

Managing Multiple Sclerosis: Treatment Initiation, Modification, and Sequencing

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ABSTRACT: Recent therapeutic advances in the management of multiple sclerosis (MS) have raised questions about the selection of appropriate patient candidates for various treatments and, if the plan is to move from one treatment to another, the appropriate sequencing of these therapies. The selected approach should provide optimal disease management without limiting future therapeutic options based on safety concerns, and recognize potential future treatments and the possibility of combination therapies. Additional challenges include incorporation of patient needs and preferences into the overall therapeutic approach, in order to ensure optimal outcomes in the short and long term. The objective of this manuscript is to provide an overview of what is currently known regarding the impact of various therapies for MS on future therapeutic choices (sequencing). In this context, we reviewed the available evidence in support of various treatments and, based on the presence of disease activity, suggested a scheme for switching or escalating therapy with the main focus on sequencing of therapeutic approaches.

RÉSUMÉ: **Prise en charge de la sclérose en plaques du début d'un traitement à sa modification : considérations par rapport aux séquences thérapeutiques envisagées.** Des avancées thérapeutiques récentes dans la prise en charge de la sclérose en plaques (SP) ont soulevé des questions relatives à la sélection appropriée de patients en regard avec divers traitements. Dans l'hypothèse où l'on opérerait pour une série de traitements, il y a aussi lieu de se questionner quant à la séquence la plus appropriée. À cet égard, toute approche thérapeutique devrait pouvoir fournir une prise en charge optimale de la maladie sans pour autant exclure d'autres traitements futurs en raison de préoccupations en matière de sécurité. Toute approche thérapeutique devrait aussi reconnaître l'existence de traitements potentiels et la possibilité de combiner des traitements. D'autres défis additionnels incluent notamment le fait d'incorporer les besoins et préférences des patients dans une approche d'ensemble afin d'assurer, à court et à long terme, une évolution optimale de leur état de santé. L'objectif de cette étude est donc de fournir un aperçu de l'état actuel des connaissances en ce qui a trait aux impacts des divers traitements de la SP quant à de futurs choix thérapeutiques (leur séquence). Dans cette perspective, nous nous sommes penchés sur des données probantes au sujet de ces divers traitements. Une fois des cas de SP détectés, nous avons suggéré un plan de modification ou d'intensification des traitements en mettant l'accent sur leur séquence.

Keywords: Multiple sclerosis, Long-term outcome, Relapsing remitting

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INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neurodegeneration.^{1,2} The disease is heterogeneous in its clinical manifestation and progression. The key pathological mechanism involves infiltration of autoreactive immune cells into the CNS where, with varying degrees of severity, they cause demyelination, gliosis, neuronal loss, and eventually cerebral atrophy.¹⁻⁴

Since the publication of the Canadian MS Working Group Updated Recommendations regarding treatment optimization in MS,⁵ several new therapies have become available while others are imminent. The advent of new therapeutic options has created a need for guidance on treatment sequencing, including algorithms to assist clinicians when deciding on therapeutic approaches for a particular patient. The selected approach should provide optimal disease management while not limiting future therapeutic options based on safety concerns. It should also recognize potential future treatments and the possibility of combinations.

Taking this into consideration, we developed an approach that assesses patients' risk for imminent progression (low vs. high) and

then evaluates their response to treatment (Figure 1) as outlined by Freedman et al.⁵

TREATMENT INITIATION

The clinical course of MS is highly variable, ranging from patients with relatively mild disease even years after the diagnosis to those with an early aggressive course and rapid accumulation of disability. Before initiating MS therapy, clinicians must consider the nature of the disease and long-term treatment plan, which is likely to be influenced by patient- and disease-related characteristics. Depending on the anticipated course of the disease, two different therapeutic approaches can be considered for treatment

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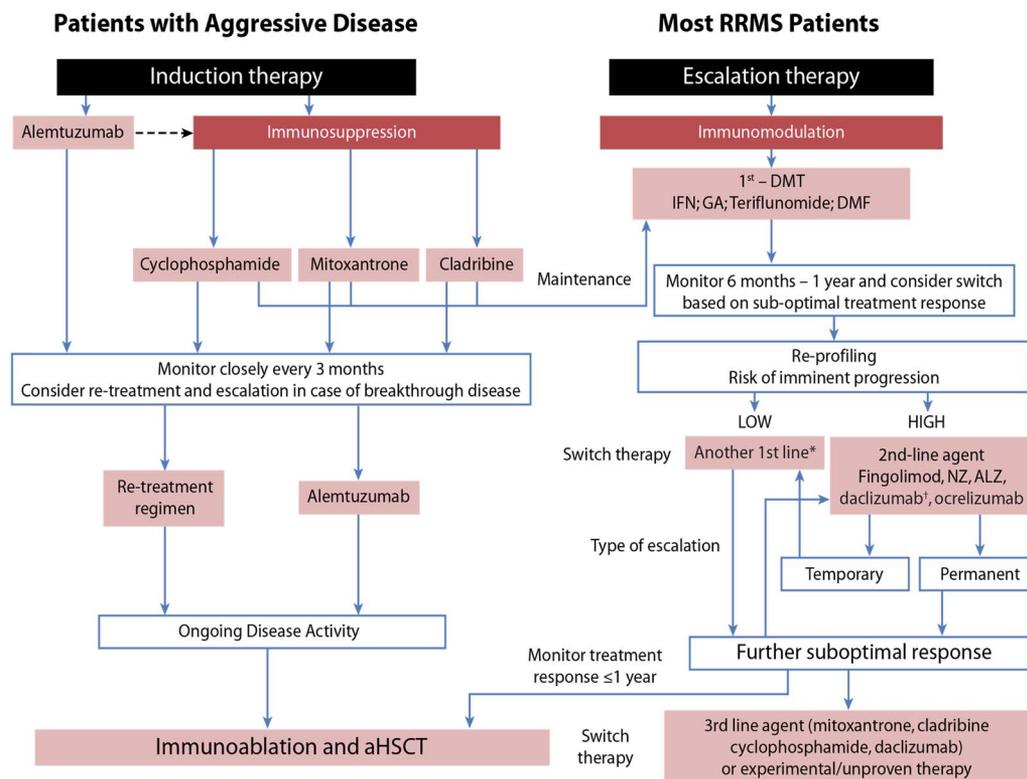


Figure 1: Sequencing algorithm. No monitoring and laboratory tests at baseline is requested when initiating or switching to glatiramer acetate (GA) and only thyroid testing, complete blood count and liver function test are necessary when starting or lateral switching patients to interferons (IFNs). *Tolerability is often a reason for a lateral switch. †Daclizumab was voluntarily removed from the market March 2, 2018 due to safety concerns.¹⁰² aHST = autologous hematopoietic stem-cell transplantation; ALZ = alemtuzumab; DMF = dimethyl fumarate; DMT = disease-modifying therapies; MS = multiple sclerosis; NZ = natalizumab; RRMS = relapsing remitting multiple sclerosis. Adapted with permission from Freedman et al⁵ and Rush et al.⁹

initiation: induction and escalation. In addition, as the treatment course may involve more than one agent, the optimal initial treatment should be one that does not limit subsequent therapeutic options.

