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Short report

Tuberculosis screening in multiple sclerosis: effect of disease-modifying therapies and lymphopenia on the prevalence of indeterminate TB screening results in the clinical setting

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Abstract

Background: Tuberculosis screening is recommended in multiple sclerosis patients starting certain disease-modifying therapies. Disease-modifying therapies may affect interferon-gamma release assay results.

Objective: To determine the effects of multiple sclerosis disease-modifying therapies on interferon-gamma release assay results.

Methods: Indeterminate interferon-gamma release assay results among multiple sclerosis patients were compared across disease-modifying therapies by Fisher's exact test. Logistic regression evaluated the effects of lymphopenia on interferon-gamma release assay results.

Results: A total of 1058 patients underwent interferon-gamma release assay: 2.0% (21) positive, 6.1% (65) indeterminate, with 59.4% (628) on disease-modifying therapies. Results were significantly different across disease-modifying therapies ($P = 0.002$). Absolute lymphocyte count less than 0.5 k/μL had 9.39 times (95% confidence interval 5.2–17.0) increased odds of indeterminate interferon-gamma release assay results.

Conclusions: Disease-modifying therapies affecting lymphocytes had a higher risk of indeterminate interferon-gamma release assay results.

Keywords: Multiple sclerosis, disease-modifying therapies, risk assessment, tuberculosis testing

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Introduction

Disease modifying therapies (DMTs) for multiple sclerosis (MS) have diverse effects on the immune system, and can increase the risk of latent tuberculosis (TB) reactivation.[1] TB screening is recommended prior to the initiation of certain DMTs,[1] but generally occurs in the setting of prior DMTs. TB screening, including by serum interferon-gamma release assay (IGRA), is affected by immunosuppression.[2–4] One study examined the in vitro effects of teriflunomide on IGRA in latent TB; teriflunomide led to conversion from positive to negative.[5] The effect of MS DMTs on IGRA has not otherwise been investigated.

In latent or active TB infection, T cells are sensitized to TB-specific antigens. IGRA measures interferon-gamma release in response to TB-specific antigen exposure in vitro (antigen response).[6] The mitogen response determines the adequacy of serum T-cell response as a positive control. Patients with anergy or lymphocyte hyporesponsiveness can have a false negative or indeterminate test.[4,7,8]

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Our study objectives were to determine the frequency of positive or indeterminate IGRA testing in a MS clinic population and the effects of DMTs on IGRA.

Patients and methods

An electronic medical record search for MS patients who underwent TB screening by means of Quantiferon-TB Gold testing (our site's IGRA platform) between 1/1/17 and 5/1/18 was conducted. Data were extracted by chart review, including demographics, clinical characteristics, concurrent DMT, methylprednisolone within 30 days, IGRA result (interpretation (positive/negative/indeterminate), TB antigen response (IU/mL), mitogen response

Table 1. Patient characteristics and IGRA results.

