Sex differences in outcomes of disease-modifying treatments for multiple sclerosis: a systematic review

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Abstract:

Background: Multiple sclerosis (MS) is a chronic immune mediated demyelinating disease of the central nervous system that exhibits sexual dimorphism and may benefit from sex-specific treatment. To investigate a potential influence of sex on immunomodulatory therapeutic effects in patients with MS, we performed a comprehensive analysis of published studies examining sex differences in the effects of disease-modifying treatments (DMTs) for MS. **Methods:** PubMed, Cochrane Library, and Web of Science databases were searched for clinical studies involving patients with MS who were undergoing DMTs. Studies were included if they investigated sex differences in DMT outcomes. **Results:** Fourteen studies with 11,425 participants were included; 11 of these studies were randomized controlled trials, and 3 were cohort studies. Although the studies did occasionally show sex-specific differences for some clinical outcomes in patients with MS who received DMTs, the limitation of subgroup analysis design made it difficult to draw conclusions on the direction or the extent of the sex-based effect. **Conclusion:** No clear sex-based differences in response to DMTs have been documented to date. More studies will be needed to better elucidate the presence of sex differences on the DMT effects.

Keywords: Sex difference; disease-modifying treatment; multiple sclerosis

1 Introduction

Multiple sclerosis (MS) is a chronic immune mediated demyelinating disease of the central nervous system. It is more prevalent in women than men, and onset occurs later in men than in women¹. However, men experience more rapidly progressive clinical and radiological courses¹. Such sexual dimorphism in MS prevalence and course indicates differences in the immune system or nervous system between women and men, which may be caused by the effects of gonadal hormones or genetic differences as well as by different environmental exposures and modern lifestyles of men and women^{2, 3}. The gender differences in MS raise the question of whether gender, via sex hormones and other gender-related factors, may affect the treatment response. However, to date, there are few and conflicting results from studies examining gender effect on the response to currently used disease-modifying treatment (DMTs). In this study, we performed a comprehensive analysis of published articles that investigated sex differences on the effects of DMTs in MS to determine whether gender affects immunomodulatory therapy.

2 Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA; <http://www.prisma-statement.org/>).

2.1 Literature search

The PubMed, Cochrane Library, and Web of Science databases from inception to December 30, 2015, were searched for relevant articles. The following search terms and their medical subject headings (MeSH) were used: “multiple sclerosis”; “disease modifying drugs”; “treatment/therapy”; “interferon beta (IFN β)”; “glatiramer acetate (GA)”; “dimethyl fumarate”; “mitoxantrone”; “alemtuzumab”; “fingolimod”; “natalizumab”; “teriflunomide”; “mitoxantrone”; “sex differences”; “gender differences”; “sex”; “male”; “female”; “men”; “women.” Only papers published in English were included. There were no restrictions on publication date. Only completed, published, and peer-reviewed studies were included to ensure high-quality evidence. Additional manual searches were performed based on the relevant references provided in the articles identified in the initial search to improve the recall ratio and precision ratio.

2.2 Data collection

Two of us (Rui Li and Xiaobo Sun) independently reviewed articles at each screening stage, and disagreements were resolved by consensus. Data were extracted in duplicate using a data extraction form following the “participants, interventions, comparisons, outcomes, study design, and time” principles. Studies not meeting the inclusion criteria were excluded, and the reasons for exclusion were recorded. Information was obtained on study characteristics and design, sample population, and disease-modifying treatment outcomes.

2.3 Quality assessment

The included randomized controlled trials (RCTs) and cohort studies were evaluated using the Cochrane collaboration’s tool for assessing risk of bias (<http://community.cochrane.org/handbook>) and the Newcastle-Ottawa assessment scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The criteria used to score the subgroup analysis (SGA) for comprehensiveness, based on the criteria of Yusuf et al.⁴ with some modifications, were as follows: (i) the SGA was prestated or planned a priori to the study commencement; (ii) the hypothesis or rationale for the analysis was provided; (iii) a statistical test for interaction was performed between the subgroups (for RCTs), or a statistical analysis was conducted to compare the treatment effects between the subgroups (for cohort studies); and (iv) the overall treatment results were emphasized more than the findings of the SGA. Proper SGA is defined as one that includes (i) a statistical test for interaction to test subgroup differences (for RCTs), or a statistical analysis to compare the clinical endpoints between the subgroups (for cohort studies), and (ii) conclusions that emphasize the overall results of the RCT and not the results of the SGA⁵.

