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Review article

Teriflunomide vs injectable disease modifying therapies for relapsing forms of MS

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ABSTRACT

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory disease affecting the white and gray matter of the central nervous system. Several disease modifying therapies (DMTs) have been shown to significantly reduce relapse rates, slow disability worsening, and modify the overall disease course of MS. Decision-making when initiating a DMT should be shared between the patient and physician. Important factors such as prognostic indicators, safety, patient preferences, adherence, and convenience should also be considered. Treatment guidelines recommend switching a DMT when a patient experiences breakthrough disease activity, but also for patients who experience adverse events. Compared with injectable therapies, oral DMTs are often associated with increased treatment adherence and patient satisfaction, due to a less burdensome route of administration and greater tolerability. This review will summarize the available scientific evidence for injectable DMTs and the oral DMT teriflunomide, including considerations for both treatment-naïve patients initiating a DMT and patients switching from an injectable DMT.

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease affecting the white and gray matter of the central nervous system (Compston and Coles, 2008; Thompson et al., 2018b). While no curative treatment exists for MS, several disease-modifying therapies (DMTs) significantly reduce relapse rates, slow disability worsening, and modify the overall disease course. Injectable DMTs, which include interferon beta (IFNβ)-1a, IFNβ-1b, and glatiramer acetate (GA), were the first therapies to be approved for relapsing- remitting MS (RRMS) by the U.S. Food and Drug Administration and European Medicines Agency in the 1990s, and are traditionally considered first-line treatments (Bayer HealthCare Pharmaceuticals Inc., 2018; Biogen Inc., 2016; EMD Serono Inc., 2015; Marta and Giovannoni, 2012; Teva Pharma, 2018; Teva Pharmaceuticals USA Inc., 2018). Since then, oral DMTs have become available. In the U.S., teriflunomide, fingolimod, dimethyl fumarate (DMF), and siponimod were approved as first-line therapies, and cladribine as second-line therapy, in patients with relapsing MS. In the European Union, teriflunomide and DMF were approved for first-line use, with fingolimod and cladribine indicated for use in highly active RRMS (Biogen, 2017; Biogen Netherlands B.V., 2019; EMD Serono Inc, 2019; EMD Serono Inc, 2019a; Novartis Pharmaceuticals, 2019; Novartis Pharmaceuticals Corp., 2018; Novartis Europharm Limited, 2019; Sanofi Genzyme, 2019; Sanofi-Aventis Groupe, 2019).

The importance of early treatment initiation following a clinically definitive diagnosis of relapsing MS is well established (Giovannoni et al., 2017; Montalban et al., 2018; MS Coalition, 2018;

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Rae-Grant et al., 2018). Many DMTs are available for treatment-naïve patients and patients early in their disease course. This review will summarize the available scientific evidence for one of the oral DMTs, teriflunomide, compared with injectable DMTs. We further discuss considerations for treatment-naïve patients initiating a DMT and patients switching treatment from an injectable DMT to teriflunomide.

2. Teriflunomide and injectable DMTs

2.1. Mechanisms of action and posology

Teriflunomide is an oral immunomodulatory agent taken once daily, available in 14 mg doses globally and additionally 7 mg in the US (Table 1). It selectively and reversibly inhibits dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme essential for *de novo* pyrimidine synthesis in rapidly dividing lymphocytes. As a result, the proliferation and function of activated T and B cells are reduced, while the resting cells of the adaptive immune system are spared (Arnold et al., 2014). Results from the TERIDYNAMIC study (NCT01863888) suggest that DHODH inhibition also corrects metabolic disturbances in T cells, and may promote recovery of an altered T cell receptor repertoire in autoimmunity (Klotz et al., 2019). Preclinical and clinical data suggest that teriflunomide also has antiviral properties (Edwards et al., 2017).

Five preparations of IFNβ are currently available, one of which is a weekly intramuscular (IM) injection, with the remaining four administrated as subcutaneous (SC) injections at frequencies ranging from every second day to once every two weeks (see Table 1). IFNβ has antiviral, immunomodulatory, and antiproliferative properties that may contribute to its mechanisms of action in MS, including increased expression of anti-inflammatory cytokines and decreased expression of proinflammatory cytokines. It may also reduce the trafficking of inflammatory cells across the blood–brain barrier and increase nerve growth factor production, leading to a potential increase in neuronal survival and repair (Kieseier, 2011).

GA is administered as a SC injection, as either a 20 mg daily dose or 40 mg three-times weekly. It is thought to compete with myelin basic protein for binding to major histocompatibility complex class II molecules on antigen-presenting cells. GA stimulates expansion of T helper 2 cells which may cross-react with myelin to stimulate release of anti-inflammatory cytokines. Evidence suggests it may also modulate antigen-presenting cells, $CD8^+$ T cells, $Foxp3^+$ regulatory T cells, and plasma cells, and promote regulatory B-cell properties (Caporro et al., 2014; Lalive et al., 2011).

2.2. Efficacy, safety, and tolerability

In addition to route of administration, dose, and convenience, teriflunomide and the injectable DMTs differ in their efficacy, safety, and tolerability profiles. Treatment outcomes of each DMT have been demonstrated in randomized, placebo-controlled trials (Tables 2–5). The data discussed here are limited to the phase 3 trials from each clinical program, plus adherence/quality of life (QoL) data from phase 4/observational real-world studies. When evaluating data from individual trials, differences in the study design, patient population, time period in which the study took place, and outcome measures used should be taken into consideration and cross-trial comparisons should be avoided.

