8 Clinical Decision-Making in the Management of Multiple Sclerosis

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Escalation Versus Early Aggressive (or Induction) Treatment in the Management of Relapsing MS (RMS)

Early in the disease course, multiple sclerosis is characterized by periods of inflammation associated with demyelination and axonal injury. However, in the later phase of the disease, inflammation becomes less prominent, and neurodegeneration arises as the defining feature of the illness. While progressive MS is primarily managed symptomatically, the early inflammatory phase in relapsing MS represents a critical period where the benefits of disease-modifying therapy (DMT) can be best realized. Several studies [1–7] have shown that early treatment with disease-modifying therapy results in better long-term outcomes in comparison with delayed treatment and consequently therapeutic strategies have evolved.

The two general approaches employed in selecting a disease-modifying therapy can be described as either an "escalation" strategy or an early aggressive strategy. An escalation approach entails the initial use of a first-line agent, generally glatiramer acetate (GA) or interferon β, and transitioning to a second-line agent in the event of disease progression or clinical relapses while on therapy [8]. This is a reasonable strategy, as a patient may be well controlled on an agent with a long safety profile history. However, this approach does not take into consideration how early or late a patient is in their disease course or the degree of initial clinical or radiographic activity. Alternatively, an early aggressive strategy utilizes initial treatment with a medication considered more potent than first-line therapies, such as fingolimod, natalizumab, or ocrelizumab, or the use of an "induction" agent. Induction therapies provide a sustained alteration of the immune system and ideally are able to provide a prolonged period free from disease activity. Three of the disease-modifying therapies are considered induction agents: mitoxantrone,

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alemtuzumab, and cladribine [9]. Stem cell transplant therapies also fall in the category of induction therapy.

In general, the newer therapies have been shown to decrease clinical relapse rates to a greater degree than the older therapies, and many of the newer therapies decrease the rate of disability progression in MS [10]. However, stronger medications also come with an increase in risk of serious adverse events. Progressive multifocal leukoencephalopathy with the use of natalizumab and the precipitation of other autoimmune conditions with alemtuzumab, for instance, are concerning for adverse outcomes related to the use of these agents. Due to variations in presentation and the fact that some patients will present with aggressive disease which cannot be adequately managed by first-line therapies, individualizing the treatment regimen for the individual is paramount. Disease severity must be considered when selecting a medication. Use of a potent agent as an initial therapy is becoming more common in an effort to minimize disability, particularly in patients with risk factors for an aggressive course [9, 11–14].

An aggressive treatment approach is often considered in an attempt to achieve a disease-activity-free status in multiple sclerosis. Criteria for such a status have been debated; however, the term "no evidence of disease activity" (NEDA) is the currently agreed upon model [15]. More specifically, NEDA-3 has been defined as (1) the absence of relapses—a new, or worsening of a previously stable, neurological abnormality, present for at least 24 h and occurring in the absence of fever or infection; (2) the absence of focal MRI activity, new or enlarged T2 lesions and/or gadolinium-enhancing lesions; and (3) the absence of confirmed disability progression (CDP)—an increase in Expanded Disability Status Scale (EDSS) score of 1.5 points from a baseline of 0, of 1.0 point from a baseline score of at least 1.0, or of 0.5 points from a baseline score of greater than 5.0 and confirmed after 3 or 6 months. While NEDA-3 captures inflammatory disease activity well, it may not fully account for the neurodegenerative component of MS. Thus, another more stringent definition, NEDA-4, incorporates the criteria included in NEDA-3, as well as an annualized rate of brain volume loss of less than 0.4% [16]. Since brain volume loss has been shown to correlate with disability progression and cognitive decline, this definition may more accurately reflect a complete cessation of disease activity. It should be noted, however, that NEDA criteria do not account for disability attributed to cognitive measures, visual function, fatigue, or pain [17, 18].

Sustained disease control with an induction agent has been demonstrated in several studies. Mitoxantrone, an intercalating agent which crosslinks DNA strands, has proven efficacious in the treatment of acute myeloid leukemia, breast cancer, liver carcinoma, and non-Hodgkin's lymphoma. For MS, it is administered intravenously every 3 months but is limited by a cumulative maximum dose. A 5-year observational trial of patients who received mitoxantrone therapy for MS showed that 32% of patient remained relapse-free after 5 years and 60% of patients did not have worsening of their EDSS score [19]. However, it should be noted that the adverse outcomes of decreased left ventricular cardiac ejection fraction and leukemia often limit mitoxantrone use [20]. Alemtuzumab, a humanized anti-CD52 monoclonal antibody which binds to the CD52 receptor on B and T lymphocytes causing a long-lasting depletion of lymphocytes, has similarly exhibited positive outcomes. The CARE-MS I study demonstrated that as an initial therapy, alemtuzumab was superior to interferon beta 1a in achieving an endpoint equivalent to NEDA-3—referred to as "freedom from disease activity"—with 39% (139/360) of patients in the alemtuzumab arm achieving this outcome at 24 months, in comparison with 27% of patients in the interferon beta 1a group [21]. In the CARE-MS II trial, alemtuzumab was utilized as a second-line therapy, and 32% (127/396) of these patients achieved freedom from disease activity at 24 months, compared to 14% of patients in the interferon beta 1a group [22]. Cladribine data thus far is encouraging with an extension study demonstrating that after 4 years after initiating treatment, 75% of patients

remained relapse-free and 72.4% of patients were free from disability progression [23].

While modern DMTs have demonstrated improved efficacy in minimizing disease progression in relapsing-remitting MS (RRMS), autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of MS has also shown encouraging results. AHSCT for MS patients, which can be considered the ultimate in induction therapies, began in 1995, and by 2008, approximately 400 cases had been performed worldwide [24]. Although protocols from early transplantations varied greatly, even initial data showed slowing of disease progression in the majority of patients following treatment. Unfortunately, transplant-related mortality in early trials was reported as high as 7.3%. This was particularly concerning due to the fact that MS patients tend to be young and otherwise unburdened by other diseases. Newer trials have fortunately shown positive outcomes with far less morbidity and mortality. A retrospective review analyzing results from 281 patients who had received AHSCT via various protocols between 1995 and 2006 and had a median follow-up of 6.6 years found that 46% of transplant patients did not progress in their EDSS after 5 years [25]. Younger age, relapsing type of MS, fewer prior immunotherapies, and lower baseline EDSS score were all associated with improved outcomes. Furthermore, 100-day mortality following AHSCT was 1.3% for transplants performed from 2001 to 2007.

