Lymphopenia and DMTs for relapsing forms of MS

Considerations for the treating neurologist

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Abstract

Purpose of review

To provide neurologists with an update on the proposed mechanisms of action (MOAs) of disease-modifying therapies (DMTs) for the treatment of relapsing MS, and their effect on peripheral blood leukocytes, in order to inform treatment decisions.

Recent findings

DMTs have vastly differing MOAs, including effects on peripheral blood leukocyte counts, particularly lymphocytes. The clinical implications of changes in lymphocyte counts need to be understood in the context of the underlying MOAs of each respective DMT, with treatment tailored to individual patient needs.

Summary

DMTs can alter lymphocyte counts, subsets, activation, and distribution, and thus can influence immune surveillance. Serial monitoring of total leukocytes and absolute lymphocyte counts (ALCs) is advisable in patients receiving DMTs. ALCs should be interpreted regarding expected immunologic changes and individual patient characteristics. Any decision to switch DMTs should consider these factors, along with drug efficacy, safety, and effect on quality of life.
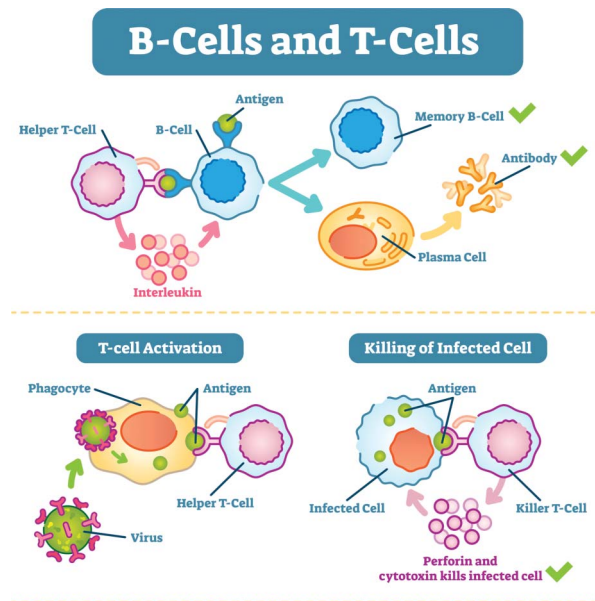
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MS is a chronic, immune-mediated, demyelinating CNS disorder[1] associated with development of neurologic deficits and subsequent accumulation of physical and cognitive disability.[2] Around 2.3 million people worldwide and 400,000 in the USA have MS,[3] with a higher incidence in women.[4] Although there are regional variations, the prevalence of MS in the US in 2012 was 149.2 per 100,000 individuals.[4] Relapsing forms of MS (RMS) account for over 80% of all MS cases at onset, and thus comprise a substantial proportion of MS cases under a neurologist's care.[1]

There is strong evidence indicating that infiltration of autoreactive immune cells into the CNS, particularly $CD4^+$ and $CD8^+$ T cells, plays an important role in MS pathogenesis.[5] In addition,

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a growing body of evidence has highlighted the involvement of B cells as important contributors to MS pathogenesis.[5–8] The proposed mechanisms of action (MOAs) of various disease-modifying therapies (DMTs) for the treatment of patients with RMS generally involve some form of immunomodulation or lymphocyte depletion involving T cells, B cells, or both. DMTs target lymphocytes by modulating their activation, proliferation, or cytokine secretion, or by reducing their trafficking across the blood–brain barrier.[5,8]

As this review indicates, a nuanced approach is necessary for interpreting changes in complete blood counts observed in relation to DMTs. There is no single "normal" lymphocyte level for each individual DMT, and it is recommended that due consideration be given to expected changes vs changes that potentially signal unfavorable clinical outcomes. It is also worth noting that lymphopenia can occur in patients with MS that is unrelated to treatment with DMTs.[9–11]

Proposed MOAs and evidence of lymphopenia for currently available DMTs

Several injectable, oral, and infusible DMTs have been approved for the treatment of RMS, based on clinical trial evidence demonstrating reductions in MS relapse frequency, magnetic resonance imaging disease activity, and ongoing disability accumulation. Many of these DMTs result in a decrease in circulating T and B lymphocytes. However, it is important to note that circulating lymphocytes represent only a small proportion (~2%) of the total population; thus, they may not be an accurate indicator of the body's total lymphocyte pool and function.[12,13] Furthermore, fluctuations in blood lymphocytes seldom correlate with changes in composition and number of lymphocyte subsets in other lymphoid and non-lymphoid organs.[13] Therefore, blood lymphocytes provide limited information on an individual's immune status.[13]

A basic understanding of the underlying MOAs of DMTs and their effects on the immune system can help to inform the management of patients with RMS. The currently understood MOAs of DMTs and their known effects on lymphocyte subsets and the immune system are summarized in the table and figure, and discussed further in the following section of this review.