Aggressive MS, affecting about 10% of MS patients, can be defined as disease leading to disability within 5 years from symptom onset and rapid transition to secondary progressive MS.^{6,7} As early aggressive disease activity drives long-term disability, it is extremely important that it be identified quickly and treated effectively (Table 1).^{8,9} Treatment of aggressive MS requires an aggressive approach (Figure 1) usually using agents more capable of eliminating disease-causing cells (immunosuppressive therapy) instead of those that only alter their functioning (immunomodulation) or prevent them from entering the brain without altering either their function or their numbers (anti-trafficking agents).

The selection of treatment(s) for even typical relapsing multiple sclerosis (RMS) has become very challenging because of the number and availability of therapies, including new agents with more complex mechanisms of action and greater risks of adverse effects that may also impact subsequent therapies. Although much remains unknown about the effects of moving between immunosuppressive and other disease-modifying therapies (DMTs), factors such as presence of co-morbidities, desire for pregnancy, previous use of other immunosuppressants (for MS

or other conditions), John Cunningham virus (JCV) antibody seropositivity, geographical parameters, health insurance coverage, and patient/neurologist preferences can influence the treatment selection and might also inform the sequencing of therapies. As the order in which treatments are used might predispose patients to increased long-term toxicity, all MS treatment strategies must be monitored to gather more safety data.

Based on the way they affect disease-causing cells, currently available therapies for MS can be divided into: (1) immunomodulators (interferon beta [IFN- β], glatiramer acetate [GA], dimethyl fumarate [DMF], teriflunomide [also a mild cell-depleting agent], daclizumab); (2) anti-trafficking agents (natalizumab, fingolimod); and (3) immune cell-depleting agents (mitoxantrone, cyclophosphamide, cladribine, ocrelizumab, alemtuzumab) (Table 2).¹⁰⁻²⁵

The mechanisms of action of different agents may also contribute to the potential risk of specific toxicities.^{26,27} In the context of sequencing, some mechanisms of action might be considered complementary whereas others might indicate increased risk. For example, the use of natalizumab confers a greater risk of progressive multifocal leukoencephalopathy (PML),²⁸ so possibly using it after another drug that has PML as a potential side effect such as DMF may confer additive PML risk. Contrast that with the use of teriflunomide, both an immunomodulator and mild cell-depleting agent, together with IFN- β , a combination shown to be

Table 1: Clinical and radiological factors suggestive of aggressive multiple sclerosis (MS)^{8,9}

Clinical features	
Demographics	
Male sex	
Older age (>40 years) at onset	
African American	
African-Latin American	
Relapse severity	
≥1-point change on EDSS, ≥2-points change on any individual functional system, or ≥1-point change on any two functional systems	
Steroid requirement	
Hospitalization	
Type of attack	
Multifocal	
Partial or incomplete recovery	
Attack affects motor, cerebellar, sphincteric, or cognitive functions	
Relapse frequency	
Frequent relapses in the first 2-5 years	
Short inter-attack interval	
Disease course	
Rapid accrual of disability, e.g., EDSS score of 3.0 within 5 years, with superimposed relapses	
MRI features	
At onset	
High T2 lesion burden	
More than two gadolinium-enhancing lesions	
Presence of T1 lesions ('black holes')	
Early discernable atrophy	
Infratentorial lesions	
At follow-up	
Presence of new T2 lesions	
One or more new gadolinium-enhancing lesions	

EDSS = Expanded Disability Status Scale.

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both safe and synergistic.²⁹ However, if the mechanism of action of an agent like GA is to produce regulatory cells that need to reach the CNS in order to work, then concomitant use of an anti-trafficking drug might counteract that ability.³⁰⁻³² On the other hand, based on their unique mechanisms of action, one could speculate that fingolimod followed by GA might be an "ideal sequence." Fingolimod might act first to round up all disease-causing cells and sequester them in lymph nodes,^{33,34} where GA has its greatest action and shifts T cells from a mostly pro-inflammatory T helper (Th) 1 pattern of cytokine secretion to a mostly anti-inflammatory Th2 pattern.³⁵

Induction Therapies: Cell-Depleting Agents and their Impact on Sequential Therapeutic Approaches

Induction therapy refers to the use of powerful cell-depleting therapy capable of eliminating disease-causing autoimmune cells up front in patients presenting with early active aggressive disease (~10 % of MS patients).³⁶ Evidence from experimental models of MS and other immune-mediated diseases suggests that this type of approach might "reset" the immune system to prevent epitope spreading and control inflammatory disease activity more effectively than immunomodulation, thus preventing early structural

damage, controlling disease progression, and preserving brain function.³⁷ However, the duration of the induction treatment is often limited by specific toxicity and by cumulative doses.³⁸ Serious side effects related to potent immunosuppressants such as mitoxantrone and cyclophosphamide are dose related, which is often a limiting factor.³⁸ In the case of mitoxantrone, the risk of cardiotoxicity appears proportional to the total lifetime cumulative dose and it is increased in patients with a history of cardiac disease. In addition to cardiotoxicity, blood malignancies have been associated with mitoxantrone. Consequently, a complete blood count is recommended before each dose and each year after mitoxantrone treatment. Due to these serious safety concerns, lifetime cumulative doses of mitoxantrone should not exceed 140 mg/m². Mitoxantrone exerts its therapeutic effect in MS through the inhibition of proliferation of B and T lymphocytes and macrophages.³⁸ In addition, several other immunosuppressive effects have been described, such as decreased secretion of IFN- β , tumor necrosis factor- α , and interleukin (IL)-2.³⁸ A full course of mitoxantrone treatment can stabilize patients with aggressive MS for 5 years or more.³⁹ However, due to its long-term safety concern, lifetime exposure to mitoxantrone is limited.⁴⁰ If maximal lifetime doses are reached, patients may require maintenance therapy with a DMT. It has been suggested that a short course of mitoxantrone followed by a first-generation immunomodulator (GA or IFN) after clinical stabilization of the disease may be an appropriate treatment strategy.³⁹⁻⁴¹ However, due to potential toxicity and the emergence of other options mitoxantrone is now rarely used.

