Multiple Sclerosis and Related Disorders 36 (2019) 101374

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The long-term effects of disease modifying therapies on disability in people living with multiple sclerosis: A systematic review and meta-analysis

Suzi B. Claflin[1], Brian Tan[1], Bruce V. Taylor*

Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, TAS 7000, Australia

ARTICLE INFO

Keywords:
Systematic review
Disease modifying therapies
Multiple sclerosis

ABSTRACT

Background: Disease modifying therapies (DMT) are a common medication class for treating people living with MS. However, although treatment with DMT can extend over more than a decade, little is known about their long-term effects. Here, we systematically review long-term (≥4 years) studies on the effect of DMT on disability progression and relapse in people living with MS.

Methods: We searched the EMBASE and Medline databases in January 2018, using search terms that included DMT and relevant outcome measures. Two authors screened all resulting studies and evaluated the risk of bias of included studies using the ROBINS-I tool for non-randomized studies. Where there was sufficient data, we performed meta-analyses using RevMan 5. Studies that could not be included in a meta-analysis were included in data synthesis.

Results: Our search returned 7,766 unique articles for review. After screening, 18 articles were included. Follow-up in these studies ranged from a mean of 3.9 years to a median of 17.8 years. Fifteen (83.3%) of the included studies had a moderate risk of bias and three (16.7%) had a serious risk of bias. Meta-analysis showed that DMT significantly reduced the risk of EDSS 6.0 and SPMS compared to no treatment.

Conclusion: There is some evidence that long-term treatment with interferon beta reduces the risk of EDSS 6.0 and SPMS compared to no treatment or placebo. More work is needed on the effect of second generation DMT and the relative effect of DMT on health outcomes.

1. Introduction

Disease modifying therapies (DMT) are a medication class used to treat multiple sclerosis (MS). (See Supplementary Table 1 for a list of FDA-approved DMT.) DMT modify, modulate or suppress the immune system, limiting inflammation in the central nervous system, and preventing relapse and the formation of new lesions (De Angelis et al., 2018). MS disease duration can exceed 40 years, and people living with MS may be treated with DMT for more than a decade. However, while there is good evidence from meta-analyses that DMT improve disability progression outcomes in adults with relapsing-remitting MS (RRMS) over 2–3 year periods compared to placebo, there is little such evidence of their long-term impact (Claflin et al., 2019). Here, we present a systematic review and meta-analysis of long-term studies (≥4 years) evaluating the effect of DMT on relapse and disability progression outcomes in people with MS.

Evidence about long-term DMT efficacy is important for risk-benefit assessment. The cost of DMT is high and continues to rise. When they were introduced, first-generation DMT (interferon β−1b, interferon β−1a IM, and glatiramer acetate) had annual costs of US $8292–11,532, and their costs have risen 21–36% per year (Hartung et al., 2015). As with other classes of medication, DMT can also have significant adverse side effects, including risk of serious infections (Pucci et al., 2011). Because their costs can be high, it is particularly important that the potential benefits of DMT are well understood.

Unfortunately, long-term DMT treatment effect studies have significant logistical and ethical challenges that make collecting the relevant data difficult (Sormani and Bruzzi, 2015). Randomized controlled trials (RCT), commonly considered the gold standard in treatment effect studies, are expensive and logistically demanding to run. Consequently, they often have short (1–3 year) follow-up durations. Additionally, placebo-controlled RCT present ethical concerns when a short-term treatment effect is observed; it is then unethical to maintain a placebo group over the long-term. These issues make placebo-controlled long-term RCT impractical.

* Corresponding author.
E-mail address: bruce.taylor@utas.edu.au (B.V. Taylor).
[1] Equal contribution.

https://doi.org/10.1016/j.msard.2019.08.016
Received 19 July 2019; Accepted 14 August 2019

Table 1
Inclusion and exclusion criteria for this review.

	Inclusion criteria	Exclusion criteria
Population	(1) Adult (18 +) MS patients with either progressive OR relapsing remitting onset, and diagnosed using either Poser OR McDonald criteria (2) If a mixed population with pediatric patients, MUST have > 80% adults to be included (3) Each study arm must have > 25 patients	(1) Contains > 20% pediatric (17 and under) MS patients (2) Patients were not diagnosed with MS using the Poser or McDonald criteria (3) Any study arm with < 25 patients
Intervention	(1) Any of the following DMTs licensed to be used for the treatment of MS: Aubagio (Teriflunomide) Avonex (Interferon beta-1a) Azasan (Azathioprine) Betaferon (Interferon beta-1b) Copaxone (Glatiramer acetate) Gilenya (Fingolimod) Lemtrada (Alemtuzumab) Leustatin (Cladribine) Novantrone (Mitoxantrone or Mitozantrone) Ocrevus (Ocrelizumab) Plegridy (PEGylated Interferon beta-1a) Rebif (Interferon beta-1a) Tecfidera/BG-12 (Dimethyl fumarate) Trexall (Methotrexate) Tysabri (Natalizumab) Zinbryta (Daclizumab)	(1) Does not have at least one study arm treated with ONLY DMT
Comparators	(1) One or more placebo/no treatment/usual care groups (NO DMT), OR head-to-head studies comparing two or more DMTs	(1) Does not compare DMT treated group to EITHER placebo/no treatment/usual care OR another DMT
Outcomes	(1) Must report on at least one of the primary outcomes: EDSS, MSSS, ARR, and MRI, or one of the secondary outcomes: QoL and AE	(1) Does not assess any of the following: EDSS, MSSS, ARR, MRI, QoL or AE
Study duration	(1) A follow-up (treatment period plus any extended follow-up) period of a minimum of 4 years	(1) Has follow-up (treatment period plus any extended follow-up) of less than 4 years
Study design	(1) Anything but review articles, systematic reviews, cross-sectional, case-control studies, and case studies	(1) Is a review article, systematic review, cross-sectional, case-control, or case study (2) Is a study looking at DMT adherence, discontinuation, or rescue therapies
Language	(1) Study published in English	(1) Study published in a language other than English

Observational studies and other non-randomized study designs present alternative methodologies for assessing the long-term treatment effects of DMT. However, these approaches are more vulnerable to bias (summarized in Sormani and Bruzzi, 2015). Despite these potential pitfalls, the data collected in these studies is valuable and makes an important contribution to our understanding of the impact of DMT on health outcomes.

However, to date, there are have been few meta-analyses of the long-term effects of DMT (Claflin et al., 2019). A notable exception is the systematic review and meta-analysis conducted by Signori et al. (2016), who reviewed the long-term treatment effects of interferon beta and glatiramer acetate in studies published before April 2015. In this study, we build on Signori et al.'s work, presenting a systematic review and meta-analysis of long-term (≥ 4 years) studies exploring the effect of DMT on disability and relapse outcomes in people living with MS.