Beta IFNs

Numerous studies have demonstrated that anti-inflammatory properties of the beta interferons (IFNs) are mediated through downregulation of pro-inflammatory CD4$^+$ and CD8$^+$ memory T cells, memory B cells, and a concomitant increase in regulatory T cells (Tregs).[14,15,18,51] Dose-related reductions in all cell lineages, predominantly leukocytes, have been observed with IFNs, with the most notable effect

seen in total leukocyte and lymphocyte counts.[14] It has been estimated that approximately two-thirds of patients treated with IFNs will develop cytopenia/lymphopenia, which generally resolves 34 months after treatment initiation.[52]

Glatiramer acetate

The synthetic polymer glatiramer acetate (GA) does not affect absolute lymphocyte counts (ALCs).[53] Instead, GA appears to promote anti-inflammatory cytokine shifts in CD4$^+$ and CD8$^+$ T cells, restores Tregs, and decreases both memory B and T cells.[20,54] Consequently, GA is infrequently associated with leukopenia, and when it does occur it is generally mild in nature.[22,55]

Daclizumab

Daclizumab binds to the alpha subunit (CD25) of the high-affinity interleukin-2 (IL-2) receptor expressed on activated T cells and modulates IL-2 signaling, resulting in an expansion of CD56^{BRIGHT} natural killer (NK) cells and a reduction in proinflammatory activated T cells.[25] In clinical trials, daclizumab was associated with reductions in total lymphocyte counts, and T and B cell counts of ≤10%, which were reversible following treatment discontinuation, and a low overall incidence of lymphopenia.[24–26]

Fingolimod

Fingolimod affects lymphocyte migration to secondary lymphoid organs via down-modulation of sphingosine 1-phosphate receptor 1 on lymphocytes, preventing egress of C-C chemokine receptor type 7+ (CCR7$^+$) lymphocytes, naïve and central memory T cells, and memory B cells, from lymph nodes.[7,14] Fingolimod does not sequester effector T cells lacking CCR7 in lymph nodes.[56] It has been shown that most patients who receive fingolimod can generate an immune response against both new and recalled antigens, and their lymphocyte functions remain largely intact.[32]

Teriflunomide

Teriflunomide, an immunomodulator, selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase and specifically targets proliferating lymphocytes (while sparing resting or slowly dividing cells), resulting in decreases in CD4$^+$ and CD8$^+$ T cells, memory B cells and NK cells.[28] Overall, teriflunomide is associated with only infrequent mild lymphopenia and neutropenia, which tends to reverse with ongoing treatment or following treatment discontinuation.[10]

Dimethyl fumarate

The small molecule dimethyl fumarate (DMF) results in selective depletion of CD8$^+$ over CD4$^+$ T cells.[34] In clinical trials with DMF, a reduction in ALC of approximately 30%

