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Multiple sclerosis

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Abstract

Multiple sclerosis is a chronic, unpredictable, and disabling disease. Significant advances have been made in recent years supporting an earlier, more accurate, diagnosis and have led to more than 15 disease-modifying therapies approved by the Food and Drug Administration for relapsing forms of multiple sclerosis. Disease-modifying therapies are now being classified into categories based on level of efficacy. Strategies to use disease-modifying therapies earlier and in a more customizable manner are also emerging. A clinical case study will be used throughout this pearl to review the disease-modifying therapies and use patient-specific factors to develop and provide recommendations on therapeutic strategies for individuals with relapsing forms of multiple sclerosis.

Keywords: multiple sclerosis, disease-modifying therapies, escalation versus induction, highly effective, modestly effective, guidelines

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Introduction

Multiple sclerosis (MS) is characterized by immune-mediated, demyelinating attacks on the central nervous system (CNS) resulting in fully or partially reversible neurologic syndromes or relapses. An MS relapse typically comes on acutely or subacutely, lasts days to weeks, and gradually remits. Radiographic evidence of inflammatory attacks can be seen anywhere in the white and grey matter of the CNS. Symptoms reflect lesion locations although silent lesions occur as well. Acute optic neuritis is the most common neurologic syndrome at onset.[1-4] Other symptoms may occur throughout the disease such as cognitive impairment, fatigue, bowel and bladder disturbances, and spasticity.[2-4]

Epidemiology, Phenotypes (Clinical Course), and Diagnosis

Nearly one million persons are currently living with MS in the United States.[5] Multiple sclerosis is most commonly diagnosed in females and at age 20 to 50 years.[6] More than 80% of persons with MS (pwMS) have relapsing remitting MS (RRMS). Approximately 15% to 30% of pwMS will gradually evolve from RR to secondary progressive (SP) 15 to 20 years after onset. Previous natural history studies reported that 25% to 40% of pwMS develop SPMS, likely reflecting the lack of earlier diagnosis and use of DMTs. Roughly 15% of pwMS have a primary progressive (PP) course from the onset.[7-10]

A relapsing or progressive phenotype has been used since 1996 to describe a person's MS. In 2013, these phenotypes were modernized to better inform prognostication and

treatment decision making by addressing limitations of the older phenotypes (Table 1).[9,10] The core clinical phenotypes of RR, SP, PP were retained, clinically isolated syndrome was officially added, but the confusing *progressive relapsing* phenotype was removed. Radiologically isolated syndrome or the incidental findings of MS-like lesions on brain magnetic resonance imaging (MRI), was not added since MRI findings without clinical evidence of demyelination may be nonspecific. Descriptive modifiers were introduced to provide more clinically useful information when communicating phenotype including *active* and *not active* to describe disease activity (recent relapse or CNS imaging activity) and *with progression* and *without progression* to describe disease worsening. As of May of 2019, the Food and Drug Administration (FDA) approved labeling of every DMT has been updated with these modifiers.

The McDonald's diagnostic criteria routinely undergoes revisions aligning the criteria with advancements in clinical and imaging technologies. Diagnosis is based on parameters such as medical history and neurological exam, as well as paraclinical parameters such as MRI, cerebrospinal fluid showing oligoclonal banding (sign of CNS inflammation), and evoked potentials (a measure of electrical activity in the brain). MRI remains the most sensitive tool available for determining events that meet diagnostic criteria for dissemination in time and space. The 2017 McDonald's diagnostic criteria[11] revision allows for earlier diagnosis of MS in individuals with typical clinically isolated syndrome if either imaging shows both symptomatic and asymptomatic MRI lesions or if cerebrospinal fluid is positive for oligoclonal banding. MRI scans may be used to obtain objective evidence to track treatment efficacy and adverse effects (Table 2).[12]

Patient Case Part 1: Risk Factors

A 27-year-old presents to the clinic with new onset numbness and tingling of the left buttock, leg, and foot along with lightheadedness and fecal incontinence. Brain MRI showed 2 new T2-lesions and cervical spine MRI showed 1 new T2-lesion, resulting in a diagnosis of RRMS. The patient exercises 4 times weekly, smokes 1 pack per day, has 2 to 3 alcoholic beverages per month, and expresses interested in natural remedies and lifestyle changes when discussing treatment options.

