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REVIEW ARTICLE

Immunological Mechanism of Action and Clinical Profile of Disease-Modifying Treatments in Multiple Sclerosis

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Abstract Multiple sclerosis (MS) is a life-long, potentially debilitating disease of the central nervous system (CNS). MS is considered to be an immune-mediated disease, and the presence of autoreactive peripheral lymphocytes in CNS compartments is believed to be critical in the process of demyelination and tissue damage in MS. Although MS is not currently a curable disease, several disease-modifying therapies (DMTs) are now available, or are in development. These DMTs are all thought to primarily suppress autoimmune activity within the CNS. Each therapy has its own mechanism of action (MoA) and, as a consequence, each has a different efficacy and safety profile. Neurologists can now select therapies on a more individual, patient-tailored basis, with the aim of maximizing potential for long-term efficacy without interruptions in treatment. The MoA and clinical profile of MS therapies are important considerations when making that choice or when switching therapies due to suboptimal disease response. This article therefore reviews the known and putative immunological MoAs alongside a summary of the clinical profile of therapies approved for relapsing forms of MS, and those in late-stage development, based on published data from pivotal randomized, controlled trials.

Key Points

Given that multiple sclerosis (MS) is a lifelong and, as yet, incurable disease, the long-term safety and tolerability profiles of treatments are clearly important considerations in therapy selection.

There are now several disease-modifying therapies (DMTs) available, or in late-stage clinical development, for the treatment of relapsing forms of MS in the US and the European Union (EU).

Each DMT has its own mechanisms of action and, as a consequence, each has a different efficacy and safety profile. Understanding the immunological mechanisms and associated clinical profiles of each therapy for MS is important, in order to select and manage patients' therapy appropriately.

Few comparative head-to-head trials have been undertaken to assess the superiority or non-inferiority of one therapy over another, and there is a need for such evidence now that numerous treatments for relapsing MS are available.

There is a need for treatment algorithms to help physicians and their patients decide on a therapy for optimal disease management.

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1 Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease affecting the central nervous system (CNS) [1]. While the exact cause is unknown, extensive study of the pathology of MS has implicated autoimmune processes in disease progression. These are thought to be mediated by autoreactive lymphocytes that cross the blood–brain barrier (BBB) and enter the CNS where they cause localized inflammation resulting in demyelination, gliotic scarring, and axonal loss [2, 3]. According to this model, as the disease advances, and with repeated inflammatory episodes, CNS repair processes begin to fail, becoming less and less effective, and neurodegeneration results in progressive and irreversible disability [4].

An increased understanding of the pathophysiology of MS has allowed the development of new immunomodulating agents with unique mechanisms of action (MoA). The most effective drugs have tended to have the most profound effects on the immune system, which can result in treatment-limiting adverse events [5]. Clearly, it is important to weigh up the beneficial effects of specific drugs against the potential adverse events so that therapies can be prescribed in an informed manner and to the appropriate patients.

There are several disease-modifying therapies (DMTs) currently available, or in late-stage clinical development, for the treatment of relapsing forms of MS in the US and the European Union (EU). Interferon (IFN) β-1a and β-1b and glatiramer acetate (GA) administered by subcutaneous (SC) or intramuscular (IM) injection are the established first-line therapies for relapsing MS [6–15]. Natalizumab intravenous infusion has also been approved for nearly 10 years and is used mainly as a second-line therapy [16, 17]. Several oral drugs are also available. In 2010, fingolimod became the first oral drug to be approved for the treatment of relapsing forms of MS [18, 19]. More recently, oral teriflunomide [20] (2012) and dimethyl fumarate [21] (2013; US only) have also been approved. Alemtuzumab, administered as a course of infusions, was also recently approved within the EU [22] (2013). In addition, a number of experimental therapies are undergoing phase III clinical trials.

This paper reviews the MoA of the approved therapies and those in late-stage development for the treatment of relapsing MS (Table 1). The clinical efficacy of each therapy is also summarized, as well as the potential associated adverse effects and safety issues.

2 Parenteral Therapies

2.1 Interferon β-1a/b

2.1.1 Mechanism of Action and Immunological Effects

Type I IFNs are endogenous cytokines produced by eukaryotic cells in response to viral infections and related biological stimuli. Synthetic IFNs, synthesized via recombinant DNA technology in mammalian cells (known as IFNβ-1a) and via bacterial fermentation (known as IFNβ-1b), are used in the treatment of relapsing MS. The biological activity of IFN is mediated via interaction with specific cell surface receptors. Physiological and pathophysiological effects induced by IFNs are likely to reflect divergences in the downstream signaling induced by IFN type I-receptor binding and resulting pleiotropic transcriptional effects. As a result, the precise MoA of IFNs in MS is not yet understood. IFNs exert direct and indirect effects on lymphocytes, and may involve the expansion of immunomodulatory cells such as natural killer cells and T regulatory cells, inhibition of B-cell stimulatory capacity and secretion [23], and inhibition of the inflammasome [24]. IFNs also profoundly and directly influence CD8+ T-cell responses [25]. This T-cell subset predominates in MS lesions and is associated with permanent neurological deficits [26, 27].

It has been shown that IFNβ increases the production of anti-inflammatory cytokines and suppresses the production of proinflammatory cytokines. In an ex vivo study, the production of the anti-inflammatory cytokines interleukin (IL)-10 and IL-4 were enhanced significantly in the IFNβ-treated myelin basic protein-reactive T cells, while production of the proinflammatory cytokine, tumor necrosis factor (TNF)α, was unaffected [28]. Such preclinical data are supported by those from clinical studies. For example, in blood and cerebrospinal fluid (CSF) samples collected from patients with MS who were receiving treatment with IFNβ-1a, serum and CSF IL-10 levels increased with increasing treatment exposure [29]. Further studies showed that administration of IFNβ down-regulates expression of the proinflammatory cytokines IL-17 and osteopontin [30], and reduced serum IFNγ and TNFα in patients with MS, while increasing production of IL-10 [31].

The pharmacological actions of IFNβ described above have been attributed to its direct action on CD4+ T cells [30] and myeloid cells [32] through the type I IFN receptor, although IFNβ signaling with other cell types within the immune system is also thought to contribute to its therapeutic effects [33]. IFNβ is likely to have a limited direct

Table 1 Mechanisms of action of approved and phase III disease-modifying therapies for multiple sclerosis

Therapy	Summary	First approved
Interferon β-1a/b	Increases production of anti-inflammatory cytokines and suppresses production of proinflammatory cytokines [28, 30, 31]	1993
	Reduces inflammatory cell migration across the blood–brain barrier [175]	
Glatiramer acetate	Is a synthetic peptide with amino acid analogs to myelin basic protein	1996
	Increases production of anti-inflammatory cytokines and decreases production of proinflammatory cytokines [23]	
Mitoxantrone	Cytotoxic agent that intercalates with DNA, causing strand breaks, and inhibits DNA repair via inhibition of topoisomerase II [55]	2000[a]
	Inhibits proliferation of B and T lymphocytes and macrophages [54]	
Natalizumab	Is a monoclonal antibody, which selectively inhibits VLA-4 (α4β1) integrins and prevents lymphocyte migration across the blood–brain barrier [59]	2004
Fingolimod	Is a sphingosine 1-phosphate receptor modulator that reversibly redistributes lymphocytes into lymphoid tissue, whilst preserving lymphocyte function [98]	2010
	Prevents naïve and central memory T cells from circulating to non-lymphoid tissues, including those of the CNS, where they could cause inflammatory tissue damage [98, 101]	
Teriflunomide	Is an active metabolite of leflunomide	2012
	Inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis, which has a cytostatic effect on proliferating T and B cells [124]	
Dimethyl fumarate (BG-12)	Dimethyl fumarate is a methyl ester of fumaric acid	2013
	Thought to exert neuroprotective action in addition to anti-inflammatory effects, via the activation of the Nrf-2 pathway [138, 139]	
Alemtuzumab	Is a monoclonal antibody that targets CD52, a cell surface protein predominantly found in B and T lymphocytes [89]	2013[b]
	Depletes lymphocyte populations and leads to a distinctive pattern of lymphocyte repopulation [90]	
Laquinimod	Is thought to work by increasing production of anti-inflammatory cytokines and decreasing production of proinflammatory cytokines [23, 154]	–
	May also reduce leukocyte migration into the CNS [153, 155]	
Daclizumab	Is a humanized monoclonal antibody which binds to the α-subunit (CD25) of the IL-2 receptor expressed on activated T cells and regulatory T cells [156]	–
	Inhibits several IL-2-dependent T-cell functions, including antigen- and mitogen-induced proliferation and cytokine secretion by activated T_h1 and T_h2 lymphocytes [157]	
Ocrelizumab	Is a humanized, recombinant monoclonal antibody reactive against CD20, which is widely expressed on B cells [162]	–
	Depletes B cells [163]	