Table Overview of the disease-modifying therapies in RMS

Treatment	Patient-years of drug exposure	Proposed mechanism of action	PK profile	Effect on circulating leukocytes	Effect on immune system/vaccine response	Rate of recovery of lymphocytes	Rate of serious infections
IFNs (Betaseron, Rebif, Avonex, Extavia, Plegridy)	Figures not readily available—widely used for over 20 years[14]	Recombinant cytokine[14]		1 month after treatment:	Leukopenia (lymphopenia)[14]	NA	NA
		Downregulation of immune recognition molecules such as MHC Class II antigens, co-stimulatory molecules and adhesion molecules[14]		Considerable reduction vs baseline in memory B cells[15]	Normal humoral and cellular response to influenza vaccine[16,17]		
		Promotes a TH1 (pro-inflammatory)–TH2 (anti-inflammatory) shift in cytokine response[14]		Decreases $CD4^+$ and $CD8^+$ T cells producing IFN-gamma and IL-4[18]			
		Reduction of lymphocyte migration across the blood–brain barrier[14]					
		Potential stimulation of neuronal growth factor release[14]					
Glatiramer acetate (Copaxone)	>2,000,000[19]	Synthetic polymer that diminishes the expression of MHC Class II molecules, deactivates monocytes and macrophages[14]	T_{max}: 15–30 min[20]	After 3 mo of treatment:[21]	Rare leukocytosis or mild leukopenia[14]	NA	1%–2%[22]
		Promotes a TH1 (pro-inflammatory)–TH2 (anti-inflammatory) shift in cytokine response[14]	Limited PK data in patients with MS[20]	Major increase in regulatory $CD8^+$ T cells over baseline	Decreases response to influenza vaccines (pandemic and seasonal)[23]		
		Exerts neuroprotective effects[14]		Treatment activates the transformation of conventional $CD4^+CD25$ T cells to regulatory $CD4^+CD25^+$ T cells[14]			
Daclizumab (Zinbryta)	5,214 (clinical trials only, data cutoff 2016)[24]	Humanized monoclonal antibody[14]	Median T_{max}: 5–7 days[25]	Increase in CD56^BRIGHT NK cells (0.6% of lymphocytes at baseline to 3.6% at end of treatment). Increase apparent by week 4[26]	Potential lymphopenia and leukopenia (generally mild)[24]	8–12 weeks after discontinuation[25]	3% vs 0 for placebo[26]
		CD25 antagonist that modulates IL-2 signaling, leading to an expansion of CD56^BRIGHT NK cells, which are thought to eliminate pathogenic T cells that contribute to inflammation in MS[14,26]	Time to steady state: 3–4 months[25]	7%–10% decrease in $CD4^+$ and $CD8^+$ T-cell counts at week 52[26]			

Table Overview of the disease-modifying therapies in RMS *(continued)*

Treatment	Patient-years of drug exposure	Proposed mechanism of action	PK profile	Effect on circulating leukocytes	Effect on immune system/vaccine response	Rate of recovery of lymphocytes	Rate of serious infections
			$T_{1/2}$: 21 d[25]	CD4$^+$/CD8$^+$ ratio remained constant[26]			
Teriflunomide (Aubagio)	~162,000 (as of October 2017)[27]	Active metabolite of leflunomide[14]	Median T_{max}: 1–4 hours[10]	During first 6 weeks of treatment:[10]	Potential mild lymphopenia and neutropenia[10,14]	May resolve with ongoing treatment or after discontinuation[10]	1.4% (7 mg) and 2.2% (14 mg) vs 2.1% for placebo[10]
		Pyrimidine synthesis inhibition by inhibiting DHODH and thereby reducing replication of high-avidity lymphocytes[14,28]	Time to steady state: ~3 months[10]	15% mean decrease in WBCs, mainly lymphocytes and neutrophils	Patients able to mount a response to neoantigen (rabies vaccine); immune response weaker vs placebo-treated patients[29]		
			$T_{1/2}$ ~ 18 and 19 days for 7 and 14 mg, respectively[10]				
Fingolimod (Gilenya)	480,000 (as of August 2017)[30]	Sphingosine 1-phosphate antagonist[7]	T_{max}: 12–16 h[9]	After 1 mo of treatment:[31]	Lymphocyte redistribution[14]	1–2 mo after discontinuation[9]	2.3% vs 1.6% for placebo[9]
		Redistribution of lymphocytes in secondary lymphoid tissue[7]	Time to steady state: 1–2 mo[9]	CD3$^+$ T cells decreased from 78% to 39% (50% overall reduction from baseline)	Immune responses mounted to tetanus and influenza[32]		
			$T_{1/2}$: 6–9 d[9]	CD4$^+$ T cells decreased from 59% to 12% (80% overall reduction from baseline)	Reduced response rates vs placebo-treated patients[32]		
				CD19$^+$ B cells decreased from 8% to 3% (63% overall reduction from baseline)			
				CD4$^+$/CD8$^+$ ratio decreased from 3.6 to 0.6 (83% overall reduction from baseline)			
				NK cells increased from 11% to 51% (364% overall increase from baseline)			
Dimethyl fumarate (Tecfidera)	>464,000 (as of January 2017)[33]	Fumaric acid methyl ester[14]	Median T_{max}: 2–2.5 h[11]	After 12 mo of treatment:[34]	Potential leukopenia (lymphopenia)[11,14]	4 wk after discontinuation in clinical trials (lower than baseline)[11]	2.0% vs 2.0% for placebo[11]