2.4 Analysis

A meta-analysis or other statistical calculations were not performed to combine or analyze data. Instead, the data were reviewed and analyzed only descriptively because of the methodological heterogeneity of the studies.

3 Results

3.1 Search results and study characteristics

We included 3 cohort studies and 11 RCTs. The flow chart for the literature screening is shown in Figure 1. The DMTs included IFN β , GA, dimethyl fumarate, natalizumab, fingolimod, and alemtuzumab. No studies were found examining sex differences in response to teriflunomide or mitoxantrone in patients with MS patients. The sample size for each study ranged from 91 to 2,570 participants. Patients' mean or median ages varied from 27.1 to 39 years in relapsing-remitting MS (RRMS), 42.8 to 45.7 years in secondary progressive MS (SPMS), and 50.4 years in primary progressive MS (PPMS). There was a predominance of females in most studies. The characteristics of the 14 studies are presented in Table 1⁶⁻¹⁹.

3.2 Study design, statistical analysis, and clinical outcomes

Only 35.7% (5/14) of the studies performed proper SGA. Most of studies used post hoc analysis, and only one study stated the SGA a priori. Nine of 14 included studies testing the effect of DMTs in male and female subgroups separately, without performing statistical tests for this subgroup difference. Four studies (28.6%) provided a rationale for performing the SGA. In 14 included studies, 42.9% (6/14) did not report or balance sex-specific baseline characteristics. Cox regression analysis was used in 11 (78.6%) studies, logistic regression in 5 studies (35.7%), Poisson regression in 3 studies (21.4%), analysis of covariance (ANCOVA) in 1 study (7.1%), other statistical analyses, such as *t* test, chi-square test, and ANOVA, in 3 studies (21.4%). The clinical outcomes are shown in Table 2.

3.2.1 Interferons

Four RCTs and three cohort studies exploring the effects of IFN β in patients with MS analyzed using sex SGA were included. The participants in these studies included patients with RRMS and SPMS.

3.2.1.1 Studies exploring the effects of IFN β in patients with RRMS

In the Cleveland Clinic study, there were no sex differences for relapse (time to first relapse and annualized relapse rate), confirmed disability (time to disability progression), or the proportion of patients with gadolinium-enhanced lesions⁶. In the Italian cohort study, which had a larger sample population and longer follow-up period than those in the Cleveland Clinic study, men exhibited a significantly ($P = 0.0097$) lower risk for first relapse and a trend ($P = 0.0897$) for a higher risk to reach confirmed disability (one-point Expanded Disability Status Scale [EDSS] progression) compared with women⁷. In the COGIMUS study, a significantly higher proportion of males than females with RRMS who received IFN β therapy had cognitive impairment at year 5 (26.5% vs. 14.4%, $P = 0.046$)⁸. However, this study used a chi-square test, which is a less exact statistical method, focusing on only the occurrence (or not) of the event, regardless of other covariant effects to evaluate sex difference. A Brazilian cohort study found no statistically significant correlation among response or non-response to IFN β according to gender⁹. However, the clinical endpoint (non-response to IFN β) selected by the Brazilian cohort study, which was defined as the presence of any relapse or increase in the EDSS(at least one-point) at one year, was not optimal. It may be

more accurate if analyzing relapse and confirmed disability respectively. All of these four studies had properly performed the SGA according to the criteria suggested by Yusuf et al.⁴. However, these four studies conducted post hoc analyses that did not state sex SGA a priori to ensure that there were sufficient numbers of participants in both sex/gender subgroups to actually determine a veritable difference between the groups.

3.2.1.2 Studies focused on the effects of IFN β in patients with SPMS

The clinical trial results from the SPECTRIMS study showed that IFN β -1a may preferentially benefit women in preventing confirmed disability¹⁰. But male patients had consistently better outcomes (time to confirmed disability) than female patients receiving placebo (selection bias), which may lead to the result that females were prone to obtain benefit from IFN β treatment. In the study by Li and his colleagues, women showed highly significant reductions at both doses (22 μ g and 44 μ g) of IFN β 1a in the T2 lesions (burden of disease, BOD) and T2 active lesions compared with the placebo group, whereas men showed treatment benefits only at the high dose compared with the placebo group¹¹. However, this result may have been affected by the differences in magnetic resonance imaging (MRI) activity in the placebo group, in which men showed less MRI activity than women, having fewer active lesions and lesser accumulation of BOD¹¹(selection bias). The additional limitations of these two studies were post hoc analyses and no statistical tests for interaction between sex subgroups. The Nordic SPMS study did not note statistical significance for a gender difference in the risk to confirmed disability progression in patients with SPMS who received IFN β treatment¹². But the Nordic SPMS population studied was clinically less active than populations studied in other trials of patients with SPMS(selection bias), and was treated with a low dose of IFN β 1a (22 μ g), which may result in ineffectiveness of IFN β treatment in both male and female patients with SPMS.