As the studies of GA and several of the IFNβ studies took place over 20 years ago when no approved DMT options were available, patient populations have since evolved (Zhang et al., 2019). A substantial downward trend in annualized relapse rate (ARR) in the placebo arms of phase 3 trials has occurred in this timeframe due to changes in diagnostic and study criteria, understanding of MS etiology, and selection biases. In addition, compared with the IFNβ studies, the time from first MS symptoms to study inclusion was longer for teriflunomide in the TEMSO (NCT00134563) and TOWER (NCT00751881) studies, the

Table 1
Phase 3 trials of injectable DMTs and teriflunomide.

DMT	Route of administration, dose, and frequency	Trial	Trial details	Reference
IFNβ-1b SC[a]	SC injection, 250 μg every other day	IFNB Multiple Sclerosis Study (1993)	2-year, multicenter, double-blind, placebo-controlled study with three parallel treatment groups (two doses of IFNβ-1b; 1.6 MIU or 8 MIU)	Betaferon SmPC; Betaferon PI; Extavia SmPC; Extavia PI; The IFNB Multiple Sclerosis Study Group, 1993
IFNβ-1a IM	IM injection, 30 μg 1 × /week	The Multiple Sclerosis Collaborative Research Group Study	2-year, multicenter, double-blind, placebo-controlled study	Avonex SmPC; Avonex PI; Jacobs et al. 1996
IFNβ-1a SC	SC injection, 44 μg 3 × /week	PRISMS	2-year, randomized, double-blind, placebo-controlled study with three parallel treatment groups (two doses of IFNβ-1a; 22 μg or 44 μg)	Rebif SmPC; Rebif PI; PRISMS Study Group 1998; Panitch et al. 2002
Peg-IFNβ-1a	SC injection, 125 μg once every 2 weeks	ADVANCE (2014) (NCT00906399)	2-year, multicenter, double-blind, parallel-group study, with a placebo-controlled design with three parallel treatment groups (two dosing intervals of Peg-IFNβ-1a; every 2 weeks and every 4 weeks) for the first 48 weeks	Plegridy SmPC; Plegridy PI; Calabresi et al., 2014; Kieseier et al. 2014
GA	SC injection; 20 mg 1×/day SC injection; 40 mg 3 × /week (or 20 mg 1 × /day, data not shown)	Phase 3 trial GALA (NCT01067521)	2-year, multicenter, randomized, placebo-controlled trial 1-year, multicenter, randomized, placebo-controlled, parallel-group study	Copaxone SmPC; Copaxone PI; Johnson et al., 1995 Copaxone SmPC; Copaxone PI; Khan et al., 2013; Comi, Filippi, and Wolinsky, 2001
Teriflunomide	Oral, 14 mg 1 × /day (or 7 mg 1 × /day, data not shown)	TEMSO (NCT00134563)	108-week, randomized, double-blind, placebo-controlled study with three parallel treatment groups (two doses of teriflunomide; 7 mg or 14 mg)	Aubagio SmPC; Aubagio PI; O'Connor et al., 2011
		TOWER (NCT00751881)	48 week, randomized, double-blind, placebo-controlled study with three parallel treatment groups (two doses of teriflunomide; 7 mg or 14 mg)	Aubagio SmPC; Aubagio PI; Confavreux et al., 2014

DMT, disease modifying therapy; GA, glatiramer acetate; IFNβ, interferon beta; IM, intramuscular; MIU, Million International Units; Peg-IFNβ-1a, pegylated interferon beta-1a; SC, subcutaneous.
[a] IFNβ-1b is available as two marketed drug products: Betaseron/Betaferon and Extavia.

Table 2
Efficacy outcomes from placebo-controlled phase 3 trials of injectable DMTs and teriflunomide.

DMT/Trial	Relapse rate	Disability	MRI
IFNβ-1b (IFNB Multiple Sclerosis Study) (The IFNB Multiple Sclerosis Study Group, 1993)	34% reduction in ARR over 2 years ($p=0.0001$) (primary endpoint)	29% decrease in EDSS change from baseline (NS)	No Gd+ lesions outcomes, 59% reduction in N/NE T_2 lesions
IFNβ-1a IM (MSCRG Study) (Jacobs et al., 1996)	18% reduction in ARR at 2 years ($p=0.02$)	37% relative reduction in risk of accumulating disability at the end of 2 years ($p=0.02$) (primary endpoint: time to sustained EDSS worsening)	Mean number of Gd+ lesions: 1.65 placebo; 0.80 treated ($p=0.05$). Median percent change T_2 lesion volume: −6.5% placebo; −13.2% treated (NS) at 2 years
IFNβ-1a SC (PRISMS)	33% reduction in relapse rate over 2 years ($p<0.001$)	Time to sustained disability worsening was significantly longer ($p<0.05$) in both IFNβ-1a treatment groups than in the placebo group	78% reduction in N/NE T_2 lesions at 2 years ($p<0.0001$)
Peg-IFNβ-1a (ADVANCE) (Calabresi et al., 2014a) (NCT00906399)	36% reduction in ARR at 48 weeks ($p=0.0007$) (primary endpoint)	38% relative risk reduction in disability worsening at 48 weeks ($p=0.0383$)	86% relative reduction in Gd+ lesions ($p<0.0001$), 67% relative reduction in N/NE T_2 lesions ($p<0.0001$) at 48 weeks
GA (phase 3 study) (Johnson et al., 1995)	29% reduction in ARR at 2 years vs placebo (ARR = 0.59 vs 0.86, $p=0.007$)	No disability worsening at 24 months: 75.4% placebo; 78.4% treated (NS)	Not assessed
GA (GALA, except for disability) (Khan et al., 2013) (NCT01067521)	34% reduction in ARR at 12 months ($p<0.0001$) (primary endpoint)	Not assessed for 40 mg. For 20 mg: no disability worsening at 24 months: 75.4% placebo; 78.4% treated (NS)	35% reduction in Gd+ lesions ($p<0.0001$), 30% reduction in N/NE T_2 lesions ($p<0.003$) at 9 months, *post hoc* SIENA analysis of the open-label extension showed early start patients had less GM volume loss compared with delayed start patients (−2.01 vs −2.33, $p=0.073$ [baseline to Month 36]; −1.16 vs −1.53, $p=0.015$ [Month 12 to 36])
Teriflunomide (TEMSO) (O'Connor et al., 2011) (NCT00134563)	31.5% relative risk reduction in ARR at 2 years ($p<0.001$) (primary endpoint)	29.8% reduction in risk of 12-week confirmed disability worsening ($p=0.03$)	80% reduction in Gd+ lesions ($p<0.001$), 77% reduction in N/NE T_2 lesions, *post-hoc* SIENA analysis showed teriflunomide 14 mg significantly slowed BVL compared with placebo (33.3% risk reduction from baseline to Year 2; $p=0.0001$)
Teriflunomide (TOWER) (Confavreux et al., 2014) (NCT00751881)	36.3% relative risk reduction in ARR at 2 years ($p=0.0001$) (primary endpoint)	31.5% reduction in risk of 12-week confirmed disability worsening ($p=0.044$)	Not assessed

