Short Report

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Thyroid autoimmunity and dysfunction in multiple sclerosis patients during long-term treatment with interferon beta or glatiramer acetate: an Italian multicenter study

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Abstract

Few long-term follow-up data are available on thyroid dysfunction (TD) in multiple sclerosis (MS) patients treated with glatiramer acetate (GA) or with interferon-beta (IFNb). In a cohort of 787 relapsing–remitting MS (RRMS) patients whom were followed up for 8 years, we observed an increased prevalence of TD and thyroid autoimmunity (TA) within the first year of IFNb treatment, regardless of the dose or frequency of administration, while no change was observed with GA treatment. The increased prevalence of TD and TA within the first year of IFNb treatment suggested the need for close monitoring of thyroid function and autoimmunity, though only during the first year of IFNb treatment.

Keywords

Adverse effects, autoimmunity, glatiramer acetate, interferon beta, multiple sclerosis, thyroid

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Introduction

The association of multiple sclerosis (MS) with systemic and organ-specific autoimmune disorders has been frequently reported and specific autoantibodies were identified in MS patients.[1] Several studies assessed the presence of thyroid dysfunction and anti-thyroid antibodies in MS patients, finding a prevalence of 2.5–10% of hormonal dysfunction and 4–21% of specific auto-antibodies.[2]

Autoimmune thyroid disease has been frequently reported in MS patients receiving interferon beta (IFNb), but not glatiramer acetate (GA);[3–5] however, few data are

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Table 1. Prevalence of thyroid dysfunction and autoimmunity developed during DMTs.

Treatment	TD, *n* (%)			TA, *n* (%)		
	Baseline	After therapy	*P* value	Baseline	After therapy	*P* value
Glatiramer acetate (*n* = 172)	4 (2.3)	3 (1.7)	NS	3 (1.7)	1 (0.5)	NS
IFN beta-1b (*n* = 76)	1 (1.3)	8 (10.5)	0.002	1 (1.3)	7 (9.2)	0.0008
IFN beta-1a i.m. (*n* = 279)	4 (1.4)	26 (9.3)	0.005	2 (0.7)	25 (8.9)	0.003
IFN beta-1a s.c. 22 µg (*n* = 153)	3 (1.9)	10 (6.5)	0.05	2 (1.3)	12 (7.8)	0.003
IFN beta-1a s.c. 44 µg (*n* = 107)	2 (1.8)	6 (5.6)	NS	2 (1.8)	10 (9.3)	0.001

DMT: Disease-modifying therapy; IFN: interferon; i.m.: intramuscular; NS: not significant; s.c.: subcutaneous; TA: thyroid autoimmunity; TD: thyroid disease

available on thyroid autoimmunity in MS patients that were treated with GA or with IFNb over a long follow-up period.

The current study was conducted on a large cohort of relapsing–remitting MS (RRMS) patients, in whom thyroid function and autoimmunity have been regularly assessed during long-term disease-modifying treatments (DMTs). The aim of this retrospective observational study was to assess the occurrence of thyroid dysfunction and autoimmunity during long-term DMTs.

Methods

Patients

We conducted a retrospective observational study on clinically-defined RRMS patients whom were enrolled by 12 Italian MS centers. All patients received at least 2 years of DMTs (IFNb1a intramuscular (im) once a week, IFNb1a subcutaneous (sc) at 22 mcg three times weekly (tiw). IFNb1a sc. at 44 mcg tiw, IFNb1b sc once daily (od) and daily GA sc), and they were screened for thyroid dysfunction (free-T4, free-T3, thyroid stimulating hormone (TSH)) and autoimmunity (anti-thyroglobulin, anti-thyroid peroxidase and anti-TSH antibodies) at baseline and during DMT treatment every 3–6 months. Thyroid dysfunction (TD) was defined as overt or subclinical hyper- or hypothyroidism, while thyroid autoimmunity (TA) was considered only when thyroid autoantibodies were confirmed in two consecutive analyses.

Statistical analysis

Comparison of the clinical features between different treatment groups was assessed using the student *t* test. We performed a multiple logistic regression analysis using sex, MS onset, pre-treatment annualized relapse rate and the Expanded Disability Status Scale (EDSS) as covariates. We used the 2-sample test of proportion to compare TA/TD percentages in MS patients who were treated with different DMTs. A p value ≤ 0.05 was considered to be statistically significant.