Additional studies have further supported a freedom from disease progression over the long term. A 2009 study with 21 patients who were treated with AHSCT at Northwestern University found that 62% of patients had no disease progression as measured by EDSS, no clinical relapses, and no new MRI lesions at 3-year mean follow-up [26]. A 2015 Northwestern University study of 145 patients, primarily with RRMS, treated with AHSCT found that 52% (14/27) of patients showed improvements in EDSS of at least 1.0 point at the 5-year follow-up point [27]. The HALT-MS trial studying AHSCT in 24 patients with RRMS reported that 78% of patients achieved an endpoint comparable with NEDA—termed "event-free survival"—after 3 years and 69.2% of patients achieved this endpoint after 5 years [28]. Lastly, a trial with 24 patients with aggressive disease as predicted by a dataset from London, Ontario, Canada, showed that 69.6% of patients were free from clinical relapse, new or Gd-enhancing lesions on MRI, and progression of EDSS at 3 years following AHSCT [29]. Overall AHSCT has demonstrated NEDA status rates of 78–83% at 2 years and 60–68% after 5 years [30].

Can Disease-Modifying Treatment Be Discontinued in Non-active RRMS/SPMS Patients?

Among the reasons for discontinuing disease-modifying therapy (DMT) in multiple sclerosis (MS) patients, stopping in those who are deemed to have stable disease is perhaps the most controversial. The concept of "no evidence of disease activity" (NEDA) has made this topic even more relevant in recent years. This, combined with the extreme costs and potential complications of DMTs, means that stopping treatment if it is safe and reasonable to do so may be in our patients' best interests. Expert opinion [31–33] has long dominated this area, but evidence is slowly starting to emerge to provide clinicians with some guidance in select patient groups. That being said, a prospective, randomized study of DMT discontinuation has yet to be completed, though one is currently in process (DISCO-MS, NCT03073603).

While starting DMT early in young, nondisabled patients is widely advocated in order to achieve the best long-term outcomes, it is unclear whether older, more disabled patients with inactive or secondary progressive MS derive any benefit [34, 35]. The concept of immune senescence may explain why disease activity seems to decline with age [36] and why DMT may become unnecessary at a certain point. Cerebrospinal fluid (CSF) biomarkers of inflammation and axonal injury have been shown to decline with age, particularly with MS patients over age 54 [37]. Accordingly, age has been shown to be the most

significant predictor of gadolinium (Gd) enhancement on MRI in natural history studies, with the probability of enhancement decreasing by 36% for each additional decade. The frequency of enhancement was 12% in the group aged 50 and older compared to 55% in the 20–30-year-old group. As expected, relapse rate similarly peaked in the 20s and 30s and declined by approximately 34% per decade. Patients aged 55 and older who had been deemed to have secondary progressive disease for 5 or more years had only a 5% probability of relapse [38]. The unique pathologic basis underlying progressive disease, with chronic activation of macrophages and microglia, could potentially help explain the lower likelihood of relapses in this group [39]. Patients who are newly diagnosed with MS at an older age suggest that there is more to this story [40], but these data seem to support that older, inactive patients and patients with progressive disease may be less likely to relapse while off DMT.

Several recent observational studies have evaluated outcomes for patients who have discontinued DMT, mostly involving injectable medications. In one US center, 77 patients with secondary progressive MS who had no evidence of disease activity for at least 2 years had an 11.7% rate of new lesions or relapses after stopping DMT. These patients had a median age of 61 and range of 2–20 years of disease inactivity prior to discontinuation [41]. A French study on 100 patients with secondary progressive MS for at least 2 years who stopped DMT showed that 33% had a relapse or new enhancing lesion at 3 years, but only five of those patients had relapses that resulted in sustained increases on the Expanded Disability Status Scale (EDSS) at 6 months. Factors significantly associated with relapses following discontinuation included enhancing lesions within 3 years of stopping and EDSS less than 6 prior to stopping. Notably, changes in T2 lesion load were not considered in this study. Whether new, non-enhancing T2 lesions have implications for disability progression in secondary progressive MS remains unclear [42].

A larger analysis of 485 patients across 28 sites used data from MSBase, an international prospective Internet-based registry. These patients stopped injectable DMTs after having no relapses for at least 5 years. They had been treated continuously for at least 3 years prior to discontinuation and were followed for at least 3 years after stopping DMT. The relapse risk was 36.4% after stopping DMT, and 33.5% of patients who stopped DMT had confirmed disability progression. Only 10.8% of patients experienced both relapse and confirmed disability progression. Younger age and lower baseline disability were significant predictors of relapse risk. Survival time to confirmed disability progression was shorter among patients who stopped DMT, with patients who had a stable EDSS for 5 years prior to discontinuation contributing significantly to this observation. Notably, the MSBase registry did not include the reasons for discontinuing treatment for the majority of patients who were included in this study. Of those for whom it was listed, reasons were multifactorial including perceived disease progression, intolerance, and adverse events [43].

An Austrian study of 221 patients with relapsing–remitting MS (RRMS) who discontinued DMT identified possible criteria for selecting patients who may be more likely to remain relapse-free after doing so. These patients were treated continuously for at least 12 months prior to discontinuation and did so for a variety of reasons including adverse events or patient preference. Only 27% of the cohort discontinued DMT due to stable disease. Relapses occurred in 44% of patients during a mean of 3.8 years of follow-up. Age over 45 years and the absence of clinical relapses or enhancing lesions for at least 4 years prior to discontinuation were felt to predict freedom from relapses after stopping DMT with a hazard ratio of only 0.06. Disability progression occurred in 20.8% of patients and was associated with higher EDSS, age over 45 years, and longer disease duration at the time of discontinuation [44].