ARR, annualized relapse rate; BVL, brain volume loss; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; GM, gray matter; IFNβ, interferon beta; IM, intramuscular; MRI, magnetic resonance imaging; N/NE, new or newly enlarging; NS; not significant; Peg-IFNβ, pegylated interferon beta; SC, subcutaneous.

mean baseline Expanded Disability Status Scale score was higher, and a greater percentage of patients had previous DMT use (Table 3).

2.2.1. Efficacy

2.2.1.1. Clinical relapses. The phase 3 placebo-controlled trials were of 2 years duration for the earlier injectable DMTs (GA 20 mg and IFNβ) and teriflunomide, and 1 year duration for pegylated IFNβ-1a and GA 40 mg. The reduction in ARR was similar among the therapies, ranging from a 29% to 36% reduction compared with their respective placebo groups (Calabresi et al., 2014a; Confavreux et al., 2014; Khan et al., 2013; O'Connor et al., 2011; Panitch et al., 2002; PRISMS Study Group, 1998; The IFNB Multiple Sclerosis Study Group, 1993).

A trial of IFNβ-1b (8 MIU [250 μg]; the approved dose) showed a significant 34% reduction in ARR over 2 years compared with placebo (0.84 vs. 1.27; $p=0.0001$) (The IFNB Multiple Sclerosis Study Group, 1993). In the PRISMS study, the mean number of relapses after 2 years was 2.56 for placebo, and 1.82 and 1.73 for three-times weekly IFNβ-1a SC 22 μg and 44 μg, respectively ($p<0.005$) for a percentage reduction of 27% with the 22 μg dose and 33% with the 44 μg dose against placebo (PRISMS Study Group, 1998).

GA 20 mg daily demonstrated a 29% reduction in ARR vs placebo at Year 2 (0.59 vs. 0.84, $p=0.007$) (Johnson et al., 1995). For GA 40 mg (three-times weekly), patients showed a 34% reduction in ARR versus placebo at Year 1 (0.33 vs 0.51; $p<0.0001$) (Khan et al., 2013).

Teriflunomide showed significant reductions in ARR across clinical trials, with similar findings between the phase 3 TEMSO and TOWER studies. In the core TEMSO study, patients receiving teriflunomide 14 mg experienced a 31.5% relative reduction in ARR over 2 years versus placebo (0.54 for placebo and 0.37 for teriflunomide; [$p<0.001$]) (O'Connor et al., 2011). In the TOWER study, patients receiving teriflunomide 14 mg experienced a 36.3% relative reduction in ARR over 1 year versus placebo (0.50 for placebo, 0.32 for teriflunomide [$p=0.0001$]) (Confavreux et al., 2014). In other phase 3 trials, teriflunomide yielded ARRs of 0.22 and 0.25 over 30 months (ASCLEPIOS I and II; respective ARRs for ofatumumab were 0.11 and 0.10 [$p<0.001$ between treatments in both studies]) (Hauser et al., 2019) and 0.29 over 108 weeks (OPTIMUM; ARR for ponesimod was 0.20 [$p=0.0003$ between treatments])(Kappos et al., 2019).

2.2.1.2. Disability. Compared with placebo, significant reductions in time to confirmed disability worsening were seen for IFNβ-1a (IM, SC, and pegylated products) and teriflunomide, but not for IFNβ-1b and GA (Table 2).

Both doses of IFNβ-1a SC demonstrated significantly longer time to 3-month confirmed disability worsening compared with placebo over 2 years ($p<0.05$); (PRISMS Study Group, 1998). In the ADVANCE study (NCT00906399), the proportion of patients treated with pegylated IFNβ-1a who had 12 weeks of confirmed disability worsening at 48 weeks (0.068 in both intervention groups [125 μg every 2 weeks or every 4 weeks]) was reduced compared with placebo (0.105; $p=0.038$ for both comparisons) (Calabresi et al., 2014a).

In TOWER, teriflunomide 14 mg reduced the risk of 12-week confirmed accumulation of disability (hazard ratio [HR] 0.68 [95% CI 0.47–1.00]; $p=0.04$) over 1 year compared with placebo (Confavreux et al., 2014). In TEMSO, the proportion of patients with 12-week confirmed disability worsening over 2 years was 27.3% with placebo, and 20.2% with teriflunomide 14 mg ($p=0.03$) (O'Connor et al., 2011).

2.2.1.3. Magnetic resonance imaging (MRI). Significant reductions in the number of MRI lesions were seen across all treatments compared with placebo. In the IFNB Multiple Sclerosis Study, patients treated with

Table 3
Baseline characteristics from phase 3 RRMS trials of injectable DMTs and teriflunomide.