Table Overview of the disease-modifying therapies in RMS *(continued)*

Treatment	Patient-years of drug exposure	Proposed mechanism of action	PK profile	Effect on circulating leukocytes	Effect on immune system/vaccine response	Rate of recovery of lymphocytes	Rate of serious infections
		Activation of Nrf2 signaling pathway[14]	T$_{1/2}$: 1 hour[11]	~30% decrease in mean ALC	Adequate humoral response to tetanus vaccine; response rate comparable to IFN-treated patients[35]	Prolonged lymphopenia after discontinuation is common in clinical practice[36]	
		Protects against oxidative stress-induced cellular injury in neurons[14,37]		44% decrease in CD3$^+$ T cells			
		Promotes a TH1 (pro-inflammatory)–TH2 (anti-inflammatory) shift in cytokine response[14,37]		55% decrease in CD8$^+$ T cells			
				39% decrease in CD4$^+$ T cells			
				36% increase in the CD4$^+$/CD8$^+$ ratio			
				38% decrease in CD19$^+$ B cells			
				54% decrease in eosinophils			
Natalizumab (Tysabri)	559,749 (as of February 2017)[38]	Humanized monoclonal anti-α4 integrin antibody[14]	Time to steady-state: 24 wks[39]	3–6 mo after starting treatment:[40]	Diminished immune surveillance in the CNS[14]	CNS reconstitution in 6–12 mo[8,41]	3% for natalizumab and placebo[39]
		Inhibits α4β1 (VLA-4)[14]	T$_{1/2}$: ~11 days[39]	Considerable increase in WBC, lymphocytes and lymphocyte subsets (CD3$^+$, CD3$^+$CD4$^+$, CD3$^+$CD8$^+$, CD19$^+$, CD16$^+$CD56$^+$)	Normal humoral response to influenza vaccine; adequate response to tetanus and KLH[42,43]	Increase in lymphocytes persists for 30 months[40]	
		Restricts the extravasation of lymphocytes into CNS[14]		Greater increase from baseline in B cells (3.20) vs T cells (1.92 fold) or NK cells (1.88 fold)			
Alemtuzumab (Lemtrada)	~6,500 (clinical trials only, data cutoff October 2013)[44]	Humanized immunoglobulin G1 monoclonal anti-CD52 antibody[8]	T$_{1/2}$: ~2 weeks[42]	After 7 days of treatment:[45]	Lymphopenia[45]	After discontinuation:[45]	3% vs 1% for IFN[45]
		Results in rapid lysis of lymphocytes[46]		99.8% decrease in CD4$^+$ T cells	Normal vaccine responses to influenza, DTP, meningococcus and pneumococcus[47]	B cells: ~6 months	
				98.5% decrease in CD8$^+$ T cells		CD4$^+$ T cells: up to 1–2 y	

Table Overview of the disease-modifying therapies in RMS *(continued)*

Treatment	Patient-years of drug exposure	Proposed mechanism of action	PK profile	Effect on circulating leukocytes	Effect on immune system/vaccine response	Rate of recovery of lymphocytes	Rate of serious infections
Ocrelizumab (Ocrevus)	6,467 (clinical trials only; as of June 2016)[48]	Humanized immunoglobulin G1 monoclonal anti-CD20 antibody[49]; Results in antibody-dependent lysis of B cells[45]	$T_{1/2}$: 26 d[49]	Within 14 days of treatment: Decreases immature and mature B cells[49]	Studies ongoing	Median of 72 wk (range 27–175 wk) after discontinuation[49]; CD8$^+$ T cells: 2–3 mo	1.3% vs 2.9% for IFN[50]