Alemtuzumab, a humanized monoclonal antibody that reduces circulating cluster of differentiation (CD) 52-positive cells, is another reasonable induction strategy.⁴² It can be used for a set number of courses and re-treatment is needed only in the context of return of disease activity.⁴³ With alemtuzumab, CD52 cell depletion is sustained for up to 1 year, followed by lymphocyte repopulation and homeostatic resetting of the immune system. The biggest concern with this agent is the emergence of new autoimmune disorders, which occur in approximately one-third of patients and can develop several years after the last dose.⁴⁴ Although the reason for this is unknown, it is speculated that it takes time for regulatory cells to return to normal.⁴⁵ Most autoimmune events with alemtuzumab are thyroid related and are generally mild or moderate and manageable with timely detection and treatment.⁴⁶ Unlike other agents with maximal lifetime exposure limits, alemtuzumab can be used beyond 2 years, as a 3-day annual treatment, in case of return of disease activity. A recent study demonstrated that alemtuzumab can also be used in patients previously treated with mitoxantrone.⁴⁷

Other approaches with high efficacy and more selective lymphocyte depletion include agents such as cyclophosphamide. Cyclophosphamide is an alkylating agent that binds to deoxyribonucleic acid, interfering with mitosis and the cell cycle.^{48,49} Although extensive experience with cyclophosphamide in MS patients has been accumulated over the past 40 years, conclusive efficacy data are lacking.⁵⁰ Yet, because of the differential risk for leukemia with mitoxantrone, cyclophosphamide may be preferred to mitoxantrone as induction therapy in rapidly progressing patients.⁵¹ Cyclophosphamide should also be considered in the event that approved first- and second-line drugs fail or when fingolimod, natalizumab, or mitoxantrone are contraindicated.⁵² It is important to remember, however, that previous use of

Table 2: Immunosuppressants and immunomodulators in the treatment of relapsing remitting multiple sclerosis (RRMS): potential implication of differences in mechanisms of action

Agent (brand name)	Target/mechanism of action	Dose/frequency of administration	Study (phase; control)	Relapses/disease progression (RRR)	MRI outcomes	Main AEs	Most commonly used line of therapy	Sequencing considerations
Immunosuppressants								
Alemtuzumab (Lemtrada) sc	CD52 Recombinant humanized antibody	12 mg annual course	CARE-MS II (Phase III vs. sc IFN- β -1a) ¹⁰	ARR 0.26 vs. 0.52 with IFN- β -1a RRR 42%	Reduction in new T2 MRI lesions: 32% fewer patients Reduction in Gd + MRI lesions: 61% fewer patients	Infusion reactions, cytopenia, secondary autoimmunity, infections	Induction; second or third line	The biggest concern is the emergence of new autoimmune disorders Can be used beyond 2 years, as a 3-day annual treatment, in case of return of disease activity A recent study demonstrated that alemtuzumab can also be used in patients previously treated with mitoxantrone ⁴⁷ When switching from fingolimod to alemtuzumab, a minimum 4-week washout period is advised When switching from natalizumab to alemtuzumab a bridging strategy with an alternative DMT may be used to prevent reactivation of the disease
Cladribine (Mavenclad)	A synthetic analogue of deoxyadenosine that preferentially reduces circulating T and B lymphocytes	CLARITY trial: tablets 3.5 mg/kg or 5.25 mg/kg	CLARITY (Phase III vs. placebo) ¹¹	ARR 0.15 vs. 0.33 with placebo RRR 31%	Reduction in new T2 MRI lesions: 75% Reduction in Gd + MRI lesions: 87%	Lymphocytopenia, herpes zoster; isolated cases of malignancy were reported	Induction; second or third	There are some concerns about the durability of therapy but re-treatment after 1-2 years is possible Risk of malignancy is potential concern
Cyclophosphamide iv	An alkylating agent that binds to DNA, interfering with mitosis and the cell cycle	700 mg/m ² monthly	Northeast Cooperative MS Treatment Group trial (iv cyclophosphamide induction with or without outpatient iv cyclophosphamide boosters (700 mg/m ² every other month for 2 years) ¹² The Canadian Cooperative Multiple Sclerosis Study Group ³ (prospective, double-blind, placebo-controlled, randomized trial) ¹³	TTTF after 1 year was significantly prolonged in the booster vs. the non-booster group ($p = 0.03$) No statistically significant effect on disability progression at 2 and 3 years	Not reported	Nausea, vomiting; amenorrhea, infertility; alopecia	Induction; second or third	Myelotoxicity; hepatotoxicity; infections; hemorrhagic cystitis; bladder cancer
Mitoxantrone (Novantrone) sc	Intercalates with DNA; inhibits topoisomerase II	12 mg/m ² every 3 months until a maximum cumulative dose of 140 mg/m ² is reached	Randomised trial (IFN- β -1b) ¹⁴	ARR 0.44 vs. 1.15 for IFN- β -1a RRR 65%	Patients without Gd-enhancing lesions at 3 years; 75%	URTI, leucopenia, nausea	Induction; second or third	Myelotoxicity; infections; cardiotoxicity; acute leukemia The risk of cardiotoxicity appears proportional to the total lifetime cumulative dose and it is increased in patients with a history of cardiac disease Lifetime cumulative doses of mitoxantrone should not exceed 140 mg/m ²