3.2.2 Glatiramer acetate (GA)

The results of an originally unplanned post hoc analysis of the PROMISE trial suggested that GA may have slowed clinical progression in male but not female patients with PPMS¹³. However, the observation that men showed more rapid progression than women when untreated allowed a treatment effect to be more easily discerned in male MS patients in that trial. The researchers further explored the data from that trial in an attempt to determine if this outcome could have been an expression of a gender-dependent treatment effect. Subsequent analyses found no effect of sex on the response (relapse, confirmed disability progression, gadolinium-positive lesions, and T2 lesion volume) to GA in either PPMS or RRMS¹⁴.

3.2.3 Other disease-modifying drugs

Five RCTs were included that explored the effects of other disease-modifying drugs in patients with RRMS and that used sex SGA: two examined dimethyl fumarate(DEFINE and CONFIRM study)^{15, 16}, whereas the other three investigated natalizumab(AFFIRM and SENTINEL study)¹⁷, fingolimod(FREEDOMS study)¹⁸, and alemtuzumab(CAMMs223 study)¹⁹. In subgroup analyses of the AFFIRM and SENTINEL trials, an effect of natalizumab on confirmed disability was present only in women¹⁷. In the FREEDOMS study, the risk of confirmed disability was numerically lower in the fingolimod treatment group than that in the placebo group of men, a result that was not observed in women¹⁸. The other three clinical trials did not find a gender

difference for DMT response^{15, 16, 19}. All five of these studies conducted post hoc analyses, and none of them performed statistical tests for an interaction between the sex subgroups. Thus, the strength of the evidence from such analyses was considered low.

4 Discussion

Exploring the effects of gender on the response to therapy has implications for treatment of patients with MS. However, very little has been known about the potential effect of gender on the response to DMTs. In this review, we summarized the results from 14 studies that examined sex differences in DMT outcomes for patients with MS.

The results from current studies pertaining to a gender effect on the response to DMTs in patients with MS have, on occasion, shown sex-specific differences. However, the limitation of subgroup analysis design made it difficult to draw conclusions on the direction or the extent of these effects. The findings on a gender effect in response to DMTs in patients with MS from the included studies should be interpreted with caution for several reasons. First, the gender difference observed in most of included studies arose from post hoc analysis rather than an a priori hypothesis, resulting in an inherent limitation. Additionally, men comprised only a third of the participants in most of the trials (between 25.3 and 38% in patients with RRMS), and this relatively small sample size may have been underpowered to detect important differences between women and men. Second, RCT results based on carefully defined patient selection criteria may be confounded by selection bias, that may limit the generalizability of their findings to the typical MS population in real-world medical practice. In this review, three RCTs had selection biases, affecting the result on the sex difference of DMTs response¹⁰⁻¹²(table 2). Due to this weak point of RCT design, more observational studies representing large diverse populations are needed^{20, 21}. Third, the gender difference in DMTs response may reflect sex disparity in the natural history of MS rather than in treatment effects. Men have worse prognoses than women, and are enriched for PPMS²²⁻²⁴. It is not surprising that male patients had poorer clinical outcomes despite receiving the same treatment as females. Therefore, any worse response by males should have been compared with the placebo arm response. The cohort studies included in this review could not clarify this issue due to lacking the data of placebo group^{7,8}. The fourth interpretation caution is that half (50.0%, 5/10) of the included RCT studies did not conduct statistical tests examining interactions to help ascertain whether a significant treatment difference existed between men and women. Fifth, considering the inconsistencies within published work regarding subgroup effects, some of the suggested differential treatment effects were probably due to chance. Finding approximately one significant subgroup-by-treatment interaction after undertaking many independent statistical interaction tests (α level of 0.05) across subgroups would have been expected by chance if the null hypothesis (i.e., no effect of subgroups in reality) were true¹⁷. Sixth, some (42.9%, 6/14) of the included studies did not report or balance sex-specific baseline characteristics, and the effects of potential confounding factors (such as baseline EDSS) could not be assessed. Finally, less exact statistical methods may affect the results of sex SGA.