The incidence of MS in the United States is greater at higher latitudes.[5] This prevalence gradient may be related to less ultraviolet B-induced vitamin D production in the skin due to less sun exposure. Vitamin D appears to have protective anti-inflammatory and immunoregulatory effects.[2] Other immunologic, infectious, genetic, and environmental etiological factors have also been identified.[1-4] Patients should be educated on the etiological factors that are modifiable if applicable, where interven-

Take Home Points

- Treatment of multiple sclerosis is centered around disease-modifying therapies (DMTs) that are either immunomodulating or immunosuppressive by mechanism. DMTs are further classified into modestly or highly effective based on annualized relapse reduction, decrease in new magnetic resonance imaging lesions, and decreased disability progression over time.
- Treatment strategies are evolving. Current published data suggests using a risk-stratified approach to determine an escalation or induction therapy approach.
- Risk of adverse effects, financial burden to the patient, and family planning desires should also be considered when choosing a DMT.
- Newer DMTs have challenges associated with their management such as screening and monitoring requirements and significant infectious risks compared to the older self-injectable, immunomodulating DMTs.

TABLE 1: The 2013 update to the phenotypic classifications of MS[10]

Terminology	Definition
Relapsing remitting (RR)	Characterized by relapses from onset that are partially or completely reversible.
Secondary progressive (SP)	Gradual progression (disability accumulation) following an initial relapsing disease course.
Primary progressive (PP)	Gradually evolving progression without discrete relapses.
Clinically isolated syndrome (CIS)	The first neurologic syndrome lasting at least 24 hours with or without lesions on magnetic resonance imaging (in an MS-like distribution).
Radiologically isolated syndrome (RIS)[a]	Incidental findings of lesions occurring in an MS-like distribution.

MS = multiple sclerosis.

[a]Not considered an official MS phenotype as of 2013 update.

TABLE 2: Various types of magnetic resonance imaging scans and what they show[12]

Terminology	Definition
T1-weighted without GAD	*Hypointense* or dark areas on magnetic resonance imaging. Considered to be areas of permanent damage or neurodegeneration. Sometimes called *T1-black holes*.
T1-weighted with GAD	*Hyperintense* or enhancing lesions. Consider to be areas where the blood brain barrier has broken down and acute inflammation has occurred.
T2-weighted	Images showing all new and old lesions.
FLAIR	Similar to the T2-weighted image, but increases the detection of new lesions without interference from cerebrospinal fluid.
Brain atrophy	Shows overall reduction in volume of both white and gray matter.
Spinal cord	Assists with showing dissemination in time and space.

FLAIR = fluid attenuated inversion recovery; GAD = Gadolinium contrast agent.

tion may either lower the risk of developing MS or if diagnosed, may weaken its influence on the rate of disease progression (Table 3).[13,14]

Predicting the course of a pwMS is difficult since the disease manifests heterogeneously from one individual to another. Several factors can discern which pwMS may be at greater risk for a more aggressive course.[15,16] The strongest and most consistent negative prognostic factors include: frequent relapses during the first 2 to 5 years postonset, short interval between relapses, incomplete relapse recovery, sphincter-type symptoms (ie, bowel, bladder), progression at onset, and rapidly worsening disability.[15,16] Imaging characteristics include increasing size of T2 lesion burden from baseline, GAD lesions, cerebellar and/or spinal cord lesions, and brain atrophy.[16] Identifying the presence of negative prognostic factors and, thereby, patients at greater risk of disease worsening, informs clinicians which patients may benefit from earlier initiation of higher efficacy DMT.

Patient Case Part 2: Too Many Choices

Based on formulary options, copay assistance programs, and patient preference for route of administration, interferon-betas, fingolimod, and teriflunomide are DMT options discussed with the patient during a shared-decision making conversation.