Ocrelizumab (Ocrelizumab) iv	CD20 Recombinant humanized antibody	Not approved by Health Canada for MS	OPERA I and OPERA II (Phase III vs. IFN- β -1a) ¹⁵	ARR 0.16 vs. 0.29 with IFN- β -1a RRR 40%	Reduction in Gd + MRI lesions: 95% Reduction in new T2 MRI lesions: 80%	infusion-related reaction, nasopharyngitis, URTI, headache, UTI, malignancy**	Induction; second or third line	Potential increase in risk of cancer (to be confirmed)
First-generation injectable immunomodulators								
Glatiramer acetate (Copaxone) sc	Amino acid copolymer, shifts innate and adaptive immune responses toward anti-inflammatory pathway	20 mg daily or 40 mg 3 \times /week	Copolymer 1 MS Study Group (Phase III placebo) ¹⁶	ARR 0.59 vs. 0.84 with placebo RRR 12%	Reduction in new T2 and Gd + MRI activity: 30%	Injection-site reactions; post-injection reaction (chest pain, flushing and dyspnea)	First line	Cutaneous lipoatrophy, anaphylaxis (rare)
IFN- β -1b (Extavia) sc	Modulates expression of anti-and pro-inflammatory cytokines; reduces trafficking of inflammatory cells across blood-brain barrier	250 μ g every other day	The IFNB MS Study Group ¹⁷	ARR 0.43 RRR 29%	Reduction in new T2 and Gd + MRI activity: 83%	The most common side effects of IFN- β include injection-site reactions (redness, pain, pruritus, swelling, lump) and flulike symptoms (low-grade fever, chills, myalgia, arthralgia, fatigue)	First line	Leukopenia, liver or thyroid abnormalities, depression
IFN- β -1a (Avonex) im		30 μ g weekly	MSCRG (Phase III placebo) ¹⁸	ARR 0.29 RRR 37%	Reduction in new T2 and Gd + MRI activity: 52%			
IFN- β -1a (Rebif) sc		22/44 μ g 3 \times /week	PRISM (Phase III placebo) ¹⁹	ARR 0.37/0.42 RRR 30%	Reduction in new T2 and Gd + MRI activity: 78%			
Pegylated IFN- β -1a (Plegridy) sc		125 μ g every 2 weeks	ADVANCE (Phase III placebo) ²⁰	ARR 0.18 vs. 0.49 with placebo RRR 38%	New or newly enlarging T2 hyperintense lesions: mean 3.6 vs. 10.9 placebo			
Oral immunomodulators								
Dimethyl Fumarate (Tecfidera) oral	Nuclear-related factor-2/inhibits T cell antigen presentation; shifts T cells toward an anti-inflammatory cytokine profile; promotes antioxidant responses	240 mg twice a day	DEFINE (Phase III placebo) ²¹	ARR 0.17 vs. 0.36 with placebo RRR 38%	Reduction in new T2 MRI lesions: 85% Reduction in Gd + MRI lesions: 90%	GI symptoms, flushing, LFT \uparrow Lymphopenia, UTI	First line	Lymphopenia; progressive multifocal leukoencephalopathy
Fingolimod (Gilenya) oral	Sphingosine 1-phosphate receptor/ leads to receptor downregulation in lymph nodes, preventing egress of certain populations of lymphocytes in the circulation	0.5 mg/daily	TRANSFORMS (Phase III; i.m. IFN- β -1a) ²³	ARR 0.18 vs. 0.33 with IFN- β -1a RRR 30%	Reduction in new T2 MRI lesions: 74% Reduction in Gd + MRI lesions: 82%	Bradycardia, AVB, macular edema, infections, BP \uparrow , lymphopenia, LFT \uparrow	Second line	Risk of lymphopenia; viral infections; cardiac effects; liver enzyme elevations, macular edema and isolated cases of PML When switching from fingolimod to alemtuzumab, a minimum 4-week washout period is advised

Table 2: *Continued*

Agent (brand name)	Target/mechanism of action	Dose/frequency of administration	Study (phase; control)	Relapses/disease progression (RRR)	MRI outcomes	Main AEs	Most commonly used line of therapy	Sequencing considerations
Teriflunomide (Aubagio) oral	Dihydroorotate dehydrogenase (DHODH)/DHODH is relevant for <i>de novo</i> synthesis of pyrimidine; cytostatic effect on proliferating B and T cells	14 mg daily	TEMSO (Phase III placebo) ²²	AAR 0.37 vs. 0.54 with placebo RRR 30%	Reduction in new T2 MRI lesions: 67% Reduction in Gd + MRI lesions: 80%	GI symptoms, alopecia, BP ↑, LFT↑, PN	First line	Myelotoxicity; hepatotoxicity; infections; peripheral neuropathy; pancreatic fibrosis; teratogenicity (requires accelerated elimination procedure)
Injectable immunomodulators								
Daclizumab (Zinbrya) sc*	CD25	150 mg every 4 weeks	DECIDE (Phase III vs. im IFN-β-1a) ²⁴	ARR 0.22 vs. 0.39 with im IFN-β-1a RRR 25%	Reduction in new T2 MRI lesions: 54% Reduction in Gd + MRI lesions: 65%	Infections, cutaneous events, LFT↑	Second or third line	Recommended as 2nd or 3rd line of therapy
Natalizumab (Tysabri) iv	Very late antigen-4 Blocks transmigration of T cells into the CNS	300 mg iv every 4 weeks	AFFIRM (Phase III; placebo) ²⁵	ARR 0.23 vs. 0.73 with placebo RRR 42%	Reduction in new T2 MRI lesions: 83% Reduction in Gd + MRI lesions: 90 %	Infections (PML, Herpes), infusion reactions, hepatotoxicity	Second line	Rebound and return of activity after treatment interruption Risk of PML Duration of washout period when switching to another treatment is of a concern—assess risk of rebound vs. risk of PML When switching from natalizumab to alemtuzumab a bridging strategy with an alternative DMT may be used to prevent reactivation of the disease

*Daclizumab was voluntarily removed from the market March 2, 2018 due to safety concerns.¹⁰² **The true risk of malignancy, particularly breast cancer, requires further data. ARR = annualized relapse rate; BP = blood pressure; CD = cluster of differentiation; DMF = dimethyl fumarate; DMT = disease-modifying therapy; Gd = gadolinium; GI = gastrointestinal; im = intramuscular; INF = interferon beta; iv = intravenous; LFT = liver function tests; PML = progressive multifocal leukoencephalopathy; PN = peripheral neuropathy; RRR = relative risk reduction; sc = subcutaneous; TTF = time to treatment failure; URTI = upper respiratory tract infections; UTI = urinary tract infection.

non-selective immunosuppressive drugs increases the risk of PML in natalizumab-treated patients²⁸ and may also confer risk of PML with other agents such as DMF or fingolimod.⁵³⁻⁵⁵

Cladribine, a synthetic purine nucleoside and antimetabolite that acts as an antineoplastic agent with immunosuppressive effects, might be used in a similar manner to alemtuzumab.^{56,57} Animal data suggest that the drug is capable of crossing the blood-brain barrier,⁵⁸ and it was found to be beneficial for patients with RMS.^{13,59,60} Cladribine is an option for patients with aggressive MS,⁶¹ although the cladribine tablet formulation was previously rejected in 2011 because of malignancy concerns.⁶² A recent meta-analysis of Phase III trials of licensed DMTs for MS and the CLARITY trial did not support an increased cancer risk from cladribine in the doses used in CLARITY.⁶³ The latest data from the extension phase of CLARITY showed that two to four short oral courses (one dose per day for 4-5 days) of cladribine in year 1 and two short courses in year 2 were associated with durable efficacy.⁶⁴ There are some data concerning the durability of therapy but re-treatment after 1-2 years is possible. Cladribine tablets have now been approved in Europe and Canada for RMS^{65,66}

Escalation Therapies: Immunomodulators and their Impact on Sequential Therapeutic Approaches

Due to the limitations of immunosuppressive/ablative therapies, disease-causing cells may not be completely eliminated in many cases, resulting in breakthrough disease. In some instances, re-treatment with another course of the same therapy may be possible (e.g. alemtuzumab, cladribine). Given the risk of disease return, an appropriate alternative is to consider long-term maintenance following induction therapy, generally with safer immunomodulatory agents, to extend the benefit obtained with aggressive treatment; but such an approach has not been subjected to any form of rigorous study to date. The concept of escalation and maintenance therapy represents a strategy that gives precedence to safety over efficacy and, if necessary, to sequentially advance in the treatment pyramid.⁶⁷⁻⁶⁹ In this approach, individuals start with first-line agents and are switched to second- or even third-line agents if they exhibit breakthrough disease that pushes them from low to high in terms of the risk for imminent disease progression. For the purpose of this paper, the definitions and categorization of MS medications as first-, second-, and third-line drugs previously outlined in Freedman et al⁵ have been used. It should be noted that the designation of first, second, and third-line agents is not evidence-based as all of the available treatments licensed for MS have been studied primarily as first-line agents. Escalation and maintenance therapy is appropriate for most patients with non-aggressive RMS, provided that they are closely monitored to detect suboptimal response or disease progression.