2. Methods

2.1. Identification of included studies

In January 2018, we searched the Medline and EMBASE databases. Our search terms included terms for approved DMTs and disability progression outcome measures. For complete search terms, see Appendix 1. We used EndNote (Version 8.0) to deduplicate search results and used Covidence (Cochrane Collective), an online systematic review software, to conduct further deduplication and title/abstract and full text screening.

We screened articles using the inclusion and exclusion criteria presented in Table 1. We defined our primary health outcomes as disability progression measures and relapse rates, two variables frequently measured in clinical studies as markers of MS course. Secondary health outcomes were magnetic resonance imaging (MRI) metrics, quality of life (QoL), and adverse events (AE). Two researchers (BT and SBC) carried out the search and screening process. Any discrepancies in inclusion/exclusion assignment were resolved through discussion. In the case of continued disagreement, a third researcher (BVT) determined inclusion/exclusion status.

After the initial full text screening, we made the post hoc decision to further exclude extension studies that re-randomized treatment arms, went open-label, permitted regular care after a core study phase, or predicted long-term data from short-term studies. We felt that these study designs, while interesting and important, did not address our research question by testing the long-term effects of specific DMT. Hence, we only included long-term follow-up (LTFU) and extension studies that assessed patients according to their original treatment arm without re-randomization. A citation review of screened studies was conducted to find additional relevant papers.

2.2. Risk of bias assessment

Two authors (SBC and BT) performed bias assessments on included studies using the ROBINS-I tool, which was designed by the Cochrane Collective for use on non-randomized studies of interventions (Sterne et al., 2016a). The authors assigned a risk level (low, moderate, serious, critical, or not enough information) for seven bias categories (confounding, selection, classification, deviation, loss to follow-up, measurement, and selection of reported results), according to the tool's rating criteria (Supplementary Table 2). The authors assigned an overall risk of bias rating according to the detailed guidance available for the ROBINS-I tool. A overall rating of low risk of bias was assigned to studies with a low risk of bias in all domains; a moderate rating was assigned to studies with a moderate risk of bias in at least one domain; a serious rating was assigned to studies with a serious risk of bias in at least one domain; and a critical rating was assigned to studies with a critical risk of bias in at least one domain (Sterne et al., 2016b). Because

Table 2
Characteristics of included studies.

Study	Citation	Study design	Sample size (total)	Loss to follow-up	MS course	Inclusion criteria
	Bergamaschi et al. (2016)	retrospective cohort	1178	NA	RRMS	1) diagnosis of MS according to Poser criteria; 2) initial RRMS course; 3. 10+ years disease duration; 4. 1 year or less between clinical onset and first neurological examination
European IFNb-1a Dose-Comparison Study	Clanet et al., (2004)	RCT extension study	493	47 (9.5%)	relapsing MS	1) CDMS for at least one year; 2) at least 2 medically documented relapses within the 3 years prior to randomization; 3) an EDSS score between 2.0 and 5.5, inclusive
	Cocco et al., (2015)	retrospective cohort	2516	NA	relapsing MS	1) inclusion in MS Clinic of Cagliari database before 31 December 2012 2) diagnosis of MS by Poser or McDonald criteria 3) relapsing MS
CAMMS223	Coles et al., (2012)	LTFU	198 (enrolled in extension)	15 lost to follow-up at month 60 (7.6%)	RRMS	At study initiation: 1) EDSS score ≤3.0; 2) disease duration ≤3 years; 3) ≥2 relapses in the previous 2 years; 4) presence of ≥1 gadolinium-enhancing lesion on a screening MRI scan
	Drulovic et al., (2013)	prospective cohort	419	0 (not discussed)	RRMS	1) RRMS patients recruited consecutively from January 2004; 2) diagnosis with McDonald criteria; 3) EDSS ≤3.5; 4) active disease (≥2 functionally relevant relapses within the last 2 years); 5) age ≥18
ASA Study	Havrdova et al., (2009)	RCT	181	109 by 4 years (60.2%) 126 by 5 years (69.6%)	CDMS	1) 18–55 with CDMS; 2) EDSS≤ 3.5; 3) active disease, defined as 2 relapses in the last 12 months or 3 relapses in the last 24 months; 3) naïve to IFNB and GA
IFNB MS study	IFNB Study Group (1995)	RCT	372	125 by year 4 (33.6%) 206 by year 5 (55.4%)	CDMS	1) CDMS of short duration (mean of 4.4 years); 2) EDSS 0.0–5.5
	Kalincik et al., (2017)	retrospective, matched study on mostly prospectively collected data	4332	NA	RRMS	1) definite RRMS; 2) exposure to one of the study therapies; 3) no previous haemopoietic stem-cell transplantation; 4) no participation in randomized clinical trials; 5) minimum required recorded follow-up; 6) minimum dataset; 7) ≥6 months of continuous study therapy; 8) ≥1 relapse in the year before treatment; 9) age 65 years or younger; 10) ≤10 years from first MS symptom; 11) EDSS ≤6.5
CombiRx	Lublin et al. (2017)	LTFU	687 (enrolled in extension)	103 (15.7%)	RRMS	1) age 18–60; 2) RRMS by Poser or McDonald; 3) EDSS ≤6; 4) least 2 relapses in the prior 3 years
	Moccia et al. (2018)	retrospective	507	NA	RRMS	1) CD RRMS; 2) use of IFNB as first prescribed DMT after diagnosis
BCMS	Palace et al. (2015)	prospective cohort compared to natural history comparator	5035	treated cohort: 604 (15%) to year 4 1498 (38%) to year 6	RRMS/SPMS	RRMS: 1) 18 or older; 2) 2 clinically significant relapses in previous 2 years; 3) EDSS 5.5 or lower SPMS: 1) ambulant and with relapses as the main driver of advancing disability
	Patti et al. (2006)	open–label, non–randomized observational study: retrospective for years 0–3 and prospective for years 4–6	126	0 (not discussed)	RRMS	1) clinically stable for 4 weeks before treatment initiation; 2) RRMS according to Poser criteria
	Rio et al. (2005)	prospective	236	Unclear	RRMS	1) RRMS; 2) active disease with two or more relapses in the previous two years; 3) EDSS score between 0 and 5.5; 4) between 1995 and September 1998, Avonex was only approved to treat patients with EDSS between 0 and 3.5, but was extended to EDSS 5.5 after that
BCMS	Shirani et al. (2012)	retrospective cohort (based on prospectively collected data)	2656	NA	RRMS	1) definite RRMS; 2) age 18 or older; 3) EDSS ≤6.5