As attempts are made to identify groups of MS patients who may not be benefitting from DMT, particularly with prospective, randomized-controlled trials, clinicians will hopefully be able to

make evidence-based decisions with their patients to stop treatment. Such data will be particularly important for patients who are on medications such as natalizumab and fingolimod which are associated with a risk of disease "rebound" on cessation [45, 46]. The newer drugs ocrelizumab and siponimod which have been shown to slow disability progression even in the absence of objective evidence for inflammatory activity raise additional questions about the perceived lack of benefit of DMT in certain populations [47, 48]. Whichever group of patients may seem suited for a trial of discontinuation, what is clear is the need for close clinical and radiological monitoring after stopping.

Rebound Disease Activity in Patients Discontinuing Disease-Modifying Drugs

Though many effective treatments are now available to inhibit multiple sclerosis disease progression, reports have emerged concerning for exaggerated disease activity upon cessation of treatment with these agents. Some patients treated with fingolimod or natalizumab, which target trafficking of lymphocytes from lymphoid tissues and across the blood–brain barrier, respectively, have demonstrated "rebound" or disease activity that exceeded pretreatment rates based upon both clinical assessment and contrast-enhanced MRI analysis [49]. As studies continued to profile risks of discontinuation of fingolimod and natalizumab, new cases began to emerge that also identified increased activity in multiple sclerosis patients who discontinued treatment with dimethyl fumarate and teriflunomide [50–52]. The potential for severe exacerbation upon drug withdrawal is particularly concerning for patients who must stop treatment or change to a different medication due to inadequate response to therapy, JC virus positivity, or desire for pregnancy.

The nature of this rebound disease upon medication discontinuation is not well characterized. Some discordance in the literature reflects disagreement in definition of "rebound" versus "reactivation" or inevitable progression of an unpredictable disease. Some have suggested that those with severe reactivation compared to pretreatment status might simply be demonstrating a variant of natural disease progression that is independent of medication use [53], but comparison of large populations of patients who were on different doses of fingolimod versus placebo demonstrated that disease activity exceeded predicted disease progression [54]. Additionally, the time of increased disease activity seems to correlate with expected withdrawal from the discontinued medications. A large cohort study demonstrated significant relapse rate of disease between 2 and 8 months after cessation of natalizumab therapy with 10% of patients suffering rebound, corresponding with the 3-month decrease in concentrations of natalizumab and changes in the immune system that have been documented up to 6 months after cessation of treatment [55, 56]. Studies exploring rates of rebound with fingolimod washout are largely similar but vary from 5% to 10% [46, 50, 53, 57]. Research continues to debate whether the rebound phenomenon is of the same etiology across patient populations, John Cunningham virus (JCV) and Epstein–Barr virus (EBV) status, medication used, and other yet uncharacterized variables that could affect patient outcome.

Controversy similarly surrounds whether rebound activity is related to immune reconstitution inflammatory syndrome, or IRIS. While IRIS previously described an immune response to infectious agents, it was proposed as the culprit for rebound activity upon cessation of immunomodulatory therapies as a result of an *endogenous* antigenic cause of new activity. Characterizing "rebound" activity versus IRIS sparked a debate within the community: Was rebound an exaggerated immune response after ending therapy or was an independent mechanism to explain the increase in disease activity in excess of pretreatment levels [49, 50]? What were these endogenous antigens? According to the field hypothesis, an unidentified compound or molecule in tissue, possibly of viral origin, triggers focal inflammation [1]. Some authors favor an exogenous cause, having isolated EBV-

infected cells and T cell binding in white matter lesions in a fatal case of rebound after cessation of natalizumab [58, 59]. Others refuted the connection to IRIS and a viral antigenic etiology through description of a severe, fatal disease they characterized in a postmortem study as inconsistent with IRIS or PML. The lesional damage was extensive yet characteristic of active demyelinating MS progression. Additionally, CCR5 inhibitors have shown efficacy in treating PML/IRIS, but researchers detected low levels of expression in sampled brain tissue, suggesting that such treatment would have been ineffective in their rebound case [60].

Other hypotheses regarding disease mechanism and etiology are more specific to the distinct treatments. Long-term natalizumab therapy may change the dynamics of cell adhesion molecules in leukocytes [61], and changes in cell adhesion molecule expression might also explain the cases of rebound disease upon cessation of dimethyl fumarate [62], though these may be through different mechanisms. Individual patient variables may also affect outcomes. A case report describing an affected patient's neutralizing antibodies against natalizumab suggested that acceleration of T cells into CSF caused disease exacerbation beyond the patient's baseline. They also noted that natalizumab promotes immune activation by giving a costimulatory signal to T cells, causing a pro-inflammatory state so its withdrawal (and thus prevention of effector cell migration into CSF) results in an increase of disease activity above pretreatment baseline [63]. Immune cell populations also undergo changes with treatment that may contribute to rebound phenomena. Research has shown an increased peripheral Th17 cell population and IL-17 levels after use of natalizumab, while disease reactivation was associated with a drop in Th17 and decrease in serum IL-17, suggesting reentry into CSF that was confirmed in a postmortem pathologic study [60, 64]. Others note the contributions of a reduction of regulatory T cells and upregulation of effector T cells [65].

Rebound activity after cessation of fingolimod may be due to a completely different immune dysregulatory effect. A predisposition for severe exacerbations may arise from compensatory overexpression of sphingosine-1-phosphate receptors involved in lymphocyte trafficking due to chronic receptor blockade by fingolimod [66]. These rebounds can be particularly severe, producing tumefactive demyelinating lesions (i.e., lesions that are larger than 2 cm, with edema or mass effect) [67] even during active fingolimod treatment [65]. A postmortem case report following a fatal discontinuation of fingolimod describes astrocytic gliosis within the tumefactive lesions with intense sphingosine-1-phosphate receptor 1 expression. Of note, researchers also found astrocytic gliosis within white matter regions that appeared grossly normal [68].