Personalizing Treatment

The newer DMTs affect immune system functioning more directly compared to older self-injectable DMTs by targeting T-cell activation, T-cell migration, T- and/or B-cell depletion. When selecting a DMT, consider patient-specific factors and treatment approach. In the case example, affordability as well as oral and injectable options were discussed given the patient did not want to consider an infused therapy option. Although self-injectable interferon-betas were the mainstay of MS management for many years, the self-injectable administration may not be ideal, primarily because of the risk of flu-like symptoms and injection-site reactions. Teriflunomide and fingolimod provide oral options but differ in their efficacy, safety, and side effect profiles (Table 4).[17-29] While teriflunomide does have a risk of some worrisome side effects, (eg, hepatotoxicity, leukopenia, paresthesia), overall it has demonstrated similar or better tolerability compared to other oral DMTs in observational studies.[30,31] The most important clinical risks with teriflunomide include hepatotoxicity (managed with routine laboratory monitoring), and teratogenicity. Another important factor for DMT decision-making is desire/plan for pregnancy. While specific management strategies for managing MS in preparation of and during pregnancy are out of the scope of this review, contraception and family planning should be discussed with every patient. Although safety of DMT use in pregnancy varies among agents, experts recommend highly effective contraception should be considered in all patients starting DMTs.[32]

TABLE 3: Potentially modifiable environmental etiologic factors[13,14]

- Individuals with decreased cutaneous production or consumption of vitamin D
  - Increased risk of relapses
  - Empiric vitamin D_3 is 800 IU to 4000 IU daily is recommended
- Tobacco smoking
  - Progress to secondary progressive MS at a faster rate than non-smokers with greater risk of increasing disability
  - May not achieve optimal benefit of MS disease-modifying therapies
  - Quitting smoking delays experiencing disability progression and lessens the influence on relapses.
- Obesity
  - Occurring especially during childhood and adolescence (and in females) increases the risk for developing MS and for disease activity in persons with MS

MS = multiple sclerosis.

TABLE 4: Disease-modifying therapies[17-29]

