1075–1084. [PubMed: 26827074]

34. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol. 2018;17(5):405–415. [PubMed: 29545067]

35. Faissner S, Gold R. Progressive multiple sclerosis: latest therapeutic developments and future directions. Ther Adv Neurol Disord. 2019;12:1756286419878323. [PubMed: 31598138]

36. Faissner S, Plemel JR, Gold R, Yong VW. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. Nature reviews Drug discovery. 2019;18(12):905–922. [PubMed: 31399729]

37. Schwartzbach CJ, Grove RA, Brown R, Tompson D, Then Bergh F, Arnold DL. Lesion remyelinating activity of GSK239512 versus placebo in patients with relapsing-remitting multiple sclerosis: a randomised, single-blind, phase II study. J Neurol. 2017;264(2):304–315. [PubMed: 27888416]

38. Neumann B, Baror R, Zhao C, et al. Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells. Cell Stem Cell. 2019;25(4):473–485 e478. [PubMed: 31585093]

39. Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. Mult Scler. 2016;22(13):1719–1731. [PubMed: 27589059]

40. MedDay Reports Top-Line Data from Phase III Trial "SPI2" for Treatment of Progressive Forms of Multiple Sclerosis. https://www.medday-pharma.com/2020/03/10/medday-reports-top-line-data-from-phase-iii-trial-spi2-for-treatment-of-progressive-forms-of-multiple-sclerosis/. Published 2020. Updated 03/10/2020. Accessed.

41. Cadavid D, Mellion M, Hupperts R, et al. Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2019;18(9):845–856. [PubMed: 31285147]

42. Petrillo J, Balcer L, Galetta S, Chai Y, Xu L, Cadavid D. Initial Impairment and Recovery of Vision-Related Functioning in Participants With Acute Optic Neuritis From the RENEW Trial of Opicinumab. J Neuroophthalmol. 2019;39(2):153–160. [PubMed: 30095536]

43. Green AJ, Gelfand JM, Cree BA, et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. Lancet. 2017;390(10111):2481–2489. [PubMed: 29029896]

44. Cohen JA, Tesar PJ. Clemastine fumarate for promotion of optic nerve remyelination. Lancet. 2017;390(10111):2421–2422. [PubMed: 29029894]

45. Mansoor SR, Zabihi E, Ghasemi-Kasman M. The potential use of mesenchymal stem cells for the treatment of multiple sclerosis. Life Sci. 2019;235:116830. [PubMed: 31487529]

46. Harris VK, Stark J, Vyshkina T, et al. Phase I Trial of Intrathecal Mesenchymal Stem Cell-derived Neural Progenitors in Progressive Multiple Sclerosis. EBioMedicine. 2018;29:23–30. [PubMed: 29449193]

47. Baldassari LE, Cohen JA. Mesenchymal Stem Cell-derived Neural Progenitor Cells in Progressive Multiple Sclerosis: Great Expectations. EBioMedicine. 2018;29:5–6. [PubMed: 29496459]

48. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet. 2014;383(9936):2213–2221. [PubMed: 24655729]

49. Fox RJ, Coffey CS, Conwit R, et al. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. N Engl J Med. 2018;379(9):846–855. [PubMed: 30157388]

50. Raftopoulos R, Hickman SJ, Toosy A, et al. Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(3):259–269. [PubMed: 26822749]

51. Spain R, Powers K, Murchison C, et al. Lipoic acid in secondary progressive MS: A randomized controlled pilot trial. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e374. [PubMed: 28680916]

52. Chataway J, De Angelis F, Connick P, et al. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. Lancet Neurol. 2020;19(3):214–225. [PubMed: 31981516]

Key Points

- Multiple sclerosis is a chronic, immune-mediated neurologic disease that affects nearly 1 million people in the US, is a major cause of disability and can lead to a reduced quality of life.

- There are currently over a dozen approved disease modifying therapies for MS, with varying mechanisms of action, routes of administration, dosing schedule, efficacy, and side-effect profiles

- The vast majority of disease modifying therapies target active, inflammatory disease that defines relapsing remitting MS, with less treatments available to target neurodegenerative disease.

- The treatment targets, goals, and algorithms are changing as the field learns more about the pathophysiology of the disease.

- New therapies that target remyelination and neurodegeneration are being developed, but more robust data is needed before they are integrated into routine clinical care.

Synopsis

Multiple sclerosis is a relatively common, immune-mediated neurologic disease of the central nervous system that can cause significant disability and lead to reduced quality of life. There are a number of currently approved disease modifying therapies, and more in the pipeline being developed and tested. As the field learns more about the pathophysiology and natural course of the disease, the treatment approaches are also being investigated. This review will review data on available treatments along with a discussion of future treatment targets under investigation.

Table 1:

An overview of currently approved oral DMTs (as of April 2020)

DMT	Year Approved	Dosing	Medication Class	Phase 3 Trial	Trial design	Main Outcome	Main Side Effects
Fingolimod[10]	2010	0.5 mg daily	Sphingosine 1-phosphate receptor modulator	• FREEDOMS • TRANSFORMS	• RRMS, placebo-controlled • RRMS, active control with interferon beta-1a	• 54% decrease in annualized relapse rate • 48% decreased in annualized relapse rate	Bradycardia/Heart block with first dose, macular edema, elevated liver enzymes, hypertension, headache. VZV reactivation
Siponimod[11]	2019	Initial titration with a final dose of 2mg daily for CYP2C9 genotypes 1/1, 1/2, 2/2 or 1mg daily for genotypes 1/3 or 2/3	Selective sphingosine 1-phosphate receptor modulator	EXPAND	SPMS, placebo-controlled	21% decrease in risk of 3 month confirmed disability progression	Bradycardia with first dose, lymphopenia, elevated liver enzymes, macular edema, hypertension, VZV reactivation
Ozanimod[12,13]	2020	1mg daily	Selective sphingosine 1-phosphate receptor modulator	• RADIANCE • SUNBEAM	• RRMS, active-controlled with interferon beta-1a • RRMS, active-controlled with interferon beta-1a	• 38% reduction in ARR • 48% reductions in ARR	Elevated liver enzymes, nasopharyngitis, hypertension
Dimethyl fumarate[14,15]	2013	240mg BID	Anti-inflammatory/cytoprotective	• DEFINE • CONFIRM	• RRMS, placebo-controlled • RRMS, placebo-controlled	• 53% reduction in ARR • 44% reduction in ARR	Flushing, GI upset, elevated liver enzymes, lymphopenia
Diroximel fumarate[7]	2019	462mg BID	Converted to same active metabolite as DMF	EVOLVE-MS-2	RRMS, head-to-head comparison to DMF	46% reduction in days with Individual Gastrointestinal Symptom and Impact Scale score of 2	Flushing, GI upset, elevated liver enzymes, lymphopenia
Teriflunomide[16]	2012	7mg or 14mg daily	Interferes with de-novo pyrimidine synthesis	• TOWER • TEMSO	• RRMS, placebo-controlled • RRMS, placebo-controlled	• 36% reduction in ARR • 31.5% reduction in ARR	Elevated liver enzymes, hair thinning, Headache
Cladribine[9]	2019	1.75mg/kg in 2, 5-day courses 23–27 days apart in year one and again 43 weeks later	Inhibits DNA synthesis and promote apoptosis in lymphocytes	CLARITY	RRMS, placebo-controlled	57.6% reduction in ARR	Lymphopenia, VZV reactivation, infections