Due to the lack of clarity and seeming disparity in etiologies of rebound cases, clinicians should be cautious when selecting patients who are appropriate candidates for immunomodulatory therapies. Patients with disease rebound tend to have more pretreatment disease activity, as indicated by higher Expanded Disability Status Scale (EDSS) scores, higher annualized relapse rate, and mean enhancing lesions before treatment, demonstrating a correlation between prior disease activity and likelihood of rebound activity [55, 56]. These patients should be monitored with extra caution when discontinuing a medication regimen, especially with fingolimod or natalizumab. Prevention and treatment of rebound are not yet optimized, but current studies considering specific medication withdrawal and JCV status recommend that alternative therapy should be started as 2–4 weeks after cessation of fingolimod and within 4 months after ending natalizumab to align timing of treatment with washout [49]. This can be challenging if patients end treatment with these regimens due to JCV positivity: alemtuzumab, cladribine, and mitoxantrone may cause long-term lymphocyte depletion, thus hindering CD8-dependent T-cell defense against JCV. B-cell therapies, rituximab and ocrelizumab, may provide immunity against JCV escape variants, so transitioning or discontinuing therapies safely with these options is a unique challenge [49].

Additionally, prevention of rebound has proven difficult at best. After stopping fingoli-

mod therapy, patients have rebounded even with treatment with rituximab or two courses of steroids [46]. A case study of a patient's transition from fingolimod to alemtuzumab with methylprednisolone after a 5-week fingolimod washout still resulted in unexpected high activity as T cells displayed an activated HLA phenotype. However, this immune response may be connected with fingolimod insufficiency in this patient [69]. Similar difficulties have been documented in transitioning to other therapies from natalizumab. A patient who discontinued natalizumab and started daclizumab suffered rebound on his new therapy, but he responded well to methylprednisolone and alemtuzumab [70]. In JCV-positive patients who must switch from natalizumab to alemtuzumab or other induction therapies, some recommend bridging with fingolimod, citing its efficacy in controlling disease after stopping natalizumab [71], though others have found relapse during use of fingolimod in patients transitioning from natalizumab [72]. One study did not find any significant reduction in disease activity with preventative methylprednisolone treatment, and glatiramer acetate, fingolimod, nor interferon beta offered appropriate protection against resumption of disease activity [55]. However, while some cases of rebound respond poorly to steroids, rebound upon discontinuation of teriflunomide responded well in a patient to two courses of IV steroids and 60 mg oral prednisone daily for 2 weeks followed by rituximab [52]. Research suggests that dimethyl fumarate might be effective if started after a short (1 month) washout of natalizumab [73], but a case report has also demonstrated inefficacy of dimethyl fumarate in controlling rebound activity after natalizumab cessation when used after a cyclophosphamide bridge [74]. Other work suggests that a short course of treatment with 60 mg cladribine effectively suppresses inflammatory activity and allows partial recovery in a patient with progressive multiple sclerosis with rebound disease from fingolimod with no short-term safety issues or adverse events [75]. Further work is necessary to explicate the relationships among patient factors, rebound etiology, medication effects, immunologic characteristics, and risk profiles with different bridging regimens to clarify which patients would benefit most from specific transition protocols and who would be less likely to respond to certain treatments.

Extended/Reduced Dosing of DMD

Several of the disease-modifying agents have been associated with serious side effects related to sustained immunosuppression including but not limited to PML. One possible approach to mitigate the risk is to reduce the overall dose of the agents by extending dosing intervals. Although definite data is lacking, several small studies provide some supportive evidence for this approach.

A subset of patients on fingolimod have a higher risk of developing severe lymphopenia, infections, and liver function abnormalities. Reducing the frequency of dosing (alternate day) may improve laboratory abnormalities although there may be a higher risk of breakthrough disease activity [76–78]. Several observational studies have evaluated the risk of breakthrough disease in patients treated with natalizumab who were dosed less frequently (up to 8-week intervals) and found no significant increase in disease activity [79–82]. More recently, a statistical analysis of the large TOUCH registry (US REMS program) revealed a significant reduction of risk of developing PML in JCV-positive patients who are treated with extended dosing compared to standard dosing [83]. Less frequent dosing prior to discontinuation has also been shown to reduce the risk of developing rebound disease activity after natalizumab discontinuation [84]. Infrequent dosing for B-cell-targeted therapies is even less well studied. Both rituximab and ocrelizumab are dosed at fixed 6-month intervals. While this dose effectively maintains B-cell depletion in the majority of patients, the minimum dose required to achieve complete and persistent B-cell depletion is unclear. One small study showed 97% depletion of B cells in patients who were treated with 1 mg/m^2 (a fraction of the standard dose) although cells recovered to 60% of baseline within 4 weeks [85]. Similarly, several small

studies have suggested increasing the intervals between treatments (up to 9 months) or reducing the dosage (50%) of rituximab in RRMS patients maintains B-cell depletion and efficacy [85–87]. Some suggest flexible dosing based on CD19/20 counts [88].

Less frequent dosing seems to be a reasonable option in patients who are at risk of or are experiencing significant side effects on DMDs.

Management of PML in MS Patients and Subsequent Disease-Modifying Treatment

Among the most feared complications of disease-modifying therapy (DMT) in multiple sclerosis (MS) patients is progressive multifocal leukoencephalopathy (PML), a rare but severely disabling disease of the central nervous system caused by the John Cunningham virus (JCV) [89]. Patients treated with natalizumab, one of the most effective treatment options for MS, are the third largest population at risk of developing PML after patients with HIV and hematologic malignancies [90]. Besides natalizumab, PML has also been reported to occur in a few cases of patients treated with dimethyl fumarate and fingolimod [91, 92]. However, natalizumab has the most well-established association with PML as an adverse effect among the immunomodulatory therapies, with over 800 cases reported since 2005 [93]. The incidence of PML associated with natalizumab ranges from 0.1% for patients without additional risk factors to 1.3% among patients who are JCV antibody-positive, have a history of prior immunosuppressive therapy, and have received more than 4 years of treatment [94, 95]. With significant disability being incurred by two-thirds of the approximately 80% of patients who survive natalizumab-associated PML, early diagnosis and institution of appropriate treatment are of paramount importance [93, 96].