Table 2 (*continued*)

Study	Citation	Study design	Sample size (total)	Loss to follow-up	MS course	Inclusion criteria
	Tedeholm et al. 2013	retrospective cohort	916	NA	RRMS/SPMS	1) definite MS
	Trojano et al. (2005)	prospective cohort	1086; efficacy evaluated in 943	109 (56 Betaferon; 25 Avonex; 28 Rebif-22)	CDMS (RRMS and SPMS), efficacy only evaluated in RRMS cases	1) CDMS; 2) about to begin therapy with an IFNb
	Trojano et al. (2007)	Unclear	1504	NS	RRMS	1) RRMS according to Poser or McDonald criteria
BCMS	**Zhang et al. (2015)**	retrospective cohort study	2564	NA	RRMS	NS

Study	Exclusion criteria	Follow-up duration	Comparisons	Outcome measures	Overall risk of bias	Notes
	NS	median 16.5 years for treated and 17.8 years for untreated	All DMD (azathioprine, cyclophosphomides, GA, immunoglobins, IFNB, methotrexate, mitoxantrone, and natalizumab, analyzed as a group) **VS** those never treated with immune therapies	conversion to SP	**Serious**	The primary aim of this study is to confirm the capability of the BREMS score to predict MS progression.
European IFNb-1a Dose-Comparison Study	1) had progressive disease for longer than 6 months; 2) had a relapse within 2 months prior to randomization; 3) were pregnant or breastfeeding	48 months (4 years)	IFNB-1a 30 mcg **VS** IFNB-1a 60 mcg	sustained disability progression (defined as time to a sustained increase of ≥1 point on EDSS persisting for 6 months for patients with baseline EDSS scores of ≤4.5, or a 0.5 point increase for patients with baseline EDSS score of ≥5.0); sustained progression to EDSS score of ≥4.0 and ≥6.0; change in EDSS	**Moderate**	
	NS	median 12 years	**1)** Immunomodulatatory therapy (IM; IFNB-1a, IFNB-1b, GA, natalizumab) **VS** untreated (never treated or discontinued treatment after less than 1 year) **2)** Immunosuppressive therapy (IS; azathioprine, methotrexate, mitoxantrone, cyclophosphamide) **VS** untreated **3)** IM and/or IS vs untreated	time from onset to EDSS 3.0; EDSS 6.0	**Moderate**	
CAMMS223	NS	60 months	**1)** Alemtuzumab 12 mg vs IFNB-1a 44 μg **2)** Alemtuzumab 24 mg vs IFNB-1a 44 μg	proportion with and time to sustained accumulation of disability (SAD); ARR; change in EDSS	**Moderate**	Alemtuzumab dosing suspension from September 2005 until April 2008 (occurred during study period)
	NS	median 6.0 years, both groups	IFNB products (IFNB-1a 44 mcg and IFNB-1b 250 mcg) vs untreated	time from onset to sustained progression to EDSS 4.0 and EDSS 6.0; time from MS onset to conversion to SPMS	**Moderate**	
ASA Study	1) IFNB use in the previous 12 months before study; 2) received immunosuppressive treatment with either pulse cyclophosphamide or mitoxantrone in the previous 6 months	4–5 years, no mean stated	1) IFNB-1a vs IFNB-1a + azathioprine 2) IFNB-1a vs IFNB-1a +azathioprine + prednisone 3) IFNB-1a +azathioprine vs IFNB-1a + azathioprine +prednisone	ARR; time to first relapse; proportion of patients with clinical relapses; time to sustained progression	**Moderate**	

Table 2 (*continued*)

Study	Exclusion criteria	Follow-up duration	Comparisons	Outcome measures	Overall risk of bias	Notes
IFNB MS study	NS	median placebo: 3.83 years; low dose: 3.75 years; high dose: 4 years	1) IFNB-1b 1.6 MIU vs placebo 2) INFB-1b 8 MIU vs placebo 3) IFNB-1b 1.6 MIU vs IFNB-1b 8 MIU	time to EDSS worsening 1 point or more; mean change in EDSSS from baseline; annual exacerbation rate; proportion of exacerbation-free subjects; severity of exacerbation; activity and lesion burden	**Moderate**	
	NS	5 years; no mean stated	**1)** Alemtuzumab (12–24 mg) vs IFNB-1a (44 μg) **2)** Alemtuzumab (12–24 mg) vs fingolimod (0.5 mg) **3)** Alemtuzumab (12–24 mg) vs natalizumab (300 μg)	on-treatment ARR; cumulative hazard of relapses; disability accumulation events; disability improvement events; proportion of patients free from disability accumulation; proportion of patients with disability improvement during follow-up while on treatment	**Moderate**	
CombiRx	NS	mean and median = 3.9 years	**1)** GA 20 mg vs IFNB-1a 30 μg **2)** GA 20 mg vs GA 20 mg + IFNB-1a 30 μg **3)** IFNB-1a 30 μg vs GA 20 mg + IFNB-1a 30 μg	ARR; confirmed worsening (min 1.0 increase in EDSS from baseline); MSFC; MRI; clinical and disease activity free status; adverse events	**Moderate**	
	1) progressive form of MS at baseline; 2) age at diagnosis <18; 3) incomplete clinical records; 4) previous use of DMT	mean 8.5 ± 3.9 (SD) years	IFNB-1a 44 mcg vs IFNB-1a 30 mcg	ARR; 1-point EDSS progression;% reaching EDSS 4.0;% conversion to SPMS	**Moderate**	
BCMS		6 years (mean 5.1 ± 1.4 (SD) years for prospectively followed participants)	prospective cohort treated with IFNB and GA vs natural history comparator	accumulation of disability (EDSS progression and loss of utility)	**Moderate**	
	1) previous therapy with immunosuppressive drugs	6 years mean not given	IFNB-1a vs IFNB-1b	relapse; disease progression; percentage conversion to SPMS; safety (therapy change, discontinuation)	**Moderate**	
		at least 4 years	**1)** IFNB-1b vs IFNB-1a (Avonex) **2)** IFNB-1b vs IFNB-1a (Rebif) **3)** IFNB-1a (Avonex) vs IFNB-1a (Rebif)	proportion of relapse-free patients at 2 and 4 years; confirmed and sustained disability progression at 2 and 4 years; changes in ARR; proportion of decrease in relapse rate; proportion of patients reaching EDSS 6.0 at 4 years; number of patients who discontinued treatment due to inefficacy	**Serious**	Unclear what drop-out from this group is, as the group that was followed-up past 4 years is a subset of the initial 495 participants
BCMS	1) Fewer than 2 prospective EDSS measurements from baseline to study end; 2) exposed to a non-interferon beta DMD, a cytotoxic immunosuppressant for MS or an MS clinical trial prior to baseline	median treated: 5.1 years; contemporary untreated: 4.0; historical: 10.8 years	1) IFNB (any) vs contemporary untreated 2) IFNB (any) vs natural history comparator	hazard of disease progression to EDSS 4.0 and 6.0	**Moderate**	
	1) primary progressive and undefined course; 2) began DMD treatment after onset of SP	12 years	IFNB or GA vs untreated	kaplan-meier estimates of time to SP	**Serious**	
	NS	up to 6 years (analysis of >4 years)	**1)** IFNB-1b vs IFNB-1a (Avonex) **2)** IFNB-1b vs IFNB-1a 22 mcg (Rebif) **3)** IFNB-1a (Avonex) vs IFNB-1a 22 mcg (Rebif)	EDSS; relapse number, duration and severity; sustained and confirmed disability progression (increase of ≥1.0 EDSS point for at least 3 months)	**Moderate**	184 participants switched treatments by 6 years of follow up (analysis showed that switching did not affect results)
	NS	median 5.7 years	IFNB vs untreated		**Moderate**	

