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Multiple Sclerosis Management: Current Clinical Approaches to Disease-Modifying Therapy

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Abstract

Purpose of Review The treatment landscape for multiple sclerosis has evolved and expanded significantly over the past 30 years, with now over 20 disease-modifying therapies available on the market. This review is meant to provide an update on disease-modifying therapy management.

Recent Findings Multiple sclerosis presents heterogeneously and it is impossible to predict the disease course on an individual basis. However, there are some clinical and radiographic findings which suggest a more severe and disabling course warranting high-efficacy treatment.

Summary Treatment is chosen based on shared decision-making between the patient and provider based on various clinical, radiographic, safety, and socioeconomic factors. Multiple emerging therapies are currently being studied to address the progressive and neurodegenerative component of MS.

Keywords Multiple sclerosis treatment · Disease-modifying therapy

Introduction

Multiple sclerosis is a heterogeneous disease caused by various genetic and environmental factors leading to an aberrant immune response involving T cells, B cells, and other immune cells, such as microglia [1••, 2]. The treatment landscape has evolved and expanded significantly over the past 30 years, with now over 20 disease-modifying therapies available on the market. Disease-modifying therapy (DMT) decisions are made through shared decision-making between the patient and provider, taking into account other medical comorbidities and quality of life goals.

One approach to treating MS is to start with lower efficacy treatments, such as first-generation injectable DMTs, with escalation to higher efficacy therapies only after clinical relapses and disease progression occur. Unfortunately, because disability accumulation may not always be obvious early on, this approach may result in some patients being under-treated for their MS. There has been a shift towards using higher efficacy therapies earlier to prevent disability before it becomes evident, particularly in patients in which various clinical and radiographic factors suggest a potentially more aggressive disease course.

This review is by no means comprehensive but is meant to provide a brief review of current MS treatment options and an updated and pragmatic approach to DMT management in MS.

Current MS Treatment Options

First-Generation Injectable MS DMTs

Beta interferons and glatiramer acetate were the first MS disease-modifying therapies, FDA-approved in the 1990s. They are only moderately effective compared to more modern MS treatment options, but they are felt to be generally safe and well tolerated. Injection-related side effects are common.

Beta Interferons

Interferon-β was the first disease-modifying therapy approved for relapsing MS in 1993, and multiple

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formulations of interferon (IFN) have followed since [1••]. There are currently 5 IFNs available (BETASERON, EXTAVIA, AVONEX, REBIF, PLEGRIDY), which are administered as subcutaneous or intramuscular injections. While they differ in their administration frequency and doses, they have similar side effects (flu-like symptoms, fatigue, injection site reactions) and require similar monitoring (liver and thyroid function tests). They all have the potential for developing neutralizing antibodies and can result in reduced efficacy and breakthrough disease activity [1••].

Glatiramer Acetate

Glatiramer acetate is a synthetic injectable medication first approved in 1996. It is currently available under two different brand names (COPAXONE and GLATOPA) as well as a number of generics with different doses and administration frequency. Side effects may include injection site reactions with fibrosis and lipoatrophy, or a post-injection syndrome of shortness of breath, flushing, and palpitations. No laboratory monitoring is generally required [1••, 2].

Oral MS DMTs

Oral therapies for MS have been available for over a decade. They are at least as effective, if not more effective, than first-generation injectable medications. They may require slightly more rigorous screening and monitoring, but these once- or twice-daily pills are generally well tolerated with relatively modest side effects.