DMT	Trial	Arm	Age, y, mean (SD)	Female sex, %	MS disease duration, y, mean (SD)	Baseline EDSS Score, mean (SD)	Number of MS relapses over past 24 months, mean (SD)	Number of T2 lesions, mean (SD)	Number of Gd+ lesions, mean (SD)
IFNβ-1b	IFNB Multiple Sclerosis Study	PBO (n = 123)	36.0 (0.6)[a]	71.5	3.9	2.8	3.6	N/A	N/A
					(0.3)[a,b]	(0.1)[a]	(0.1)[a]		
		0.25 mg IFNβ-1b (n = 124)	35.2 (0.6)[a]	69.4	4.7	3.0	3.4	N/A	N/A
					(0.4)[a,b]	(0.1)[a]	(0.2)[a]		
IFNβ-1a IM	MSCRG Study	PBO (n = 143)	36.9 (0.64)[a]	72	6.4	2.3	1.2	N/A	2.32
					(0.49)[a]	(0.07)[a]	(0.05)[a]		(0.37)[a]
		30 μg IFNβ-1a (n = 158)	36.7 (0.57)[a]	75	6.6	2.4	1.2	N/A	3.17
					(0.46)[a]	(0.06)[a]	(0.05)[a]		(0.62)[a]
IFNβ-1a SC	PRISMS	PBO (n = 187)	34.6 (28.8–40.4)[c]	75	4.3	2.4	3.0	N/A	N/A
					(2.4–8.4)[d]	(1.2)	(1.3)		
		22 μg IFNβ-1a (n = 189)	34.8 (29.3–39.8)[c]	67	5.4	2.5	3.0	N/A	N/A
					(3.0–11.2)[d]	(1.2)	(1.1)		
		44 μg IFNβ-1a (n = 184)	35.6 (28.4–41.0)[c]	66	6.4	2.5	3.0	N/A	N/A
					(2.9–10.3)[d]	(1.3)	(1.1)		
	EVIDENCE	30 μg IFNβ-1a IM (n = 338)	37.4 (18–55)[e]	74.6	4.1	2.0	2.0	0 (1.1)	0
					(6.7)	(2.3)	(2.6)		(2.5)
		44 μg IFNβ-1a SC (n = 339)	38.3 (18–55)[e]	74.9	4.0	2.0	2.0	0 (1.2)	0
					(6.5)	(2.3)	(2.6)		(1.9)
Peg-IFNβ-1a	ADVANCE	PBO (n = 500)	36.3	72	3.5[b]	2.44	2.6	50.6 (35.7)	1.6
			(9.7)		(4.6)[b]	(1.18)	(1.00)[e]		(3.8)
		Peg-IFNβ-1a Q2W (n = 512)	36.9	71	4.0	2.47	2.6	48.7	1.2
			(9.8)		(5.1)	(1.26)	(0.99)[e]	(36.8)	(3.4)
GA	Phase 3	PBO (n = 126)	34.3 (6.5)	76.2	6.6	2.4	2.9	N/A	N/A
					(5.1)	(1.3)	(1.1)		
		GA 40 mg (n = 125)	34.6	70.4	7.3	2.8	2.9	N/A	N/A
			(6.0)		(4.9)	(1.2)	(1.3)		
	GALA	PBO (n = 461)	38.1	67.9	7.6[c]	2.7	1.9	N/A	1.4
			(9.2)		(6.4)	(1.2)	(0.9)		(3.7)
		GA 40 mg (n = 943)	37.4	68.0	7.7[c]	2.8	1.9	N/A	1.7
			(9.4)		(6.7)	(1.2)	(0.9)		(4.7)
Teriflunomide	TEMSO	PBO (n = 363)	38.4	75.8	8.6[c]	2.68	2.2	N/A	1.66
			(9.0)		(7.1)	(1.34)	(1.0)		(3.55)
		Teri 14 mg (n = 359)	37.8	71.0	8.7[c]	2.67	2.2	N/A	1.81
			(8.2)		(6.7)	(1.24)	(1.0)		(5.17)
	TOWER	PBO (n = 389)	38.1	70	7.64[c]	2.69	2.1	N/A	N/A
			(9.1)		(6.70)	(1.36)	(1.1)		
		Teri 14 mg (n = 372)	38.2	69	8.18[c]	2.71	2.1	N/A	N/A
			(9.4)		(6.73)	(1.35)	(1.2)		

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; IFNβ, interferon beta; IM, intramuscular; MS, multiple sclerosis; N/A, not available; PBO, placebo; Q2W, every 2 weeks; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneous; SD, standard deviation; y, year.

[a] Standard error of the mean
[b] Duration since diagnosis
[c] Duration since first MS symptoms
[d] Median (interquartile range)
[e] Relapses within the previous 3 years (not reported for previous 24 months).

IFNβ-1b experienced a 59% reduction in the number of new or enlarging T_2 hyperintense lesions over 2 years (gadolinium-enhancing [Gd+] lesion outcomes were not investigated) (The IFNB Multiple Sclerosis Study Group, 1993). In the MSCRG study, mean number of Gd + lesions over 2 years was 0.80 in patients receiving IFNβ-1a IM, compared with 1.65 in patients receiving placebo ($p = 0.05$). The median percent change in T_2 lesion volume was –6.5% for placebo and –13.2% for IFNβ-1a IM (non-significant) (Jacobs et al., 1996). For patients receiving IFNβ-1a 44 μg SC, a 78% reduction in new or newly enlarging T_2 lesions compared with placebo was demonstrated at 2 years ($p < 0.0001$) (PRISMS Study Group, 1998); this treatment was associated with fewer overall active MRI lesions compared with IFNβ-1a IM ($p < 0.001$ at 24 and 48 weeks) (Panitch et al., 2002).