Name of Drug Route of Administration Mechanism of Action Indication	Adverse Effects	Monitoring	Author Clinical Pearls and Other Highlights
ME-DMT			
Interferon-betas SC, IM Reduce activation and entry of T cells into central nervous system; reduces adhesion molecules and helper T cells Relapsing forms of MS	Common: ISR, flu-like symptoms Less common: depression, abnormalities, abnormalities in CBC, LFTs, TFTs	Baseline: CBC, LFTs, TSH Routine: CBC, LFTs, TSH	Encourage hydration to reduce severity/frequency of flu-like symptoms May worsen psoriasis and MS-related spasticity Use with caution in persons with severe depression
Glatiramer acetate SC Copolymer mimics myelin basic protein triggers shift toward type 2 helper T cells Relapsing forms of MS	Common: ISR, lipoatrophy, Less common: transient 15 to 30 min postinjection reaction (anxiety, chest pain, palpitations, flushing)	None	FDA-approved generics available Product-specific auto-injectors are not interchangeable Postinjection reaction is not cardiac and is temporary
ME-DMT or HE-DMT[a]			
Dimethyl fumarate PO Antioxidant and anti-inflammatory effects mediated through nuclear factor 2 pathway Relapsing forms of MS	Common: flushing, nausea, diarrhea, abdominal pain Less common: lymphopenia, elevated LFTs, rash	Baseline: CBC, LFTs Routine: CBC, LFTs Consider interruption of therapy if ALC less than 500/μL for more than 6 mo	Poorer tolerability (GI toxicity) compared to other oral DMTs per observational studies[31,44] Low PML risk, may be related to severe lymphopenia[b] Take aspirin for flushing Use with caution in persons with GI-related disorders (eg, irritable bowel syndrome)
Teriflunomide PO Inhibits pyrimidine synthesis; prevents proliferation of T-cells and B-cells Relapsing forms of MS	Common: alopecia, diarrhea, nausea, paresthesia, nasopharyngitis Less common: leukopenia, increased BP, hepatotoxicity	Baseline: CBC, LFTs, BP, pregnancy test, TB test Routine: alanine transaminase monthly for first 6 mo, then LFTs and/or CBC as needed	Serum concentrations persist for up to 2 y Accelerated elimination procedure option available if needed (ie, pregnancy) Effective contraception needed, even in women whose male partners are on teriflunomide Avoid if pregnancy desired given teratogenicity concerns Low PML risk[b]
HE-DMT			
Alemtuzumab IV Anti-CD52 monoclonal antibody decreases B-cells and T-cells Relapsing forms of MS for patients with an inadequate response to 2 or more DMTs	Common: IRR, nasopharyngitis, nausea, vomiting, urinary tract infection, fatigue, URI, herpes viral infections, urticaria, pruritus, secondary thyroid autoimmunity fungal infection, arthralgia, diarrhea, paresthesia, rash Less common: ITP, autoimmune kidney disease	Baseline: CBC, LFTs, SCr, UA, TFT, skin examination, VZV serology, TB test, HIV screen, pregnancy test REMS required monitoring: Starting after the first infusion series and for 48 mo after last treatment cycle: CBC, SCr, UA monthly, TSH every 3 mo, skin examination yearly	Low PML risk[b] Use with caution in persons with thyroid disorders
Cladribine PO Purine nucleoside analog; selectively depletes peripheral lymphocytes RRMS and active SPMS[c] for patients who have had inadequate response to, or unable to tolerate, at least 1 other DMT	Common: URI, headache, nausea, lymphopenia Less common: liver injury, infections, opportunistic infections, nephrotoxicity, severe dermatologic reactions, malignancy	Baseline: CBC, TB, HIV and hepatitis B screen, pregnancy test, LFTs Between/after treatment courses: CBC 2 and 6 mo after start of each treatment course, LFTs if clinically indicated Administer anti-herpes prophylaxis if ALC <200/μL	

TABLE 4: Disease-modifying therapies[17-29] (continued)

Name of Drug Route of Administration Mechanism of Action Indication	Adverse Effects	Monitoring	Author Clinical Pearls and Other Highlights
Fingolimod PO S1P nonselective receptor modulator; sequesters lymphocytes in lymphoid tissue Relapsing forms of MS	Common: headache, diarrhea, back pain, elevated LFTs, cough, lymphopenia Less common: bradycardia, AV conduction slowing, HSV infections, macular edema, asthma exacerbation, seizure, BCC, melanoma	Baseline: CBC, LFTs, VZV serology, OCT test, ECG, BP, pulse Initiation: FDO; observe for bradycardia for 6 h after first dose monitoring pulse, BP and ECGs Routine: CBC, LFTs; OCT 3 to 4 mo after starting	Must discontinue 2 mo prior to trying for conception Risk of severe MS rebound with discontinuation FDA approved for 10 y and older, with dose adjustment Low PML risk[b] Avoid or use with caution in persons with skin cancers
Natalizumab IV Selective adhesion molecule inhibitor; prevents migration of inflammatory cells across blood brain barrier Relapsing forms of MS	Common: rash, arthralgia, headache, respiratory tract infection Less common: PML, leukocytosis, hepatotoxicity	Baseline: CBC, LFTs, anti-JCV antibody Routine: anti-JCV antibody every 6 mo (per REMS); CBC, LFTs as needed	Highest risk of PML of all DMTs Risk is directly associated to anti-JCV antibody positive status, duration of therapy, and history of immunosuppressant use Avoid use if anti-JCV antibody positive
Ocrelizumab IV Anti-CD20 humanized monoclonal antibody; depletes B-cells Relapsing forms of MS, PPMS	Common: IRR, infection Less common: hypogammaglobulinemia, hepatitis B reactivation	Baseline: HBV screening, CBC, immunoglobulins Routine: CBC; immunoglobulins as needed	May monitor B-cells Low PML risk[b]
Rituximab IV Anti-CD20 chimeric monoclonal antibody; depletes B-cells *Not FDA approved for MS*	Common: IRR, infection Less common: hypogammaglobulinemia, hepatitis B reactivation	Baseline: HBV screening, CBC, immunoglobulins Routine: CBC; immunoglobulins as needed	Multiple variations of off-label dosing have been used, however, 1000 mg × 1 then 500 mg every 6 mo OR 500 mg every 6 mo may be the most used regimens at present May monitor B-cells Low PML risk[b], no cases of PML with Rituximab used for MS indication
Siponimod PO S1P1 and S1P5 selective receptor modulator; sequesters T-cells in lymphoid tissue Relapsing forms of MS	Common: headache, hypertension, elevated LFTs Less common: bradycardia, AV conduction slowing, HSV infections, macular edema, asthma exacerbation, risk of BCC	Baseline: CYP2C9 genotype, CBC, LFTs, VZV serology, OCT test, ECG, BP, pulse Initiation: FDO only if presence of heart block, sick sinus syndrome or pacemaker Routine: CBC, LFTs, OCT 3 to 4 mo after starting	Starter pack with slow dose titration reduces need for FDO requirement Despite increased receptor selectivity, risk of adverse effects appears similar to fingolimod Suspect rebound will be a concern here too (given mechanism of action) and risk of skin cancers