(*continued on next page*)

Table 2 (*continued*)

Study	Exclusion criteria	Follow-up duration	Comparisons	Outcome measures	Overall risk of bias	Notes
				time to EDSS 4.0; time to EDSS 6.0; time to SP		It is unclear if this was a prospective or retrospective study; untreated control refused treatment or was not eligible for it
BCMS	NS	median treated: 5.7 years; untreated contemporary: 3.7; historical: 7.3 years	**1)** IFNB (all) vs contemporary untreated **2)** IFNB (all) vs historical comparator	time from baseline to SPMS	**Moderate**	

the included studies received a rating of not enough information for a maximum of1 domain, the authors decided that a rating of not enough information would not influence the overall rating.

2.3. Data extraction and meta-analysis

Two authors (BT and SBC) extracted data from all included studies using a standard form. This included citation, study name, study design, population data, follow-up duration, treatment arms, and outcome measures (Table 4; Supplementary Table 2). The authors compared the extracted data and resolved any discrepancies through discussion. We contacted corresponding authors to obtain additional data that would allow us to evaluate these studies in a meta-analysis, however we received few responses and data received was not used in subsequent analysis.

When a study made comparisons to both a historical and contemporary control group with follow-ups of four years or greater, we extracted the results of the contemporary comparison. Our aim was to present a conservative assessment of DMT efficacy.

We conducted meta-analysis on outcomes assessed by three or more included studies. Funnel plots were created for each of meta-analysis to evaluate possible publication bias. All analysis was performed in Review Manager 5 (Cochrane Collective).

2.4. Data synthesis

The studies that were not included in meta-analysis were aggregated based on their study design: DMT compared to placebo/untreated or head-to-head comparison. The primary outcomes from these studies were then synthesized.

3. Results

3.1. Search results and study selection

Our search returned 7766 unique articles for review (Fig. 1). During the title and abstract screening, 7101 articles were excluded, leaving 665 articles for full text screening. Six hundred and twenty-seven articles were excluded during the full text screening. A further 24 articles were excluded upon closer assessment, leaving 14 articles. We reviewed the citations of these 14 articles and found four additional studies meeting the inclusion criteria, resulting in a total of 18 included studies.

3.2. Characteristics of included studies

Of the 18 studies included in this review, 14 (77.8%) had inclusion criteria that only allowed relapsing MS cases. Of the 4 remaining studies, three had inclusion criteria that allowed all clinically definite MS cases (16.7%), one of which only assessed efficacy in RRMS cases; and 1 study (5.6%) that allowed both RRMS and SPMS cases. Follow-up ranged from a mean of 3.9 years to a median of 17.8 years (Table 2). Four studies (22.2%) compared a contemporary treated cohort to a historical control group (Palace et al., 2015; Shirani et al., 2012; Tedeholm et al., 2013; Zhang et al., 2015). Three of these (Palace et al., 2015; Shirani et al., 2012; Zhang et al., 2015) conducted different analyses on the same dataset and used both a contemporary and historical control group.

A range of DMT were assessed in the included studies, but interferon beta was the most common. Five studies (27.8%) compared the efficacy of interferon-beta products in head-to-head trials. Four studies (22.2%) conducted head-to-head comparisons of other DMT, including combination therapies. Nine (50%) studies evaluated the effect of a DMT or group of DMT compared to an untreated or placebo group (Table 2).

The most commonly assessed disability progression measures were time to EDSS 4.0, EDSS 6.0, and SPMS. Three studies (16.7%) analyzed progression to EDSS 4.0 (Drulovic et al., 2013; Shirani et al., 2012;