Although the results of our qualitative review of these data might not convincingly demonstrate that there were sex differences in response to DMTs (i.e., 64.3% [9/14] of the studies performed improper SGA, and 50% [7/14] of the studies reported no sex differences), sex bias did exist in

some studies, including a few higher-quality studies. More interesting is that the potential subgroup difference was consistent (in favor of females) across several studies for patients with MS patients who received IFN β therapy^{7, 8, 10, 11}. We therefore cannot absolutely rule out the possibility of a gender effect on DMT (i.e., IFN β) in patients with MS. This potential gender difference for patients with MS patients receiving IFN β therapy, if real, may be due to several factors. (1) The immune response in men and women display differences in the regulation of T-helper (Th) cell network homeostasis. Contasta et al.²⁵ noted that the efficacy of IFN β treatment in the re-establishment of the Th-network balance and in delaying the progression of neurological disability is linked to the interleukin 6 pathway in women and to the IFN γ pathway in men. These findings underscore the need for treatment approaches that take gender into account. (2) Female patients with MS report better awareness of disease symptoms and have more positive perceptions of their ability to manage DMTs than do male MS patients²⁶. (3) Lifestyles may be different between men and women, which may further influence IFN β treatment effects. For instance, smoking is associated with an increased risk of developing neutralizing antibodies (Nabs) to IFN β -1a, which are associated with a loss of biological and clinical efficacy²⁷. Epidemiological survey data from the World Health Organization showed that smoking prevalence in males is much higher than that in females²⁸.

Because of the weak evidence from the sex SGA included in this systematic review, we cannot convincingly conclude that a gender effect exists for the response to DMTs in patients with MS. Nevertheless, the preexisting biological rationale (i.e., the aforementioned sexual dimorphism in immunologic status in patients with MS) and the sex bias of the DMT response alluded to in some clinical studies indicate that better studies are warranted to explore possible differences in the effect of DMTs on clinical outcomes between men and women with MS.

Conclusion

To date, no clear sex-based therapy response differences have been documented. More studies are needed to better elucidate the presence of sex differences for the effects of DMT. Such studies would be helpful in improving individualized treatment for patients with MS.

Conflict of interest

The authors have no conflict of interest to report.

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Figure 1. Literature screen flow chart.

Table 1 Characteristics of the 14 studies included in the systematic review

Study	Study location	Study design	Study title	Phase	Clinical subtype	No. of participants (F/M)	Intervention	Age of onset, mean±SD	Follow-up
Rudick et al. 2010 ⁶	Ohio, USA	RCT*	Cleveland Clinic study	III	RRMS	1406(1027/379)	IFNβ1a(Avonex 30 μ g IM once weekly)	--	2 years
Trojano et al. 2009 ⁷	Bari, Italy	Cohort	Italy cohort study	--	RRMS	2570(1774/796)	IFNβ1b(Betaferon 250 μ g SC every other day), IFNβ1a(Avonex 30 μ g IM once weekly; Rebif 22 μ g SC three times weekly; Rebif 44 μ g SC three times weekly)	27.1±8.6	7 years
Patti et al. 2013 ⁸	Catania, Italy	Cohort	COGIMUS	--	RRMS	179(111/68)	IFNβ1a(Rebif 22 μ g SC three times weekly; Rebif 44 μ g SC three times weekly)	39±8.2	5 years
Pereira et al. 2012 ⁹	Brazil	Cohort	Brazil cohort study	--	RRMS	91(68/23)	IFNβ(IFNβ1b: Betaferon 250 μ g SC every other day; IFNβ1a: Avonex 30 μ g IM once weekly; Rebif 22 μ g SC three times weekly; Rebif 44 μ g SC three times weekly)+GA	30(5,51)	--
(SPECTRIMS) Study Group. 2001 ¹⁰	Europe, Canada, and Australia	RCT	SPECTRIMS study	III	SPMS	618(389/229)	IFNβ1a(Rebif 22 μ g SC three times weekly; Rebif 44 μ g SC three times weekly)	42.8±7.1	2 years
Li et al. 2001 ¹¹	Europe, Canada, and Australia	RCT	SPECTRIMS study	III	SPMS	618(389/229)	IFNβ1a(Rebif 22 μ g SC three times weekly; Rebif 44 μ g SC three times weekly)	42.8±7.1	3 years
Andersen et al.	Denmark and	RCT	Nordic SPMS	III	SPMS	364(218/146)	IFNβ1a(Rebif 22 μ g SC three times	45.7	3 years