Although JCV is widespread throughout the world, with most individuals infected by age 30–40 likely via a urine or fecal–oral route, pathological transformation occurs only in immunosuppressed individuals by poorly understood mechanisms [90, 97]. Replication of the transformed JCV then leads to axonal demyelination via lysis of infected oligodendrocytes. Large plaques are thereby formed in the subcortical white matter, often involving U fibers. The multifocal destruction leads to the variable symptomatology, ranging from hemiparesis to visual deficits depending on the areas involved. Neuroimaging and PCR detection of JCV DNA from CSF combined with the clinical picture make diagnosis possible without the need for biopsy [97].

Patients receiving natalizumab are risk stratified for PML at regular intervals using quantitative JCV antibody testing. The cutoff values for a positive test and when to halt further treatment evolve over time based on available evidence. Several studies have documented a very low risk of PML in patients who remain JCV negative [98]. There are several potential limitations to this method of PML risk stratification, including variability in testing methodologies and the possible effect of natalizumab on JCV indices. It also does not take into account other PML risk factors, such as prior immune suppression and duration of treatment with natalizumab [98]. While it is currently unclear whether JCV antibody testing has resulted in significantly earlier detection of PML, such is the goal of risk stratification methods and will hopefully be the case as they are further refined. Given the small number of PML cases associated with fingolimod and dimethyl fumarate, monitoring parameters for the purposes of PML risk stratification have not yet been established, though a possible association with lymphopenia has been observed [89, 99].

Currently, there is no treatment for PML. The general approach once PML has been diagnosed, regardless of etiology, consists of immune reconstitution in order to support the body's natural response to JCV [89, 97]. In natalizumab-associated PML, this was historically achieved by plasma exchange (PLEX) with the aim of removing the drug as quickly as possible. As the half-life of natalizumab is ~11 ± 4 days, it would take 2–3.5 months to naturally clear 95% of the drug. Modeling based on a study of PLEX in

patients treated with natalizumab suggested that five sessions would reduce serum natalizumab concentrations to <1 μg/mL in >95% of patients [95, 100]. Whether this approach is superior to simple drug cessation remains uncertain. Recent retrospective analyses have failed to support the use of PLEX for improving clinical outcome and survival [101, 102]. It is noteworthy that biological effects of natalizumab may persist for 6 months or more despite drug cessation [95, 103]. Newer treatments, including antiviral agents, immune response modulators, and even immunization strategies, are currently being investigated and will hopefully result in some positive outcomes [90].

A common complication in the treatment of PML is PML-immune reconstitution inflammatory syndrome (PML-IRIS). The majority of natalizumab-treated patients with PML go on to develop PML-IRIS upon removal of the drug within days to weeks. In this entity, the demyelination induced by PML is paradoxically enhanced by a robust immune response with macrophages and CD4 and CD8 lymphocytes [97]. Radiologically, PML-IRIS is more likely than PML to cause edema or mass effect and to enhance with contrast, particularly at the borders of an established PML lesion [104]. Treatment usually consists of high doses of corticosteroids followed by a prolonged taper while being mindful of the potential for exacerbating any coexistent infection [97]. This approach has not been evaluated in any controlled trials [90].

For the 80% of patients who survive PML, a standardized approach to resuming treatment of their MS does not exist. Not only are there concerns about which agent to choose, but there are also questions regarding how long to delay treatment following PML. A recent retrospective study evaluated outcomes in 23 patients treated with various DMTs following PML. Though only three patients had been treated with each, both dimethyl fumarate and fingolimod were used without any clinical or radiological worsening of PML. Of note, the mean duration of treatment with both drugs was shorter than the mean time to PML associated with these drugs in the cases described thus far. The mean delay in switching ranged from 2.9 months with IFN-ß 1B to 11.6 months with dimethyl fumarate. The length of delay should likely differ depending on the pre-natalizumab severity of disease activity [105].

While there is a need for prospective controlled trials on many fronts to inform PML diagnosis, treatment, and resumption of MS DMT for PML survivors, the small population for recruitment and the lack of an adequate PML animal model are major limitations [97]. What is perhaps most clear at present for the successful treatment of PML is the need for early detection and subsequently providing the immune system the ability to fight JCV, just not too well.

Management of Issues Related to Pregnancy in MS

Normal Pregnancy and Reproduction in Multiple Sclerosis

Multiple sclerosis (MS) is nearly three times more common in women than in men where onset typically occurs during childbearing years (20 and 40 years of age), a time when many individuals consider starting a family [106–108]. Many patients may wonder how MS will affect their ability to reproduce; thus, providers should thoroughly discuss pregnancy and its implications with patients and tailor specific disease management to the individual.

In starting this conversation, women should be reassured that the diagnosis of multiple sclerosis does not affect fertility. Studies have shown that MS females have normal fertility rates with no increase in spontaneous abortions or fetal abnormalities [107].

Although the etiology of MS still remains unclear, it is thought to involve the interaction between multiple genes and environmental factors [108, 109]. According to certain studies, the lifetime risk of developing MS in the normal population is about 100–300 cases per 100,000 [110, 111]. Individuals with first-degree relatives with MS have a 2–4% chance for developing the disease, although this is much higher (up to 20%)

in children that are born to two MS parent [110, 112]. MS patients should be reassured that their own diagnosis, however, does not increase their child's risk of developing the disease. Per expert opinion, MS patients carry a 96% chance of having a completely normal child [106, 110].