Abbreviations: ALC = absolute lymphocyte count; DHODH = dihydroorotate dehydrogenase; DMT = disease-modifying therapy; DTP = diphtheria, tetanus, pertussis; FDA = Food and Drug Administration; IFN = interferon; IL = interleukin; KLH = keyhole limpet hemocyanin; MHC = major histocompatibility complex; NA = not applicable; NK = natural killer; PK = pharmacokinetic; RMS = relapsing forms of MS; T_{max} = time taken to reach maximum concentration; $T_{1/2}$ = time required for the concentration to fall to 50%; TH = T helper; VLA-4 = very late antigen-4; WBC = white blood cells.

was observed in the first year of treatment.[11] In addition, prolonged lymphopenia (≥6 months) was seen in 2.2% of patients.[57] One month after stopping treatment, mean counts increased, but did not return to baseline levels in all patients.[11]

Natalizumab

Natalizumab, an anti-α4 integrin monoclonal antibody (mAb), affects lymphocyte migration to the CNS. Distinct from other mAbs, it leads to considerable increases in CD4$^+$ and CD8$^+$ T cells, CD19$^+$ B cells, and NK cells, with no effect on the CD4$^+$/CD8$^+$ T-cell ratio in the periphery but a reduction in the CNS.[40,41] The increases in ALC following natalizumab infusion likely occur as a result of increased release of CD34$^+$ progenitor cells from bone marrow as well as impaired egress of lymphocytes from the periphery, with concomitant reduction in lymphocytes in the CSF and notable reduction in the CSF CD4$^+$/CD8$^+$ ratio.[39,58] After discontinuation, circulating lymphocytes usually return to baseline levels within 16 weeks; the CD4$^+$/CD8$^+$ ratio normalizes within 6 months.[8,39,41]

Alemtuzumab

Alemtuzumab, an anti-CD52 mAb, causes near-complete depletion of circulating lymphocytes: dramatic drops in CD4$^+$ and CD8$^+$ T cells, CD19$^+$ B cells, and NK cells have been observed after treatment, followed by variable reconstitution of leukocyte subpopulations, generally over 6–12 months.[45,59] During alemtuzumab treatment, ALC decreases rapidly after the first infusion; however, all cell types, including memory CD4$^+$ and CD8$^+$ T cells, start to recover within the first month post-infusion, with a selective delay in CD4$^+$ T cell reconstitution (taking ≤2 years to normalize vs CD8$^+$ T cells, which return to normal after 3 months of treatment). B cells are restored approximately 6 months post-discontinuation.[8,45]

Ocrelizumab

Ocrelizumab, an anti-CD20 mAb, leads to pronounced B-cell lymphopenia that has been shown to persist for a median of 72 weeks after last infusion.[49] Following the first infusion, B cell counts are reduced within 2 weeks and remain depleted throughout ongoing treatment. B cells have been shown to recover to baseline levels/lower limit of normal 2.5 years after discontinuation in 90% of patients.[49]

Clinical implications of lymphopenia

DMTs alter normal immune responses and thus have the potential to increase infection risk. However, rates of serious infections reported in clinical trials are low (1%–3%) and similar between DMTs (table). Nevertheless, there are some important differences between DMTs with respect to the risk of some serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML), a demyelinating disease associated with John Cunningham virus (JCV) infection. Ongoing clinical and postmarketing safety studies continue to collect information on infections in patients receiving DMTs.

Serious opportunistic infections associated with DMTs

Extensive experience with GA and IFNs has not elicited safety concerns with respect to opportunistic infections or PML; to date, neither teriflunomide, daclizumab, nor ocrelizumab has been associated with increased risk of opportunistic infections or PML in the RMS population.[14,25,49,60] However, further long-term data are needed for ocrelizumab.[61] Daclizumab was voluntarily withdrawn from the market following reports of inflammatory encephalitis and meningoencephalitis.[62]

Fingolimod has been associated with opportunistic infections including herpes viruses and cryptococcal infections.[14] In clinical trials, 2 patients died of herpetic infections, and cases of fatal cryptococcal meningitis and disseminated cryptococcal infections have been reported in the postmarketing setting.[9] The overall risk of PML not attributed to prior natalizumab treatment remains very rare, and is estimated to be ∼1:12,000 patients. As of August 2017, 15 fingolimod-treated patients

were reported to have developed PML in the absence of natalizumab treatment in the preceding 6 months.[30] However, these cases of PML were not associated with sustained grade 4 (ALC <0.2 × 10^9/L) lymphopenia.[9,30,61] An additional 4 cases of PML were later reported.[63]