Results

We included in the study 787 RRMS patients: 262 (33%) male and 525 (67%) female.

The mean ± SD age at onset was 29.1 ± 10.5 years. The mean baseline EDSS score was 1.7 ± 1.0. The mean baseline annualized relapse rate (RR) was 0.97 ± 0.64. The mean duration of follow-up was 51.2 ± 29.8 months. The mean EDSS score at the end of the follow-up period was 2.1 ± 1.1.

There was no difference between demographic and clinical characteristics among RRMS patients whom were treated with different DMTs. The number of RRMS patients affected by TD and TA was significantly higher during, rather than before the beginning, of IFN treatment (7% versus 13.2%; $p < 0.02$ and 3.5% versus 13.4%; $p = 0.01$, respectively). On the contrary, no difference in the percentage of TD and TA was observed in RRMS patients before and after the beginning of GA treatment. The frequency of TD and TA were significantly higher during therapy with IFNb1a im, with IFNb1b sc and with IFNb1a sc at 22 mcg; than they were before the onset of these treatments. During therapy with IFNb1a at 44 mcg the frequency of TA, but not of TD, was significantly higher than baseline (Table 1).

Comparing the pre-treatment with the on-treatment proportions of patients with TD and TA within drug groups, we found the patients undergoing therapy with IFNb1a im ($p = 0.02$ and $p = 0.003$, respectively), IFNb-1b sc ($p = 0.002$ and $p = 0.009$, respectively), IFNb1a sc at 22 mcg ($p = 0.003$ and $p = 0.04$, respectively), and with IFNb1a sc at 44 mcg ($p = 0.04$ and $p = 0.001$, respectively) developed TD/TA more frequently than GA. Moreover, we did not observe a significant difference in development of TD/TA among IFNb drugs. We observed no interaction among TA/TD and sex, disease duration, baseline annualized RR and EDSS.

The development of TA/TD occurred within the first year of treatment with IFNs (Figure 1). Only 8 out of 787 patients, and 1 out of 787 patients, developed TD or TA after 1 year and 2 years of treatment, respectively.

We did not observe TA nor TD development after the first year of treatment, in both IFNb and GA groups. No