ALC = absolute lymphocyte count; AV = atrioventricular; BCC = basal cell carcinoma; BP = blood pressure; CBC = complete blood count; DMT = disease-modifying therapy; ECG = electrocardiogram; FDA = Food and Drug Administration; FDO = first dose observation; GI = gastrointestinal; HBV = hepatitis B virus; HE = highly effective; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IM = intramuscular; IRR = infusion related reaction; ISR = injection site reactions; ITP = immune thrombocytopenic purpura; IV = intravenous; JCV = John Cunningham virus; LFTs = liver function tests; ME = modestly effective; MS = multiple sclerosis; OCT = optical coherence tomography; PML = progressive multifocal leukoencephalopathy; PO = oral; PP = primary progressive; REMS = Risk Evaluation and Mitigation Strategy; RR = relapsing remitting; S1P = sphingosine 1-phosphate; SC = subcutaneous; SCr = serum creatinine; SPMS = secondary progressive multiple sclerosis; TB = tuberculosis; TFT = thyroid function test; UA = urinalysis; URI = upper respiratory infection; VZV = varicella zoster virus.

[a]ME-DMT and HE-DMT classification is controversial. Higher efficacy outcomes in clinical trials appear to not always correlate to what's seen in clinical practice or observational studies. For this reason, these DMTs are listed as they are in this table.

[b]The vast majority of PML cases occur in patients previously exposed to natalizumab. For some, the switch from natalizumab was prompted by an anti-JCV antibody positive status and/or more than 2 years of treatment. In cases of no prior natalizumab exposure, some PML cases were associated rarely with severe lymphopenia (as with dimethyl fumarate) or with prior history/concomitant use of immunosuppressing therapies. For these reasons, risk of PML for nonnatalizumab DMTs is overall considered to be low.

[c]Relapsing forms of MS are considered to be clinically isolated syndrome, RRMS, and active SPMS per the 2013 update in MS phenotypes. While it may appear that siponimod and cladribine were the first DMTs to be approved for use in SPMS, that is not the case as patients meeting the definition for active SPMS, a relapsing form of MS, were enrolled in these clinical trials. With the phenotype updates, all package labeling of DMTs for relapsing MS were updated in May of 2019 to include active SPMS as a relapsing form.

Determining Modestly Effective Versus Highly Effective DMTs

The variable efficacy and side effect profiles of currently approved DMTs (Table 4) have introduced the idea of *personalizing* MS care.