CNS central nervous system, *IL* interleukin, *Nrf-2* nuclear factor (erythroid-derived 2)-like 2, T_h T helper, *VLA* very late antigen

[a] Mitoxantrone was approved for use in the US only in 2000

[b] Alemtuzumab received marketing authorization in the EU only in 2013

effect on the CNS. The brain is relatively isolated from the immune system by the BBB, and it has not been established what doses of IFN would be needed to achieve physiologically relevant concentrations in CSF. It is possible that IFNs cross the BBB at sites of CNS inflammation. Alternatively, and not mutually exclusively, CNS effects of IFNs may be related to inhibition of inflammatory cell migration across the BBB [34].

2.1.2 Clinical Effects in Relapsing MS

Injectable IFNs have been the mainstay of MS treatment for around 20 years, and are frequently used as first-line therapy. Table 2 summarizes data regarding clinical efficacy (effect on disease relapses and disability progression) of the IFNβ formulations from randomized, placebo-controlled, phase III trials. The clinical efficacy in comparative randomized trials is summarized in Table 3. Meta-analyses show that IFNβ is associated with a significant effect on MS relapses and disability progression compared with placebo [38, 39]; however, the effect of IFNβ therapy on disability progression has been disputed, as a large-scale, retrospective study of prospectively collected data demonstrated that IFNβ was not associated with a reduction in disability progression [35–37]. A consideration relating to the efficacy of the IFNβ formulations is the potential for

Table 2 Clinical outcomes of randomized, placebo-controlled, phase III trials of approved or late-stage disease-modifying therapies in previously untreated patients with relapsing multiple sclerosis[a]

Active therapy	Trial name/ study group [reference]	Regimen	*n*	ARR over 2 years (*p* value vs placebo)	Mean baseline EDSS score	EDSS score change over 2 years (*p* value vs placebo)	MSFC change over 2 years (*p* value vs placebo)	Confirmed disability progression at 2 years % (*p* value vs placebo)* [based on KM estimates][†]	Reduced disability progression vs placebo at 2 years*	Publication date
Dimethyl fumarate	CONFIRM [148]	Oral dimethyl fumarate 240 mg twice daily	359	0.22 ($p < 0.001$)	2.6	N/R	N/R	13 (N/R)[b] HR 0.79 (0.52–1.19)	No	2012
		Oral dimethyl fumarate 240 mg thrice daily	345	0.20 ($p < 0.001$)	2.5			13 (N/R) HR 0.76 (0.50–1.16)	No	
		Glatiramer acetate SC 20 mg once daily (reference arm)	350	0.29 ($p = 0.01$)	2.6			16 (N/R)[b] HR 0.93 (0.63–1.37)	No	
		Placebo	363	0.40	2.6			17	–	
	DEFINE [147]	Oral dimethyl fumarate 240 mg twice daily	410	0.17 ($p < 0.001$)	2.4	N/R	N/R	16 (N/R)[b] HR 0.62 (0.44–0.87) $p \leq 0.005$	Yes[‡]	2012
		Oral dimethyl fumarate 240 mg thrice daily	416	0.19 ($p < 0.001$)	2.4			18 (N/R) HR 0.66 (0.48–0.92) $p = 0.01$	Yes[‡]	
		Placebo	408	0.36	2.5			27	–	
Fingolimod	FREEDOMS [114]	Oral fingolimod 1.25 mg once daily	429	0.16 ($p < 0.001$)	2.4	–0.03 ($p = 0.002$)	0.01 (0.02)	16.6 ($p = 0.01$)[c] HR 0.68 (0.50–0.93) $p = 0.02$	Yes[‡]	2010
		Oral fingolimod 0.5 mg once daily	425	0.18 ($p < 0.001$)	2.3	0.00 ($p = 0.002$)	0.03 (0.01)	17.7 ($p = 0.03$) HR 0.70 (0.52–0.96) $p = 0.02$	Yes[‡]	
		Placebo	418	0.40	2.5	0.13	–0.06	24.1	–	
Glatiramer acetate	MSSG [176]	Glatiramer acetate SC 20 mg once daily	125	1.19 ($p = 0.007$)	2.8	–0.05 ($p = 0.023$)	N/R	21.6 (N/R)[d]	No[§]	1995
		Placebo	126	1.68	2.4	0.21		24.6	–	

Table 2 continued

Active therapy	Trial name/ study group [reference]	Regimen	*n*	ARR over 2 years (*p* value vs placebo)	Mean baseline EDSS score	EDSS score change over 2 years (*p* value vs placebo)	MSFC change over 2 years (*p* value vs placebo)	Confirmed disability progression at 2 years % (*p* value vs placebo)* [based on KM estimates][†]	Reduced disability progression vs placebo at 2 years*	Publication date
IFNβ-1a IM	MSCRG [177]	IFNβ-1a IM 30 μg weekly	158	0.61 ($p = 0.002$)	2.4	0.25 ($p = 0.02$)	N/R	21.9 ($p = 0.02$)[e]	Yes[‡]	1996
		Placebo	143	0.90	2.3	0.74		34.9	–	
IFNβ-1a SC	PRISMS [178]	IFNβ-1a SC 44 μg 3 times per week	184	1.73 ($p < 0.005$)	2.5	0.23 ($p \leq 0.05$)	N/R	N/R	Yes[‡]	1998
		IFNβ-1a SC 22 μg 3 times per week	189	1.82 ($p < 0.005$)	2.5	0.24 ($p \leq 0.05$)			Yes[‡]	
		Placebo	187	2.56	2.4	0.48			–	
IFNβ-1b SC	MSSG [179]	IFNβ-1b SC 8 MIU every other day	124	0.84 ($p = 0.0001$)	3.0	N/R	N/R	N/R	Marginal[¶]	1993
		IFNβ-1b SC 1.6 MIU every other day	125	1.17 ($p = 0.01$)	2.9				No	
		Placebo	123	1.27	2.8				–	
Mitoxantrone	MIMS [55]	Mitoxantrone IV 12 mg/m^2 every 3 months	63	0.35 ($p = 0.001$)	4.5	–0.13 ($p = 0.0194$)	N/R	8.3 ($p = 0.036$)[d]	Yes	2002
		Mitoxantrone IV 5 mg/m^2 every 3 months	66	N/R	4.6	N/R	N/R	N/R	–	
		Placebo	65	1.02	4.7	0.23	N/R	22.0	–	
Natalizumab	AFFIRM [69]	Natalizumab IV 300 mg every 4 weeks	627	0.23 ($p < 0.001$)	2.3	N/R	N/R	17 (N/R)[b] HR 0.58 (0.43–0.77) $p < 0.001$	Yes[‡]	2006
		Placebo	315	0.73	2.3			29	–	
Teriflunomide	TEMSO [132]	Oral teriflunomide 7 mg once daily	365	0.37 ($p < 0.001$)	2.7	N/R	N/R	21.7 ($p = 0.08$)[c] HR 0.76 (0.56–1.05)	No	2011
		Oral teriflunomide 14 mg once daily	358	0.37 ($p < 0.001$)	2.7			20.2 ($p = 0.03$) HR 0.70 (0.51–0.97)	Yes[‡]	
		Placebo	363	0.54	2.7			27.3	–	