DMF-associated lymphopenia and PML have been a recent area of focus; CD8$^+$ T lymphocytes, which are likely critical to defend against JCV,[64] are selectively depleted by DMF, and their sustained reduction may result in an increased risk of developing PML.[34] To date, one case of PML in a patient with prolonged lymphopenia has been reported in a clinical trial,[11] and 4 cases have been reported in the postmarketing setting in the presence of lymphopenia (<0.8 × 10^9/L) persisting for >6 months.[11,61]

Natalizumab prescribing information indicates a general increased risk of developing infections,[39] and the risk of PML is known to be higher for natalizumab (approximately 4 in 1,000 patients) than other DMTs, increasing with treatment duration (>24 months), prior immunosuppressant exposure, JCV antibody positivity, and older age (>44 years).[39,61,65] As of February 2017, there have been 711 cases of PML reported in patients with MS exposed to natalizumab, with a mortality rate >20%.[38] The mechanisms underlying PML development in natalizumab-treated patients remain unclear; it is assumed that impaired immunosurveillance in the CNS and mobilization of premature B cells infected by JCV into the CNS may be involved.[61]

Although no cases of PML following alemtuzumab treatment have been reported in patients with MS, several cases of *Listeria*-associated infections during or soon after an

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Figure Simple schematic depicting the general effects of selected DMTs on lymphocytes
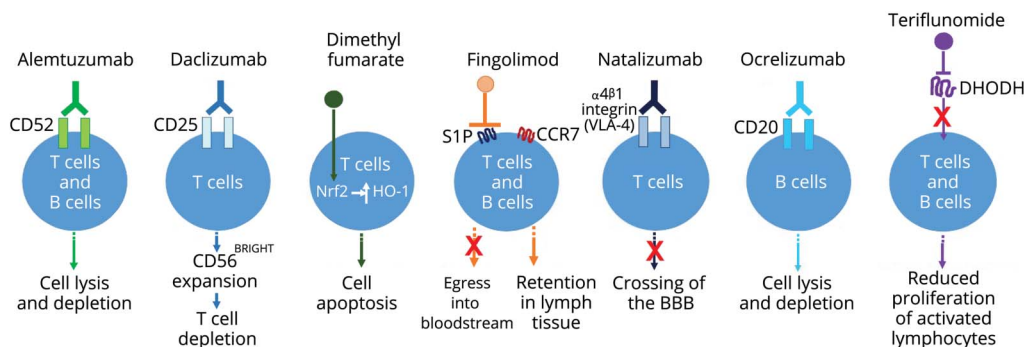
The mechanisms of action of each DMT have not been fully elucidated in relapsing MS; the depiction shown in this schematic with respect to effects on lymphocytes is based on currently available evidence. Alemtuzumab is a humanized immunoglobulin-1 monoclonal anti-CD52 antibody that results in rapid lysis of lymphocytes.[42] Daclizumab is a humanized monoclonal anti-CD25 antibody that leads to CD56^{BRIGHT} expansion via interleukin-2 modulation, and consequently, to activated T-cell depletion.[14] Dimethyl fumarate is believed to exert its lymphopenic effect through activation of the Nrf2 pathway, which leads to induction of the anti-inflammatory stress protein HO-1 and consequently apoptosis of primarily CD8$^+$ T cells.[8,34] Fingolimod is a sphingosine 1-phosphate (S1P) agonist; after binding to and activating S1P1, fingolimod acts as a functional antagonist and prevents CCR7$^+$ lymphocytes, including naïve and central memory T cells and B cells, from exiting lymph nodes.[7,8] Natalizumab is a humanized monoclonal anti-α4 integrin antibody that binds α4β1 integrin (very late antigen-4 [VLA-4]) and prevents lymphocytes from crossing the blood–brain barrier (BBB) and entering the CNS.[14] Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells; it results in antibody-dependent cellular cytolysis following cell surface binding to B lymphocytes.[49] Teriflunomide inhibits de novo pyrimidine synthesis in rapidly dividing cells by inhibiting the enzyme dihydroorotate dehydrogenase (DHODH), causing a cytostatic effect on activated/proliferating T and B cells.[14]

alemtuzumab treatment cycle have emerged in the post-marketing setting.[14] In clinical trials with alemtuzumab, antiviral prophylaxis reduced the frequency of herpes simplex infections.