Based on the available evidence, there is a generally accepted categorization of modestly effective (ME)-DMTs versus highly effective (HE)-DMTs (Table 4), however controversy and differences in clinical opinion still exists.[15,33] The increased efficacy of many of the newer DMTs exposes pwMS to DMTs with higher risks (eg, adverse effect potential, more complex safety monitoring needed). This increased risk potential is related to the newer agents having more immunosuppressing mechanisms (suppressing the immune response) versus the immunomodulating mechanisms (adjusting level of immune response) of the first available DMTs.

Determining ME-DMT versus HE-DMT for relapsing type of MS is not entirely straightforward given an overall lack of head-to-head trials between newer and older DMTs. Previous head-to-head trials[34-38] between older self-injectable agents have shown similar efficacy across agents. While one trial[38] showed superiority of one interferon-beta over another (eg, high-dose interferon vs low-dose interferon) this trial had design limitations lessening the strength of the result. The available phase III head-to-head trials and comparative effectiveness research between interferon-betas and the oral DMTs suggest teriflunomide is as effective as the interferon-betas and fingolimod is more effective than interferon-betas.[39,40] The placebo-controlled studies[24-27] of dimethyl fumarate included glatiramer acetate as a reference comparator, and thus were not designed to test the superiority or noninferiority of dimethyl fumarate versus glatiramer acetate. Prospective head-to-head studies among the HE-DMTs remain absent. Fortunately, observational and comparative effectiveness studies[30,31,39,44,45] showing HE-DMTs are more effective than ME-DMTs and describing long-term safety are providing real world data and supplementing the evidence given the limited number of head-to-head phase III trials.

With limited head-to-head data, clinicians are also left with comparing DMT efficacy outcomes such as annualized relapse reduction, incidence of new brain lesions on MRI, and disability scores, across placebo-controlled clinical trials. This practice comes with its own set of confounding factors and limitations making it difficult to compare these agents. For example, clinical trials vary by patient population and inclusion/exclusion criteria. Additionally, the diagnostic criteria for MS and definition of clinical relapse have changed and evolved over the years, making it difficult to compare recent studies to older clinical trials.

Patient Case Part 3: To Induce or Not to Induce

At the next clinic visit, the clinician and the patient discussed the goals and expectations of therapy and compared the efficacy and safety of the DMT options.

Given the approval of more efficacious DMTs, a broad evolution of the current MS treatment paradigm is underway. The key evolving concepts include treatment initiation and goals, stratifying treatment on disease phenotype and DMT efficacy, and managing use of riskier DMTs.

Goals of Treatment and Treatment Strategy

Prior to the availability of HE-DMTs, treatment response was demonstrated by achieving limited reduction in relapse rates and minimal effects on disability accumulation. Following the approval of HE-DMTs, the goals of treatment response have started to shift from reluctant acceptance of a partial response to the expectation of achieving as close to complete cessation of disease activity and progression as possible.[46] The *no evidence of disease activity* (NEDA) treatment goal remains controversial because of a lack of definition for how to measure disability progression clinically, MRI sensitivity for detecting lesions associated with disability, and real-world application.[46] The most agreed upon definition includes the absence of relapses, no confirmed disability progression, and no new GAD lesions or new or worsened T2 lesions.[46,47] Using NEDA as a treatment goal means any evidence of relapse, progression, and/or active lesions should prompt reconsideration of the current DMT. Two therapeutic strategies are being examined to determine which best achieves a NEDA-like target.

The *escalation* strategy means starting with *safer* ME-DMTs and then transitioning to *higher risk* HE-DMTs only if disease breakthrough occurs. The argument against this strategy is that the early use of subpotent DMTs may expose individuals unnecessarily to the loss of functional years from disability accumulation because relapses are frequently underreported and silent lesions often occur.[48,49]