Prior to the 1960s, it was believed that pregnancy worsened the clinical progression of multiple sclerosis, and these patients were highly discouraged from becoming pregnant [109]. Instead, research in the modern era has shown that pregnancy is actually protective due to increased levels of immunosuppression and a state of immune tolerance [109]. Several retrospective and prospective studies show that pregnancy is associated with decreased MS relapses, particularly in the second and third trimesters. This was first demonstrated in 1998 through the *Pregnancy in Multiple Sclerosis* (PRIMS) study. In this trial, 254 pregnant MS patients were prospectively followed and were found to have a 70% reduction in annualized relapse rates during their third trimester of pregnancy compared to their prepregnancy year [106, 108, 109, 113]. Reduced relapse rate during pregnancy is thought to be due to estriol and progesterone, two female sex hormones which are found in higher concentrations in late pregnancy. These hormones are thought to increase anti-inflammatory cytokines and reduce pro-inflammatory cytokines [107–109]. After delivery, there is a sudden decline in these hormones which most likely accounts for the increased relapse rates observed in the 3- to 6-month postpartum period [107, 109]. Although MS relapse rates increase temporarily postpartum, the *PRIMS* study further showed there was no change in the overall course of the disease during the 3-year follow-up period. Thus, pregnancy, delivery, and postpartum relapse rates appear to have no effect on long-term MS disease progression or disability [108, 114].

Another common question asked by patients is whether babies born to MS mothers will have long-term health consequences compared to the normal population. Between 1967 and 2002, a study was conducted comparing birth outcomes in women with MS to those without by using the Norwegian Medical Birth Registry [108, 110, 115]. Other than finding that MS mothers had higher rates of small-for-gestational age babies, this study showed there was no difference in Apgar scores, rates of birth defects, or neonatal mortality [108]. From this research, the general consensus is that babies born to MS mothers have no greater long-term health consequences compared to the normal population [106, 108, 110, 114, 115].

Testing and Treatment of Acute Relapse During Pregnancy

When concern for acute MS exacerbation arises in pregnancy, providers must suggest appropriate testing which poses minimal to no harm on the developing fetus. In the past, use of MRI was avoided during the first trimester due to concern over the negative health ramifications on the growing baby. Instead, newer research has shown that *non-contrast* MRI poses no increased risk to the developing neonate and is considered safe throughout all stages of pregnancy. Use of gadolinium contrast, however, is strongly discouraged throughout pregnancy (in any trimester) due to an assortment of negative effects on the fetus including inflammatory/skin disorders, rheumatologic conditions, and neonatal death. Evoked potentials and lumbar puncture are other tests that can be pursued and considered safe throughout pregnancy [107].

MS relapses that occur during pregnancy can be effectively treated with intravenous (IV) methylprednisolone but should be reserved for severe exacerbations and are safest when used only in the second and third trimesters [114]. IV steroid use should be avoided in the first trimester of pregnancy as studies have shown an increased risk for craniofacial abnormalities, such as cleft palate [107, 108, 114, 116]. Instead, relapses occurring in the first trimester of pregnancy can be effectively treated with intravenous immunoglobulin (IVIG) as there are no effects on the developing fetus and very low rate of maternal side effects [107, 110, 111]. Testing and treatment of acute MS exacerbations during pregnancy

should be carefully discussed with the patient and tailored to each individual.

Risks of Disease-Modifying Therapy During Conception, Pregnancy, and Lactation

Risk of disease-modifying therapy (DMT) should be thoroughly discussed with MS patients who are trying to conceive or discover they are pregnant. Available data regarding these risks are mainly based on incidental exposure to the drug or animal research. Each DMT has varying effects on the growing fetus and differ in length of time they should be discontinued prior to attempts at conception [107]. There is general agreement from the FDA and National MS Society that most DMTs should not be used in MS patients who are pregnant or breastfeeding and should be discontinued at least 3 months prior to conception [108, 110].

IFN-βs, the oldest class of injectable DMT, are contraindicated in pregnancy and should be discontinued at least 3 months prior to conception [114]. Various animal studies show increased rates of miscarriage and spontaneous abortion with supra-therapeutic dosages (as high as 40 times the human therapeutic dose), leading to its category C rating by the FDA [114]. Certain reports show higher incidence of low birth weight and premature births in women incidentally exposed to these agents prior to conception or within the first trimester of pregnancy [110, 114, 117]. However, other studies do not confirm these findings such as the German Multiple Sclerosis and Pregnancy Registry, Betaseron Pregnancy Registry, or Avonex Pregnancy Exposure Registry [107, 114]. As a result, some providers still choose to continue interferon therapy up until conception, while others stop these agents at least 3 months prior [110]. The exact decision regarding discontinuation of therapy should be made between the provider and the patient and can be based largely on the severity of the patient's disease [108, 110].

Glatiramer acetate (GA) is the only MS disease-modifying agent labelled category B. It does not cross the placenta and is shown to be safe during both pregnancy and lactation [106–108, 114]. In animal studies and human case reports, exposure to this agent during conception and throughout pregnancy has shown no teratogenic effects to the growing fetus, including no association with congenital abnormalities, low birth weight, premature birth, or spontaneous abortion [107, 108, 114]. Being a large amino acid polymer, GA is unable to be absorbed through the neonatal gastrointestinal tract and is thus safe during lactation and breastfeeding [114].

Fingolimod is rated category C by the FDA due to strong evidence showing increased teratogenicity (cardiovascular malformations) and spontaneous abortions during pregnancy [106, 107, 110, 114]. This agent has the ability to cross the placenta and should be discontinued at least 3 months prior to conception [114]. Fingolimod takes at least 2 months to be completely eliminated from the body after drug discontinuation [108, 110]. MS patients wanting to become pregnant should be counseled on the importance of drug discontinuation prior to conception and informed of its negative effects on a growing fetus. In over 50 human exposure cases, this agent was associated with high rates of cardiovascular fetal malformations at birth including Tetralogy of Fallot, persistent truncus arteriosus, ventricular septal defects, and even fetal death [114, 118]. When used during conception and pregnancy, fingolimod likely precipitates cardiovascular malformations due to its action on specific sphingosine-1-phosphate receptors, which are involved in fetal angiogenesis [110]. As this drug is also secreted in breast milk, breastfeeding while using fingolimod is strongly contraindicated [114].