Table 2 continued

Active therapy	Trial name/ study group [reference]	Regimen	*n*	ARR over 2 years (*p* value vs placebo)	Mean baseline EDSS score	EDSS score change over 2 years (*p* value vs placebo)	MSFC change over 2 years (*p* value vs placebo)	Confirmed disability progression at 2 years % (*p* value vs placebo)* [based on KM estimates][†]	Reduced disability progression vs placebo at 2 years*	Publication date
Laquinimod	ALLEGRO [158]	Oral laquinimod 0.6 mg once daily	550	0.30[¥] ($p = 0.002$)	2.6	2.68[¥] ($p = 0.05$)	0.06[¥] ($p = 0.59$)	11.1 (N/R)[e] HR 0.64 (0.45–0.91) $p = 0.01$	Yes[‡]	2012
		Placebo	556	0.39[¥]	2.6	2.79[¥]	0.04[¥]	15.7 (N/R)	–	

ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *HR* hazard ratio, *IFNβ* interferon beta, *IM* intramuscular, *IV* intravenous; *KM* Kaplan–Meier, *MIU* million international units, *MS* multiple sclerosis, *MSFC* Multiple Sclerosis Functional Composite, *N/R* not reported, *SC* subcutaneous

See Table 5 for full trial names

* As disability progression criteria varied across studies, caution should be applied when making direct comparisons

† HRs were calculated using Cox's proportional hazards model, with baseline EDSS score, adjusted region, and baseline age as continuous variables

‡ Significantly reduced the risk of sustained disability progression or delayed progression of disability over the study period

§ Significantly more patients taking placebo declined by 1.0 point in the EDSS score during the trial, while significantly more patients taking glatiramer acetate increased by 1.0 point in the EDSS score. However, there was no difference in sustained disability progression between the two groups

¶ There was no significant change in the mean EDSS score. There was a weak trend suggesting lessened disability at the 3-year time point ($p = 0.043$). However, this was not confirmed (i.e., sustained) over two consecutive EDSS scores

¥ These values are actual scores at study endpoint

[a] Phase III studies involving daclizumab [165] and ocrelizumab [168] are ongoing, and clinical outcomes are not included in this table

[b] Disability progression was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later

[c] Disability progression was defined as an increase of 1.0 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months

[d] Disability progression defined as an increase of 1.0 point in the EDSS score confirmed after 3 months

[e] Disability progression defined as an increase of 1.0 point in the EDSS score confirmed after 6 months

Table 3 Clinical outcomes from comparative randomized trials of approved disease-modifying therapies in patients with relapsing multiple sclerosis[a]

Trial name/study group [reference]	Study masking	Regimen	*n*	ARR over 2 years (differences not significant unless stated)	Mean baseline EDSS score	EDSS change over 2 years (differences not significant unless stated)	MSFC change over 2 years (differences not significant unless stated)	Confirmed disability progression at 2 years % (*p* value vs placebo)[b] [based on KM estimates][c]	Differences in disability progression between arms over 2 years	Publication date
BECOME [49]	Single blind (outcomes assessor)	IFNβ-1b SC 250 μg every other day	36	0.37	2.0[b]	N/R	N/R	N/R	Not studied	2009
		Glatiramer acetate SC 20 mg once daily	39	0.33	2.0[b]					
BEYOND [50]	Double blind (subject, caregiver, outcomes assessor)	IFNβ-1b SC 500 μg every other day	899	0.33	2.3	N/R	N/R	22[d]	No differences	2009
		IFNβ-1b SC 250 μg every other day	897	0.36	2.4			21		
		Glatiramer acetate SC 20 mg once daily	448	0.34	2.3			20		
BRAVO [159]	Double blind (subject, caregiver, outcomes assessor)	Oral laquinimod 0.6 mg once daily	434	0.28	2.7	N/R	N/R	HR 0.67 (0.45–0.99) $p = 0.04$ vs placebo	$p = 0.04$ vs placebo No differences	2011
		IFNβ-1a SC 44 μg 3 times per week	447	0.26 ($p = 0.007$ vs placebo)	2.7					
		Placebo	450	0.34	2.7					
CARE-MS I [91]	Single blind (outcomes assessor)	Alemtuzumab IV 12 mg once daily for 5 days, then once daily for 3 days at 12 months	386	0.18	2.0	–0.14	0.15 ($p = 0.01$)	8[e] 0.70 (0.40–1.23)	No differences	2012
		IFNβ-1a SC 44 μg 3 times per week	187	0.39	2.0	–0.14	0.07	11		
CARE-MS II [92]	Single blind (outcomes assessor)	Alemtuzumab IV 12 mg once daily for 5 days, then once daily for 3 days at 12 months	426	0.26	2.7	2.9	0.08	12.1[e] 0.58 (0.38–0.87)	$p = 0.0084$ vs IFNβ	2012
		IFNβ-1a SC 4 μg 3 times per week	202	0.52	2.7	2.6	–0.04	21.13		

Table 3 continued

Trial name/study group [reference]	Study masking	Regimen	*n*	ARR over 2 years (differences not significant unless stated)	Mean baseline EDSS score	EDSS change over 2 years (differences not significant unless stated)	MSFC change over 2 years (differences not significant unless stated)	Confirmed disability progression at 2 years % (*p* value vs placebo)[b] [based on KM estimates][c]	Differences in disability progression between arms over 2 years	Publication date
Danish study [180]	Single blind (outcomes assessor)	IFNβ-1a SC 22 μg weekly	143	0.66	–	N/R	N/R		No differences	2006
		IFNβ-1b SC 250 μg every other day	158	0.66	–					
EVIDENCE [181]	Single blind (outcomes assessor)	IFNβ-1a SC 44 μg 3 times per week	339	0.54[f]	2.3	N/R	N/R	12.7 0.87 (0.58–1.31)	No differences	2002
		IFNβ-1a IM 30 μg weekly	338	0.64[f]	2.3			14.5		
INCOMIN [182]	Single blind (outcomes assessor)	IFNβ-1b SC 250 μg every other day	96	0.50 ($p < 0.001$)*	2.0	2.1 ($p = 0.004$)*	N/R	13[g] ($p = 0.005$)	Higher EDSS score at 24 months with IFNβ-1a (2.5) vs IFNβ-1b (2.1) at 24 months; $p = 0.004$	2002
		IFNβ-1a IM 30 μg weekly	92	0.70	2.0	2.5		30 0.44 (0.25–0.80) $p < 0.005$ vs IFNβ-1b		
REGARD [51]	Single blind (outcomes assessor)	IFNβ-1a SC 44 μg 3 times per week	386	0.30	2.4	2.4	N/R	11.7[h]	No differences	2008
		Glatiramer acetate SC 20 mg once daily	378	0.29	2.3	2.3		8.7		
TENERE [183, 184]	Single blind (outcomes assessor)	Oral teriflunomide 7 mg once daily	109	0.41	2.0	N/R	N/R		No differences	2013
		Oral teriflunomide 14 mg once daily	111	0.26	2.3					
		IFNβ-1a SC 44 μg 3 times per week	104	0.22 ($p = 0.03$)**	2.0					

Table 3 continued

Trial name/study group [reference]	Study masking	Regimen	*n*	ARR over 2 years (differences not significant unless stated)	Mean baseline EDSS score	EDSS change over 2 years (differences not significant unless stated)	MSFC change over 2 years (differences not significant unless stated)	Confirmed disability progression at 2 years % (*p* value vs placebo)[b] [based on KM estimates][c]	Differences in disability progression between arms over 2 years	Publication date
TRANSFORMS [115]	Double blind (subject, caregiver, outcomes assessor)	Oral fingolimod 1.25 mg once daily	420	0.20 ($p < 0.001$)***	2.2	–0.11 ($p = 0.02$)	0.08 ($p < 0.001$)	6.7[i]	No differences	2010
		Oral fingolimod 0.5 mg once daily	429	0.16 ($p < 0.001$)***	2.2	–0.08 ($p = 0.06$)	0.04 ($p = 0.02$)	5.9		
		IFNβ-1a IM 30 μg weekly	431	0.33 (at 1 year)	2.2	0.01	–0.03	7.9		

ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *HR* hazard ratio, *IFNβ* interferon beta, *IM* intramuscular, *IV* intravenous, *KM* Kaplan–Meier, *MSFC* Multiple Sclerosis Functional Composite, *N/R* not reported, *SC* subcutaneous

See Table 5 for full trial names

* $p = 0.03$ for SC IFNβ-1b versus IM IFNβ-1a

** $p = 0.03$ for SC IFNβ-1b versus 7 mg teriflunomide

*** $p < 0.001$ for both doses of oral fingolimod versus IM IFNβ-1a

[a] Phase III studies involving daclizumab [165] and ocrelizumab [168] are ongoing, and clinical outcomes are not included in this table

[b] Median

[c] HRs were calculated using Cox's proportional hazards model, with baseline EDSS score, adjusted region, and baseline age as continuous variables

[d] Disability progression was defined as a 1.0 point change in the EDSS score that was sustained for 3 months

[e] Sustained accumulation of disability was defined as an increase from baseline of at least 1.0 point in the EDSS score (or 1.5 points if baseline EDSS score was 0) confirmed over 6 months

[f] ARR over 48 weeks; difference not significant at this time point

[g] Disability progression was defined as an increase of at least 1.0 point in the EDSS score sustained for at least 6 months and confirmed at the end of follow-up

[h] Disability progression was defined as an increase of 1.0 point in the EDSS score that was confirmed after 3 months

[i] Disability progression was defined as a 1.0 point increase in the EDSS score (or a half-point increase for patients with a baseline score = 5.5) that was confirmed 3 months later in the absence of relapse

Table 4 Adverse events commonly associated with each disease-modifying therapy and occurring more frequently than placebo in placebo-controlled studies[a]

Therapy	Most common[b] adverse events
Interferonβ-1a/b	Flu-like symptoms, headaches, injection-site reactions, and elevated liver enzymes
	Flu-like symptoms and depression were the most common causes of discontinuation
Glatiramer acetate	Injection-site reactions, vasodilatation, rash, dyspnea, and chest pain (not of cardiac origin)
	Injection-site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity were the most common causes of discontinuation
Mitoxantrone	Nausea, vomiting, alopecia, and urinary tract infections
	Leucopenia, depression, decreased left-ventricular ejection fraction, bone pain, repeated urinary tract infections, and hydronephrosis were the causes of discontinuation
Natalizumab	Headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash
	Urticaria and other hypersensitivity reactions were the most common causes of discontinuation
Fingolimod	Headache, flu-like symptoms, diarrhea, back pain, liver enzyme elevations, cough, and bradycardia at treatment onset
	Serum transaminase elevation was the most common cause of discontinuation
Teriflunomide	Serum alanine aminotransferase increased, alopecia, diarrhea, flu-like symptoms, nausea, and paresthesia
	Alopecia was the most common cause of discontinuation
Dimethyl fumarate	Flushing, abdominal pain, diarrhea, and nausea
	Gastrointestinal events, flushing, and elevated hepatic transaminases were the most common causes of discontinuation
Alemtuzumab	Rash, headache, pyrexia, and respiratory tract infections
	Immune thrombocytopenic purpura, thyroid disorders, nephropathies, cytopenias, infusion-associated reactions, and infections were also associated with infusions
Laquinimod	Headaches, nasopharyngitis, and back pain
	Elevations in alanine transaminase were the most common cause of discontinuation

[a] Phase III studies involving daclizumab [165] and ocrelizumab [168] are ongoing, and adverse events commonly associated with these drugs are not included in this table

[b] The reported common adverse events include those occurring at a frequency of >1/10 and ≥1/100, based on product labels where available, or from pivotal publications for therapies yet to gain an indication

patients to produce neutralizing antibodies. Although the role of neutralizing antibodies is not fully understood, it is thought that they lead to treatment resistance and can therefore reduce treatment efficacy over the long term [38, 39].

All three forms of IFNβ are generally well tolerated. The most common adverse events are flu-like symptoms, headaches, and injection site reactions, as summarized in Table 4. However, due to the effect of IFNβ on circulating lymphocyte numbers, formulations are also associated with mild lymphopenia.

More recently, a formulation of IFNβ-1a conjugated to polyethylene glycol (PEG) was developed as a potential treatment for relapsing–remitting MS (RRMS). This pegylation process was designed to extend the half-life of IFNβ-1a and enable a less frequent dosing schedule. The ongoing phase III ADVANCE study (see Table 5 for full trial names) aims to determine the clinical efficacy of PEG-IFNβ-1a administered once every 2 weeks or every 4 weeks via SC injection in patients with relapsing MS [40].

2.2 Glatiramer Acetate

2.2.1 Mechanism of Action and Immunological Effects

GA was first approved as a daily injectable treatment for RRMS in 1996 and, like the IFNs, it is a frequently used first-line agent [10, 11]. More recently, a higher dose formulation (40 mg) administered three times per week has been approved in the US for use in patients with RRMS [41]. GA consists of a heterogeneous polypeptide mixture made of glutamic acid, lysine, alanine, and tyrosine that was designed to simulate myelin basic protein, one of the major myelin auto-antigens classically used to induce experimental autoimmune encephalomyelitis (EAE) in animal models, and also thought to be involved in MS.

The exact MoA of GA is not fully understood [42]; however, it appears to shift the GA-reactive lymphocyte population from a pro-inflammatory T helper (T_h) 1 state to an anti-inflammatory T_h2 state. In various studies, GA has also been shown to increase levels/expression of

Table 5 Acronyms and full trial names/study groups

Acronym	Full trial name/study group
ADVANCE	Efficacy and Safety Study of BIIB017
AFFIRM	Natalizumab Safety and Efficacy in Relapsing–Remitting Multiple Sclerosis
ALLEGRO	Safety and Efficacy of Orally Administered Laquinimod for Treatment of Relapsing Remitting Multiple Sclerosis
BECOME	Betaseron vs Copaxone in MS with Triple-Dose Gadolinium and 3-T MRI Endpoints
BEYOND	Betaferon Efficacy Yielding Outcomes of a New Dose in multiple sclerosis patients
BRAVO	Benefit and Risk Assessment of Avonex and Laquinimod
CARE-MS	Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis
CombiRX	Combination Therapy in Patients With Relapsing–Remitting Multiple Sclerosis
CONFIRM	Comparator and an Oral Fumarate in RRMS
DEFINE	Efficacy and Safety of Oral BG00012 in Relapsing–Remitting Multiple Sclerosis
EVIDENCE	Evidence of Interferon Dose-Response: European North American Comparative Efficacy
FREEDOMS	FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis
INCOMIN	Independent Comparison of Interferon
MIMS	Mitoxantrone in Multiple Sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
MSSG	Multiple Sclerosis Study Group
PRISMS	Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis
REGARD	Rebif vs Glatiramer Acetate in Relapsing MS Disease
TEMSO	Teriflunomide Multiple Sclerosis Oral
TENERE	Teriflunomide and Rebif®
TOWER	Teriflunomide Oral in People With Relapsing Remitting Multiple Sclerosis
TRANSFORMS	Trial Assessing Injectable Interferon vs FTY720 Oral in RRMS

anti-inflammatory IL-10 and IL-4 cells, and decrease levels of proinflammatory TNF and IL-12 cells [23]. Daily usage appears to selectively promote trans-endothelial migration of T_h2 cells across the BBB [43] and stimulate the release of anti-inflammatory cytokines [44]. There is no information regarding the absorption, distribution, metabolism, or excretion profiles of GA in humans as there is currently no direct and sensitive analytical method for measuring the compound in biological fluids. Therefore, it is also not known whether GA crosses the BBB.