The *induction* strategy means that the *higher risk*, HE-DMTs are started immediately following diagnosis, in order to achieve the NEDA-like target as early as possible. Alemtuzumab and cladribine are considered induction-specific DMTs given their relatively rapid suppression of

multiple cell lines and persistent immunosuppression. Repopulation of these cell lines may take months to years thus, fostering long term suppression of disease activity. Induction therapy is then followed by long-term maintenance treatment, such as with a ME-DMT.[50] Rituximab and ocrelizumab are also HE-DMTs, though these agents have partial induction effects. While they do not suppress multiple immune cell lines, their duration of effect is prolonged and repeat dosing can be given at extended intervals (ie, every 9 to 12 months or longer if needed) over time. Natalizumab and fingolimod are HE-DMTs and are used as initial treatments for aggressive disease in a manner similar to induction-specific DMTs, but they do not have true induction effects. Both natalizumab and fingolimod (and likely siponimod) appear to have rapidly reversible effects that predispose patients to a rebound of disease activity upon discontinuation.[50] The overall concern with the induction approach is that an otherwise young, healthy person may be exposed to serious adverse effects including risk of opportunistic infections.

The recently updated treatment guidelines published by the American Academy of Neurology (AAN)[51] and the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) in cooperation with the European Academy of Neurology (EAN)[43] do not advocate for any particular therapeutic strategy. Both advise treating individuals with clinically isolated syndrome who have MS-like lesions with an injectable DMT. Both recommend treating RRMS as early as possible to improve outcomes based on data from trials of individuals with clinically isolated syndrome who had MS-like lesions and trials showing DMT efficacy is greatest when using the HE DMTs early in the disease.[33,52,53] And both guidelines address switching DMTs. EAN/ECTRIMS endorses switching therapy for pwMS on a self-injectable who experience breakthrough disease activity (relapses, disability progression, or MRI activity) to a HE-DMT rather than between self-injectables. Without providing a definition of *highly active* MS, the AAN advises identifying persons with *highly active* MS and treating individuals with DMTs they consider having greater efficacy but did not use the term *highly effective*.[51] Neither of these guidelines provide specific treatment algorithms for personalization. The MS Coalition, an affiliation of independent MS organizations including the National Multiple Sclerosis Society, updated their consensus paper in 2019. The consensus paper[1] advocates for initiating DMT early, recognizes specific DMTs as HE-DMTs and supports using HE-DMTs if disease is highly active and opposes any restrictions to therapy choice. Neither AAN nor EAN/ECTRIM guidelines support one strategy (*escalation* or *induction*) over the other, and both strategies are an option. Use of a ME-DMT at onset (*escalation* strategy) can be considered either for patients presenting with milder symptoms (ie, optic neuritis or numbness/tingling sensory symptoms), who have no negative prognostic factors, for patients already stable on ME-DMTs who have no negative prognostic factors, or for patients who are risk averse. Consider escalating to a HE-DMT when a new relapse and/or new MRI lesion(s) occur. Additionally, inform the patient that even though the disease may appear dormant, silent inflammatory attacks and progression may be ongoing.[15,16] For pwMS with any negative prognostic factor, we suggest HE-DMT from the start (*induction* strategy) along with education of the risks and careful monitoring of side effects.

Patient Case Part 4: De-Risking the Risk

The clinician supports the choice of fingolimod as an *induction therapy* given findings of spinal cord lesions and sphincter symptoms (fecal incontinence). Appropriate screening is completed and fingolimod is initiated with the recommended first dose observation (FDO) including a baseline electrocardiogram, blood pressure, and heart rate followed by blood pressure and heart rate checks hourly for 6 hours after the first dose is taken, and finally a repeat electrocardiogram at the 6 hour mark. The FDO of fingolimod is tolerated and treatment is started, after which the clinical pharmacy specialist assists with implementation of safety monitoring.

The clinical pharmacy specialist recommends absolute lymphocyte count (ALC) and liver function test (LFT) monitoring every 6 months while on fingolimod. At 6 months postinitiation, LFTs remain normal however, ALC falls to 300/μL. The patient denies any signs or symptoms of infection. The primary care provider orders a repeat complete blood count in 2 weeks and shows stable ALC, which remained at 300/μL.