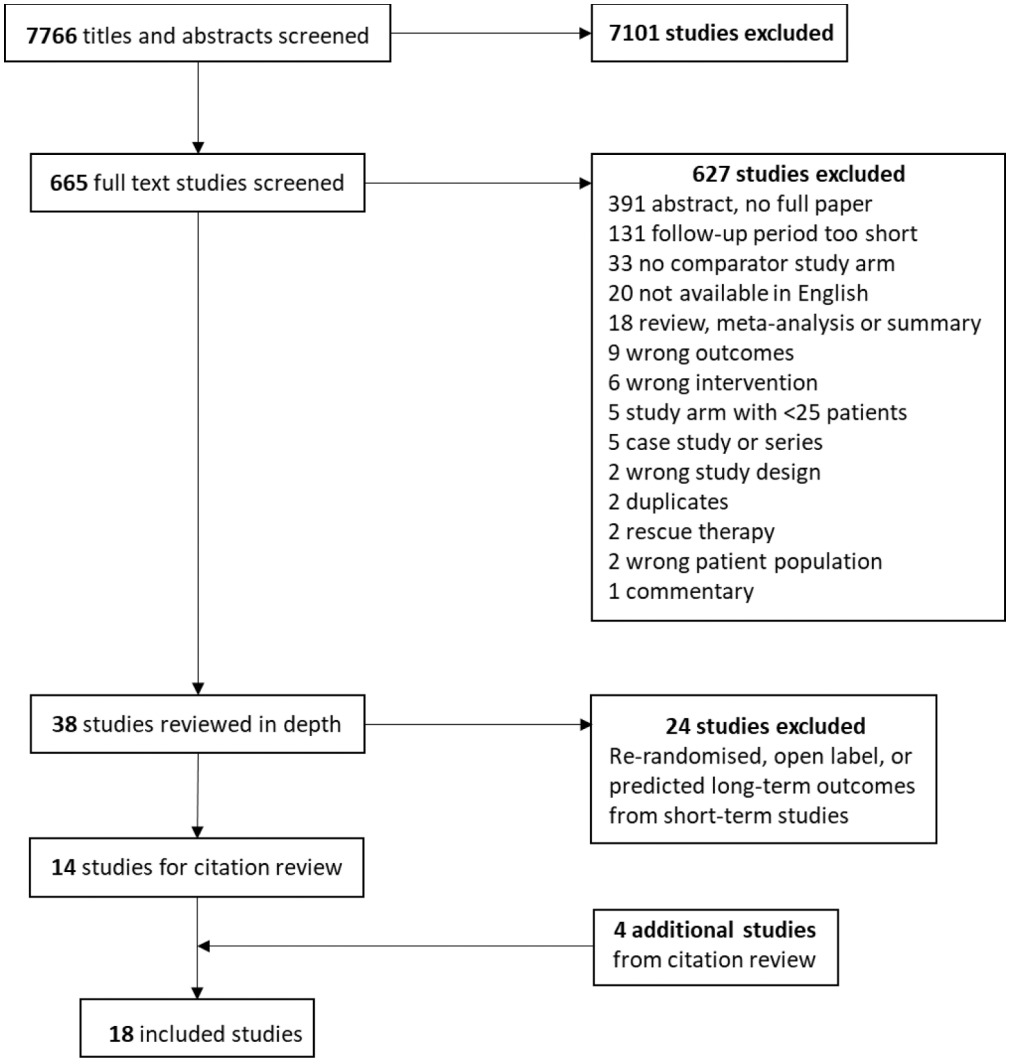

Fig. 1. Inclusion Flowchart.

Trojano et al., 2007), four studies (22.2%) evaluated progression to EDSS 6.0 (Cocco et al., 2015; Drulovic et al., 2013; Shirani et al., 2012; Trojano et al., 2007), and four (22.2%) evaluated conversion to SPMS (Drulovic et al., 2013; Trojano et al., 2007; Zhang et al., 2015). Less frequently assessed outcome measures included ARR, EDSS progression and the proportion of patients with EDSS $\geq$6.0 (Table 2).

4. Methodology

The included studies used a range of methodologies to correct for the potential biases of non-randomized studies. All but 5 studies corrected for baseline covariates in their analyses (Bergamaschi et al., 2016; IFNB Study Group, 1995; Patti et al., 2006; Rio et al., 2005; Trojano et al., 2005). Five studies used intention-to-treat analysis (ITT) or its equivalent (Havrdrova et al., 2009; IFNB Study Group, 1995; Palace et al., 2015; Rio et al., 2005; Trojano et al., 2005), and three studies used propensity weighting (Cocco et al., 2015; Moccia et al., 2018; Trojano et al., 2007). One study matched participants for baseline covariates using individual propensity scores (Kalincik et al., 2017). One study stratified their final analysis by sex (Tedeholm et al., 2013). Four studies compared the treatment group to historical cohorts (Palace et al., 2015; Shirani et al., 2012; Tedeholm et al., 2013; Zhang et al., 2015). Three studies used the same historical cohort (Palace et al., 2015; Shirani et al., 2012; Zhang et al., 2015) as a control group. Two of these also compared the treatment group to a similar cohort of contemporary controls (Shirani et al., 2012; Zhang et al., 2015), although one did not have sufficient follow-up with the contemporary controls to meet our inclusion criteria (Zhang et al., 2015).

4.1. Risk of bias assessment

Fifteen (83.3%) of the included studies received an overall rating of moderate risk of bias and 3 included studies (16.7%) received an overall rating of serious risk of bias (Table 2). Most (91.3%) of the bias domain ratings for the included studies were either low or moderate risk of bias. The bias domain that was best addressed by the included studies was classification bias; all included studies received a low risk of bias rating for this domain.

Of the 3 studies that received a serious risk of bias rating, two received it for risk of bias due to confounding (Bergamaschi et al., 2016; Rio et al., 2005), and one for risk of bias due to participant selection (Tedeholm et al., 2013). Eight studies (44.4%) received a rating of not enough information for one of the bias domains: one for the risk of bias due to confounding (Trojano et al., 2005), two for the risk of selection bias (Bergamaschi et al., 2016; Shirani et al., 2012), two for the risk of bias due to deviation from the intervention (IFNB Study Group 1995; Patti et al., 2006), and three for risk of bias due to loss to follow-up (Lublin et al., 2017; Rio et al., 2005; Trojano et al., 2007). None of the included studies received a rating of critical risk of bias. For a complete recording of the risk of bias assessment for each study, including rationale, please see Supplementary Table 2.