Together, these studies provide evidence that, for the majority of currently available DMTs, there is no obvious link between ALC and overall risk of opportunistic infections. Nevertheless, continuous assessment of infection risk before, during, and after administering DMTs is advisable and has profound clinical relevance given the link between MS exacerbations and infection.[66] To minimize infection risk, a comprehensive analysis of patient characteristics is required for deciding on the optimal DMT, including any history of infectious disorders, prior exposure to immunosuppressants, age, and immune status. For example, patients with low baseline lymphocyte counts and women with low body mass index may be at particular risk of developing clinically significant lymphopenia with fingolimod.[67] In patients receiving natalizumab, prior immunosuppressant use has also been associated with increased risk of PML,[68] and the recent American Academy of Neurology (AAN) practice guidelines on DMTs in MS state that a discussion regarding switching to a DMT with a lower risk of PML should take place for patients who are or become JCV antibody-positive while receiving natalizumab.[69] It is important that healthcare providers look beyond lymphocyte count and remain vigilant to detect clinical signs and symptoms in order to act swiftly in cases of opportunistic infection.

Lymphopenia and relationship with DMT efficacy

Because lymphocytes appear to be important contributors to MS pathology, elucidating the significance of DMT-induced lymphopenia and predicting which patients are at risk of serious or opportunistic infections, and who might benefit most from certain treatments, are important for clinical decision-making. Based on currently available data, there does not appear to be a link between lymphopenia and DMT efficacy, although such a link cannot be excluded given the complex mechanisms involved. Despite long-standing clinical experience with IFN-beta, immunologic markers that predict treatment efficacy have not been identified.[51] Similarly, lymphopenia associated with DMF treatment was not predictive of good clinical response or breakthrough MS activity,[36] and no association between the degree of lymphopenia and clinical outcomes was observed in patients treated with fingolimod.[70] Additionally, earlier evidence of IL-21 and differential lymphocyte reconstitution as potential biomarkers for relapse risk after alemtuzumab treatment has not been validated.[71]

Advances are being made towards establishing clinically relevant markers of treatment response in RMS, with neurofilaments representing a particular focus.[72] However, in the absence of reliable biomarkers, close patient monitoring

> With the exception of prolonged lymphopenia with DMF, lymphopenia alone is not a signal to switch treatments or reduce dosage in the majority of cases.

and comprehensive patient education are of paramount importance.

Alternative dosing strategies to address lymphopenia

With the exception of prolonged lymphopenia with DMF, lymphopenia alone is not a signal to switch treatments or reduce dosage in the majority of cases. Rather, lymphopenia may be an expected consequence of the MOA of several DMTs and does not necessarily signify clinically significant loss of immunity. Nevertheless, some physicians have devised alternative dosing strategies to reduce lymphopenia risk. A recent observational study reported that fingolimod-associated lymphopenia could be mitigated by utilizing an every-other-day dosing regimen; however, there was a considerable increase in risk of relapse or new magnetic resonance imaging lesions. Furthermore, it is also currently unknown whether alternate-day dosing has any additional effect on overall safety outcomes.[73]

Switching DMTs

Suspending or switching between DMTs may become necessary when patients fail to respond to therapy or when concerns emerge about actual/potential adverse events (such as opportunistic or recurrent infections, hepatotoxicity, renal insufficiency, and cardiovascular diseases—see individual product labels). When switching between therapies, it is important to consider both MOA and duration of action (table) of each therapy and understand the risks and benefits associated with each. To avoid inadvertent additive treatment effects, ALC monitoring and an optimal washout period should be elucidated for each drug-switching combination: a long washout period may cause disease rebound, and a shorter period may be associated with safety issues due to the synergetic effect of more than one drug on the immune system.[74] No evidence-based guidelines for recommended washout periods between DMTs currently exist, and clinical practice varies widely. The recent AAN practice guidelines on DMTs in MS make no recommendations for switching in cases of lymphopenia.[69] As each treating physician has their own approach to patient management, such as low lymphocyte counts that would prompt discontinuation, switching DMTs due to lymphopenia is more likely to be based on personal protocols rather than set guidelines. Monitoring of normalization of lymphocyte counts after DMT switches may help guide sequence timing.