2004 ¹²	Norway		study					weekly)		
Wolinsky et al.	Texas, USA	RCT	PROMISE	III	PPMS	943(483/460)	GA(20mg SC daily)	50.4±8.3	3 years	
2007 ¹³										
Wolinsky et al.	Texas, USA	RCT+meta	PROMISE	III	PPMS+RR	PPMS:943(483/4	GA(20mg SC daily)	--	3 years	
2009 ¹⁴		-analysis			MS	60) RRMS:540(392/148)				
Bar-Or et al.	Montreal, Canada	RCT	DEFINE	III	RRMS	1234(908/326)	BG-12(240mg bid/240mg tid)	Placebo:38.5 ±9.1 Treatment:38.1 ±9.1/38.8±8.9	96 weeks	
2013 ¹⁵										
Hutchinson et al.	Dublin, Ireland	RCT	CONFIRM	III	RRMS	1067(746/321)	BG-12(240mg bid/240mg tid)	37.8±9.4	2 years	
2013 ¹⁶										
Hutchinson et al.	Dublin, Ireland	RCT	AFFIRM and SENTINEL	III	RRMS	627(449/178)	NA(300mg IV every 4 weeks)	35.6±8.5	2 years	
2009 ¹⁷										
Devonshire et al.	Multiple center	RCT	FREEDOMS	III	RRMS	843(--)	FIN(0.5mg daily)	Placebo:37.2 ±8.6 Treatment:: 36.6±8.8	2 years	
2012 ¹⁸										
Coles et al.	Multiple center	RCT	CAMMS223	II	RRMS	325(208/117)	Alem(24mg or 12mg IV daily)	32.5±8.6	2 years	
2011 ¹⁹										

*,pooled data from 5 RCTs; --, not reported; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; IM, intramuscular; SC, subcutaneous; IV, intravenous; IFNβ, interferon beta; GA, glatiramer acetate; BG-12, dimethyl fumarate; NA, natalizumab; FIN, fingolimod; Alem, alemtuzumab.

Table 2. Clinical outcomes of the 14 studies included in the systematic review

Study	Clinical outcomes (sex difference reported)							Strength	Limitation
	RE	CD	GL	CI	TR	T2LV	T2AL		
Rudick et al. 2010 ⁶	N	N	N	×	×	×	×	Detailed data(male vs. female) 1) %patients with relapse at year 1: 37% vs. 37%, p=0.785 2) ARR: 0.65 vs. 0.68, p=0.655 3) %progressed at year 2: 29% vs. 27%, p=0.776 4) %patients with no GD-enhanced lesions at year 2: 69% vs. 69%,p=0.806	Properly performed SGA; post hoc analysis
Trojano et al. 2009 ⁷	M	F*	×	×	×	×	×	1) 1-point EDSS progression:HR(male vs. female)=0.86,p=0.0097 2) 1 st relapse:HR(male vs. female)=1.14,p=0.0897	Properly performed SGA; larger sample and longer follow-up period; post hoc analysis
Patti et al. 2013 ⁸	×	×	×	F	×	×	×	%patients with cognitive impairment: 26.5% vs. 14.4%,p=0.0459	Properly performed SGA; post hoc analysis; less exact statistical methods
Pereira et al. 2012 ⁹	×	×	×	×	N	×	×	%nonresponders: 55.9% vs. 60.9%,p=0.466	Properly performed SGA; post hoc analysis; Not optimal clinical endpoint
(SPECTRI MS) Study Group. 2001 ¹⁰	×	F	×	×	×	×	×	Women showed delay in progression compared with placebo, whereas men did not. No p-value for comparison between female and male.	-- post hoc analysis; no statistical tests for interaction between sex subgroups; selection bias(men showed less confirmed disability than women when untreated).