Sphingosine-1-Phosphate (S1P) Agents

Fingolimod (GILENYA) was the first oral therapy for relapsing forms of MS, FDA-approved as a once-daily capsule in 2010. It is a nonselective S1P receptor modulator whose effect in MS is presumed to be a result of lymphocyte sequestration, i.e., preventing lymphocytes from leaving the lymphoid tissue. It may be associated with several "off-target effects," including an increased risk of bradycardia or heart block when treatment is initiated, necessitating first-dose observation. Siponimod (MAYZENT) is a more specific S1P receptor modulator approved for both relapsing and "active" secondary progressive MS. Siponimod is titrated over 5 days and does not require first-dose observation in most cases. CYP2C9 genotyping is necessary before starting siponimod to identify individuals who may have decreased ability to metabolize the drug. Additional selective S1P receptor modulators, ozanimod (ZEPOSIA) and ponesimod (PONVORY), have been recently approved for relapsing forms of MS [1••].

Prior to starting any S1P agent, patients must be checked for varicella-zoster virus (VZV) immunity and should be vaccinated against VZV when appropriate [1••, 2]. Hypertension, bronchospasm, VZV reactivation, elevated liver enzymes, macular edema, and skin cancer may occur. Progressive multifocal leukoencephalopathy (PML) has occurred in patients taking S1P agents [1••, 2]. Disease rebound, which can be quite severe, may occur after abrupt discontinuation of any S1P [1••]. Artifactual lymphopenia is common and expected with S1P medications based on their mechanism of action. Patients on S1P agents should get annual skin cancer screening.

Teriflunomide

Teriflunomide (AUBAGIO) was the second oral agent approved for relapsing forms of MS [1••], most commonly taken as a once-daily 14 mg tablet. There is some evidence that teriflunomide may be slightly less efficacious but better tolerated than S1P agents [3]. Side effects may include transient hair thinning, elevated liver enzymes, and mild gastrointestinal (GI) upset [1••]. Screening for latent tuberculosis should be performed prior to initiation, and liver enzymes should be checked monthly during the first 6 months of treatment. Rapid elimination may be achieved using cholestyramine or activated charcoal, if necessary [1••].

Fumarates/Fumaric Acid

Several fumarates have been approved for the treatment of relapsing forms of MS, including dimethyl fumarate (TECFIDERA), diroximel fumarate (VUMERITY), and monomethyl fumarate (BAFIERTAM). All fumarates are oral therapies with twice-daily dosing for relapsing forms of MS. Common side effects include GI upset and flushing. Diroximel fumarate and monomethyl fumarate were formulated to minimize GI upset and flushing, though these side effects are still seen to a lesser extent. Lymphopenia may occur and seems to be associated with an increased risk of PML. It has been generally recommended that fumarates should be discontinued if absolute lymphocyte counts consistently fall below 500 [1••, 2].

Oral Cladribine

Cladribine selectively targets both T and B cells and is associated with a long-term immunomodulatory effect in MS. It has been approved in oral form (MAVENCLAD) for relapsing forms of MS but is contraindicated in patients with active malignancy, pregnancy, active tuberculosis (TB), active hepatitis, and HIV [1••, 4]. Lymphopenia is a common side effect (10% of individuals) following cladribine administration, as is VZV infection (also 10%). Therefore, patients should be screened for VZV immunity and should be vaccinated against VZV (inactivated vaccine only), if indicated. Screening for TB and hepatitis B/C should be

completed prior to initiation. In phase 3 placebo-controlled trial evaluating oral cladribine in MS patients (CLARITY), one patient died from reactivation of latent TB; however, this was before tuberculosis screening measures were implemented [4]. As previously mentioned, patients with active TB and hepatitis are ineligible for cladribine [1••]. Patients with latent TB or latent hepatitis may still be eligible for cladribine with simultaneous treatment of latent infection on a case-by-case basis with infectious disease collaboration.

Unlike other oral MS therapies, which are taken continuously on a daily basis, Mavenclad is taken as two courses of treatment, 1 year apart. Dosing is dependent on body weight, with a total dose of 1.75 mg/kg per yearly course. The first treatment is typically 1 or 2 tablets daily over 4 to 5 days with a second treatment cycle 1 month later. Labs (CBC and CMP) are checked at baseline and months 2, 6, and 12 to monitor for lymphopenia, liver dysfunction, and kidney dysfunction. This two-cycle treatment course is repeated 1 year later [1••].

