



Immunomodulatory therapies are associated with comorbid autoimmune diseases in MS patients

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OBJECTIVE

To investigate type and prevalence of comorbid autoimmune diseases (AID) occurring in Multiple Sclerosis (MS) patients treated with different disease modifying therapies (DMT) compared to patients who remained DMT naïve over five years or greater of follow up.

BACKGROUND

Ramagopalan & Sadovnick (2011) describe MS as an organ-specific AID.¹ An increased number of AIDs are seen in people diagnosed with MS compared to matched population control groups.^{2,3}

Review of literature shows a coexistence of MS with other autoimmune diseases, for example systemic lupus erythematosus (SLE), thyroid disease, rheumatoid arthritis, active hepatitis, type1DM, uveitis, psoriasis, inflammatory bowel disease, pemphigus and myasthenia gravis.³⁻⁷ Bagir et al., showed that 20-25% of untreated MS patients have autoimmune thyroiditis (AIT) and/or subclinical hypothyroidism.⁵

Multiple immunomodulatory therapies are already available for MS treatment including three oral agents. IFN-beta was the first FDA approved disease modifying therapy DMT almost 20 years ago. A relation between IFN-beta and thyroid diseases has been reported in literature.⁸ Occasional cases of myasthenia gravis, and SLE⁹ following IFN-beta therapy have also been described as well as case reports in patients on glatiramer acetate therapy.¹⁰⁻¹³

The relation between the use of disease modifying therapies (DMT), including type and duration of therapy and the occurrence of comorbid AID's in MS patients is unclear.

DESIGN & METHODS

We extracted data from the state-wide New York State MS Consortium (NYSMSC) longitudinal registry. The NYSMSC database contains demographic, patient-reported, and physician-reported follow-up data from 16 MS centers throughout New York State over a period from 1996 through 2011.

Only patients with a minimum 5 years of follow-up were included (n=2,047). Patients with clinically definite MS according to McDonald criteria, including patients with relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS) types were included. Patients with unknown DMT use prior to enrollment, and patients who had an AID at time of entry into the registry were excluded.

Patients meeting group criteria were divided into two groups: those with AID after DMT initiation (ADAD, n=281) and patients with AID who were DMT naïve (ADDN, n=33).

AID types included Crohn's disease, systemic lupus erythematosus, myasthenia gravis, IBS, psoriasis, rheumatoid arthritis, thyroid disease, and type 1DM.

DMT types include Interferon beta 1-a (Avonex, Rebif), Interferon beta 1-b (Betaseron), glatiramer acetate (Copaxone), natalizumab (Tysabri), Cytoxan, Imuran, Methotrexate, and Mitoxantrone (Novantrone).

Chi-square and independent sample t-tests were conducted to examine differences between DMT naïve and DMT users. Regression modeling was used to test differences in duration between symptom onset and first AID between the DMT users group and DMT naïve subjects, while adjusting for sex, age at symptom onset, EDSS at registration, and year of registration.

