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Disease modifying therapies use associated with comorbid autoimmune diseases in multiple sclerosis patients ☆

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Abstract
Background: The relation between the use of disease modifying therapies (DMT's) and the occurrence of comorbid autoimmune diseases (AID's) in multiple sclerosis (MS) patients is still unclear.
Objective: To investigate the difference in duration from MS symptom onset to first reported AID in subjects using DMT's vs. DMT naïve. Type and prevalence of comorbid AID's was also investigated.
Methods: Data was extracted from the New York State MS Consortium (NYSMSC) registry and comprised of MS patients with a minimum of 5 years follow-up. After exclusion, 1792 patients were enrolled in the study, 1478 had no AID, and 314 patients had comorbid AID's that developed after the initial enrollment. Patients who had an AID were divided into two groups: those with an AID after DMT initiation (n=281) and patients with an AID who were DMT naïve (n=33). Logistic regression analysis was used to test differences in duration between MS symptom onset and the development of AID between the two groups while adjusting for confounders
Results: DMT use did not change the frequency of self-reported AID (17.2 vs. 20.4%). However, the duration between first MS symptom onset and the initial reported occurrence of a comorbid AID was significantly shorter in the DMT user group (192 months ± 115) compared to the DMT naïve group (262 months ± 107, p=.002).
Conclusion: There were no group differences between DMT users vs. DMT naïve subjects with regards to AID frequency. The DMT user group reported the development of an AID earlier than the DMT naïve group. Further studies that can identify patients with higher risk for developing AID's is warranted.
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1. Introduction

Multiple sclerosis (MS) is the most common disease of the central nervous system (CNS) affecting young adults and causing chronic disability. It is strongly believed that MS is an organ-specific autoimmune disease (AID) (Ramagopalan and Sadovnick, 2011) targeting the CNS. Studies have suggested genetic, environmental and infectious agents as interacting factors influencing the risk for development of MS (Ramagopalan and Sadovnick, 2011; Giovannoni and Ebers, 2007).

The classification of autoimmune diseases has varied over time, with the overall estimated prevalence in the general population being 4.5% (Hayter and Cook, 2012). An increased number of AID's are reported in people diagnosed with MS compared to the general population (Henderson et al., 2000; Somers et al., 2009; Dobson and Giovannoni, 2013). Examples of comorbid AID's in MS patients reported in the literature include: systemic lupus erythematosus (SLE), thyroid diseases, rheumatoid arthritis, active hepatitis, type 1 diabetes mellitus, uveitis, psoriasis, inflammatory bowel disease (IBD), pemphigus and myasthenia gravis (Bagir et al., 2009; Belniak et al., 2007; Nielsen et al., 2006; Kimura et al., 2000; Basiri et al., 2009).

As MS is a heterogeneous disease and the response to therapy varies between patients, an individualized therapeutic approach should be tailored on a well-defined risk-benefit balance for each therapeutic intervention. According to current literature, autoimmune complications associated with IFN-β therapy are rare and no significant autoimmune complications have been reported during the large phase III pivotal studies of IFN-β-1a and INF-β-1b in relapsing-remitting MS (RRMS) (Jacobs et al., 1995; IFNB Multiple Sclerosis Study Group, 1993), perhaps related to the short time period (18–24 months) the studies were carried out.

An increase in AID cases was found to be associated with the use of Alemtuzumab (Campath), a very potent treatment with increased efficacy for RRMS patients (Cohen et al., 2012; Coles et al., 2012; Daniels et al., 2014; Aranha et al., 2013). AID's including thyroid disease, as well as a few cases of idiopathic thrombocytopenic purpura, were more commonly seen in patients treated with Alemtuzumab compared to subjects treated with IFN-β-1a.

As most cases reported in the literature refer to sporadic instances of AID's associated with MS, we aimed to investigate the difference in duration from MS symptom onset to first reported comorbid AID in a group of subjects using DMT's in comparison to a DMT naïve group. We also evaluated the type and frequency of AID's in our large cohort followed prospectively as part of a multicenter MS patient registry. In order to investigate a potential influence of DMT use related to an occurrence of a comorbid AID, we compared the prevalence and types of AID between a DMT users group and a DMT naïve group.

2. Methods

2.1. Study population

State MS Consortium (NYSMSC) registry. Informed consent according to Institutional Review Board policy was obtained for all patients who contributed data. Only patients with at least five years of follow-up from baseline were included. The NYSMSC database contains patient-reported and physician-reported follow-up data from 12 MS centers throughout New York State over a period from 1996 through 2011. Data from 11 centers fulfilled the inclusion criteria. MS patients with clinically definite MS according to McDonald criteria, including patients with RRMS, secondary progressive (SPMS), primary progressive (PPMS), progressive relapsing (PRMS) types of MS were included in the study. Exclusion criteria included patients with unknown DMT use prior to enrollment, patients who had an AID at registration, those with less than 5 years of follow up, and patients with Devic's disease, leaving a sample size of $n=1792$ of which 314 subjects reported having an AID.

2.2. AID groups

The AID and no AID groups were compared on basic demographic and clinical characteristics to identify the presence of any inherent differences between the groups. To further ascertain the influence of DMT's on AID's, patients were divided into two groups: those with a comorbid AID after DMT initiation as DMT use was prior to reporting AID ($n=281$) and patients who developed AID while being DMT naive ($n=33$). Self-reported AID's included: Crohn's disease, SLE, myasthenia gravis, irritable/inflammatory bowel syndrome (IBS combined), psoriasis, rheumatoid arthritis, thyroid disease, and type I diabetes mellitus. DMT types included IFN-β-1a (Avonex, Rebif), IFN-β-1b (Betaseron), glatiramer acetate (Copaxone), natalizumab (Tysabri), and combinations with add-on cyclophosphamide (Cytoxan) azathioprine (Imuran), methotrexate, and mitoxantrone (Novantrone).

2.3. Statistical analyses

Statistical analyses were conducted using SPSS 21.0 software package (SPSS Inc., Chicago, IL, USA). All p-values reported were two-tailed and $p<.05$ was considered significant. Chi-square tests were used to determine whether categorical variables were significantly different between the groups. To examine differences in means for continuous variables, independent samples t-tests were used. A logistic regression model was used to test differences in duration between symptom onset and first AID diagnosed between the DMT user group and DMT naïve group, while adjusting for sex, age at symptom onset, Expanded Disability Status Scale (EDSS) at enrollment, year of enrollment and number of follow-ups.

3. Results

3.1. Demographic characteristics between AID and no AID groups

The majority of patients (1478 out of 1792, 82.1%) did not report a comorbid AID. Those with a comorbid AID were older at MS symptom onset and were more likely to be females. No other significant group differences were reported (see Table 1).