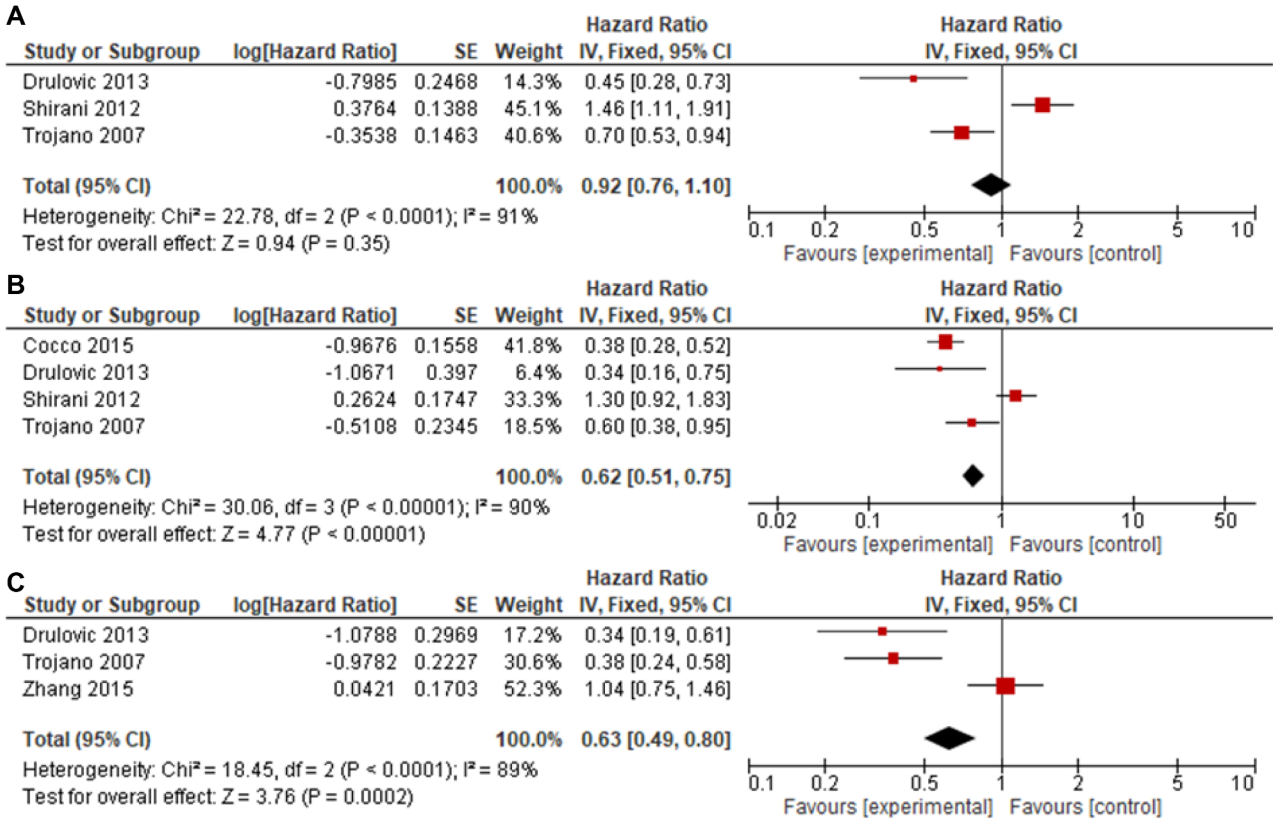

Fig. 2. Forest plot showing the results of a meta-analysis of A) the association of long-term (≥4 years) interferon-beta treatment with the hazard of progression to EDSS 4.0, measured as time to EDSS 4.0; B) the association of long-term DMT treatment with the hazard of progression to EDSS 6.0, measured as time to EDSS 6.0; and C) the association of long-term interferon-beta treatment with the hazard of conversion to SPMS, measured as time to SPMS. Data in Shirani et al. (2012) is derived from comparisons with a contemporary untreated cohort. Data in Zhang et al. (2015) is derived from comparison with a historical cohort.

4.2. Meta-analysis on the long-term efficacy of dmt

Meta-analysis demonstrates that interferon-beta is not significantly associated with a reduced hazard of progression to EDSS 4.0 for people with RRMS, measured as time to EDSS 4.0 ($p = 0.35$; Fig. 2A). The three studies included in this meta-analysis (Drulovic et al., 2013; Shirani et al., 2012; Trojano et al., 2007) all grouped interferon beta-1a and interferon beta-1b products into a single treatment group, which they compared to untreated controls over follow-up periods ranging from a median of 4 to 10.8 years.

Conversely, we found a significant association between long-term DMT treatment and the hazard of reaching EDSS 6.0 for people with relapsing MS, measured as time to EDSS 6.0 ($p < 0.0001$; Fig. 2B). Four studies assessed this relationship, two of which included more than one DMT. One study (Cocco et al., 2015) compared immunomodulant and immunosuppressant-treated cases (analyzed as a single group) with untreated cases. Another (Tedeholm et al., 2013) assessed the effect of interferon-beta products and glatiramer acetate, analyzed as a group, to untreated controls. The two remaining studies (Trojano et al., 2007; Zhang et al., 2015) evaluated the effect of interferon-beta products compared to untreated controls. The studies had follow-up periods ranging from a median of 5.7 years to 12 years.

Meta-analysis also showed that treatment with interferon-beta was significantly associated with a longer time to SPMS conversion for people with RRMS ($p < 0.001$; Fig. 2C). The three studies included in this analysis (Drulovic et al., 2013; Trojano et al., 2007; Zhang et al., 2015) evaluated the effect of interferon-beta compared to untreated controls. As with the analysis above, the follow-up period for these studies ranged from a median of 5.7 years to 12 years.

It is important to note that all three of the above meta-analyses showed substantial heterogeneity between studies ($I^2 = 91\%$, 90%, and 89%, respectively). Additionally, one study (Shirani et al., 2012) included in both the EDSS 4.0 and EDSS 6.0 meta-analyses compared the treatment group to both historical and contemporary controls. The contemporary control group analysis is included in the analysis in Fig. 2, because it is the most conservative estimate of effect. We replicated this analysis using the historical control group data (Supplementary Fig. 1). Because the direction of effect in this study is different (EDSS 4.0: HR = 0.99 (95%CI: 0.79–1.24); EDSS 6.0: HR = 0.77 (95%CI: 0.58–1.02)), the meta-analysis including the comparison with the historical control demonstrate an effect of DMT on the risk of EDSS 4.0 and 6.0 and have reduced heterogeneity (EDSS 4.0: HR = 0.80 (95%CI: 0.68–0.95), $z = 2.58$, $p = 0.010$, $I^2 = 79\%$; EDSS 6.0: HR = 0.55 (95%CI: 0.46–0.66), $z = 6.42$, $p < 0.0001$, $I^2 = 76\%$).

Due to the small number of included studies, it was not possible to rigorously assess publication bias. Funnel plots for the included meta-analyses are presented in Supplementary Fig. 2.

4.3. Data synthesis

4.3.1. DMT compared to untreated or placebo

In addition to the meta-analyses discussed above, our search returned five studies that evaluated the long-term effect of DMT on disability progression compared to placebo or no treatment. These studies also found that DMT treatment was significantly associated with improved disability outcomes in relapsing MS cases compared to placebo or no treatment.

Two studies (Bergamaschi et al., 2016; Cocco et al., 2015) analyzed all available DMT as a single group. These studies found that treatment was significantly associated with a reduced risk of secondary progression (Bergamaschi et al., 2016) and a 73–94% lower risk of EDSS 3.0 compared to untreated relapsing MS cases (Cocco et al., 2015). Two

studies grouped interferon beta and glatiramer acetate into a single treatment group in their analyses. The first (Palace et al., 2015) found that these DMT significantly reduced disability accumulation in RRMS patients compared to untreated historical controls and maintained their cost-effectiveness over 6 years. The second (Tedeholm et al., 2013) found that those treated with DMT had a significantly longer time to SPMS compared to untreated historical controls.

The final study (IFNB Study Group 1995) found that interferon-beta-1b significantly reduced the exacerbation rate in each of 5 years, reduced the 4-year progression of lesion burden, and slowed confirmed disability progression compared to placebo.

4.3.2. Interferon beta head-to-head studies

Five studies compared interferon beta products and dosages. In general, these studies found the included interferon beta products and dosages were equally effective at reducing relapse rate and disability accumulation (Clanet et al., 2004; Moccia et al., 2018; Patti et al., 2006; Rio et al., 2005; Trojano et al., 2005). However, one study (Moccia et al., 2018) found that the rate of SPMS conversion was significantly higher for interferon beta-1b compared to interferon beta-1a 44 mcg, although there was no difference between interferon beta-1a 30 mcg and interferon beta-1a 44 mcg. Additionally, one study (Trojano et al., 2005) reported that interferon beta-1b resulted in more withdrawals (19%) compared to interferon beta-1a (Avonex, 6%) or interferon beta-1a (Rebif, 7%) at 6 years.