Sequential DMT monotherapy is currently the most common treatment strategy for RMS with injectables such as IFN- β or GA, along with teriflunomide or DMF being the most frequently used first-line therapies. Injectable IFN- β or GA as well as teriflunomide and cladribine have approved indications not only for patients with RMS but also for those with early MS, including patients with clinically isolated syndrome who are at high risk for the development of more active MS.⁸ Recent evidence indicates that early initiation of DMT is beneficial over the long term, resulting in significant reduction of long-term disability.^{5,36,43,67-70}

Although the injectable mode of administration of IFN- β or GA may be inconvenient for some patients, it is important to keep in mind the wealth of experience with these drugs in regard to dosing and toxicity management. Newer formulations have attempted to increase convenience with a pegylated version of IFN- β used every 2 weeks⁷¹ and a new formulation of GA taken just thrice weekly.⁷² With DMF, for example, the management of severe flushing and/or gastrointestinal toxicities continues to be a problem and efforts continue to reduce these side effects.⁷³ The DEFINE study suggested that half dose for 1 month (240 mg daily dose)⁷⁴ is more appropriate in regard to achieving desirable gastrointestinal tolerability than the extended titration (120 mg 3 \times /day 360 mg daily dose).⁷⁵ However, doses lower than 240 mg daily are not as effective in reducing brain MRI activity.⁷⁶

First-generation immunomodulators also have well-established short- and long-term safety profiles. Therefore, even if new oral first-line drugs such as teriflunomide⁷⁷ and DMF⁷⁸ may appear more convenient from the patient perspective and have a positive effect on treatment adherence and the patient's quality of life,⁷⁹ it is important to keep in mind that there are still significant uncertainties regarding their long-term effects.

Several cases of PML have been reported with DMF, some of which were not related to previous use of immunosuppressants.^{53,54} In most, but not all cases, the patients had low lymphocyte counts (grade 2 or 3 lymphopenia).^{53,80} Lymphopenia is a frequent outcome of DMF therapy and in clinical practice lymphopenia appears to be more common than reported in clinical trials. A retrospective cohort study of 221 patients prescribed DMF at a single academic medical center suggested that the cumulative incidence of grade 3 lymphopenia exceeds 20% in adults older than 55 years; combined grade 2 and 3 lymphopenia developed in more than 40% of patients in this age group.⁸¹ A higher risk of lymphopenia was noted in patients switching to DMF from natalizumab therapy and in those with lower baseline lymphocyte counts. Fingolimod and natalizumab are involved in immune cell trafficking that impedes lymphocyte migration across the blood-brain barrier (natalizumab) and/or from exiting lymph nodes into the circulation (fingolimod), preventing CNS inflammation.⁸² While these therapies may offer substantial efficacy as a consequence of their mechanism of action, their alteration of lymphocyte distribution may influence immune surveillance and increase the risk of infections and PML.

There have been very few "head-to-head" studies using DMTs. High-dose IFN- β 1a given subcutaneously three times per week (tiw) has been proven superior to the once-weekly intramuscular IFN- β 1a.⁸³ Fingolimod was shown to be superior to intramuscular once-weekly IFN- β 1a,²³ daclizumab is superior to once-weekly IFN- β 1a²⁵ and both alemtuzumab⁸⁴ and ocrelizumab⁸⁵ were proven superior to subcutaneous IFN- β 1a tiw. Although natalizumab is believed to be more potent on clinical and MRI outcomes than first-line injectable immunomodulators,⁸⁶ this has never been shown in properly controlled studies, but is substantiated only with large, "real world" observational data sets.⁸⁷

With respect to escalation from either IFN- β or GA to natalizumab, retrospective and observational studies have indicated that switching is associated with a significant reduction in clinical and radiological activity.⁸⁸⁻⁹⁰ A switch from IFN- β to fingolimod has also been shown to produce significant reductions in clinical and radiological activity.⁹¹ However, no large head-to-head studies or evidence-based criteria exist to guide the choice between

fingolimod and natalizumab. Thus, apart from the presence/absence of anti-JCV antibodies (researched only in the context of natalizumab) the choice is empirical, although some small, observational, uncontrolled studies suggest that natalizumab may be superior to fingolimod in RMS patients not responding to first-line agents.⁹²⁻⁹⁵ According to the recent report from the MSBase registry, alemtuzumab and natalizumab seem to have similar effects on annualized relapse rates in RMS. While alemtuzumab was superior to fingolimod and IFN- β in mitigating relapse activity, natalizumab was superior to alemtuzumab in enabling recovery from disability. Thus, according to the investigators, treatment decisions between alemtuzumab and natalizumab should be primarily governed by their safety profiles.⁹⁶

Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20. The superior efficacy of ocrelizumab over IFN- β 1a was proven in two Phase III clinical trials OPERA 1 and OPERA 2 that included ~800 patients with RMS.¹⁴ However, four neoplasms (two breast cancers, one renal cancer, and one melanoma) occurred in patients treated with ocrelizumab (0.5%) versus two occurrences in the IFN- β 1a group (0.2%). Five additional malignancies were also detected during the open-label extension phase. In the ORATORIO trial involving patients with primary progressive MS, 11 neoplasms were reported, four of which were breast cancer.⁹⁷ Thus, long-term follow-up with larger numbers of patients will be necessary to assess these risks more fully. Similar to malignancies observed with cladribine, it is unknown whether the cancer risk is idiosyncratic or related to the duration of therapy. Ocrelizumab was recently approved by Health Canada for the treatment of adult patients with RMS, with active disease defined by clinical and imaging features.⁹⁸