Patients taking cladribine should undergo standard cancer screenings due to a possible risk of malignancy. Mild lymphopenia can be seen transiently following each treatment cycle; however, severe lymphopenia (below absolute lymphocyte count of 200) is rare. Although PML has not been observed in MS patients on cladribine specifically, a theoretical risk of PML exists and the John Cunningham virus (JCV) index should be checked prior to initiation [1••, 2].

Monoclonal Antibody MS DMTs

Monoclonal antibody treatments may be administered intravenously or subcutaneously and have proven to be highly efficacious in terms of relapse rate reduction, prevention of MRI activity, and reducing the risk of disability progression in MS. Although generally well tolerated, additional screening and monitoring may be necessary.

Natalizumab

Natalizumab (TYSABRI) prevents the migration of activated lymphocytes into the CNS and other organs by binding to α4-integrin on the surface of lymphocytes. Standard dosing is 300 mg IV every 4 weeks. The use of natalizumab is primarily limited by an increased risk of PML in patients with prior exposure to JCV. Screening for JCV antibodies is required prior to initiation and is repeated every 6 months. Patients with a negative titer or JCV index less than 0.9 are generally eligible for standard natalizumab dosing [1••]. Extended interval dosing of 300 mg every 6 to 8 weeks can be considered for patients with a JCV index between 0.9 and 1.2 [5]. Development of neutralizing antibodies can occur, and this possibility should be considered in any patients with disease breakthrough [1••].

Anti-CD20 Agents

Selective depletion of B lymphocytes expressing CD20 has proven to be highly effective at suppressing relapses, preventing MRI activity, and reducing disability progression in MS.

Ocrelizumab (OCREVUS) is an IV infusion given every 6 months. The first treatment is split into 2 doses, given 2 weeks apart. Premedication with steroids, acetaminophen, and antihistamines helps to mitigate infusion reactions.

Ofatumumab (KESIMPTA) is a self-administered subcutaneous injection taken monthly, after three weekly induction doses [7]. Ofatumumab injections are very well tolerated and premedication is generally not necessary.

Screening for latent tuberculosis/hepatitis B/C and checking baseline immunoglobulin levels is mandatory prior to initiating any anti-CD20 agent. An increased risk of infection (upper respiratory infection or urinary tract infection) is possible. PML can rarely occur. Initially, there was a concern for a possible increased risk of breast cancer associated with ocrelizumab [1••]; however, over time, it appears that the incidence of malignancies in MS patients on ocrelizumab is roughly the same as that of the general population [6]. Ofatumumab has not been associated with an increased risk of cancer.

Alemtuzumab

Alemtuzumab (LEMTRADA) targets circulating B and T lymphocytes that express CD52 and is administered as two courses of IV treatment (5 days and 3 days) 1 year apart. Many patients experience significant long-lasting suppression of MS disease activity after just two treatment courses. However, safety concerns, including secondary autoimmune conditions (thyroid disease, immune thrombocytopenia, hemolytic anemia, and Goodpasture's disease), infusion reactions, stroke, and malignancy, have limited its use. Monthly lab testing (CBC with differential, liver function tests, kidney function tests, thyroid function tests) is mandatory for 4 years following the last alemtuzumab infusion to monitor for the aforementioned potential side effects [1••].

Other Considerations

Progressive MS

When disability gradually increases, independent of relapse activity in MS, this is called MS progression. If progression occurs after an initial period of relapsing activity, this is referred to as secondary progressive MS. When secondary progression occurs while clinical relapses are still occurring or evidence of inflammatory disease is detected on MRI, this is considered "active" secondary progressive MS. Technically, all MS DMTs have been approved to treat active secondary progressive MS, as this is considered a relapsing form of MS.

Progression may be present at onset, with or without subsequent relapsing activity—this form of MS is called primary progressive MS. Ocrelizumab is currently the only medication FDA-approved for primary progressive MS.