In the GALA study, patients treated with GA experienced a 45% reduction in Gd+ lesion counts ($p < 0.0001$) and a 35% reduction in new or newly enlarging T_2 lesion counts ($p < 0.0001$) at 1 year (Khan et al., 2013). *Post-hoc* analysis of the open-label extension using the Structural Image Evaluation using Normalization of Atrophy (SIENA) technique also showed that patients initiating GA treatment early had less gray matter volume loss over 36 months compared with delayed-start patients (Zivadinov et al., 2015).

Gadolinium-enhancing lesion counts were reduced with teriflunomide compared with placebo over 108 weeks in both TEMSO (80.4% reduction; $p < 0.0001$) (Wolinsky et al., 2013), and in the TOPIC study (NCT00622700) of patients with clinically isolated syndrome (CIS) (58.5% reduction; $p = 0.0008$) (Miller et al., 2014). T2-hyperintense lesion volume was also reduced for teriflunomide compared with placebo in TEMSO (76.7% reduction; $p = 0.0004$) (Wolinsky et al., 2013); no significant treatment reduction was found in TOPIC (Miller et al., 2014). In a *post-hoc* analysis of TEMSO using SIENA, teriflunomide 14 mg reduced brain volume loss (BVL) over 2 years compared with placebo (30.6% relative reduction; $p = 0.0001$) (Radue et al., 2017). Slowed BVL may underlie the ability of teriflunomide to delay disability worsening (Sprenger et al., 2019). Although no effect on gray matter volume was found with teriflunomide in TEMSO (Wolinsky et al., 2013), data from the TOPIC study showed a 40.2% reduction in the loss of cortical gray matter volume for teriflunomide compared with placebo over 2 years ($p = 0.0416$) (Zivadinov et al., 2017).

2.2.1.4. Comparative efficacy. Some head-to-head trials have been conducted for first-line therapies (Table 5), but none of the therapies has consistently demonstrated superior efficacy over others. However, data suggest superiority of high frequency and high dose IFNβ treatment compared with lower doses. In the EVIDENCE study (Panitch et al., 2002) (N = 677) three-times weekly IFNβ-1a SC 44 μg demonstrated superior efficacy in the number of relapse-free patients ($p = 0.0005$) and active MRI lesions ($p < 0.001$) compared with once-weekly IFNβ-1a IM 30 μg. Studies of IFNβ-1b SC versus GA (BECOME [NCT00176592], BEYOND [NCT00099502] (Cadavid et al., 2009; O'Connor et al., 2009)) and teriflunomide versus three-times weekly IFNβ-1a SC (TENERE [NCT00883337]) (Vermersch et al., 2014), showed no differences in primary or secondary outcomes between comparators. Similarly, IFNβ-1a SC 44 μg and GA did not differ over 96 weeks in the REGARD study (NCT00078338) in time to first relapse or MRI lesion volume outcomes, but lower Gd-enhancing lesion counts in IFNβ-1a SC-treated patients were observed ($p = 0.0002$ between treatments) (Mikol et al., 2008).

2.2.2. Safety and tolerability

Each treatment has a unique safety and tolerability profile (Table 4). Patients treated with IFNβ products most frequently reported flu-like symptoms, fever, headache, nasopharyngitis, nausea, diarrhea, chills, myalgia, lymphopenia, and injection site reactions. The most commonly reported adverse events (AEs) in patients receiving GA were injection site erythema, subcutaneous lipoatrophy, nasopharyngitis, injection site pain, and headache. In teriflunomide-treated patients, the most common AEs were alanine aminotransferase (ALT) elevation, hair thinning, diarrhea, nausea, and paresthesia. In the TENERE study, increased ALT was the most common reason for treatment discontinuation in both IFNβ-1a- and teriflunomide-treated patients, with the highest frequency of discontinuations due to this AE occurring in the IFNβ-1a arm (8.9% compared with 3.6% for teriflunomide) (Vermersch et al., 2014).

For women of reproductive potential, teriflunomide is contraindicated for use during pregnancy; GA and IFNβ may be used when the benefit on MS disease outweighs any potential risk to the fetus, as neither therapy has been associated with negative pregnancy effects based on thousands of human exposures (Coyle et al., 2019). For women planning a pregnancy, or who become pregnant, while being treated with teriflunomide, an accelerated elimination procedure is recommended, based on animal data indicating teriflunomide's potential for fetal harm (Sanofi-Aventis Groupe, 2019; Sanofi Genzyme, 2019). However, in pregnant women who have been exposed to injectable DMTs or teriflunomide, pregnancy outcomes were similar to the general population (Andersen et al., 2018; Coyle et al., 2014; Herbstritt et al., 2016; Sandberg-Wollheim et al., 2005; Sandberg-Wollheim et al., 2018; Thiel et al., 2016; Vukusic et al., 2019).

2.2.3. Adherence, treatment satisfaction, and QoL

Treatment adherence is another important consideration in choice of DMT as improved adherence may lead to better clinical outcomes (Gerber et al., 2017; Steinberg et al., 2010; Tan et al., 2011). In real-world observational studies, proportions of patients with no missed doses were found to be 66% for GA and 85% for weekly IM IFNβ-1a (Devonshire et al., 2011). This is consistent with a review of studies that assessed treatment adherence for injectable DMTs, which reported patient adherence ranging from as low as 49% up to 87.5% (Menzin et al., 2013). The proportion of patients ≥80% adherent to teriflunomide was 98% (Coyle et al., 2017).