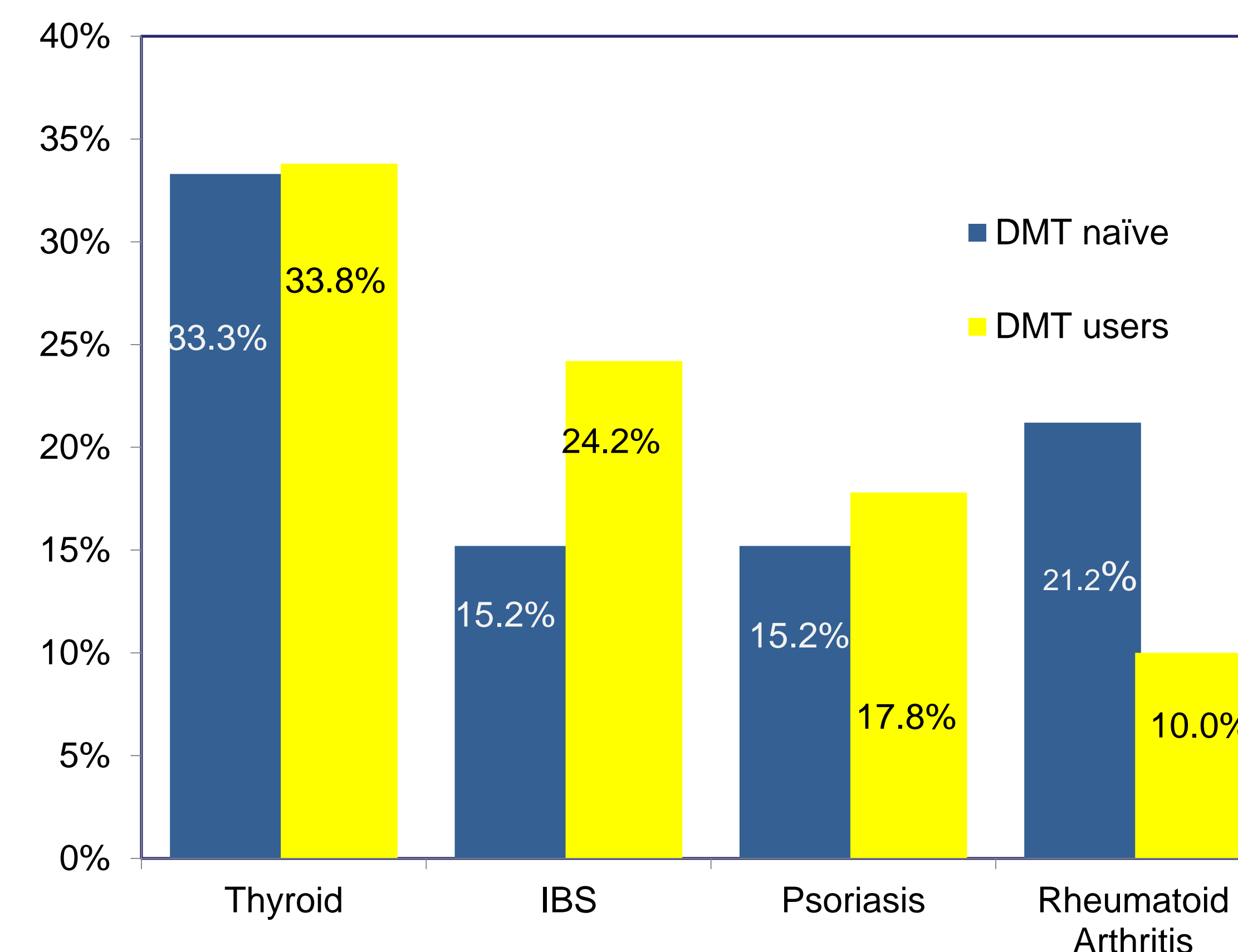
RESULTS

There were no group differences in sex, race, marital status or education between the DMT naïve group and the AID following DMT initiation group. For an overview of the characteristics, Table 1.

The most common AID in both groups group was "thyroid disease".

The mean time from MS symptom onset to first comorbid AID was significantly shorter in the group of DMT users followed by an AID (mean 192.1 months (SD=114.2) compared to DMT naïve group (mean 261.9 months (SD=106.7) (p=0.002). This effect remained after adjusting for covariates in logistic regression modeling (p<0.001).

Characteristics	n (%) or Mean (SD)		
	Group 1 AID DMT naïve	Group 2 AID after DMT initiation	
Sex, female	30 (90.9)	239 (85.1)	.364
Age at registration	60.8 (10.2)	52.2 (10.0)	<.001
Type of MS at registration			<.001
RR	17 (51.5)	2210 (78.9)	
SP	9 (27.3)	39 (13.9)	
PP/PR	7 (21.2)	20 (7.2)	
EDSS at registration	4.0 (2.5)	3.1 (1.9)	
EDSS at most recent follow-up	4.5 (2.6)	4.2 (2.2)	.017
Duration— Symptom onset (months)			
to most recent follow-up	289.9 (112.9)	230.8 (112.1)	.010



DISCUSSION

Review of literature shows an increased AID comorbidities associated with of MS. Our study was unique in investigating type and prevalence of AIDs occurring in MS patients treated with different DMTs compared to patients who remained DMT naïve in a longitudinal sample.

IFNβ therapy has been reported to induce anti-thyroid antibodies and precipitate thyroid clinical disease in patients with preexisting antibodies.^{8,14} In our study, thyroid disease was reported more frequently in both groups. Rheumatoid arthritis, psoriasis and IBS were also common AIDs in both groups.

An interesting finding is that IBS was more common in the DMT users group compared to those who were DMT naïve, while the opposite was true for rheumatoid arthritis, which was more common in the DMT naïve group vs. the DMT user group.

Our results suggest that it takes a shorter time for subjects in the DMT user group to report their first comorbid AID following DMT initiation compared to the DMT naïve group, a result that remained significant after adjusting for covariates. This warrants further investigation especially for identifying demographics and disease characteristics that may predict a higher risk for development of AID.

CONCLUSION

In this unique study we demonstrated that the duration of time to a comorbid AID is briefer for DMT users compared to the non-users. Identifying risk factors associated with the development of AID in the context of DMT use merits further understanding. Our study results may contribute to identifying more appropriate personalized therapeutic management decisions for MS patients.

NYSMSC

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