A growing body of evidence suggests that GA leads to a broader immunomodulatory effect on cells of both the innate and adaptive immune system [23]. GA-mediated modulation of antigen-presenting cells (APCs) such as monocytes and dendritic cells, CD4+ T_h cells, CD8+ T cells, Forkhead box P3+ regulatory T cells, natural killer cells, and antibody production by plasma cells have been reported [23]. In addition, most recent investigations indicate that GA treatment may also promote regulatory B-cell properties, with a reciprocal reduction in the expression of proinflammatory cytokines [45, 46]. T-cell-induced brain-derived neurotrophic factor (BDNF) secretion following GA administration has also been described in MS, EAE, and experimental cell lines [47]. However, the clinical implications of this are not fully understood.

2.2.2 Clinical Effects in Relapsing MS

The efficacy of GA in reducing relapses in patients with MS has been demonstrated in several randomized, controlled clinical trials (Tables 2, 3) and post hoc analyses [48]. The efficacy of GA on relapse reduction was similar to that of IFN therapy in the BECOME, BEYOND, and REGARD trials, with similar annualized relapse rates (ARRs) [49–51]. Combined GA and IFN therapy did not reduce the risk of relapse compared with GA therapy alone over 3 years in the CombiRX trial [52]. The most common adverse events associated with GA therapy are injection site reactions, vasodilation, and rash (summarized in Table 4). Following GA injection, an immediate systemic reaction can occur in some patients, leading to chest tightness, dyspnea, and bradycardia lasting up to 20 minutes, but this reaction is not considered to be life threatening [53]. Rates of discontinuation were similar to those

for IFN formulations in clinical studies [49–51]. No new adverse events appeared in patients treated with a high-dose formulation of GA administered three times per week [41].

2.3 Mitoxantrone

2.3.1 Mechanism of Action and Immunological Effects

Mitoxantrone was approved in the US in 2000 for use in "patients with secondary progressive, progressive relapsing or worsening relapsing–remitting multiple sclerosis" [54]. It is a synthetic anthracenedione traditionally used as an anti-neoplastic agent. Mitoxantrone intercalates with the DNA of both proliferating and non-proliferating cells causing strand breaks, and also inhibits DNA repair via inhibition of topoisomerase II [55]. It is thought that the mechanism by which mitoxantrone exerts its therapeutic effect in MS is through inhibition of proliferation of B and T lymphocytes and macrophages [54]. Additionally, several other immunosuppressive effects have been described, such as decreased secretion of IFNγ, TNFα, and IL-2 [56].

2.3.2 Clinical Effects in Relapsing MS

Mitoxantrone is administered by intravenous infusion every 3 months at a dose that is body-weight dependent (12 mg/m^2). Table 2 summarizes data regarding clinical efficacy on disease relapses and disability progression of mitoxantrone from the randomized, placebo-controlled, phase III MIMS trial [55]. Meta-analyses show that mitoxantrone is associated with a significant effect on MS relapses and disability progression compared with placebo [57].

The most common adverse events are nausea, vomiting, alopecia, and urinary tract infections, as summarized in Table 4 [54]. Cardiotoxicity, neutropenia, amenorrhea, which in some cases may be permanent, and the potential for late-occurring leukemia are the major safety concerns associated with mitoxantrone use [57].

2.4 Natalizumab

2.4.1 Mechanism of Action and Immunological Effects

Natalizumab is a recombinant humanized monoclonal antibody produced in murine myeloma cells [17]. Natalizumab is a selective adhesion molecule inhibitor; it binds specifically to α4-subunits of α4β1 and α4β7 integrins expressed on the surface of all white blood cells (WBCs), except neutrophils [58]. This inhibits α4-mediated adhesion of WBCs to their counter-receptors, including vascular cell adhesion molecule-1 (VCAM-1) [59], and reduces very late antigen-4 expression on all investigated immune cells, including B cells [60]. This produces a number of phenotypic changes in the immune composition of peripheral blood [61].

Natalizumab increases the percentage of activated leukocytes producing pro-inflammatory cytokines, which has been attributed to sequestration of activated lymphocytes in the peripheral circulation [62, 63]. The CD4/CD8 ratio is reduced with long-term therapy [64], and serum immunoglobulin (Ig) M and IgG levels decrease significantly with continued therapy [65]. Natalizumab also increases the number of circulating CD34+ hematopoietic progenitors by interfering with homing to bone marrow [66]. In addition, increases in peripheral natural killer cells have been observed with natalizumab treatment. This effect may play a role in its efficacy, but further investigation is required [23].

Through the disruption of various molecular interactions, natalizumab is believed to directly inhibit transmigration of leukocytes into the CNS and inflamed parenchymal tissue [59], thus reducing the formation of MS lesions. Treatment with natalizumab may also inhibit the ongoing inflammation mediated by leukocytes already present in the CNS by interrupting their interaction with the extracellular matrix proteins [67]. One study has shown that natalizumab can cross the BBB, although the full implications of this finding are yet to be determined [68].

2.4.2 Clinical Effects in Relapsing MS

Natalizumab intravenous infusion was approved as a treatment for RRMS in 2007, and is used mainly as a second-line therapy [16, 17]. The phase III, placebo-controlled AFFIRM study demonstrated the efficacy of natalizumab in reducing disease relapses and preventing disability progression [69], and subsequent meta-analyses confirmed these findings [70, 71]. At present, there are no direct head-to-head comparisons of natalizumab with other DMTs (Table 3), but the numerical differences in the findings seen in AFFIRM suggest this agent may be more effective than the IFNβs and GA in terms of reducing relapses (Table 2).

In a prospective, observational cohort study of 73 MS patients treated with natalizumab, development of antibodies to the agent occurred by week 24 in 58 % of the patients [72]. The majority of these patients reverted to an anti-natalizumab-negative status at follow-up. However, the persistence of anti-natalizumab antibodies in the minority of patients correlated with a reduction in serum natalizumab levels and decreased drug efficacy [72, 73].

The most common adverse events associated with natalizumab therapy are headache, fatigue, and respiratory tract infections (summarized in Table 4). The immune

system effects of natalizumab may increase the risk of infections, including pneumonia, urinary tract infections, gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections [17, 69].

Most notably, long-term exposure to natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the John Cunningham virus (JCV), which can reactivate in patients who are immunocompromised [74]. As of September 2013, over 120,500 patients worldwide had received natalizumab and, as of November 2013, there had been 418 confirmed post-marketing cases of PML among these individuals leading to 96 deaths (23 %) [75]. Risk factors for development of PML in natalizumab-treated MS patients include a positive anti-JCV antibody test, prior use of immunosuppressants, and exceeding 24 months of natalizumab treatment [76]. Presence of all three factors increases the risk of PML by about 20-fold compared with having a positive anti-JCV antibody test alone, and by over 100-fold compared with a negative test for JCV antibodies [77]. Given that anti-JCV antibodies are found in 50–60 % of the general population, healthcare providers are advised to stratify their patients to treatment according to anti-JCV status and other risk factors. Additionally, it is recommended that patients receiving natalizumab who test negative for anti-JCV antibodies should be retested every 6 months [76] as seroconversion rates are estimated to be between 2.0 % and 14.5 % per year [78, 79]. Immune reconstitution inflammatory syndrome after withdrawal of natalizumab has been observed in at least 90 % of patients with PML, leading to death in 29 % [17, 80, 81].

Due to the risk of infections following natalizumab therapy, it is suggested that a washout period may be required before switching from natalizumab to another immunomodulatory therapy [82]. The pharmacodynamic effects of natalizumab are reported to last for 12 weeks according to the European Summary of Product Characteristics, but some reports suggest that some effects may continue for as long as 6 months [83]. However, this must be balanced with the risk of severe relapse if treatment with the new agent is delayed for too long [78, 84–88]. Therefore, the optimal time to initiate a new therapy after natalizumab discontinuation requires further investigation, and should also be considered on an individual patient basis to maximize efficacy and reduce risk of disease relapse and residual natalizumab effects.