One factor that may affect treatment adherence is patient satisfaction. An observational, retrospective study of patients on injectable DMTs using the Treatment Satisfaction Questionnaire for Medication version 1.4 (TSQM v1.4), in which higher scores indicate greater satisfaction, found that patients were reasonably satisfied with their treatment and that the main source of dissatisfaction was the inconvenience of injections. The highest overall satisfaction for injectable treatments was reported for IFNβ-1a SC (mean ± SD: 72.4 ± 20.3) and the lowest for IFNβ-1b SC (61.7 ± 23.7). For the TSQM side effects sub-scale, GA had the highest score (80.6 ± 22.2) and IFNβ-1a IM the lowest (63.9 ± 24.6). For the effectiveness sub-scale, patients were most satisfied with IFNβ-1a SC (70.1 ± 16.9) and least satisfied with IFNβ-1b SC (63.2 ± 17.9). For the convenience sub-scale, IFNβ-1a SC scored highest (69.4 ± 17.4) and IFNβ-1b scored lowest (55.5 ± 17.2) (Fernández et al., 2017).

In the phase 3 TENERE study and the real-world Teri-PRO and TAURUS MS-I studies, patient-reported treatment satisfaction with teriflunomide 14 mg using the TSQM was consistent, with particularly high scores for side effects (93.2 in TENERE and 84.1 in Teri-PRO; side effects not reported in TAURUS) and convenience (89.9, 90.4, and 90.2, in the TENERE, Teri-PRO, and TAURUS studies, respectively) (Coyle et al., 2017; Kallmann et al., 2019; Vermersch et al., 2014). In the comparative TENERE study, mean TSQM v1.4 scores were significantly improved at Week 48 with teriflunomide 14 mg compared with SC IFNβ-1a for global satisfaction (least squares [LS] mean difference 7.84; $p = 0.02$), side effects (21.77; $p < 0.0001$), and convenience (27.96; $p < 0.0001$) (Vermersch et al., 2014). In patients who received previous MS treatments in TAURUS MS-I, TSQM v9 values at 24 months improved by 8.1 points for effectiveness, 17.0 points for convenience, and 15.3 points for global satisfaction ($p \leq 0.001$ each) compared with study entry (Kallmann et al., 2019). Additional

Table 4
Adverse events from phase 3 trials of injectable DMTs and teriflunomide 14 mg.

DMT	Trial[a]	Adverse events with incidence >10% in any treatment group
IFNβ-1b	IFNB Multiple Sclerosis Study (1993) (The IFNB Multiple Sclerosis Study Group, 1993)	Injection site reactions, inflammation at injection site, fever, myalgia, flu-like symptoms, chills, sweating, malaise
IFNβ-1a IM	The Multiple Sclerosis Collaborative Research Group Study[b] (1996) (Jacobs et al., 1996)	Headache, flu-like symptoms, muscle aches, nausea, fever, asthenia, chills, diarrhea
IFNβ-1a SC	PRISMS (1998) (PRISMS Study Group, 1998)	Headache, flu-like symptoms, injection site reactions, fatigue
	EVIDENCE (2002) (Panitch et al., 2002)	Injection site reaction and inflammation, flu-like symptoms
Peg-IFNβ-1a	ADVANCE (2014) (Calabresi et al., 2014b) (NCT00906399)	Injection site erythema, influenza-like illness, pyrexia, headache, MS relapse, myalgia, chills, injection site pain, asthenia, back pain, injection-site pruritus, nasopharyngitis, arthralgia, fatigue, pain in extremity
GA	Phase 3 study (Johnson et al., 1995)	Injection site reactions, transient self-limited systemic reaction (including flushing, chest tightness, plus dyspnea, palpitations or anxiety)
GA	GALA (2013) (Khan et al., 2013) (NCT01067521)	Injection site erythema, nasopharyngitis, injection site pain, headache
Teriflunomide	TEMSO (2011) (O'Connor et al., 2011) (NCT00134563)	Nasopharyngitis, headache, diarrhea, fatigue, elevated ALT level,[c] nausea, hair thinning or decreased hair density, influenza, back pain, urinary tract infection, pain in arms or legs
	TOWER (2014) (Confavreux et al., 2014) (NCT00751881)	ALT increase, hair thinning, headache, nasopharyngitis, diarrhea, fatigue, nausea, upper respiratory tract infection, urinary tract infection

AEs with incidence >10% in any treatment group.
AE, adverse event; ALT, alanine aminotransferase; DMT, disease modifying therapy; GA, glatiramer acetate; IFN-β, interferon beta; IM, intramuscular; MS, multiple sclerosis; IFNβ-1a, pegylated interferon beta-1a; SC, subcutaneous.
[a] Year refers to year of study publication
[b] Publication reports symptoms seen in >10% of total population and at least 5% higher in treatment group than in placebo group
[c] Elevated levels were reported as AEs by the investigators.

measures of QoL used in the Teri-PRO study include the Multiple Sclerosis International Quality of Life and Stern Leisure Activity Scale (Coyle et al., 2018). Total scores for these measures remained stable over 48 weeks in patients switching to teriflunomide from other DMTs, including injectable DMTs (Coyle et al., 2018). Higher treatment satisfaction with oral treatments such as teriflunomide compared with injectable DMTs may reflect different adverse effects and/or the lack of discomfort or pain associated with injections.

3. Considerations when initiating a DMT in treatment-naïve patients

A patient's prognostic profile, which includes demographic, clinical, and MRI characteristics, should be used to guide individual treatment decisions (Butterworth et al., 2016; Comi et al., 2017). All newly diagnosed patients with relapsing MS should start a DMT (Thompson et al., 2018a). Patients presenting with moderately active RRMS (at least one relapse in the previous 2 years but fewer than two relapses in the last year) would be suitable to start a first-line DMT (Brownlee et al., 2019; Confavreux and Vukusic, 2014; Gajofatto and Benedetti, 2015). Those with unfavorable prognosis (based on potential predictors of disease severity such as male gender; a late age at onset; motor, cerebellar, and sphincter involvement at onset; early progression of disability; a short inter-attack interval; a high number of early attacks; a high number of MRI lesions, and MRI evidence of brain atrophy [Bergamaschi, 2007; Ziemann et al., 2011]) and with highly active disease (at least two relapses in the last year) should start a high efficacy second-line DMT (Gajofatto and Benedetti, 2015).