Dimethyl fumarate has been labeled category C by the FDA due to animal studies showing increased embryonic lethality at supra-therapeutic dosages (two times higher than the approved human dose) [114]. Limited data exists on the effects of this drug when taken during or after conception. However, no adverse effects were found in a case series of 45 women who were incidentally exposed to this therapy during the

first trimester of pregnancy [114, 119]. Despite this, based mainly on animal studies, consensus recommendations are to stop this DMT 3 months prior to conception. Due to its short half-life, at least 1 month is indicated prior to discontinuation. As effects on the growing neonate remain unclear, women are further advised to avoid breastfeeding while on this medication [114].

Teriflunomide is contraindicated during conception, pregnancy, and lactation. Due to its mechanism of action (inhibition of pyrimidine synthesis), this drug has increased teratogenicity during embryogenesis and is labeled category X by the FDA [107, 110, 114]. In animal studies, teriflunomide was able to cross the placenta and caused multiple fetal abnormalities (craniofacial, axial, and appendicular skeletal malformations) at doses lower than those used for MS therapy [114, 120]. However, human exposure studies have not shown serious malformations or increased rate of spontaneous abortions compared to the general population [107, 110]. Despite this, caution when using teriflunomide is still advised. A pregnancy test should be administered prior to initiation of this agent in female MS patients, and it should not be used in patients with unreliable methods of contraception [107, 114]. Moreover, small amounts of this drug are found in male semen, although it is not known to damage human sperm or affect male fertility [110, 114]. Because of its long half-life, teriflunomide may stay in a patient's body between 8 months and 2 years after drug cessation. Because of this, discontinuation of the drug is advised at least 2 years prior to conception and pregnancy in both male and female patients [110, 114]. In cases of unplanned pregnancy or conception desired within 1 year of DMT, the rate of drug elimination from the body can be increased with use of cholestyramine or activated charcoal [107, 110, 114]. Teriflunomide has also been detected in rat milk and is thus contraindicated during breastfeeding [110, 114].

Alemtuzumab is an anti-CD52 humanized monoclonal antibody labeled category C by the FDA. In animal studies, early use of alemtuzumab during conception and pregnancy leads to increased rates of fetal loss and decreased lymphocytes in offspring upon birth [121]. In a case series involving over 130 pregnant women (where conception occurred at least 4 months after last alemtuzumab infusion), there was no evidence of increased spontaneous abortions or birth defects [114, 120]. Since this drug has been found in milk of lactating mice, breastfeeding is strongly contraindicated [114].

Natalizumab is considered category C by the FDA, and consensus recommendations include discontinuation of this DMT 3 months prior to conception and during breastfeeding [107, 110, 114]. In animal studies, supra-therapeutic doses were shown to decrease fertility and reduce neonatal survival [114]. In humans, the *Tysabri Pregnancy Exposure Registry*, which enrolled 369 MS patients exposed to the drug, showed minimal increase in spontaneous abortions and fetal malformations when compared to the general population. However, transient hematologic abnormalities were observed in patients with severe MS who were on this medication during the second and third trimesters of pregnancy [107, 110, 114]. This DMT has been found in breast milk and should be avoided during breastfeeding [110, 114].

Rituximab (an anti-CD20 chimeric monoclonal antibody) and ocrelizumab (the humanized version of rituximab) are labeled category C by the FDA [114]. Animal studies demonstrate that rituximab crosses the placenta but show no increased risk of spontaneous abortions or teratogenicity. However, transient B-cell depletion was observed in newborns when mothers were exposed to the drug during the second or third pregnancy trimesters [114, 122]. Ocrelizumab is a relatively newer agent with limited information available regarding its effect on the developing fetus and on the neonate while breastfeeding. Due to its unknown effects, patients are currently advised to discontinue treatment 6 months prior to conception and to avoid use while breastfeeding [114].

All chemotherapeutic agents are contraindicated in pregnancy and lactation and should be discontinued at least 3 months prior to conception. Mitoxantrone and azathioprine are placed in FDA category D where azathioprine has been associ-

ated with increased risk of intrauterine growth retardation [108, 110]. Methotrexate (FDA category X) is known to be teratogenic and carries a high risk of spontaneous abortion [108, 110].

Overall, choosing when to discontinue disease-modifying agents prior to conception can be a difficult decision for many patients with MS due to the risk of relapse that may occur if therapy is held for a prolonged period [114]. For MS patients hoping to become pregnant, a visit should be scheduled at least 6 months to 1 year prior to conception to discuss the various risks and benefits of DMT [107]. The risk of relapse due to DMT discontinuation can often be offset by the reduced rate of relapse during pregnancy [107]. Regardless of the DMT, advice must be tailored to each individualized patient.

Managing Postpartum Relapse

Although MS relapse rates are known to decrease during pregnancy, numerous studies have shown higher rates of relapse in the 3 months postpartum [109, 110]. Acute disease exacerbation during this period has the potential to worsen postpartum depression or can interfere with the developing bond between both mother and child [110]. Three variables correlate with increased postpartum relapse: increased relapse rate in the year prior to pregnancy, increased relapse rate during pregnancy, and a higher Expanded Disability Status Scale score at pregnancy onset [109, 114]. In turn, women on DMT prior to or during conception and throughout pregnancy have shown lower relapse rates than those not on therapy [109]. Acute exacerbation in the postpartum period can effectively be treated with intravenous methylprednisolone [110, 123]. This is considered safe when breastfeeding as only small concentrations pass into milk from mother to child [123]. Based on retrospective studies, intravenous immunoglobulin can also be administered postpartum with no adverse effects and the ability to reduce relapse rates by about 50% [110, 124].

Limited evidence and no clear consensus exist on how to prevent postpartum relapse [109, 110]. After delivery, many practitioners decide to resume DMT; however, the optimal time to restart these agents remains unclear [109]. As discussed earlier, many maintenance therapies are contraindicated during breastfeeding. Although it is generally recommended to resume DMT in patients with highly active disease prepregnancy, there is evidence that exclusive breastfeeding reduces MS relapse [108, 125, 126]. A prospective study showed fivefold relapse rate reduction in patients who exclusively breastfed in the 2-month postpartum period [108, 110, 126]. However, earlier studies suggested no effect on postpartum relapse rates during lactation. Although this is still an area of controversy, the decision regarding breastfeeding versus reinitiation of DMT should be tailored to the individual and thoroughly discussed between patient and provider [108, 110].