Clinically Isolated Syndrome

A first clinical attack, or clinically isolated syndrome (CIS), is currently considered a relapsing form of MS. All of the MS DMTs mentioned earlier can be considered in patients with CIS, except for cladribine and alemtuzumab, which are recommended to be used as second- or third-line treatments in MS.

Emerging Therapies

Bruton's tyrosine kinase (BTK) inhibitors are being evaluated as oral therapies in phase III clinical trials in patients with relapsing and progressive MS. The rationale behind using BTK inhibitors in MS is to inhibit B-cell activation and release of cytokines involved in promoting a proinflammatory macrophage phenotype [8••]. A phase II study evaluating evobrutinib vs. placebo or dimethyl fumarate met its primary endpoint by demonstrating significantly fewer gadolinium-enhancing T1 lesions at weeks 12 and 24 [8••]. Fenebrutinib, with a mechanism distinct from evobrutinib, triggers a change in BTK morphology over time and is currently being evaluated in primary progressive MS in comparison to ocrelizumab [9]. Results of these studies are expected around 2024 [9].

The use of stem cells in MS is controversial. In the experimental autoimmune encephalomyelitis (EAE) mouse model, there was a reduction in disease activity. However, this was found to be a result of immunomodulation more so than myelin repair [1••]. This treatment is not commercially available currently and is only performed at clinical trial sites.

Remyelination remains an elusive target. Several therapeutics are being evaluated to guide oligodendrocyte precursor cells (OPCs) to differentiate into effective myelin-regenerating cells to mitigate axonal degeneration and, optimistically, reverse disability [2]. Anti-LINGO-1 (Opicinumab) advanced to a phase III study however failed to meet its primary endpoint. There are several medications being evaluated (e.g., clemastine, miconazole, clobetasol) for their potential to guide OPCs into myelinating oligodendrocytes and are currently in phase II studies [2, 11•], but these molecules are not routinely used as remyelinating agents in clinical practice at this time.

Discontinuation of Therapy

There are no current guidelines for treatment de-escalation and discontinuation and it is currently evaluated on a case-by-case basis. Over the age of 55, the immune system seems to weaken over time, a phenomenon known as immunosenescence. This poses an increased risk for infection while on disease-modifying therapy. Retrospective observational studies have provided mixed results. Results of a prospective randomized study (DISCO MS) will be released this year.

Discussion

Multiple sclerosis presents heterogeneously and it is impossible to predict the disease course on an individual basis. However, there are some clinical and radiographic findings which suggest a more severe and disabling course warranting high-efficacy treatment [1••, 2].

Observationally, patients of male gender and/or African American race tend to be diagnosed later in their disease course and thereby present with a worsened disability, though the reasons for this are not fully understood. Given the fact that MS was historically thought of as a disease affecting young, Caucasian women, unconscious bias leading to a delayed diagnosis in other groups remains one contributing factor. Regardless, because men and African Americans tend to have a more disabling course, some have recommended that they be started on a "high-efficacy treatment" such as anti-CD20 agents, S1P modulators, natalizumab, or cladribine. Patients with infratentorial lesions, spinal cord lesions, and "black holes" on T1 imaging suggest a more severe course and also may warrant higher efficacy therapies.

Although there are many DMTs available on the market, there is a need for better biomarkers for disease progression. MRI of the brain is not sensitive to inflammation specifically; rather, it is a marker for the breakdown of the blood–brain barrier after inflammation has been ongoing [1••]. There is a push for employing precision medicine, i.e., classifying disease and choosing treatment based on underlying biologic factors as opposed to presenting phenotype, for an individualized treatment approach [13•]. However, more biomarkers to make these classifications and prognosticate an individual's disease course are needed for precision medicine to be used in the treatment landscape of multiple sclerosis.