Li et al. 2001 ¹¹	×	×	×	×	×	F	F	For women, percent change in T2 lesion volume and T2 active lesions from baseline to month 36 differed between each IFNβ1a dose and placebo (p < 0.0001). Men showed treatment benefit compared with placebo only at the high dose (p = 0.01). No p-value for comparison between female and male.	--	post hoc analysis; no statistical tests for interaction between sex subgroups; selection bias(men showed less MRI activity than women when untreated)
Andersen et al. 2004 ¹²	×	N	×	×	×	×	×	Time to confirmed disability(IFNβ vs. placebo):HR(female)=1.11(0.73-1.69)(p=0.62),HR(male)=1.24(0.73-2.10)(p=0.43).No p-value for comparison between female and male	Stated SGA a priori	selecion bia(the SPMS population studied was clinically less active than populations studied in other trials); low dose of IFNβ that may not reach statistical significance
Wolinsky et al. 2007 ¹³	×	M	×	×	×	×	×	Time to confirmed disability(GA vs. placebo):HR(female)=1.08(0.79-1.46)(p=0.630),HR(male)=0.71(0.53-0.95)(p=0.093).No p-value for comparison between female and male	--	post hoc analysis
Wolinsky et al.	N	N	N	×	×	N	×		Properly performed SGA	

2009¹⁴

Bar-Or et al. 2013¹⁵

N

×

×

×

×

×

1) %patients relapsed at two years(dimethyl fumarate vs. placebo):
HR(female)=0.53(0.40-0.70),
HR(male)=0.47(0.28-0.79)
2) ARR(dimethyl fumarate vs. placebo): HR(female)=0.499
(0.375-0.663),
HR(male)=0.376(0.209-0.674)
3) %patients with confirmed disability progression at two years (dimethyl fumarate vs. placebo):
HR(female)=0.73(0.49-1.06),
HR(male)=0.4(0.21-0.77)
No p-value for comparison between female and male.

post hoc analysis; no statistical tests for interaction between sex subgroups; referral bias due to the RCT design

Hutchinson et al. 2013¹⁶

N

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1) %patients relapsed at two years(dimethyl fumarate bid vs. placebo):
HR(female)=0.67(0.49-0.91),
HR(male)=0.62(0.39-1.01)
2) ARR(dimethyl fumarate bid vs. placebo):
HR(female)=0.561(0.402-0.784),
HR(male)=0.570(0.343-0.948)

post hoc analysis; no statistical tests for interaction between sex subgroups; referral bias due to the RCT design

								No p-value for comparison between female and male.		
Hutchinson et al. 2009 ¹⁷	N	F	×	×	×	×	×	<p>1) relapse rate(natalizumab vs. placebo): HR(female)=0.32(0.25-0.42)(p<0.001), HR(male)=0.38(0.25-0.59)(p<0.001)</p> <p>2) disability progression (natalizumab vs. placebo):HR(female)=0.54(0.38-0.75)(p<0.001), HR(male)=0.68(0.40-1.17)(p=0.166)</p> <p>No p-value for comparison between female and male.</p>	--	post hoc analysis; no statistical tests for interaction between sex subgroups; referral bias due to the RCT design
Devonshire et al. 2012 ¹⁸	N	M	×	×	×	×	×	<p>1) ARR(natalizumab vs. placebo): HR(female)=0.50(0.39-0.65)(p<0.001), HR(male)=0.33(0.22-0.50)(p<0.0001)</p> <p>2) %patients with confirmed disability progression at two years:HR(female)=0.77(0.53-1.10)(p=0.15), HR(male)=0.43(0.22-0.81)(p=0.009)</p>	--	post hoc analysis; no statistical tests for interaction between sex subgroups; referral bias due to the RCT design

								7) No p-value for comparison between female and male.	
Coles et al. 2011 ¹⁹	N	N	×	×	×	×	×	1) relapse rate(alemtuzumab vs. IFN β): HR(female)=0.274, HR(male)=0.285 2) sustained accumulation of disability (alemtuzumab vs. IFN β):HR(female)=0.399, HR(male)=0.198 No p-value for comparison between female and male.	-- post hoc analysis; no statistical tests for interaction between sex subgroups; referral bias due to the RCT design

RE, relapse; CD, confirmed disability, progression; GL, GD-enhancement lesions; CI, cognitive impairment; TR, treatment response; T2LV, T2 lesion volume; T2AL, T2 active lesions; SGA, subgroup analysis; *: showed a trend of favoring women, but did not reach statistical significance; RCT, randomized controlled trial; IFN β , interferon beta; ARR, annual relapse rate; HR, hazard ratio; F, favor female; M, favor male; N, no sex difference, ×, not reported.