Use of Medical Marijuana in Multiple Sclerosis Patients

Although cannabis has been used medicinally for thousands of years, evidence of its role in the treatment of multiple medical and psychiatric disorders has only recently begun to accumulate. Over the last several decades, many randomized clinical trials (RBCs) have attempted to test the effectiveness of cannabinoid-based medications in treating neuropathic pain, cancer pain, inflammation, spinal cord injury, spasticity in multiple sclerosis (MS), and other conditions [127]. Notably, most of these novel medications still lack government approval, which limits their clinical usage. Nonetheless, there is both anecdotal and scientific evidence that cannabis extract or cannabinoid-based medication may be beneficial in managing symptoms such as spasticity, chronic pain, and bladder function and may improve overall quality of life [128].

In the United States, about 20% of MS patients either inhale or ingest cannabis, while an estimated 1–4% of MS patients in the United Kingdom and 14–16% of patients in Canada use cannabinoid-based medications [129, 130]. Cannabinoids come in multiple formulations aside from inhaled marijuana. Cannabis extract,

dronabinol (Marinol), and nabilone (Cesamet) are orally administered, while nabiximols (Sativex) is administered through an oromucosal spray [131]. More than 60 cannabinoids have been identified from the *Cannabis sativa* flowering plant, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the major compounds [132]. The effects of cannabinoids are mediated through G protein-coupled receptors, specifically CB1 and CB2. Receptor activation inhibits adenylate cyclase, which converts cAMP to ATP and inhibits the release of neurotransmitters such as acetylcholine, dopamine, and glutamate [131]. The highest density of CB1 receptors is found in the cerebral cortex, cerebellum, basal ganglia, and hippocampus, while CB2 receptors are found not only predominantly in lymph tissue but also in the periaqueductal gray and other brain regions [131, 133, 134]. Cannabinoids also have indirect effects on opiate, serotonin, NMDA, and gamma-aminobutyric acid, which help explain the various physiologic responses seen with cannabis use [131].

THC is a partial CB1 receptor agonist shown to induce psychotic activity, analgesia, muscle relaxation, and hunger [135]. CBD, on the other hand, is a CB1/CB2 receptor antagonist with antipsychotic activity and has been shown to have anxiolytic, antioxidant, neuroprotective, and anticonvulsant effects [135]. Genetic knockout mice studies have demonstrated the neuroprotective effects of cannabinoids [136]. In relation to MS in particular, knockout models have shown that cannabinoids may improve inflammation, increase re-myelination of axons, and decrease apoptosis of oligodendrocytes [136].

The evidence around using cannabinoids as a therapeutic treatment for symptoms of MS is limited. However, a systemic review conducted by Nielsen et al. in February 2018 synthesizing the findings from high-quality 11 systemic reviews and 32 studies examining the efficacy and safety of cannabinoid use in MS found evidence that cannabinoids have modest efficacy in treating spasticity and chronic pain [137]. A meta-analysis of moderate-certainty evidence conducted by da Rovare et al. in 2017 including 16 placebo-controlled RCTs (2597 patients) found that cannabinoid use in MS patients is associated with non-statistically significant improvements in spasticity, cognitive function, and pain [128]. A systemic review and meta-analysis of the benefits and adverse events of cannabinoids for medical use conducted by Whiting et al. in 2015 including 79 RCTs (6462 patients) found that cannabinoid use in MS patients was correlated with non-statistically significant improvements in spasticity and chronic neuropathic pain [138]. Lastly, a systemic review of the safety and efficacy of cannabinoids in the treatment of MS and other neurological disorders conducted by Koppel et al. in 2014 found that cannabis extract is effective and nabiximols and THC are probably effective in reducing patient-centered measures of spasticity, central pain, and painful spasms [131].

Although spasticity affects the majority of MS patients at some point in their disease course, conventional antispastic agents are often not efficacious or have intolerable side effects. Currently, Sativex, which contains CBD and THC in a 1:1 ratio, is the only commercially available formulation of cannabinoids available to MS patients who have spasticity refractory to first-line antispastic therapies. A literature review by Giacoppo et al. found that Sativex is effective in treating spasticity and also improves quality of life. In addition, it has a low incidence of adverse effects. Additionally, a double-blind, placebo-controlled RCT conducted by Markovà et al. in 2018 found that using Sativex as an add-on therapy improved spasticity significantly more than adjusting conventional antispastic agents in resistant MS spasticity ($p < 0.01$) [138, 139].

Notably, research has consistently demonstrated that when compared to treatment with placebo or usual care, cannabinoids are associated with a significantly greater number of adverse effects such as headaches, dry mouth, dizziness, nausea, and somnolence [128, 138]. In addition, preliminary research with fMRI suggests that smoked cannabis may compromise information processing speed and memory, but in the absence of a high-quality clinical trial, the effects of cannabinoids on cognition are unknown [130]. Importantly, the side effects associated with can-

nabinoid use are considerably more tolerable than the side effects of conventional antispastic therapies such as baclofen, benzodiazepines, gabapentin, and tizanidine [128].

In summary, there is limited data on topics surrounding cannabis use in patients with MS despite the high prevalence of cannabinoid-related medications in the MS population across the globe. There is both anecdotal and scientific evidence that cannabis extracts may be effective in providing symptom relief for MS patients; however, more evidence in the form of large-scale RCTs is needed to better understand the effectiveness of cannabinoids in treating patient outcomes such as spasticity, pain, cognition, and bladder function. The classification of marijuana as a Schedule I drug in the United States makes research into its effects on MS and other neurological conditions more complicated, although more and more states are legalizing medical use of marijuana. Ultimately, it is up to individual physicians to weigh the constellation of evidence related to cannabinoid use and determine, for themselves, the role cannabis may play in patient care within the MS population.

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