Daclizumab is a humanized IgG1 monoclonal antibody directed against CD25, the alpha subunit of the high-affinity IL-2 receptor.⁹⁹ As demonstrated in the Phase III DECIDE trial, 25 mg once-monthly subcutaneous daclizumab was superior to once-weekly intramuscular IFN- β -1a in reducing the clinical relapse rate and radiological measures of disease in patients with RMS. In addition, daclizumab has demonstrated efficacy in reducing disability progression and in improving health-related quality of life. Toxicity profile includes hepatic, infectious, and cutaneous events. Despite its availability, the place of daclizumab, functioning mainly as an immunomodulator in MS treatment remains to be fully determined. Based on available evidence, EMA advised against using daclizumab in patients with pre-existing hepatic disease or hepatic impairment and in patients with autoimmune diseases other than MS, and they urge caution when using the drug in combination with drugs that can damage the liver.¹⁰⁰ In Canada, daclizumab was approved as second- or third-line option.¹⁰¹ However, as of March 2, 2018, Biogen and AbbVie voluntarily removed daclizumab from the market worldwide due to safety concerns voiced by the European Medicines Agency after 8 patients in Europe presented with encephalitis and/or meningoencephalitis.¹⁰²

Suggested Strategies to Decrease the Risk of PML with Natalizumab

The increased risk of the development of PML with different DMTs, especially natalizumab, is well established.⁵³ As of December 7, 2017, there have been 756 confirmed PML cases (753 MS, three Crohn's Disease).¹⁰³ As of November 30, 2017, ~177,800 patients received natalizumab, yielding an incidence of

4.22 in 1000 treated patients. The global overall incidence of PML in natalizumab-treated patients is 4.22 per 1000 patients (95% confidence interval 3.93-4.54 per 1000 patients).¹⁰³ The risk is particularly high in patients treated with natalizumab for longer than 12 months, those who had previous exposure to immunosuppressive therapies, and those with a high anti-JCV antibody index.¹⁰³⁻¹⁰⁵ With the availability of several other DMTs, it is now possible to reduce the risk of PML by switching JCV-seropositive patients treated with natalizumab to another agent. One caveat is that previous exposure to natalizumab may have prolonged effect risk, also referred to as "carryover PML."¹⁰⁶⁻¹⁰⁸ Carryover PML is the result of the complex pathogenesis of PML, which develops over months to years.¹⁰⁴ One strategy to reduce the risk of carryover PML is to washout natalizumab before starting another DMT, allowing immune reconstitution of the CNS.¹⁰⁶ The obvious downside of this strategy is rebound effect and return of disease activity.^{108,109} To overcome this risk, several approaches have been tried.¹¹⁰⁻¹¹³ Yet, currently the only effective method to prevent rebound appears to be either fingolimod¹¹² or teriflunomide¹¹³ without any washout period. It is important to be aware that the risk of PML after stopping natalizumab is unlikely to disappear completely.

As JCV reactivation in the CNS is not fully understood, clinical pharmacovigilance is warranted as there might be a risk from either current or previous therapy. Furthermore, it appears that, despite stratification algorithms and the available test for JCV serology, the incidence of PML in natalizumab-treated MS patients has continued to increase, likely because patients are kept on the drug too long.^{114,115} In their recent editorial, Mowry and McArthur¹¹⁵ suggest the development of Apps or online calculators for PML risk, as has been done for cardiovascular risk. Clinicians need to acknowledge that the incidence of PML remains high and not to rely on cutpoints, but rather appreciate that risk continues to accumulate with increased treatment duration. Given that PML may develop even after natalizumab discontinuation, it is possible that the longer a patient waits after becoming JCV antibody-positive before switching, the higher the risk of PML will become.¹¹⁵

COURSE TO FOLLOW WHEN CONSIDERING TREATMENT MODIFICATION

Factors to Consider When Moving to the Next Line of Therapy

The excitement surrounding new effective DMTs is tempered by concerns about both known and unknown additional risks. Although in many instances the rationale after relapse is to try a DMT with a different mechanism of action, the impact of a previous therapy on potential toxicity profile needs to be considered. In addition, washout period and potential for rebound effect present additional challenges when moving to the next line of therapy. For example, as fingolimod traps lymphocytes in the lymph nodes,¹¹⁶ efficacy of subsequent agents that target circulating lymphocytes such as alemtuzumab¹¹⁷ may be compromised. Fingolimod has a pharmacologic half-life of 6-9 days and lymphocytes would be expected to normalize 2-4 weeks after discontinuation.¹¹⁸ Therefore, it is recommended to stop fingolimod for 4 weeks, checking peripheral lymphocyte counts to ensure that they are returning towards normal before giving the first course of alemtuzumab, in order to maximize its effect on

circulating lymphocytes.¹⁰⁷ From a safety standpoint, moving from natalizumab or fingolimod (and probably DMF)—agents that have proven in monotherapy to cause PML—to alemtuzumab requires additional consideration. Should latent PML (i.e. active copies of JCV) be present and a patient switched to alemtuzumab, the patient will be immunocompromised and the PML can be life threatening. Such patients should probably undergo a lumbar puncture, with measurement of CSF for JCV polymerase chain reaction, before starting alemtuzumab or any other potent immunosuppressant, as a precautionary measure.

Managing pregnancy-related issues in patients with RMS

The theoretical potential for teratogenicity is relevant for all DMT when considering the treatment of female patients of childbearing age, but the risk varies among agents. In general, patients should be advised to discontinue DMTs before conception although there are suggestions that IFN- β ¹¹⁹ and GA¹²⁰ can be continued throughout pregnancy in patients with severe or highly active disease. Fingolimod should be discontinued 2-3 months before the cessation of contraception,¹²¹ and evidence regarding the discontinuation of natalizumab is not clear considering the high risk of disease recurrence even during pregnancy.¹²² Teriflunomide is associated with a theoretical risk of teratogenicity, despite little evidence for this in the treatment of MS,¹²³ and the Food and Drug Administration regulation changed in regard to labeling all pharmaceuticals regarding the risk during pregnancy.¹²⁴ Most of the warnings for teriflunomide derive from those tagged to the parent drug, leflunomide, used for the treatment of rheumatoid arthritis.¹²⁵ Without going through an accelerated 11-day elimination procedure,¹²⁵ teriflunomide is eliminated slowly from plasma and it can take up to 2 years to achieve systemic clearance at a level where teratogenicity is theoretically unlikely. Across nine Phase II/III clinical studies with teriflunomide a total of 71 pregnancies were reported.¹²⁶ Upon learning of their pregnancies, patients were instructed to discontinue their study treatment and undergo an accelerated elimination procedure (cholestyramine or activated charcoal). In total, 44 of the 71 pregnancies were reported in patients exposed to teriflunomide; the remaining pregnancies occurred in patients treated with placebo, IFN- β , or blinded therapy. In the 17 live births, including 12 exposed to teriflunomide, no structural defects or functional deficits have been reported. The duration of fetal exposure was up to 11 weeks and newborns had birth weights between 2780 and 4150 g. Thus far there is no signal for teratogenicity in newborns with prenatal teriflunomide exposure following accelerated elimination although more prospective data are needed with respect to pregnancy outcomes. The recent report on the outcomes of pregnancies occurring in the teriflunomide clinical program ($n=69$ pregnancies) and in the post-marketing setting ($n=171$ pregnancies) confirmed these observations.¹²⁷