The presence of lymphopenia following initiation of DMTs known to cause cell lysis or redistribution is not usually sufficient to warrant switching drugs or reducing dosage. However, per the DMF prescribing information, interruption of treatment should be considered in patients with lymphocyte counts less than 0.5×10^9/L persisting for more than 6 months. Although fingolimod treatment was interrupted in patients with ALCs $<0.2 \times 10^9$/L in the pivotal clinical trials,[75–77] post-marketing safety analysis and further studies have not shown a clear correlation between the degree of lymphopenia and opportunistic infections.[78] The prescribing information contains no language regarding the necessity for discontinuation of fingolimod for lymphopenia; however, due to treatment interruptions in the pivotal clinical trials, information on patients with ALCs $<0.2 \times 10^9$/L who continued fingolimod therapy is limited.

To conclude, a nuanced approach is proposed, where the underlying MOA of the DMT and key patient characteristics are considered. There might not be a "normal"-lymphocyte count for patients with RMS on DMTs; the implications of any changes in lymphocyte count need to be understood in the context of the underlying MOA of prescribed DMTs, and treatment tailored to individual patient needs.

Author contributions

E.J. Fox: drafting/revising the manuscript. G. Buckle: drafting/revising the manuscript; study concept or design; analysis or interpretation of data. B. Singer: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data. V. Singh: drafting/revising the manuscript. A. Boster: drafting/revising the manuscript.

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Disclosure

TAKE-HOME POINTS

→ On the basis of the proposed MOAs of many of the DMTs used in the treatment of RMS, lymphopenia is an anticipated side effect. However, not all patients experience lymphopenia, and its severity may vary between individuals.

→ Lymphopenia is usually reversible after discontinuation of most DMTs, with infrequent exceptions. However, the length of time for complete reversal of lymphopenia varies between individuals and depends greatly on the specific DMT.

→ Despite differences in MOAs of the various DMTs, overall rates of serious infection appear to be low, as reported in clinical trials.

→ There is currently no direct evidence to suggest that DMT efficacy, in terms of either clinical response or breakthrough MS activity, is related to the presence or severity of lymphopenia.

→ The presence of lymphopenia following initiation of DMTs known to cause cell lysis or redistribution is not usually sufficient to warrant switching drugs or reducing dosage.

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Things to consider before treating MS with DMTs

B and T lymphocytes are important to **multiple sclerosis (MS)** pathogenesis, and thus are often targeted by **disease modifying therapies (DMTs).**

2.3 million people affected.

Relapsing forms of MS (RMS) account for **>80%** of MS cases at initial diagnosis.

MS DMTs target B and T cells via different MOAs and preferentially affect certain subtypes.

Treatment conundrum

Should DMT's effect on lymphocytes and immune systems be considered when managing patients with RMS?

Lymphocytes should be monitored in patients receiving DMTs.

Ocrelizumab — CD20 — B cells — Cell lysis and depletion
Alemtuzumab — CD52 — ↓CD4⁺ CD8⁺ T cells
Dimethyl fumarate — Nrf2→↑HO-1 — ↓CD3⁺ T cells
Natalizumab — α4β1 integrin (VLA-4) — ↓Crossing of blood-brain barrier
Teriflunomide — DHODH*⊥ — ↓CD3⁺, CD3⁺CD4⁺ CD3⁺CD8⁺ CD19⁺ CD16⁺CD56⁺ / ↓Proliferation of activated lymphocytes
Fingolimod — S1P CCR7 — ↓Egress into bloodstream / ↑Retention in lymphoid tissue
Beta interferons — ↓CD4⁺ T cells CD19⁺ B cells
Glatiramer acetate — ↓CD4⁺ CD8⁺ T and B cells / ↑Memory T and B cells

T cells **and** B cells

*Dihydroorotate dehydrogenase

DMTs alter lymphocyte counts, but overall rate of serious infection appeared low.

A nuanced treatment approach that considers the underlying mechanisms of action of specific DMTs and individual patient characteristics is essential.