

Clinical / Scientific note

Lymphopenia in treatment-naive relapsing multiple sclerosis

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DISCLOSURES

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INTRODUCTION

Lymphopenia accompanies some autoimmune diseases¹. A number of studies^{2, 3}, but not others^{4, 5}, have suggested that lymphopenia occurs in treatment-naive multiple sclerosis (MS), so the issue remains unresolved. This is important since lymphopenia may identify an immunologically distinct subset of MS. Also, lymphopenia may emerge as a risk factor for serious viral infections of the brain during dimethyl fumarate treatment². We therefore embarked on a retrospective controlled study of pre-treatment lymphopenia in relapsing MS.

METHODS

Data was collected retrospectively during an institutionally-approved service evaluation of blood-test monitoring of patients with relapsing MS in a regional MS service in Southampton, UK over a two year period (2012-2014). MS diagnosis was by McDonald criteria. The following data was collected: age, sex, comorbidities, type of relapsing MS, date of first MS symptom onset, number of functional systems affected, pre-treatment and post-treatment lymphocyte counts and their dates, relapse date and severity (three categories⁶), and date of treatment initiation. To calculate a relapsing disease severity index, mean relapse severity was multiplied by relapse rate. Control lymphocyte data was derived from pre-operative blood counts of age and sex-matched individuals undergoing septoplasty in the same hospital for structural reasons, excluding neoplastic and infective operative indications. Lymphopenia was classified according to CTCAE v4. Statistical analysis was conducted in SPSS v22. Null hypotheses were rejected at $p < 0.05$.

RESULTS

764 patients were identified with blood test data (Table 1). Baseline and post-treatment blood tests were available in 466 and 247 patients respectively. Average blood test frequency was 4/year. Lymphocyte counts were relatively stable with time, with a coefficient of variation of 7.5%.

The mean lymphocyte count in treatment-naive MS patients was $2.18 \times 10^9/L$ with a standard deviation of 0.66×10^9 . Lymphopenia was present in 10% (47 patients; 46 Grade I, one Grade II, one Grade III). A detailed retrospective review of the medical records of all lymphopenic patients was undertaken to look for recognized causes of lymphopenia¹. In only three cases steroids were administered in the month prior to lymphopenia; one case with borderline baseline lymphocytes developed a Grade III lymphopenia two days after steroids, while blood tests prior to steroids were unavailable in two cases with a Grade I lymphopenia.

There was no association between pre-treatment lymphocyte count and any patient characteristic (age, sex, MS type, autoimmune comorbidities, age at onset of first MS symptom, disease duration, time since last relapse, number of functional systems affected, relapse rate, last relapse severity, and severity index) or month or season (using correlation coefficients, group comparison tests and linear or logistic regression). In the UK, during the study period, patients with higher disease activity (≥ 2 disabling relapses in 1 year) received natalizumab, and treatment options for lower disease activity included interferon-beta, glatiramer acetate and fingolimod. This binary treatment destination was used as a marker of disease activity. In a multivariate logistic regression, pre-treatment lymphocyte count or

lymphopenia did not predict natalizumab use, while younger age and higher relapsing disease severity index did (Odds ratios of 0.9 and 25 respectively, $p < 0.0001$).

We compared the lymphopenia observed in the pre-treatment MS population with an age and sex-matched control hospital population undergoing cosmetic septoplasty who had pre-operative blood tests on the same haematology analyser. There was no statistical difference in mean lymphocyte count or prevalence of lymphopenia (Table 1).

After treatment with interferon-beta or glatiramer acetate, the prevalence of sustained lymphopenia rose to 28% (26% Grade I, 2% Grade 2). Lymphocytes decreased after starting interferon-beta (mean decrease of $0.3 \times 10^9/L$, $p < 0.0001$, paired t-test), but not glatiramer acetate. Multiple logistic regression identified low pre-treatment lymphocyte count as the only predictor of post-treatment lymphopenia (Odds ratio of 0.1, $p = 0.001$).

Fingolimod caused a lymphopenia in all patients (range: $0.3-1.4 \times 10^9/L$; median decrease of $1.5 \times 10^9/L$ compared to baseline, $p < 10^{-6}$, Wilcoxon); using multiple linear regression, pre-treatment lymphocyte count was the only predictor of post-treatment count ($R^2 = 0.22$, $B = 0.1$, $p = 0.003$). Natalizumab increased lymphocyte count (median decrease of $1.3 \times 10^9/L$ compared to baseline, $p < 10^{-14}$, Wilcoxon; lymphocytosis $> 4 \times 10^9/L$ in 23% vs 0%).

DISCUSSION

Since the lymphocyte reference range covers 95% of values in a healthy population, lymphopenia is expected in 2.5%¹. In our treatment-naïve relapsing MS population, we

found lymphopenia in 10%. However, this was not different from a well-matched healthy control population. Moreover, lymphopenia was not associated with relapsing activity. Hence the lymphopenia in MS patients is unlikely to be related to autoimmunity. A more likely explanation is stress-induced lymphopenia in both cohorts, through cortisol or EBV activation⁷.

We found that pre-treatment lymphopenia predicts post-treatment lymphopenia; this is useful since it identifies at-risk patients needing frequent monitoring. Due to this study's retrospective nature, lymphocyte subsets were not available, and these are important^{4, 5}. Further work is needed to determine whether lymphocyte subsets during lymphopenia differ in MS patients versus controls.

Table 1

| Characteristic | Total MS population | MS patients with baseline lymphocyte count | Control population | p |
|---|----------------------|--|------------------------|-------------------|
| N | 764 | 466 | 102 | |
| Age (mean \pm SD, range) | 44 \pm 10, 21-67 | 43 \pm 9, 19-67 | 42 \pm 14, 19-67 | 0.17 ^a |
| Sex (female, male, in %) | 76, 24 | 73, 27 | 75, 25 | 0.71 ^b |
| Pretreatment lymphocyte count (mean \pm SD, range, in $\times 10^9/L$) | | 2.18 \pm 0.66, 0.4-5.9 | 2.06 \pm 0.56, 1-3.2 | 0.14 ^a |
| Prevalence of lymphopenia | | 10.1% | 13.7% | 0.29 ^b |
| Type of relapsing MS (RR, SP with relapses, PR, not recorded, in %) | 73, 7, 1, 19 | | | |
| Age at onset of MS (mean \pm SD, range) | 32 \pm 9, 14-66 | | | |
| Disease duration (mean \pm SD, range) | 10 \pm 8, 0-43 | | | |
| Relapse rate (mean \pm SD, range) | 0.68 \pm 0.56, 0-6 | | | |

| | |
|---|--------------------|
| EDSS* (mean \pm SD, range) | 4.1 \pm 2.3, 0-8 |
| Treatment (IFN, GA, FING, NAT, OTHER, in %) | 49,25,10,15,1 |

* Data only available in 18% of cases

^a Mann-Whitney

^b Fisher exact test

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