	All ($n = 1058$)	Negative IGRA ($n = 972$)	Indeterminate IGRA ($n = 65$)	Positive IGRA ($n = 21$)	P value[a]
Age (years), mean (SD)	47.9 (11.8)	47.9 (11.8)	49.5 (10.8)	46.5 (14.1)	0.486
Gender (female), % (n)	68.1 (721)	68.3 (664)	70.8 (46)	52.4 (11)	0.269
Race					0.342
Caucasian	78.7 (833)	78.9 (767)	76.9 (50)	76.2 (16)	
African-American	15.8 (167)	15.9 (155)	15.4 (10)	9.5 (2)	
Asian	0.5 (5)	0.5 (5)	0 (0)	0 (0)	
American Indian/Alaska Native	0.1 (1)	0.1 (1)	0 (0)	0 (0)	
Multiracial	1.2 (13)	0.9 (9)	4.6 (30)	4.8 (1)	
Native Hawaiian/Pacific Islander	0.2 (2)	0.2 (2)	0 (0)	0 (0)	
Other	0.8 (8)	0.7 (7)	0 (0)	4.8 (1)	
Unknown	2.7 (29)	2.7 (26)	3.1 (2)	4.8 (1)	
MS subtype, % (n)					0.791
Relapsing–remitting	65.6 (694)	65.4 (636)	64.6 (42)	76.2 (16)	
Primary progressive	15.3 (162)	15.4 (150)	13.8 (9)	14.3 (3)	
Secondary progressive	19.1 (202)	19.1 (186)	21.5 (14)	9.5 (2)	
Disease duration (years), mean (SD)	11.1 (28.4)	11.2 (29.5)	11.0 (7.9)	6.54 (7.2)	0.756
MS DMT status (on DMTs), % (n)	59.4 (628)	58.5 (569)	72.3 (47)	57.1 (12)	0.089
MS DMT use, % (n)					0.002
Not on MS DMT	40.6 (430)	41.5 (403)	27.7 (18)	42.9 (9)	
Dimethyl fumarate	16.2 (171)	15.4 (150)	26.2 (17)	19.0 (4)	
Fingolimod	10.7 (113)	9.7 (94)	29.2 (19)	0 (0)	
Natalizumab	9.7 (103)	10.3 (100)	0 (0)	14.3 (3)	
Glatiramer acetate	9.5 (101)	9.8 (95)	7.7 (5)	4.8 (1)	
Interferon beta	5.3 (56)	5.3 (52)	1.5 (1)	14.3 (3)	
Teriflunomide	2.5 (26)	2.5 (24)	3.1 (2)	0 (0)	
Other immunosuppressantb	1.9 (20)	1.9 (18)	1.5 (1)	4.8 (0)	
Rituximab	1.1 (12)	1.2 (12)	0 (0)	0 (0)	
Ocrelizumab	1.0 (11)	0.9 (9)	3.1 (2)	0 (0)	
Pulse IV methylprednisolone	0.9 (10)	1.0 (10)	0 (0)	0 (0)	
Cyclophosphamide	0.2 (2)	0.2 (2)	0 (0)	0 (0)	
Daclizumab	0.2 (2)	0.2 (2)	0 (0)	0 (0)	
Alemtuzumab	0.1 (1)	0.1 (1)	0 (0)	0 (0)	
Steroid use within 30 days, % (n)	8.7 (92)	7.7 (75)	21.5 (14)	14.3 (3)	<0.001
Absolute lymphocyte count (k/μL), mean (SD), $n = 942$	1.85 (1.1)	1.90 (1.0)	0.80 (0.7)	2.58 (1.3)	<0.001

DMT: disease-modifying therapy; **IGRA**: interferon gamma release assay; **MS**: multiple sclerosis; **SD**: standard deviation.

[a]P values comparing negative, indeterminate, and positive groups; proportions using Fisher's exact test and group means by analysis of variance.

[b]Other: mycophenolate mofetil ($n = 6$), methotrexate ($n = 8$), azathioprine ($n = 2$), other ($n = 4$).

(IU/mL)), and absolute lymphocyte count (ALC, k/μL) within 30 days. Follow-up testing for indeterminate IGRAs were recorded. Approval from the Cleveland Clinic institutional review board was obtained (#18-094).

Statistical analysis

Proportions of patients with indeterminate IGRA were compared across DMTs by Fisher's exact testing. Logistic regression determined the odds of indeterminate testing in the setting of specific DMTs, steroid use, or grade 3 or greater lymphopenia (ALC <0.5 k/μL). Spearman's rank correlation coefficient was calculated for ALC and mitogen response. All analyses were performed using R (version 3.5.2).

Results

Patient population

A total of 1058 patients with MS who underwent TB testing by IGRA were included (Table 1). Generally, patients underwent IGRA prior to starting a DMT for which screening is standard practice at our center (ocrelizumab, teriflunomide, alemtuzumab).