Recent treatment guidelines also recommend that physicians ascertain and consider the patient's preferences for efficacy, safety, route of administration, co-morbidities, lifestyle, cost, family planning, common adverse effects, and tolerability when initiating a DMT (Rae-Grant et al., 2018). Choosing an appropriate DMT should be a shared decision between the patient and physician (MS in the 21st Century

Table 5
Prospective, randomized head-to-head studies in relapsing MS for injectable DMTs or teriflunomide.

Trial	DMTs	Outcome
EVIDENCE (Panitch et al., 2002)	IFNβ-1a SC TIW vs IFNβ-1a IM weekly	IFNβ-1a SC TIW demonstrated superior efficacy in the number of relapse-free patients ($p=0.0005$) and active MRI lesions ($p<0.001$) (N=677)
CombiRx (Lublin et al., 2013) (NCT00211887)	IFNβ-1a IM weekly + GA 20 mg SC daily vs IFNβ-1a IM weekly or GA 20 mg SC daily	The combination was significantly better than IFNβ-1a alone in reducing the risk of relapse and superior to either agent alone in reducing new lesion activity and accumulation of total lesion volume. GA was significantly better than IFNβ-1a in reducing the risk of relapse. The combination was no better than either agent alone in reducing disability worsening
BECOME (Cadavid et al., 2009) (NCT00176592)	IFNβ-1b every other day vs GA daily	No difference in relapses or MRI outcomes (N=75)
BEYOND (O'Connor et al., 2009) (NCT00099502)	IFNβ-1b 250 μg or 500 μg every other day vs GA daily	No difference in relapse rate, EDSS progression, and MRI outcomes (N=2244)
INCOMIN (Durelli et al., 2002)	IFNβ-1b every other day vs IFNβ-1a IM weekly	IFNβ-1b demonstrated superior efficacy on risk of relapse ($p=0.03$) and MRI outcomes ($p<0.0003$) (N=188)
REGARD (Mikol et al., 2008) (NCT00078338)	IFNβ-1a SC TIW vs GA daily	No difference in time to first relapse and no significant differences for MRI outcomes, except IFNβ-1a-treated patients had significantly fewer enhancing lesions ($p=0.0002$) (N=764)
TENERE (Vermersch et al., 2014) (NCT00883337)	Teriflunomide daily vs IFNβ-1a SC TIW	No difference in the primary outcome of time to failure (first appearance of confirmed relapse or permanent treatment discontinuation for any cause); and no difference in ARR (secondary outcome) between teriflunomide 14 mg and IFNβ-1a SC (N=324)

ARR, annualized relapse rate; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFNβ, interferon beta; IM, intramuscular; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneous; TIW, three-times weekly.

Steering Group et al., 2018). Studies on patient preference in treatment decisions have shown heterogeneity of preferences. In some cases, patients most valued symptom control, in other cases, patients prioritized delaying disability, and in yet other cases, patients focused on safety and avoiding AEs. Overall, patients preferred oral administration to injections, particularly frequent injections (Garcia-Dominguez et al., 2016; Lebrun et al., 2018; Mansfield et al., 2016; Poulos et al., 2016). One independent study found patients with MS placed more importance on DMT monthly out-of-pocket costs and mode of administration than AEs or efficacy (Hincapie et al., 2017).

Injectable DMTs and teriflunomide have been shown to be efficacious in treatment-naïve patients. In the IFNβ-1a studies, significant reductions in ARR and time to confirmed disability worsening compared with placebo were observed (Jacobs et al., 1996; PRISMSStudy Group, 1998). While IFNβ-1b and GA studies demonstrated significant reductions in ARR versus placebo, neither demonstrated significant reductions in confirmed disability worsening (The IFNB Multiple Sclerosis Study Group, 1993; Zwibel, 2006). A *post-hoc* analysis of the TEMSO and TOWER trials demonstrated a significant reduction in ARR and a non-significant reduction in the probability of disability worsening with teriflunomide 14 mg compared with placebo in treatment-naïve patients (Freedman et al., 2018a). Efficacy in patients with CIS has also been demonstrated in placebo-controlled trials of IFNβ treatments (REFLEX, BENEFIT, CHAMPS, ETOMS (Comi et al., 2012; Comi et al., 2001; Jacobs et al., 2000; Kappos et al., 2007)), as well as GA (PreCISe [NCT00666224] (Comi et al., 2009) and teriflunomide (TOPIC (Miller et al., 2014)).

4. Considerations for patients switching from injectable DMTs

4.1. When and why to switch

Treatment guidelines recommend considering a DMT switch when a patient shows breakthrough disease activity, assuming the patient has been on the DMT long enough for the treatment to take full effect and is adherent to their therapy (Montalban et al., 2018; Rae-Grant et al., 2018). In the case of breakthrough disease activity on first-line therapy, the patient should switch to a more potent, high-efficacy DMT. Guidelines also recommend considering switching DMT for patients experiencing AEs that negatively influence adherence, or who report intolerable discomfort with injections or injection fatigue, as these are also common reasons for poor adherence (Rae-Grant et al., 2018). Injection fatigue is generally defined as a waning commitment to continue with the prescribed injectable treatment and can result from a number of factors such as side effects, perceived lack of efficacy, anxiety/fear or “needle phobia”, or depression (Crawford et al., 2014).