Tests to Obtain Before Attempting Treatment Modification

Detection of anti-JCV antibodies in serum or plasma using a two-step enzyme-linked immunosorbent assay has been proposed to stratify the risk of PML. Testing for JCV antibody status is recommended for all natalizumab candidates before treatment initiation as well as before starting a new therapy after having taken natalizumab, DMF, or fingolimod. Natalizumab is generally not recommended in patients who are JCV antibody-positive and

have received prior immunosuppressants, such as mitoxantrone or cyclophosphamide; however, the risk of other agents such as cladribine, alemtuzumab, or ocrelizumab are unknown.¹¹⁵

Patients considered for fingolimod should be assessed for cardiovascular disease, diabetes, and liver dysfunction. As fingolimod can also increase low-density lipoprotein and total cholesterol, evaluation of serum lipids should be part of routine monitoring for patients taking fingolimod.¹²⁸ As increased susceptibility to serious viral infections was noticed during the TRANSFORMS trial,²³ patients considering fingolimod should probably be vaccinated against the varicella zoster virus and immunity confirmed before initiating therapy.¹²⁸ Furthermore, due to the immunosuppressive mode of action of fingolimod, an increased awareness of infectious complications is required.^{129,130} Cases of cryptococcal infections, including cryptococcal meningitis, and systemic meningitis, have been reported in patients taking fingolimod.^{131,132}

Although a recent study found no increased risk of early relapse (within the first 6 months) following switch of patients previously stable on injectable therapy to oral treatment,¹³³ the longer-term (>6 months) risk of relapse is unknown. The long-term adverse event profile of most oral agents has yet to be established compared with the injectable immunomodulators IFN- β and GA.

Washout Period

Transitioning from one particular DMT to another can be complex, and a washout period may be required in certain circumstances. There is a paucity of data regarding the optimal washout period when switching from one agent to another. Furthermore, it is often unclear for which treatment transitions a washout period is required, how long it should last, or what long-term safety surveillance procedures should be implemented. Nevertheless, concomitant treatment within the washout period of the previous DMT is not advisable, owing to the potential risk of carry-over PML from previous treatment and additive effects on the immune system. Consequently, it is important to consider the half-life as well as the mechanism of action of the previous DMT when transitioning from one therapy to another.

In general, a washout period is not required when switching from first line injectable to any other treatment. As mentioned, an accelerated elimination protocol may be advisable when switching from teriflunomide to another agent due to the long half-life of the drug.¹²⁵

When switching from fingolimod to alemtuzumab, a minimum 4-week washout period is advised.^{101,134,135} Recent reports of patients treated with fingolimod who experienced significant rebound of disease activity when switched to alemtuzumab indicate that one must wait for lymphocytes to deseguester in order to get the most out of the first 5-day course of alemtuzumab.^{134,135} Because of the potential for PML in patients on fingolimod alone, it is imperative that PML be ruled out before initiating alemtuzumab for reasons outlined below. An “exit MRI” along with CSF for JCV PCR is strongly recommended.

The proposed mechanism of action of DMF (activation of the nuclear factor erythroid 2-related factor 2) would generally not foresee any issues with rapid transition to another therapy,¹³⁴ although DMF has also been shown to have a lymphopenic effect in certain patient populations.¹³⁶ Thus, similar to fingolimod, a washout period might be advisable when transitioning from DMF to

alemtuzumab.^{137,138} For both drugs, however, the time period over which lymphocytes return to normal is variable and can take many months, during which time the patient is at risk of relapse.¹³⁷ This is a significant challenge in sequencing from DMF. As DMF has also had cases of PML associated with it, an “exit MRI” and CSF for JCV PCR is recommended before initiating alemtuzumab (see below).

Teriflunomide is also associated with a reduction in lymphocytes and neutrophil counts. However, patients receiving teriflunomide have the opportunity to undergo an accelerated elimination procedure, potentially allowing the initiation of alemtuzumab relatively quickly after stopping teriflunomide.

As natalizumab does not reduce circulating lymphocyte counts, rather it blocks their entry to the CNS resulting in only mild lymphocytosis,^{137,138} there may be limited benefit in delaying initiating treatment with another DMT following natalizumab discontinuation.¹³⁸ It has also been suggested that starting

a new treatment immediately after stopping natalizumab (without washout period) may be more beneficial because the risk of developing PML is lower than the risk of a severe relapse.^{139,140}

However, despite preferred outcomes in the absence of a prolonged washout period after natalizumab, it is important when switching to confirm JCV status and exclude any PML carryover in JCV-positive patients by MRI and by cerebrospinal fluid examination for JCV DNA, before treatment initiation. This is of particular relevance when patients are switched from natalizumab to alemtuzumab as the effects of alemtuzumab cannot be reversed in the short term, and, if carry-over PML develop following alemtuzumab treatment, it is unlikely that full immune cell repopulation can occur and that patients will be unable to clear the virus. Thus, when switching from natalizumab to alemtuzumab, either this should occur swiftly, as soon as an “exit MRI” and CSF study ruling out JCV

Table 3: Level of concern according to the criteria for relapse, Expanded Disability Status Scale (EDSS) progression, and MRI findings⁵

Criteria	Level of concern		
	Low	Medium	High
Relapse			
Rate	1 relapse in the second year of treatment	1 relapse in the first year of treatment	>1 relapse in the first year of treatment
Severity	Mild Steroids not required Minimal effect on ADL 1 functional domain affected No or mild motor/cerebellar involvement	Moderate Steroids required Moderate effect on ADL >1 functional domain affected Moderate motor/cerebellar involvement	Severe Steroids/hospitalization required Severe effect on ADL >1 functional domain affected Severe motor/cerebellar involvement
Recovery (duration)	Prompt recovery No functional deficit	Incomplete recovery at 3 months Some functional impairment	Incomplete recovery at 6 months Functional impairment
EDSS progression			
EDSS score			
≤3.5	≤1 point	2 points at 6 months*	>2 points at 6 months* 2 points at 12 months*
4.0 to 5.0	<1 point	1 point at 6 months*	>1 point at 6 months* 1 point at 12 months*
>5.5		0.5 point at 6 months*	>0.5 point at 6 months
Clinically documented progression	No motor Minor sensory	Some motor, cerebellar, or cognitive Multiple EDSS domains affected	Pronounced motor, cerebellar, or cognitive Multiple EDSS domains affected
T25FW**	<20% confirmed at 6 months	>20% and <100% increase confirmed at 6 months	>100% increase confirmed at 6 months
MRI findings			
Activity on MRI*			
New Gd-enhancing lesions OR Accumulation of new T2 lesions per year	1 lesion	2 lesions	>3 lesions

ADL = activities of daily living

When considering a switch in therapy, whether it is a lateral switch between two agents in the same line of therapy (e.g., interferon beta [IFN-β] to glatiramer acetate [GA]) or treatment escalation to a second-line agent, clinicians should first determine if suboptimal treatment response warrants a switch in treatment. This can be done by determining the level of concern according to the criteria for relapse, EDSS progression, and MRI.