Prevalence of abnormal IGRA results

Of 1058 patients, 91.9% ($n = 972$) tested IGRA negative, 2.0% ($n = 21$) positive, and 6.1% ($n = 65$) indeterminate. Of the indeterminate results, 60.0% ($n = 39$) underwent follow-up testing, including repeat IGRA (79.5%, $n = 31$), tuberculin skin testing (7.7%, $n = 3$), and chest X-ray (12.8%, $n = 5$). With repeat IGRA, 74.2% ($n = 23$) were negative (one held dimethyl fumarate (DMF) at repeat testing), and 25.8% ($n = 8$) again were indeterminate (2/8 remained off DMT, and 6/8 continued DMT). All other patients remained on DMT at repeat testing.

Effect of DMTs on IGRA results

Some 59.4% ($n = 628$) of patients were on DMT at IGRA testing (Table 1). There was a significant difference in IGRA results across DMTs ($P = 0.002$). DMF (26.2%, $n = 17$) and fingolimod (29.2%, $n = 19$) had the highest incidence of indeterminate IGRA. The odds of indeterminate IGRA were significantly increased by 4.0 times (95% confidence interval (CI) 2.2–6.9) on fingolimod and 1.9 times (95% CI 1.1–3.4) on DMF compared to other patients. Fingolimod and DMF were significant