2.5 Alemtuzumab

2.5.1 Mechanism of Action and Immunological Effects

Alemtuzumab is a recombinant, DNA-derived, humanized monoclonal antibody that targets CD52, a cell surface protein predominantly found in B and T lymphocytes [89]. Alemtuzumab is administered by intravenous infusion once per year, and is currently approved for the treatment of B-cell chronic lymphocytic leukemia and has recently been approved in the EU as a therapy for RRMS [22]. Treatment with alemtuzumab results in a rapid and long-lasting depletion of lymphocyte populations, after which homeostatic reconstitution leads to alterations in cell subsets, causing long-lasting changes in adaptive immunity [90].

2.5.2 Clinical Effects in Relapsing MS

Results from two phase III trials involving alemtuzumab are available (Table 3). Both trials compared the efficacy of alemtuzumab against IFNβ-1a in the treatment of RRMS. Superiority of alemtuzumab over active comparator in terms of relapse reduction, reduced inflammatory lesion activity, and reduced rate of brain parenchymal fraction reduction (a measure of brain atrophy) was observed in both the CARE-MS I and CARE-MS II studies [91, 92]. CARE-MS II also demonstrated improvement in sustained disability progression versus IFNβ-1a [92], although a disability benefit according to the Expanded Disability Status Scale compared with IFNβ-1a was not seen in the CARE-MS I trial [91].

The most common adverse events associated with alemtuzumab were headache, diarrhea, and flu-like symptoms (summarized in Table 4). Infections were more frequent with alemtuzumab than with IFNβ; notably cutaneous herpes was more common despite prophylactic acyclovir. The most common infections in patients receiving alemtuzumab included upper respiratory and urinary tract infections, sinusitis, and herpes simplex infections. Infections were predominantly mild to moderate in severity and there were no treatment-related life-threatening or fatal infections [91, 92].

Approximately 16–19 % of alemtuzumab-treated patients developed an autoimmune thyroid-related adverse event and approximately 1 % developed a serious thyroid-related event. Approximately 1 % developed immune thrombocytopenic purpura, and patient monitoring for immune cytopenias and thyroid or renal disorders is required for all clinical trials of alemtuzumab in MS [91, 92].

Alemtuzumab treatment significantly depletes mononuclear and lymphocyte subsets. Studies have shown that CD4 cells are depleted for up to 5 years and CD8 cells for 2.5 years. Monocytes and B cells return to baseline levels within 3 months of stopping treatment [90, 93]. Presumably, the capacity for immune-cell reconstitution is age dependent, as it is well documented that thymic production of new T cells declines as part of the normal ageing process [94, 95], although appropriate studies have not been

performed on patients older than 55 years [22]. Regardless, as a result of its prolonged effects on WBCs, it is likely that a washout period of several months, at least, may be required following cessation of alemtuzumab therapy, before starting another immunosuppressant treatment.

3 Orally Administered Therapies

3.1 Fingolimod

3.1.1 Mechanism of Action and Immunological Effects

Fingolimod is an orally administered, sphingosine 1-phosphate (S1P) receptor modulator used to treat relapsing forms of MS. It is a chemical derivative of myriocin, a metabolite of the fungus *Isaria sinclairii*, known for its anti-inflammatory properties [96].

Fingolimod reversibly redistributes lymphocytes into lymphoid tissue, whilst preserving lymphocyte function [97, 98]. By inducing internalization of S1P receptors (S1PRs) expressed on lymphocytes [99], fingolimod primarily inhibits egress of naïve and central memory lymphocytes from lymph nodes back into the circulation [100–102] and thereby prevents them from circulating to other tissues, including the CNS [98, 101]. However, effector memory lymphocytes, which are less dependent on S1P signaling for egress and do not regularly recirculate between lymphoid tissues, are less affected by fingolimod [101, 102]. These cells are mainly located in peripheral tissues and play a key role in preserving immunosurveillance [102].

Animal studies suggest that fingolimod does not impair the ability of lymphocytes (including the lymphocytes that are retained in the lymph nodes) to become activated, proliferate, and produce cytokines or antibodies [100]. The evidence suggests further that fingolimod does not inhibit humoral immunity to systemic viral infection, and does not suppress, or only modestly suppresses, the generation of virus-specific cytotoxic T cells in lymph nodes [102, 103]. Additionally, it has been demonstrated that fingolimod-treated individuals can mount vaccine-specific adaptive immune responses comparable to those of healthy controls [104, 105].

As well as its immunomodulatory effects, fingolimod may have a direct effect on the CNS as it can readily cross the BBB [18]. S1PRs are widely expressed on CNS-resident cells and have been reported to regulate several processes relevant to MS pathology. In animal models of encephalomyelitis, fingolimod, acting via S1PRs, reduced disease severity, restored motor function, and preserved brain tissue [106]. In a variety of different preclinical neurodegenerative models, fingolimod has been found to reduce astrogliosis, demyelination, and axonal loss [99, 101, 107], and protect from exocytotoxic insults, as well as potentially supporting neuroregenerative processes by enhancing recovery of myelin [108], restoring the function of neural cells [109], and increasing levels of neurotrophic factors, such as BDNF [110]. In addition, there is also preclinical evidence indicating that these effects may be independent of reductions in peripheral lymphocyte counts [107]. Recent evidence suggests S1P biology is altered in the CSF and on reactive astrocytes in white and grey matter lesions of MS patients [111–113].

3.1.2 Clinical Effects in Relapsing MS

In 2010, fingolimod became the first oral drug to be approved for the treatment of relapsing forms of MS [18, 19]. Fingolimod reduced relapses by 54 %, and delayed disability progression, lesion activity, and brain volume loss versus placebo over 2 years in the pivotal, randomized FREEDOMS clinical trial (Table 2) [114]. In a head-to-head phase III study of oral daily fingolimod versus IFNβ-1a IM in patients with MS (TRANSFORMS; Table 3), there were significantly greater reductions in relapse rate (52 % relative reduction), lesion activity, and brain volume loss with fingolimod than with IFNβ after 1 year [115]. In addition, meta-analyses indicate that fingolimod is more efficacious in reducing relapses than all IFNβ formulations and GA [116, 117]. The MoA of fingolimod likely accounts for its significant efficacy profile. The ability of fingolimod to readily cross the BBB, and potentially have direct effects within the CNS, may account, at least in part, for the consistently significant reductions (occurring within 6 months) in the progression of brain atrophy observed during all phase III pivotal trials.

The most common adverse events associated with fingolimod therapy are headache, flu-like symptoms, and diarrhea (summarized in Table 4). Fingolimod is generally well tolerated and discontinuation rates due to adverse events and severe adverse events were similar to discontinuation rates in placebo groups [114]. Two fatal herpetic infections occurred in TRANSFORMS in patients who received fingolimod at a higher-than-approved dose of 1.25 mg: one case each of herpes simplex virus encephalitis and disseminated primary varicella infection. The latter occurred in a patient without previous exposure to varicella who was also receiving high-dose corticosteroids for an MS relapse at the time of exposure to primary infection [115]. These cases are reported on a background of more than 71,000 patients treated with fingolimod in both the post-marketing and clinical-trial settings [118], and in a pooled population of patients from two phase III and one phase II studies and their extensions; serious infections were reported in 2.1 % of patients [119].

A core pharmacodynamic effect of fingolimod is a reversible reduction of the peripheral lymphocyte count to

approximately 30 % of baseline values [19]. The reversible reduction in lymphocyte counts occurs without an overall increase in infections relative to placebo, suggesting that during fingolimod therapy, peripheral lymphocyte counts do not reflect immunocompetence [119]. The lymphocyte count recovers back to normal levels within 1–2 months after fingolimod treatment discontinuation, and a 6-week washout period is recommended [19].

