CLINICAL RESEARCH STUDY

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Methylprednisolone-Induced Lymphocytosis in Patients with Immune-Mediated Inflammatory Disorders

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ABSTRACT

BACKGROUND: Transient acute reversible lymphopenia occurring within hours after glucocorticoid administration is a well-known phenomenon. The objective of this study was to establish the impact of chronic methylprednisolone (mPDN) administration on lymphocyte counts in patients with immune-mediated inflammatory disorders.

METHODS: The charts of 44 women and 17 men (median age, 59 years) with several immune-mediated inflammatory disorders receiving oral mPDN for at least 4 months were reviewed. Morning lymphocyte counts measured during treatment (L_P) were compared with pretreatment values (L_A). In addition, the acute effect of mPDN on lymphocyte counts was evaluated in 43 of these patients by quantifying lymphocyte subpopulations before and 8 hours after mPDN administration. Values are expressed as median with 25%-75% interquartile range.

RESULTS: The initial daily oral mPDN dose was 28 mg (12-32 mg). An increase in morning lymphocyte counts was detected 13 days (8.5-16 days) after initiation of mPDN treatment (L_P: 2130/μL vs L_A: 1650/μL; $P = .0121$) and persisted over time. Morning lymphocytosis ($L_P \geq 4000$/μL) was observed in 15 patients, including 7 with hyperlymphocytosis ($L_P \geq 5000$/μL). The increase in morning lymphocyte counts during treatment was most marked for CD4 T cells. In the subset of patients who agreed to a second blood test after mPDN absorption, a 49% decrease in the lymphocyte count ($P < .0001$) was transiently observed at the 8-hour time point.

CONCLUSIONS: A significant increase of the morning lymphocyte count is frequently observed in patients with immune-mediated inflammatory disorders chronically treated with oral mPDN. Heightened awareness that the timing of blood sampling in corticosteroid-treated patients affects lymphocyte counts, with possible hyperlymphocytosis before absorption, should help avoid unnecessary investigations and worry.

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Glucocorticoids (GCs) were introduced in clinical practice in 1949 and rapidly became widely used for treatment of numerous conditions, including immune-mediated inflammatory disorders, allergic reactions, and organ transplant rejection.[1] Administration of GCs is known to induce a transient drop of all lymphocyte subsets, particularly T lymphocytes, within hours, accounting at least in part for treatment-induced immunosuppression.[2]

Transient lymphopenia also develops 4-6 hours after prednisolone administration during alternate-day treatment regimens, with a return to normal counts the next morning.[3] In healthy subjects, oral methylprednisolone (mPDN) given

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for 1-3 days is also followed by a rapid and reversible fall in the numbers of circulating T and B lymphocytes.[4]

In contrast, a significant increase in the lymphocyte count after 14 days of prednisolone treatment in patients with acute hearing loss has recently been reported,[5] and an increase in T-cell subpopulations was also observed in patients treated with prednisone or deflazacort for immune thrombocytopenic purpura.[6] In polymyalgia rheumatica and giant cell arteritis, chronic prednisone administration is associated with an increase of total lymphocytes with a decrease in the percentage of CD8 cells.[7]

The purpose of the present study was to investigate the prevalence and characteristics of increased lymphocyte counts relative to pretreatment values in patients receiving long-term mPDN for immune-mediated inflammatory disorders. In addition, the acute effect of mPDN on lymphocyte subpopulations was assessed in these patients, by quantifying them before and several hours after oral administration of the maintenance mPDN dose.

CLINICAL SIGNIFICANCE

- Chronic methylprednisolone treatment induces a rise in morning lymphocyte counts in the majority of patients with immune-mediated inflammatory disorders.
- Corticosteroid intake is a new cause of morning lymphocytosis and sometimes hyperlymphocytosis (>5000 cells/μL).
- Awareness that the timing of blood sampling in corticosteroid-treated patients with immune-mediated inflammatory disorders affects lymphocyte counts should help avoid unnecessary investigations and worry.

METHODS

Patients

The medical files of mPDN-treated patients with immune-mediated inflammatory disorders followed in the outpatient clinic of the Department of Internal Medicine of Erasme Hospital (the academic hospital of the Université Libre de Bruxelles) were reviewed for the purpose of this study. Reasons for exclusion from the study were as follows: mPDN treatment for <4 months, associated immunosuppressive therapy, unavailable lymphocyte count before or after mPDN initiation, mPDN withdrawal, age <18 years, and evidence for therapeutic noncompliance.

In all, 61 patients (17 men, 44 women, aged 24-86 years) were selected for further study.

Chart Review Data

The recorded value for the pretreatment lymphocyte count (L_A) for each patient was the average of 2 measurements within 45 days preceding the initiation of mPDN treatment. All lymphocyte counts measured during the first 4 months of treatment (L_P) were taken into consideration provided that blood sampling was done in the morning before mPDN intake. We recorded the L_Ps closest to 2 weeks and 1, 2, 3, and 4 months after initiation of treatment.

To assess the magnitude of the effect of mPDN on lymphocyte counts, the maximum L_P value observed during treatment was recorded for each patient.

Lymphocytosis was defined as L_P values >4000/μL, as previously reported.[8] Hyperlymphocytosis was arbitrarily defined as L_P values >5000/μL, a level that was thought likely to trigger further investigations for a possible underlying haematologic disorder.

Effects of Acute mPDN Administration

Among the 61 patients receiving long-term mPDN treatment, 43 (11 men and 32 women, aged 26-86 years) agreed to participate in this part of the study and provided informed consent. To assess the acute effects of mPDN on leukocyte counts, blood was drawn in the morning before (BT1) and 8 hours after (BT2) the usual maintenance dose of mPDN.

Blood Analysis

Leucocyte counts were obtained from the routine laboratory, and lymphocyte subpopulations (CD3, CD4, CD8, CD19, and natural killer) were determined by flow cytometry (Navios, Beckman Coulter [Brea, Calif], 3 lasers, 10 colors) in the laboratory of clinical hematology. Staining for CD127, CD25, and FoxP3 was performed in a subset of the patients for the identification of regulator T lymphocytes (ie, $CD4^+CD127^{low}CD25^{high}FoxP3^+$ cells).

Plasma cortisol and mPDN levels were determined before and after mPDN administration by liquid chromatography-tandem mass spectrometry, as reported elsewhere.[9]

Statistical Analysis

Because the data do not follow a normal distribution (according to the Kolmogorov-Smirnov test), statistical analysis was performed using nonparametric tests, Wilcoxon matched-pairs signed rank test and Mann-Whitney *U* test for paired or unpaired data, respectively (Prism 6 for Mac OS X software). The results were considered significant at $P < .05$.

Data are expressed as median (25%-75% percentile range).

Ethics Committee

The study was approved by the Erasme Hospital's institutional review board (Erasme reference: P2011/370).