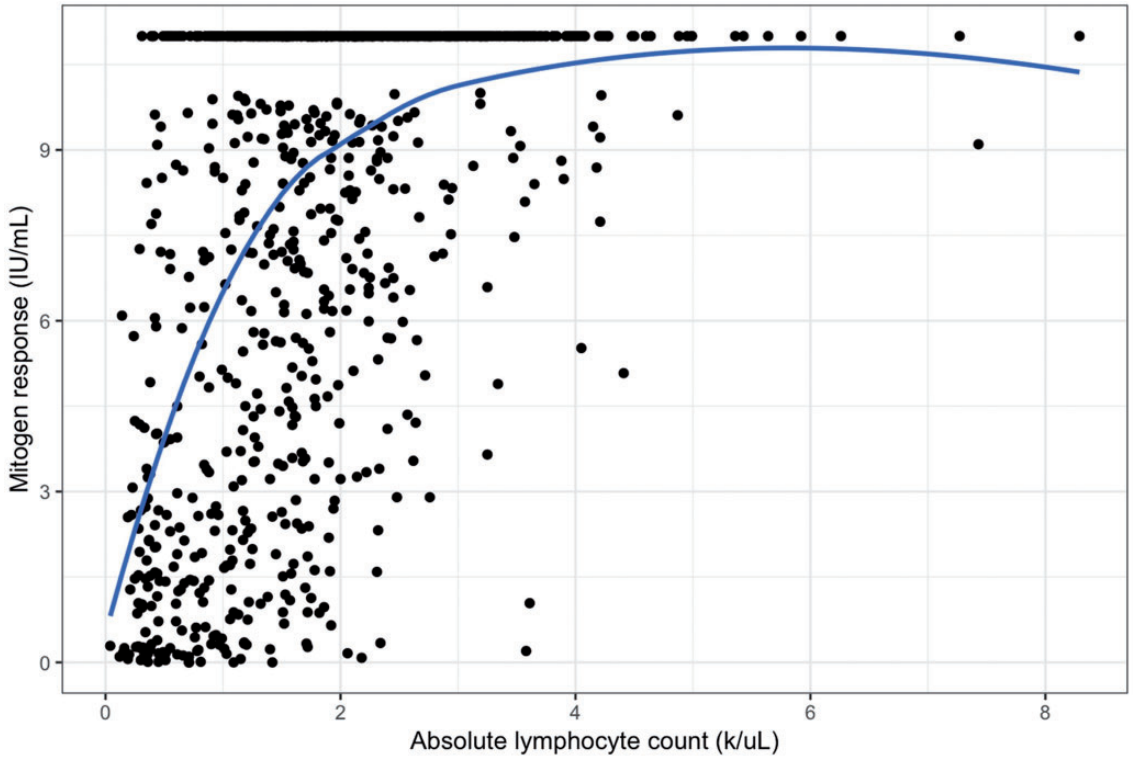

Figure 1. Correlation of mitogen response with ALC. A scatterplot of IGRA mitogen response and ALC demonstrates positive correlation between ALC and mitogen response (Spearman's rho 0.49, 95% confidence interval 0.44–0.54). Mitogen response was coded as 11 if it was reported as greater than 10, the lab standard; this ceiling effect could impact the interpretability of results. ALC: absolute lymphocyte count; IGRA: interferon gamma release assay.

univariate predictors of indeterminate IGRA, but only DMF was a significant positive predictor independent of lymphopenia.

Effect of steroid use on IGRA results

A total of 92 patients (8.7%) received methylprednisolone and of those, 75 had negative, three positive, and 14 indeterminate IGRA (Table 1). Recent methylprednisolone use resulted in 3.2 times (95% CI 1.7–5.9) the odds of an indeterminate result.

Effect of lymphopenia on IGRA results

ALC was available within 30 days of IGRA in 89.0% ($n = 942$) of patients. Patients with indeterminate IGRA ($n = 65$) had lower mean ALC (0.80 ± 0.7 k/μL) compared to negative (1.90 ± 1.0 k/μL) or positive (2.58 ± 1.3 k/μL) patients ($P < 0.001$, Table 1). ALC less than 0.5 k/μL resulted in 9.39 times (95% CI 5.2–17.0) significantly increased odds of an indeterminate IGRA result. ALC and mitogen response were positively correlated (Spearman's rho 0.49, 95% CI 0.44–0.54) (Figure 1). Mitogen response was coded as 11 if it was reported as greater than 10 (lab standard); this ceiling effect could impact the interpretability of results.

Conclusions

This is the first study to report the effects of several MS DMTs on IGRA results, specifically investigating which increase the likelihood of an indeterminate result. Grade 3 or worse lymphopenia, recent methylprednisolone use, and fingolimod or DMF use significantly increased the odds of indeterminate IGRA. Indeterminate results were driven by inadequate mitogen response in the setting of lymphopenia, which is not unexpected in the setting of medications known to interfere with lymphocyte trafficking and function. Further testing is needed in patients on certain DMTs who have a higher clinical suspicion of TB or are from endemic regions.

Our results are similar to those obtained in the literature regarding DMTs for systemic autoimmune conditions. Studies indicate impaired IGRA response and indeterminate results are associated with corticosteroids, tumor necrosis factor antagonists, and other immunosuppressive therapies.[2–4]

In a large MS center in the United States, fewer than 10% of patients had abnormal IGRA results: 2.0% were positive and 6.1% indeterminate. This latent TB prevalence by way of IGRA is similar to national estimates of 0.6% to 4.8% from the 2011–2012 National Health and Nutrition Examination Survey.[9,10] However, our population included few potentially vaccinated patients, so we cannot comment on the effect of DMTs or lymphopenia on IGRA results in this population. Individual TB exposure risk factors were not available.

Clinicians should be aware of the factors affecting IGRA results, as adequate screening for latent TB is crucial for safety with certain DMTs. In the setting of indeterminate Quantiferon-TB Gold IGRA results, the T-SPOT.TB assay may decrease susceptibility of testing to immunocompromise.[8] However, TB screening is most sensitively completed in patients not on DMTs. Our retrospective study was limited to patients on or starting DMTs, but IGRA testing pre and post-DMT exposure is needed to evaluate better how individual DMTs affect IGRA results. Sampling bias may impact result generalizability, as mandatory TB screening for certain DMTs (e.g. teriflunomide, alemtuzumab) may have resulted in their underrepresentation in this study. Further work is needed to determine optimal TB screening methods in low-risk, potentially immunocompromised patient populations such as MS.

Conflict of Interests

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