The level of concern should be reassessed and determined at regular follow-up intervals, typically every 6 or 12 months. Routine follow-up MRI with gadolinium (Gd) is recommended 6-12 months after initiating therapy for relapsing remitting multiple sclerosis (or in clinically isolated syndrome if therapy is not initiated). New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions. The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts. New T2 lesion counts require high-quality comparable MRI scans and interpretation by highly-qualified individuals.

*If EDSS progression alone is used to assess response to treatment, any change requires subsequent confirmation at 3-6 months.

**Timed 25-foot walk (T25FW) tested at baseline with aid, if required

by PCR are performed, or a bridging strategy with an alternative DMT may be required in the interim to prevent reactivation of the disease.

Given that there was a PML case described with ocrelizumab as a carryover from natalizumab¹⁴¹ switching from natalizumab to ocrelizumab should be done the same way as alemtuzumab with the same precautionary CSF analysis and MRI.

When switching from natalizumab to fingolimod, a washout period of > 3 months is associated with an increased risk of disease reactivation.¹⁴²⁻¹⁴⁴ The latest evidence suggests that no washout period is recommended.¹¹³ However, since both drugs carry a risk of PML, it would be important to perform an “exit MRI” and CSF for JCV PCR before initiating fingolimod as there have been many cases of “carry-over” PML from natalizumab-treated patients initiated on fingolimod.^{145,146}

Treatment Discontinuation

Sometimes RMS patients receiving DMT may decide to interrupt their therapy due to various personal reasons (e.g. travel, pregnancy). These patients should continue to be periodically monitored both clinically and by MRI. Pregnancy planning requires DMT discontinuation (unless the benefit to the mother outweighs the risk to the fetus) with the appropriate timing according to the drug-specific pharmacokinetics.¹⁴⁷ Discontinuation of anti-trafficking agents presents significant concern for a rebound syndrome.¹⁴⁸ Cases of fulminant relapse after stopping natalizumab, leading to death despite intensive care and immunosuppressive therapy, have been reported.¹⁰⁸ Rebound effect and the development of tumefactive demyelinating lesions were also reported in patients who stopped fingolimod in order to conceive.^{149,150}

Therefore, patients should be cautioned that some medications pose additional issues upon discontinuation. This is important especially in pregnancy planning as a bridging strategy to prevent rebound might be initiated before discontinuing anti-trafficking agents. If disease worsening is detected in patients who stopped their DMT, the decision to restart the treatment should be revisited.

Combination Therapy

Combination therapy, allowing for treatments with different mechanisms of action to accomplish better disease control, could

be an effective strategy for MS. However, limited evidence, concerns regarding potential additive effects, increased risk of toxicity, and cost concerns are all obstacles to wider uptake of combination therapy in MS. According to Phase II data, some combinations are both highly effective and safe, at least in the short term.^{151,152} Combined teriflunomide and IFN- β produce additive responses, especially on MRI.¹⁵² The combination of natalizumab and GA appeared safe and well tolerated during 6 months of therapy.¹⁵² Currently, cost is one of the main reasons prohibiting combination therapy, despite the fact that some combinations might well afford synergy due to their different mechanisms of action.

Evaluating Treatment Response

A full review of methodologies to evaluate treatment response to disease-modifying medication is beyond the scope of this paper. However, recommendations for the clinical assessment of relapses, which comprise relapse rate, severity, and recovery, have been outlined previously by Freedman et al (Table 3).⁵ Critical factors affecting the decision of changing the current DMT are listed in Table 4.²⁶ A new MRI with gadolinium is recommended 6-12 months after treatment initiation or switching to establish a new “reference” MRI for future comparison.^{5,126} Typically another MRI is recommended within a year of the new “reference” scan for full evaluation of treatment response.

CONCLUSION

The availability of new treatment options for MS provides an opportunity for improving long-term clinical outcomes. However, it has also made patient management more complex. The suggestions regarding the sequencing of MS therapies outlined in this manuscript were developed to assist clinical neurologists in their management of RMS patients.

When switching the RMS patient from one therapy to another, it is essential to consider cumulative toxicities. At the same time risk of disease reactivation and rebound effect need to be taken into consideration should too much time pass between stopping one agent and starting the next. The patient should undergo full general and neurological examinations and laboratory measurements, as well as getting either an “exit MRI” (in the case of PML

Table 4: Factors affecting the decision to modify disease-modifying therapies (DMT) for multiple sclerosis²⁶

Factors suggesting a switch from a first-line DMT to another first line (lateral switch)	Tolerability/safety issues Suboptimal efficacy with suboptimal response but still a low risk for imminent progression
Factors suggesting a switch from a first-line to a second-line DMT (i.e. escalation)	Anyone with a suboptimal response as defined by the Canadian TOR ⁵ to first-line DMT who has a moderate-higher risk for progression (as opposed to low risk) RRMS patients transitioning to the secondary progressive phase with evidence of relapses or MRI activity (such patients can also be considered for induction therapy)
Factors suggesting a switch from a second-line DMT to a third-line or higher DMT (i.e. these are the patients who moved to a higher risk for progression and the first- and second-line DMTs would not be able to change the risk)	RRMS patients continuing to experience relapses on a second-line therapy Progressive forms of MS with relapses and/or active MRI despite treatment; such patients can also be considered for induction therapy Safety issues (e.g., patients on natalizumab at high risk of developing progressive multifocal leukoencephalopathy)
Factors suggesting a switch from a second-line to a first-line DMT	Tolerability/safety issues should the patient maintain the second-line agent AND the perception that the disease is under good control and the patient's risk for imminent progression has been reduced

RRMS = relapsing remitting multiple sclerosis; TOR = Treatment Optimization Recommendations.

Adapted from: Gajofatto et al.⁹⁴

causing agents) or a new “reference” MRI (done 3-6 months after starting the new agent to allow time for it to be effective). All patients should undergo regular monitoring and follow-up so that, if needed, appropriate measures can be taken in a timely manner to offset unexpected toxicities or to treat suboptimal disease response, which is much more likely in patients already showing a lack of good treatment response to a first-line therapy.¹¹⁶

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