In patients experiencing side effects or tolerability issues, a switch to a DMT within the same efficacy class should be considered (Desai et al., 2018). Data comparing adherence rates between injectable and oral DMT classes are limited. One retrospective database claims study found that patients on injectable DMTs whose most common side effect was injection site reactions were less likely to be adherent compared with patients on oral DMTs or infusible DMTs (Higuera et al., 2016).

4.2. Efficacy and treatment satisfaction in patients switching from an injectable DMT to teriflunomide

Results of a study using MSBase registry data (N = 792) examined patients with stable disease activity on IFNβ/GA who switched to fingolimod, DMF, or teriflunomide predominantly due to lack of tolerance and/or convenience, and found no evidence of disease reactivation within the first 6 months of switching, compared with patients who remained on IFNβ/GA (Spelman et al., 2016). A study comparing relapse activity between patients who remained on injectable DMTs and patients who switched due to tolerability issues to teriflunomide or DMF, found that switchers had a lower risk of relapse (HR 0.43, $p = 0.048$) or any disease activity (HR 0.55, $p = 0.035$) compared with patients who remained on injectable therapy (Saraceno et al., 2019). In a *post-hoc* analysis of the pooled phase 3 TEMSO and TOWER studies, teriflunomide 14 mg was associated with reductions in ARR and risk of disability worsening across all subgroups defined by prior DMT exposure in the previous 2 years (≥2 prior DMTs, 1 prior DMT, or no prior DMT) compared with placebo (Freedman et al., 2018b). In the real-world Teri-PRO study, patients who switched to teriflunomide from an injectable DMT had statistically significant increases in treatment satisfaction across all four TSQM domains (effectiveness, side effects, convenience, and global satisfaction) after 48 weeks (Coyle et al., 2018). In the real-world TAURUS-MS I study, patients who switched to teriflunomide 14 mg from another DMT predominantly due to disease worsening, convenience, intolerance to prior mode of administration, or AEs demonstrated a decrease in relapses by Month 12 that was sustained at Month 24, with mean Expanded Disability Status Scale scores remaining low and stable (Kallmann et al., 2019).

4.3. Clinical guidance for patients switching from an injectable DMT

There are several important factors to consider when counseling or monitoring a patient switching from an injectable to teriflunomide.

Before initiating a switch to teriflunomide, the local label should always be followed. The authors recommend a complete blood count, a screen for latent tuberculosis with a tuberculin skin test or blood test for mycobacterium tuberculosis infection, liver function tests, and blood pressure measurements be taken. Liver function and blood pressure should also be monitored monthly in the US (Sanofi Genzyme, 2019), every 2 weeks in Europe (European Medicines Agency, 2018), for the first 6 months and then regularly thereafter with continued treatment. Because teriflunomide is contraindicated in pregnancy, counseling the patient on family planning, including the need to practice effective contraception, and carrying out a pregnancy test before switching is also advised.

No wash out period is necessary. Teriflunomide has been evaluated as an add-on therapy to IFNβ and GA in two phase 2 trials. Both doses of teriflunomide and placebo were evaluated over 48 weeks in patients already receiving a stable dose of IFNβ-1a or IFNβ-1b (Freedman et al., 2012) and in patients already receiving GA (Freedman et al., 2015). The frequency of treatment-related AEs was low across all arms in both trials, demonstrating that an immediate initiation of teriflunomide, without any wash out period, can be performed.

The most successful switches from injectable to oral DMTs are usually those initiated due to needle fatigue or AEs. Although switching generally has a positive impact on a patient's QoL, and risk of disease activity is low after switching, it is essential for the HCP to reinforce the importance of treatment adherence, and discuss with the patient any potential AEs and how they can be managed.

5. Discussion and conclusions

Teriflunomide, GA, and IFNβ have all demonstrated significant reductions in relapse rate compared with placebo in phase 3 trials, with reassuring long-term safety data. Significant reductions in time to confirmed disability worsening were seen for teriflunomide and the various IFNβ-1a drug products, but not for IFNβ-1b nor GA. These DMTs have acceptable safety profiles, but tolerability varies. Studies have demonstrated high patient satisfaction and patient preference for daily, oral administration with teriflunomide, which is the only approved oral DMT to have demonstrated a significant benefit on disability across two separate placebo-controlled, pivotal phase 3 trials of patients with relapsing forms of MS. These findings are further supported by teriflunomide's significant treatment effect on BVL in the *post-hoc* SIENA analysis of the TEMSO MRI data (Radue et al., 2017).

Slowing of BVL may have important clinical implications affecting treatment decisions, with several clinical trials now demonstrating an

effect of DMTs in reducing BVL (De Stefano et al., 2014). In clinical practice, it may therefore be important to consider the potential impact of a therapy on reducing BVL. In addition, DMT-mediated slowing of gray matter loss may also be of relevance given its association with disability, including cognitive decline (Messina and Patti, 2014).

Limitations of this review include the inability to make direct comparisons across the different studies due to dissimilarities in study design and the fact that the trials described span a period of more than 20 years. Over that time, the patient population of relapsing MS trials has shifted, and baseline patient characteristics are not always comparable among these studies. In addition, the methodologies and outcome measures used varied among the different trials. Lastly, the scope of this review was limited to a handful of DMTs for relapsing MS and is not a comprehensive guide to choosing a DMT. More treatment options are available, including high-efficacy infusible treatments and other oral treatments.

When initiating or switching a DMT, decision-making should be shared between the patient and physician to select the most appropriate therapy. It is important to consider patient factors including prognostic indicators, patient preferences, adherence, and convenience, to identify suitable options for each patient. It is important to treat patients early in the MS disease course, and to monitor them closely to ensure suboptimal response or low treatment adherence are detected promptly.

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