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Review article

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.

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 women (Bove and Chitnis, 2013). However, men experience more rapidly progressive clinical and radiological courses (Bove and Chitnis, 2013). 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 (Greer and McCombe, 2011; Harbo et al., 2013). 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 search for relevant articles. The following search terms and their medical subject headings (MeSH) were used: “multiple sclerosis”; “disease modifying drugs”; “treatment/therapy”; “interferon beta (IFNβ)”; “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

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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. (1991) 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 SGA (Aulakh and Anand, 2007).

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 Fig. 1. The DMTs included IFNβ, 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 2570 participants. Patients' mean or median ages varied from 27.1 to 39 years in relapsing-remitting MS (RRMS), 42.8–45.7 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 1 Rudick et al., 2011; Trojano et al., 2009; Patti et al., 2013; Pereira et al., 2012; Secondary Progressive Efficacy Clinical, 2001; Li et al., 2001; Andersen et al., 2004; Wolinsky et al., 2007; Wolinsky et al., 2009; Bar-Or et al., 2013; Hutchinson et al., 2013; Hutchinson et al., 2009; Devonshire et al., 2012; Coles et al., 2011.

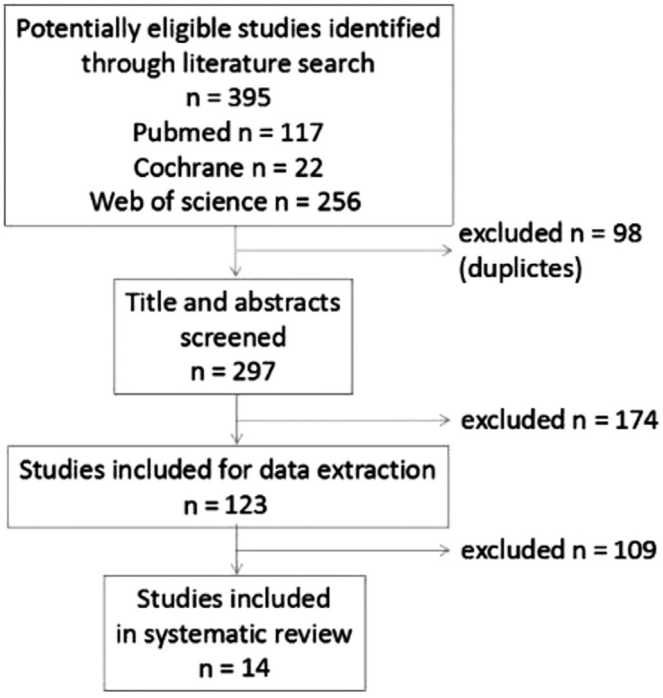

Fig. 1. Literature screen flow chart.

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 IFNβ 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 IFNβ 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 lesions (Rudick et al., 2011). 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 women (Trojano et al., 2009). In the COGIMUS study, a significantly higher proportion of males than females with RRMS who received IFNβ therapy had cognitive impairment at year 5 (26.5% vs. 14.4%, P = 0.046) (Patti et al., 2013). 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