Another expected and well characterized pharmacodynamic effect is observed at treatment initiation. This first-dose effect presents as a transient, mostly asymptomatic, and self-limiting decrease in heart rate. The transient nature of heart rate effects is explained by the initial functional agonism and subsequent rapid internalization of S1PRs on atrial myocytes [120]. Bradycardia was typically asymptomatic, observed within 6 hours of the first dose, and resolved with continued treatment. Hence, the EU label recommends a 6-hour monitoring period after the first dose and an electrocardiogram prior to treatment initiation [19]. Fingolimod is contraindicated in patients with certain pre-existing heart conditions, stroke, or who are taking certain anti-arrhythmic medications.

Other known adverse effects reported in association with the MoA of fingolimod are generally infrequent and have a known temporal profile, which allows for appropriate monitoring. This includes macular edema occurring in approximately 0.4 % of patients receiving fingolimod 0.5 mg and presenting within 3–4 months of treatment initiation (patients with a history of uveitis appear to have an increased risk), which generally resolved with or without treatment after drug discontinuation [121], and reversible elevation of liver enzymes, mainly occurring in the first 6–12 months of treatment [19].

3.2 Teriflunomide

3.2.1 Mechanism of Action and Immunological Effects

Teriflunomide is an active metabolite of leflunomide, an approved oral therapy for rheumatoid arthritis since 1998 [122]. In 2012, oral teriflunomide was approved for treatment of relapsing forms of MS [20]. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not completely understood [123]. It is believed that the drug works by inhibiting dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme involved in de novo pyrimidine synthesis. By inhibiting DHODH and reducing DNA synthesis, teriflunomide has a cytostatic effect on proliferating T and B cells [124]. However, cellular salvage pathways for proliferation exist and allow slowly dividing T memory cells to sustain ongoing pyrimidine metabolism and to survive [125]. Teriflunomide was shown to interfere with the interaction of T cells and APCs, which is central to the immune response [126].

There is also evidence that teriflunomide blocks TNFα-induced activation of nuclear factor kappa B (NF-κB) [127], inhibits adhesion molecules and matrix metalloproteinases [128], and disrupts the interaction between T cells and APCs and integrin signaling during T-cell activation [129]. In vitro studies using Jurkat and cytotoxic T-lymphocyte line-4 cells have demonstrated the inhibition of tyrosine kinase pathways following teriflunomide administration [130]. Animal experiments with leflunomide have shown that some immunosuppressive effects can be reversed by uridine as a substitute for inhibited DHODH-dependent pyrimidine synthesis, whereas others cannot, thus attesting to the in vivo relevance of the compound's interference with immune cell signaling [131].

3.2.2 Clinical Effects in Relapsing MS

Teriflunomide has been associated with significant efficacy (in terms of reducing relapses by approximately 30 % and delaying disability progression [14-mg dose only]) versus placebo in the pivotal, randomized TEMSO [132] and TOWER [133] clinical trials (Table 2). In addition, a head-to-head study has been conducted showing no superiority of oral daily teriflunomide versus IFNβ-1a SC in patients with MS (TENERE; Table 3).

The most common adverse events with teriflunomide are alopecia, diarrhea, and flu-like symptoms (summarized in Table 4). The increase in liver enzyme levels is of interest. As stated, teriflunomide is the active metabolite of leflunomide. Liver toxicity is one of the most serious safety concerns associated with leflunomide. In rare cases, leflunomide has been associated with severe hepatic injury leading to death in patients with rheumatoid arthritis. As a consequence, MS care providers should monitor liver function prior to and during treatment with teriflunomide [134].

A mean decrease in lymphocyte count of approximately 15 % and in platelet count of approximately 10 % was observed, but no overall increase in the risk of serious infections was reported in clinical trials with teriflunomide [132]. Fatal infections have been reported in the post-marketing setting in patients receiving leflunomide [134].

Teriflunomide is teratogenic in animal models and so women of childbearing potential must present a negative pregnancy test before starting the drug and use effective birth control during treatment [134].

Teriflunomide is eliminated slowly from plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations <0.02 mg/L, although because of individual variations in drug clearance it may take as long as 2 years [134]. An accelerated elimination procedure could be used at any time after discontinuation of teriflunomide. Elimination can be accelerated by using either cholestyramine or oral

activated charcoal powder for 11 days [134]. At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to a more than 98 % decrease in teriflunomide plasma concentrations.

3.3 Dimethyl Fumarate (BG-12)

3.3.1 Mechanism of Action and Immunological Effects

Dimethyl fumarate (DMF) is a methyl ester of fumaric acid. Early reports identified it as a potent cell radio-sensitizer. The large enhancement of radiation sensitivity was due to thiol depletion, thought to be responsible for radio resistance [135]. Fumaric acid esters have also been used successfully as psoriasis therapy since 1959 and are thought to have therapeutic potential for other dermatological and non-dermatological conditions [136].

The MoA by which DMF exerts its therapeutic effect in MS is not fully understood [137]. It has been proposed that fumarates may promote cytoprotection via the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription pathway [138]. DMF is rapidly metabolized to the metabolite, monomethyl fumarate (MMF). Both DMF and MMF have short half-lives, so DMF requires twice-daily administration [137]. DMF and MMF have been shown to activate the Nrf2 pathway in vitro and in vivo in animals and humans [137], with a corresponding increase in cellular redox potential, glutathione levels, adenosine triphosphate levels, mitochondrial membrane potential, and other anti-oxidative effects resulting in cytoprotective effects [138, 139]. It is worth noting that activation of the Nrf2 pathway has been implicated in tumorigenesis [140], although the clinical relevance of this in MS is unclear.

Other reported immunosuppressive effects of DMF include induction of the anti-inflammatory heme oxygenase protein via glutathione depletion [141], inhibition of cytokine-induced nuclear translocation of NF-κB apoptosis of stimulated T cells [142], and modulation of B-cell apoptosis and upregulation of monocyte superoxide anion production [143]. In vitro studies have indicated the role of DMF in promoting the T_h2-associated cytokines IL-4 and IL-5 in stimulated T cells, while down-regulating T_h1 responses and inhibiting expression of intracellular adhesion molecule-1, E-selectin, and VCAM-1 [144]. Additionally, DMF has been identified as a nicotinic acid receptor agonist in vitro [137], which may be linked to the flushing events observed in MS patients (Table 2) [145].

3.3.2 Clinical Effects in Relapsing MS

DMF was approved in 2013 for treatment of relapsing forms of MS [21, 146]. DMF has shown significant efficacy (in terms of reducing relapses by 53 %, delaying disability progression, and reducing the number of gadolinium-enhancing and new or enlarging T2-weighted hyperintense lesions) versus placebo in the DEFINE trial (Table 2) [147]. In another 2-year, phase III study with GA as a reference comparator (CONFIRM), DMF reduced inflammatory disease activity and did not significantly reduce disability progression [148].

The most common adverse events associated with DMF therapy are flushing, abdominal pain, and diarrhea (summarized in Table 4). The incidence of gastrointestinal events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with DMF versus placebo. A total of 5 and 6 % of patients in twice-daily and thrice-daily groups, respectively, discontinued DMF due to gastrointestinal events in DEFINE [147]. DMF has also been associated with elevation of hepatic transaminases (mostly <3 times the upper limit of normal) and transient increase in mean eosinophil counts was seen during the first 2 months of therapy [137].

In CONFIRM and DEFINE, mean lymphocyte counts decreased by approximately 30 % during the first year of treatment with DMF and then remained stable [137, 147, 148]. Guidance on a washout period between stopping DMF therapy and starting another MS therapy is not currently available. According to the US label, mean lymphocyte counts increased, but did not return to baseline, 4 weeks after stopping DMF [137]. The incidence of infections and serious infections was reported to be comparable to that with placebo; however, there have been a total of four reports of PML and one report of Kaposi's sarcoma [149] in patients with psoriasis who were treated with fumarates (treatment with a mixture of DMF and the calcium, magnesium, and zinc salts of ethylhydrogen fumarate with the registered trade name of Fumaderm®) in the context of 180,000 patient-years of Fumaderm® treatment [149–151]. To date, there have been no reports of PML or Kaposi's sarcoma among patients with MS treated with DMF [147, 148].