A recent longitudinal analysis evaluated the correlation between prior Epstein-Barr virus (EBV) infection and the prevalence of MS in a cohort of 10 million patients [13•]. The results of this study showed that the risk for developing MS after EBV infection was > 30 times greater than after infection with other viruses, supporting the historical observation that EBV is one major contributing cause of MS [14••]. There is no EBV vaccine currently available for the prevention of MS, though this may be a possibility in the future.

Conclusion

It is not yet possible to definitively predict the course of MS for any one individual, but various clinical and radiographic factors can suggest a more aggressive course

warranting a high-efficacy disease-modifying therapy. Treatments should be chosen based on shared decision-making between the patient and provider based on various clinical, radiographic, safety, and socioeconomic factors, and higher efficacy therapies can be considered earlier in individuals with poor prognostic features. Emerging therapies, primarily BTK inhibitors which are currently in stage III clinical trials, will add even more disease-modifying therapies to the armamentarium. The development of more biomarkers for disease progression and the use of precision medicine in multiple sclerosis will provide the best opportunity for individualizing treatment more objectively.

Declarations

Human and Animal Rights and Informed Consent This review article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Dr. Appleberry declares no conflicts of interest. Dr. Shin has accepted honoraria for consulting or speaking for the following companies: Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Horizon, Mallinckrodt, Novartis, and Sanofi Genzyme. Dr. Shin has received research support from Genentech.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Birnbaum, G: Multiple Sclerosis. In: Bielekova B, Birnbaum G, Lisak RP, editors. Neuroimmunology. Oxford: Contemporary Neurology Series; 2019. *Comprehensive textbook on neuroimmunology provides a foundation*
2. Fox RJ, Rae-Grant AD, Bethoux F. Multiple sclerosis and related disorders: clinical guide to diagnosis, medical management, and rehabilitation. Demos Medical: Springer; 2019.
3. Kappos L, Fox RJ, et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study a randomized clinical trial. JAMA Neurol. 2021;78(5):558–67. https://doi.org/10.1001/jamaneurol.2021.0405.
4. Giovannoni G, Comi G, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362:416–26. https://doi.org/10.1056/NEJMoa0902533.
5. Ryerson LZ, Li X, Goldberg JD, et al. Pharmacodynamics of natalizumab extended interval dosing in MS. Neurol Neuroimmunol Neuroinflamm. 2020;7:e672. https://doi.org/10.1212/NXI.0000000000000672.
6. Hauser SL, Kappos L, et al. Safety of ocrelizumab in patients with relapsing and primary progressive multiple sclerosis. Neurology. 2021;97:e1546–59. https://doi.org/10.1212/WNL.0000000000012700.
7. Hauser SL, Bar-Or A, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med. 2020;383:546–57. https://doi.org/10.1056/NEJMoa1917246.
8.•• Montalban X, Arnold D, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. N Engl J Med. 2019;380:2406–17. https://doi.org/10.1056/NEJMoa1901981. ()
9. BTK blockers make headway in multiple sclerosis. Nat Biotechnol 2021:39:3-12
10.•• Thebault S, Abdoli M, et al (2020) Serum neurofilament light chain predicts long-term clinical outcomes in multiple sclerosis. Nat Sci Rep 10:10381 https://doi.org/10.1038/s41598-020-67504-6 *Emerging biomarker and is being used in clinical trials and probably will be commercially available in the future*
11.• Lubetzki C, Zalc B, et al. Remyelination in multiple sclerosis: from basic science to clinical translation. Lancet Neurol. 2020;19:678–88. ()
12. Shah AA, Corboy JR (2022) Discontinuing disease-modifying therapies in multiple sclerosis. Practical Neurology.
13.• Chitnis T, Prat A. A roadmap to precision medicine for multiple sclerosis. Mult Scler. 2020;26(5):522–32. https://doi.org/10.1177/1352458519881558. ()
14.•• Bjornevik K, Cortese M, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Sci. 2022. https://doi.org/10.1126/science.abj8222. ()