4.3.3. Other DMT head-to-head studies

Four of the included studies conducted head-to-head analyses of DMT and DMT combination therapies (Coles et al., 2012; Havrdova et al., 2009; Kalincik et al., 2017; Lublin et al., 2017). Two of these evaluated the effect of alemtuzumab compared to other DMT. Both studies found that alemtuzumab significantly lowered relapse rate compared to interferon beta over 5 years (Kalincik et al., 2017; Coles et al., 2012). However, their results about disability accumulation do not agree. One study found that alemtuzumab significantly lowered the risk of sustained disability accumulation compared to interferon beta-1a, observing a 72% decrease in risk (Coles et al., 2012), and the other found that there was no significant difference between alemtuzumab and interferon beta (Kalincik et al., 2017). One study (Coles et al., 2012) reported adverse events. They found that alemtuzumab resulted in higher rates of serious infections, thyroid disorders, immune thrombocytopenia compared to interferon beta-1a in the initial study, though no additional events were reported in the study extension to 5 years of follow-up.

One study compared alemtuzumab to fingolimod and natalizumab over 5 years of follow-up (Kalincik et al., 2017). They found that alemtuzumab was associated with lower ARR than fingolimod, but similar probabilities of disability accumulation and disability improvement. They also found that alemtuzumab was associated with similar ARR and probability of disability accumulation, but a lower probability of disability improvement compared to natalizumab.

Two studies explored the effect of single DMTs compared to combination therapy. One study (Lublin et al., 2017) found that glatiramer acetate individually and in combination with interferon beta significantly reduced the risk of relapse compared to treatment with interferon beta alone. However, the effect of the combination on confirmed EDSS worsening was not significantly different from either treatment individually. The other study (Havrdova et al., 2009) compared interferon beta-1a alone to interferon beta-1a combined with low-dose azathioprine and interferon beta-1a combined with low-dose azathioprine and low-dose corticosteroids. They found no significant difference between the groups in adjusted annualized relapse rate or the cumulative probability of sustained disability progression at 5 years.

5. Discussion

Our meta-analyses suggest that the long-term use of interferon beta significantly reduces the risk of progression to EDSS 6.0 and SPMS in people with relapsing MS, but does not have a significant effect on the time to EDSS 4.0. However, there was substantial heterogeneity among the included studies and analyses could not be conducted on second generation DMT or head-to-head comparisons. Additional studies are needed to establish the long-term effects of DMT on disability progression and relapse in people living with MS.

5.1. Long-term treatment with interferon beta appears to reduce the risk of EDSS 6.0 and SPMS, but more research is required

Our meta-analyses largely support the findings of Signori et al. (2016), who found that long-term treatment with interferon beta or glatiramer acetate significantly reduced the risk of progression to EDSS 6.0 and SPMS. In large part, this agreement is explained by overlap in included studies. This overlap reflects the broader issue that—with one exception (Cocco et al., 2015)—our search did not return long-term studies of DMT other than interferon beta that met our inclusion criteria and could be included in a meta-analysis.

Similarly, disagreement with Signori et al. (2016) likely reflected a difference in included studies. While they found a significant reduction in the risk of EDSS 4.0, our meta-analysis showed no effect. This difference appears to be driven by the fact that their meta-analysis did not include Shirani et al. (2012), whose data showed no effect of interferon beta on the risk of EDSS 4.0.

As in previous meta-analyses on the long-term effects of DMT (Signori et al., 2016), our meta-analyses had substantial heterogeneity. This heterogeneity likely reflects the conflicting biases arising from different non-randomized study designs (Sormani and Bruzzi, 2015). While high heterogeneity among studies included in a meta-analysis may protect against a skewed outcome by balancing conflicting biases, it also reduces confidence in the result (Sormani and Bruzzi, 2015). Consequently, further work is needed to establish the long-term effect of interferon beta on disability progression and relapse outcomes in people living with MS.

5.2. More research is required to determine the long-term effect of second generation DMT and head-to-head comparisons

The strongest body of evidence for head-to-head comparisons in this review is around the relative effects of interferon beta products. Five studies made head-to-head comparisons. Their general findings were similar: there was little difference between products. However, there was little similarity in outcome measures, making it impossible to compare the results using meta-analysis and limiting the strength of this finding. The same is true of the wider body of evidence. There were few studies and little overlap in outcome measures between studies on second generation DMT and other head-to-head comparisons. This is likely due to the logistical and ethical challenges that long-term intervention studies present. However, it is therefore not possible draw any meaningful conclusions about long-term effects. Further work is needed to determine the impact of second generation DMT and the relative effect of DMT.

5.3. Innovative study designs are promising for future research in this area

The studies in this review included three innovative methodologies that will benefit future research. First, two studies (Shirani et al., 2012; Zhang et al., 2015) compared a prospectively followed treatment group to both a contemporary untreated group and a historical control. These comparisons have opposing biases. Comparisons with a contemporary untreated group tends to favor the control, because untreated populations often have better prognoses than treated populations. Conversely,

comparisons with historical natural history cohorts tend to favor the intervention because historical cohorts tend to have worse prognoses than modern cohorts (Sormani and Bruzzi, 2015). Presenting analyses of both strengthens the conclusions of these studies.

Second, one study (Drulovic et al., 2013) conducted a natural experiment brought about by socio-political factors rather than study design. They carried out a study of treated and untreated people living with MS in a country with limited access to DMT (interferon beta) due to the economic situation of the country. Consequently, the treated and control groups were similar in baseline demographics, reducing the risk of bias.

Finally, one study (Kalincik et al., 2017) conducted a retrospective head-to-head trial of alemtuzumab using a massive database of MS cases. This approach allowed the authors to identify a reasonable sample of contemporary cases using the DMT of interest. The large number of cases also made it possible for the authors to match participants in the treated group with participants in the various control groups by baseline factors, reducing the possibility of bias. The accessibility of large MS case databases, such as MSBase, which now includes more than 50,000 cases, may make it possible to assess the long-term effects of DMT using this or similar study designs.

5.4. The meta-analyses in this review were limited by a small sample and the biases of included studies

This review has two main limitations. First, few studies met the inclusion criteria, and fewer could be included in a meta-analysis. Second, as outlined in a previous review (Sormani and Bruzzi, 2015), non-randomized studies have significant potential biases and these biases affect meta-analyses. However, as stated above, the included studies have opposing biases that may counteract each other when aggregated.