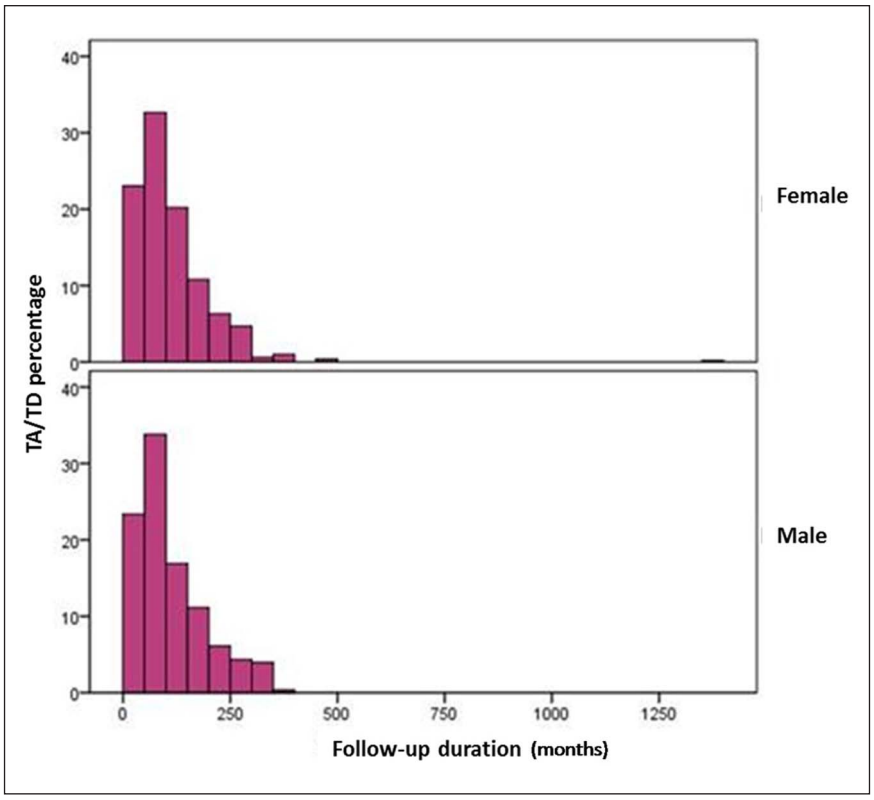

Figure 1. Percentage of TD and TA during IFN and GA treatment, in male and female patients. Both TD and TA developed during the first year of DMT in both male and female patients.
DMT: Disease-modifying therapy; GA: glatiramer acetate; IFN: interferon; TA: thyroid autoimmunity, TD: thyroid dysfunctions

difference in the time to development of TA/TD was observed among the different DMT groups.

Discussion

Although the mechanisms of thyroid damage induced by IFN have not been definitively clarified, evidence suggests that they may be due to an autoimmune reaction or immune system dysregulation induced by a chronic exposure to IFNb; however, in those patients who develop hypothyroidism without autoantibody production, a direct inhibitory effect on iodine organification may be postulated.[6] Although most studies suggest there is a relationship between IFN and thyroid diseases, some reports do not observe any increase in anti-thyroid auto-antibodies associated with IFNb-1ae and -1b therapy.[7–10]

In our study, there was an increased prevalence of TD and TA after the beginning of IFNb treatment, regardless of gender, disease duration, baseline annualized RR and EDSS, while no change was found in both TD and TA during GA treatment, suggesting a direct role for IFNb treatment in both TA and TD onset. Amongst IFNb drugs, we did not observe any significant difference in the prevalence of TD and TA, when comparing different types (IFNb-1a or IFNb-1b), methods of injection sc. or i.m.). frequency of administration (once a week, tiw, or od) and dosage, suggesting that IFNb treatment is associated with an increased incidence of TD and TA, almost exclusively within the first year of treatment. Moreover, the time of onset of TD and TA seems to be independent of gender, disease duration, baseline annualized RR and EDSS score.

In conclusion, our study conducted retrospectively on a large cohort of patients with a long follow-up period, suggests that TD and TA are not an issue in GA treated patients. Furthermore, close monitoring of thyroid function and autoimmunity is justified only in the first year of treatment with IFNb. Therefore, early detection and adequate treatments of thyroid dysfunction during the first year of IFNb-treatment are important to preserve the patients' health status and to increase the tolerability of DMTs. On the other hand, after the second year of treatment it does not appear to be necessary to continue any thyroid hormone nor auto-antibody analyses in IFNb treated patients.

Conflict of interest

G. Frisullo received honoraria for speaking and travel grants from Biogen, Sanofi-Aventis, Merck Serono, Teva, and Bayer.

M. Calabrese received honoraria for Advisory Board membership: Merck- Serono, Sanofi-Aventis, Bayer-Shering, Genzyme, Roche, Biogen Idec; Consultancy: Biogen idec, Sanofi-Aventis, Merck- Serono, Bayer-Schering, Roche; Travel/accommodation expenses covered or reimbursed:Novartis, Sanofi-Aventis, Biogen idec Merck Serono, Bayer-Schering, Roche

C. Tortorella received honoraria for speaking and travel grants from Biogen, Sanofi-Aventis, Merck Serono, Genzyme, Teva, Bayer-Shering and Novartis

D. Paolicelli received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Bayer-Schering, Teva, Genzyme and Novartis.

P. Ragonese received honoraria and travel expenses for advisory board or speaking by TEVA ph., Novartis, Merck Serono and Biogen idec.

P. Annovazzi received honoraria for speaking and travel grants from Biogen, Merck Serono, Teva and Novartis

M. Radaelli has nothing to disclose.

A. Gallo received honoraria for speaking and travel grants from Biogen, Sanofi-Aventis, Merck Serono, Genzyme, Teva, Bayer-Shering and Novartis

V. Tomassini has nothing to disclose.

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M. D'Onghia has nothing to disclose.

V. Lo Re has nothing to disclose.

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