Absolute lymphocyte count reduction is expected with fingolimod based on the mechanism of action of sequestering lymphocytes in lymphoid tissue and should not prompt therapy discontinuation. The lowest acceptable level of lymphopenia has been set to 200/μL because during clinical trials opportunistic infections were not seen even when the ALC dropped to this value. However risk of infection is unknown when ALCs are below this threshold as continuing fingolimod in this setting has not been extensively studied.[54] If ALC values fall persistently below 200/μL, an alternative DMT should be considered. Holding fingolimod therapy to allow ALC to increase within an acceptable range may be tried. However, if treatment is interrupted for more than 14 days, FDO for cardiac changes is recommended upon reinitiation.

Siponimod and dimethyl fumarate can also reduce ALC.[21,26] Because of a similar mechanism of action to fingolimod, ALC reduction with siponimod is expected and thus management recommendations are similar. Lymphopenia with dimethyl fumarate is less common. Unlike

fingolimod or siponimod where ALC returns to baseline soon after discontinuation, prolonged lymphopenia after discontinuation may occur with dimethyl fumarate.[26] In addition, rare cases of progressive multifocal leukoencephalopathy (PML; a sometimes fatal opportunistic viral infection of the CNS) has been linked to dimethyl fumarate-induced lymphopenia, and a case of PML which occurred after an ALC of less than 500/μL that persisted for greater than 6 months prompted a FDA label change in 2014, which expands on lymphocyte monitoring recommendations.[26] While severe lymphopenia as a risk factor for PML remains controversial, it does highlight the importance of appropriate laboratory monitoring and follow up.[55]

Patient Case Part 5: Rebound Relationships

After 3 years on fingolimod the patient has had no relapses, no radiographic or clinical progression of disease, and ALCs have remained at or above 200/μL without any recent illnesses. Upon follow-up, the patient shares plans to relocate out of state for a new job opportunity in 2 months. This move will involve changing insurance providers and finding a new clinician. The patient is nervous about how to continue taking fingolimod until seen by a new clinician.

Fingolimod should not be abruptly discontinued without a plan to transition to an alternative DMT because of risk of rebound in persons with relapsing MS. Clinical rebound syndrome has been reported within 4 to 16 weeks of patients stopping fingolimod and is consistent with signs/symptoms of a severe clinical relapse such as drastic increases in new and/or enhancing lesions on MRI and new or worsening MS symptoms.[23,56] Similarly, risk of disease rebound after discontinuation is also high with natalizumab as a number of case studies have reported an increase in disease activity beyond that of prenatalizumab levels.[17,57,58] While the most effective management strategy to prevent rebound syndrome remains unclear, expert clinicians recommend transitioning to an alternative HE-DMT before the effects of fingolimod or natalizumab wear off. Based on experience, it is the authors' practice to transition patients to a HE-DMT within 4 to 8 weeks after the last natalizumab infusion and within 4 weeks after the last fingolimod dose.

Since the patient will soon be without a clinician and possibly without fingolimod for an unknown length of time, switching to alternative HE-DMT prior to losing current insurance coverage would be ideal. Based on clinical experience, an anti-CD20 agent may be the best option given it may help prevent clinical rebound syndrome after discontinuing fingolimod. Anti-CD20 agents are HE-DMTs with clinical effects lasting for at least 6 months after receiving a dose, which allows the patient time to establish care. While the anti-CD20 agent, ocrelizumab, is FDA-approved for MS, rituximab was the precursor to its development and has been used off-label for many years in European countries and later in the United States.[59] Either option would be appropriate, and choice would most likely be dictated by insurance coverage, copay, and provider preference.

Conclusion

The management of MS continues to rapidly evolve. Treatment options with greater efficacy and potential for altering the course are now available. Shared decision making and patient preferences remain key factors in DMT selection. However, treatment customization should also consider patient-specific negative prognostic factors both at diagnosis and throughout the course of treatment. Identification of these factors can further stratify therapy approach using the HE-DMTs, which then requires that benefits be balanced with sometimes very serious risks. Ongoing research will provide more direction as to which strategy is the safest and most effective for achieving a NEDA-like goal of treatment.

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