4 Therapies in Late-Stage Development

4.1 Laquinimod

4.1.1 Mechanism of Action and Immunological Effects

Laquinimod is a synthetic, experimental compound being investigated as an oral treatment for MS. Laquinimod is a successor to the discontinued experimental drug linomide [152]. Linomide was tested in phase III trials, but clinical development was terminated due to severe cardiovascular toxicity [152]. Chemical modification of the linomide structure has given laquinimod a favorable toxicological profile and improved potency in EAE animal models [153].

Laquinimod is thought to work by shifting the CD4+ phenotype from the proinflammatory T_h1 pattern in favor of the T_h2/T_h3 pattern (increased IL-4 and IL-10 production) and inhibiting the infiltration of inflammatory cells into the CNS [23, 154]. Several groups have also shown that laquinimod reduces leukocyte migration into the CNS [153, 155]. Another potential MoA is the suppression of major histocompatibility complex class II antigen presentation and down-regulation of epitope spreading [156].

As well as these immunomodulatory effects, it has been postulated that laquinimod may confer a degree of neuroprotection. Treatment with laquinimod is associated with significantly higher levels of BDNF in the CNS [23]. In animal models, laquinimod crossed the BBB. In doing so, laquinimod might exert direct effects within the CNS, although it is not yet clear how this may occur, or indeed whether this has any relevance in a clinical setting [157].

4.1.2 Clinical Effects in Relapsing MS

In a phase III, randomized, placebo-controlled study in patients with RRMS (ALLEGRO), treatment with laquinimod led to a modest but significant reduction in the mean ARR, a significant reduction in disability progression, and a significantly reduced number of both gadolinium-enhancing and new or enlarging T2-weighted lesions compared with placebo (Table 2) [158]. In a second phase III, randomized, placebo- and IFNβ-1a IM-controlled study in patients with RRMS (BRAVO), laquinimod significantly reduced progression of disability and brain atrophy. In this study, laquinimod failed to reduce the ARR versus placebo in the primary analysis (Table 3). However, when the data were adjusted for baseline clinical factors associated with relapse rate that were imbalanced between treatment groups, the ARR in the placebo group increased to lead to a statistically significant advantage for laquinimod over placebo [159].

The most common adverse events associated with laquinimod therapy are headache, nasopharyngitis, and back pain (summarized in Table 4). In clinical trials, back pain, cough, headache, and depression appeared to occur more frequently with laquinimod than with placebo [158, 159]. In the phase III studies, most adverse events were similar to placebo in frequency [158, 159], although transient elevations of alanine aminotransferase ≥3 times the normal level were seen more frequently with laquinimod than placebo and IFNβ [158, 159].

4.2 Daclizumab

4.2.1 Mechanism of Action and Immunological Effects

Daclizumab is a humanized monoclonal antibody which binds to the α-subunit (CD25) of the IL-2 receptor expressed on activated T cells and CD4+CD25+FoxP3+ regulatory T cells [160]. This results in the inhibition of several IL-2-dependent T-cell functions, including antigen- and mitogen-induced proliferation, cytokine secretion by activated T_h1 and T_h2 lymphocytes, and interference with CD28-dependent CD40 ligand expression [161]. It has also been proposed that daclizumab results in expansion and activation of immunoregulatory $CD56^{bright}$ natural-killer cells, which are able to gain access to the CNS and suppress activation of pathogenic immune responses [162].

4.2.2 Clinical Effects in Relapsing MS

Daclizumab is administered by subcutaneous injection every 4 weeks. Phase II clinical trials showed that daclizumab, as add-on or monotherapy in RRMS, had a dose-dependent effect on reducing relapse rate, disability progression, and the number and volume of gadolinium-enhancing T1 and T2 lesions over 12 months [163, 164]. Adverse events were equally distributed across treatment groups; however, serious adverse events attributed to daclizumab treatment emerged. These were categorized into four main groups: infections, skin reactions, liver abnormalities, and autoimmune phenomena [160]. Phase III clinical trials in patients with RRMS are ongoing [165].

4.3 Ocrelizumab

4.3.1 Mechanism of Action and Immunological Effects

Ocrelizumab is a humanized, recombinant monoclonal antibody reactive against CD20, which is widely expressed on B cells [166]. It is administered as an intravenous infusion on days 1 and 15 at approximately 6-month intervals [167]. Treatment with ocrelizumab results in B-cell depletion [167], but the precise role of this activity in MS is not known.

4.3.2 Clinical Effects in Relapsing MS

A phase II clinical trial showed that ocrelizumab had a dose-dependent effect on reducing the number of gadolinium-enhancing T1 lesions over 24 weeks compared with placebo in patients with RRMS [167]. A similar proportion of patients had adverse events across treatment groups, although a higher proportion of patients receiving ocrelizumab had infusion-related adverse events than in the placebo group [167]. Phase III clinical trials in patients with RRMS are ongoing [168].

5 Discussion

Several injectable, and now oral, DMTs are currently available, or in late-stage clinical development, for the

treatment of relapsing forms of MS. All of the therapies described in this review are believed to suppress autoreactive peripheral lymphocyte activity in CNS compartments, which remains a critical step in the process of demyelination and tissue damage in MS. Yet each therapy has its own MoA and, as a consequence, each has a different efficacy and safety profile. In some cases, the exact pharmacological mechanisms accounting for the therapeutic effects of an MS treatment remain unknown. For example, studies on IFN, GA, DMF, and laquinimod have demonstrated widespread effects within the immune system. Other therapies, such as natalizumab, fingolimod, teriflunomide, and alemtuzumab seem to exert a more direct effect on lymphocytes. Additionally, some therapies might have neuroprotective effects, although via differing mechanisms and with different levels of supporting evidence [23, 110, 169].

All the DMTs described here are able to reduce the risk of inflammatory disease activity, as assessed by relapse rate and magnetic resonance (MRI) lesion activity, compared with placebo. However, few comparative head-to-head trials have been undertaken to assess the superiority or non-inferiority of one therapy against another, and there is a need for such evidence now that numerous treatments for MS are available. Those trials that have been undertaken indicate that alemtuzumab and fingolimod provide greater efficacy than IFNβ [92, 115].

The ability of DMTs to reduce markers of disease activity early in the disease course is an important long-term efficacy consideration because the presence of these markers, such as MRI lesion burden and clinical parameters, correlate with severe disability in the long term [170–172]. Early identification of probable treatment response using these markers enables patients with a poor response to be switched to an alternative therapy at an early stage [170–172]. Additionally, brain atrophy has been shown to correlate with long-term disease progression [173]. In this regard, fingolimod is the only MS DMT to have demonstrated consistently reduced brain-volume loss (a measure of atrophy) across all of its phase III trials compared with placebo and IFNβ [114, 115].

Finally, the route of drug administration is usually a significant determinant of a patient's therapy preference. IFNβ-1a and 1b and GA are administered by SC or IM injections; natalizumab and alemtuzumab are administered by intravenous infusion; fingolimod, teriflunomide, and laquinimod are administered orally once daily; and DMF twice daily. As such, deciding on an MS treatment pathway to match patients' needs may also require physicians to evaluate the potential for a particular treatment regimen to affect patients' long-term adherence to therapy, which in turn directly affects clinical outcomes, such as relapse rate [174].

6 Conclusions

Understanding the immunological mechanisms and associated clinical profiles of each therapy for MS is important, as treatment tailored to provide optimal efficacy for patients and potential adverse events can be readily identified and managed appropriately. In light of our evolving knowledge of the immunological mechanisms of some of the newer therapies for MS, there appears to be a need for the development of treatment algorithms to help physicians decide on the most effective treatment pathway from the earliest stage of MS, so that patients can benefit from high efficacy, high tolerability treatments throughout the course of their disease.

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