6. Conclusions

There is some evidence that long-term treatment with interferon beta reduces the risk of EDSS 6.0 and SPMS compared to no treatment or placebo. However, further research is necessary to confirm these conclusions. Additionally, more work is needed to establish the long-term effect of second generation DMT and the relative effect of DMT on progression and relapse outcomes in people living with MS.

Declaration of Competing Interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.08.016.

References

Bergamaschi, R., Quaglini, S., Tavazzi, E., Amato, M.P., Paolicelli, D., Zipoli, V., Romani, A., Tortorella, C., Portaccio, E., D'Onghia, M., Garberi, F., Bargiggia, V., Trojano, M., 2016. Immunomodulatory therapies delay disease progression in multiple sclerosis. MSJ 22 (13), 1732–1740.

Claflin, S.B., Broadley, S., Taylor, B.V., 2019. The effect of disease modifying therapies on disability progression in multiple sclerosis: a systematic overview of meta-analyses. Front Neurol. 9, 1150.

Clanet, M., Kappos, L., Hartung, H.-P., Hohlfeld, R., 2004. the European IFNβ-1a dose-comparison study investigators. interferon β-1a in relapsing multiple sclerosis: four-year extension of the European IFNβ-1a dose-comparison study. Mult. Scler. 10, 139–144.

Cocco, E., Sardu, C., Spinicci, G., Musu, L., Massa, R., Frau, J., et al., 2015. Influence of treatments in multiple sclerosis disability: a cohort study. MSJ 21 (4), 433–441.

Coles, A.J., Fox, E., Vladic, A., Gazda, S.K., Brinar, V., Selmaj, K.W., et al., 2012. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology 78 (14), 1069–1078.

De Angelis, F., John, N.A., Brownlee, W.J., 2018. Disease-modifying therapies for multiple sclerosis. BMJ 363, k4674.

Drulovic, J., Kostic, J., Mesaros, S., Dujmovic Basuroski, I., Stojsavljevic, N., Kisic-Tepavcevic, D., et al., 2013. Interferon-beta and disability progression in relapsing-remitting multiple sclerosis. Clin. Neurol. Neurosurg. 115 (Suppl 1), S65–S69.

Hartung, D.M., Bourdette, D.N., Ahmed, S.M., Whitham, R.H., 2015. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: too big to fail? Neurology 84 (19), 2185–2192.

Havrdova, E., Zivadinov, R., Krasensky, J., Dwyer, M.G., Novakova, I., Dolezal, O., et al., 2009. Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiples sclerosis. Mult. Scler. 15 (8), 965–976.

INFB Multiple Sclerosis Study Group, 1995. University of british columbia MS/MRI analysis group. interferon beta-1a in the treatment of multiple sclerosis. Neurology 45, 1277–1285.

Kalincik, T., Brown, J.W.L., Robertson, N., Willis, M., Scolding, N., Rice, C.M., et al., 2017. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. Lancet Neurol. 16 (4), 271–281.

Lublin, F.D., Cofield, S.S., Cutter, G.R., Gustafson, T., Krieger, S., Narayana, P.A., et al., 2017. Long-term follow-up of a randomized study of combination interferon and glatiramer acetate in multiple sclerosis: efficacy and safety results up to 7 years. Mult. Scler. Rel. Dis. 18, 95–102.

Moccia, M., Palladino, R., Carotenuto, A., Saccà, F., Russo, C.V., Lanzillo, R., Morra, V.B., 2018. A 8-year retrospective cohort study comparing interferon-β formulations for relapsing-remitting multiple sclerosis. Mult. Scler. Rel. Dis. 19, 50–54.

Palace, J., Duddy, M., Bregenzer, T., Lawton, M., Zhu, F., Boggild, M., et al., 2015. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK multiple sclerosis risk sharing scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol. 14 (5), 497–505.

Patti, F., Pappalardo, A., Florio, C., Politi, G., Fiorilla, T., Reggio, E., Reggio, A., 2006. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. Acta Neurol. Scand. 113 (4), 241–247.

Pucci, E., Giuliani, G., Solari, A., Simi, S., Minozzi, S., Di Pietrantonj, C., et al., 2011. Natalizumab for relapsing remitting multiple sclerosis (Review). Cochrane Database Systematic Rev. 10, CD007621. https://doi.org/10.1002/14651858.

Río, J., Tintoré, M., Nos, C., Téllez, N., Galán, I., Montalban, X., 2005. Interferon beta in relapsing-remitting multiple sclerosis: an eight years experience in a specialist multiple sclerosis centre. J. Neurol. 252, 795–800.

Shirani, A., Zhao, Y., Karim, M.E., Evans, C., Kingwell, E., van der Kop, M., Oger, J., et al., 2012. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. JAMA 308 (3), 247–256.

Signori, A., Gallo, F., Bovis, F., Di Tullio, N., Maietta, I., Sormani, M.P., 2016. Long-term impact of interferon or Glatiramer acetate in multiple sclerosis: A systematic review and meta-analysis. Mult. Scler. Relat. Disord. 6, 57–63.

Sormani, M.P., Bruzzi, P., 2015. Can we measure long-term treatment effects in multiple sclerosis? Nature Rev. Neurol. 11 (3), 176–182.

Sterne, J.A.C., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., et al., 2016a. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919.

Sterne J.A.C., Higgins J.P.T., Elbers R.G., Reeves bc and the development group for ROBINS-I. risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance, updated 12 October2016b. Available fromhttp://www.riskofbias.info [accessed 2018].

Tedeholm, H., Lycke, J., Skoog, B., Lisovskaja, V., Hillert, J., Dahle, C., Fagius, J., Fredrikson, S., Landtblom, A.-.M., et al., 2013. Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. MSJ 19 (6), 765–774.

Trojano, M., Paolicelli, D., Zimatore, G.B., De Robertis, F., Fuiani, A., Di Monte, E., Livrea, P., 2005. The IFNβ treatment of multiple sclerosis (MS) in clinical practice: the experience at the MS center of Bari, Italy. Neurol. Sci. 26, S179–S182.

Trojano, M., Pellegrini, F., Fuiani, A., Paolicelli, D., Zipoli, V., Zimatore, G.B., et al., 2007. New natural history of interferon-β-treated relapsing multiple sclerosis. Ann. Neurol. 61 (4), 300–306.

Zhang, T., Shirani, a., Zhao, Y., Karim, M.E., Gustafson, P., Petkau, J., et al., 2015. Beta-interferon exposure and onset of secondary progressive multiple sclerosis. Eur. J. Neurol. 22 (6), 990–1000.