Methotrexate for Steroid-Resistant Systemic Lupus Erythematosus

M. HASHIMOTO, S. NONAKA, E. FURUTA, T. WADA, Y. SUENAGA, M. YASUDA, M. SHINGU, M. NOBUNAGA

Summary We here report two patients with steroid-resistant systemic lupus erythematosus (SLE) who were successfully treated with methotrexate (MTX). In both cases, a steroid resistant high fever, associated with mild myositis and pancytopenia were the main common findings, and all these symptoms were alleviated within a few days either by 7.5 mg or 5 mg MTX per week. The number of CD4+ cells increased along with the clinical improvement, whereas the number of CD20+ cells and HLA-DR expressing cells also decreased. Taking into account the side effects of high dose corticosteroids and cyclophosphamides, treatment with a weekly low dose of MTX is known to contribute to an improvement in the long-term prognosis for patients with refractory SLE.

Key words Systemic Lupus Erythematosus, Methotrexate, Steroid-resistance, Surface Markers.

INTRODUCTION

Cytotoxic agents are employed in the management of steroid resistant systemic lupus erythematosus (SLE), and cyclophosphamides have been most commonly used to treat this problem. In spite of its efficacy for rheumatoid arthritis, polymyositis, and psoriasis (1), methotrexate (MTX) has been rarely used in SLE. Although it is possible that low doses of MTX may increase the risk of malignancy (2), in contrast to cyclophosphamide, MTX has fewer side effects related to oncogenicity, permanent sterility, and bone marrow suppression (3,4). We report on two cases of young SLE women in which treatment with low doses of MTX yielded remarkable results without any side effects. We therefore consider that MTX might be of benefit to patients with steroid-resistant SLE, especially young women who wish to bear children.

CASE REPORTS

Case 1

A 25-year-old woman was admitted to our Institute Hospital on October 23, 1991, with a high fever, polyarthralgia, and myalgia. On admission she was found to have both, butterfly-like erythema and discoid lupus erythema. An antinuclear antibody was positive at 1:5120 with homogeneous and speckled patterns. Tests for anti-DNA antibody, anti-cardiolipin IgG antibody, and false STS were also positive. The patient's clinical course is shown in Figure 1. Although she was treated with prednisolone at a dose of 30 mg per day, followed by 50 mg prednisolone per day, a recurrence of high fever, arthralgia, and myalgia occurred. An examination of the blood showed a haemoglobin level of 9.6 g/dl, a white blood cell count of 1,400/ul. She was treated with 3 daily pulses of 500 mg methylprednisolone intravenously without any positive effect. Therefore, 5 days after being admitted, 7.5 mg MTX began to be administered weekly with 20 mg paramethasone daily. The high fever disappeared on the following day, while the arthralgia, myalgia, and erythema all resolved within 1 week. Five weeks later, however, a high fever and pancytopenia reappeared. Since the pulse therapy of methylprednisolone (1000 mg intravenously for 3 days) was not effective, MTX was increased to 10 mg weekly. By the fifth day, she became afebrile again and pancytopenia began to resolve with a normalization of the lymphocyte subpopulations within 2 months. The antinuclear antibody and anti-DNA antibody titers decreased and complement values almost reached their normal ranges. Since being discharged from our hospital on Feb-

Department of Clinical Immunology, Medical Institute of Bioregulation, Kyushu University 69, Beppu, Japan 874.
Methotrexate for SLE

CLINICAL COURSE (CASE 1)

<table>
<thead>
<tr>
<th>Admitted</th>
<th>1991 Nov.</th>
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<tr>
<td>Prednisolone</td>
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</tr>
<tr>
<td>Hydrocortisone</td>
<td>20mg</td>
<td>50mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2mg</td>
<td>1mg</td>
</tr>
<tr>
<td>MTX</td>
<td>10mg</td>
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</tbody>
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CASE 2

A 34-year-old woman was admitted on September 10, 1992, with a high fever, hair loss, polyarthralgia, myalgia, and erythema. Laboratory test results showed a positive LE cell test, a falsepositive STS, and hypocomplementemia [CH50 13.1 U/ml (normal 30.0-40.0), C4 6 mg/dl, and C3 of 57 mg/dl]. An antinuclear antibody was positive in a titer of 1:2560, with a homogeneous pattern, and anti-DNA antibody titer was 6400 IU/ml (normal <7.0). The direct Coomb's test was negative. Her urine contained 0.98 g/24 hrs. of protein, as well as hyaline and granular casts, while the creatinine clearance was 67 ml per day. Although prednisolone, 50 mg/day followed by 100 mg/day was temporarily effective, a high fever reappeared and the pancytopenia became more severe, 7.5 g/dl haemoglobin, 1000/µl leukocytes, and 91,000/µl platelet. Methylprednisolone pulse therapy (500 mg, 3 days and 300 mg, 3 days) was also ineffective, as shown in Figure 2. On August 13, oral MTX therapy (5 mg/week) was therefore begun with 80 mg prednisolone daily. The fever disappeared on August 16 and the pancytopenia also improved, with a normalization of the lymphocyte subpopulations and proteinuria by mid-September. Subsequently, the dose of prednisolone was tapered to 30 mg without any flare-up.

DISCUSSION

MTX has been documented as having a variety of effects on the immune system. MTX can interfere with antibody responses to a variety of antigens (5). Besides, its effects on T lymphocyte function and NK cell activity have also been demonstrated (6,7). These studies support the notion that a significant reduction in rheumatoid factor titers concurrent with clinical improvement are noted in the MTX treatment of RA. Moreover, MTX inhibits both monocyte and neutrophil chemotaxis (8,9), and leukotriene B4 synthesis (10). The exact role of MTX in the treatment of autoimmune diseases, as well as in its mechanism of action, still awaits further study. These anti-inflammatory effects could however be related to the rapid responses, with signs of SLE activity disappearing within a few days.

Throughout the clinical course, we traced the surface markers of the peripheral blood mononuclear cells in these two cases. As shown in Figures 1 and 2, in association with clinical improvement, both patients showed an increment in the percentages of CD4 positive cells (from 39.2% to 45.7% for case 1, and from 34.1% to 34.1% for case 2), and a decrease in the percentages of CD20 positive cells (from 23.0% to 9.5%, and from 18.9% to 6.2%, respectively) as well as the percentages of HLA-DR expressing cells (from 30.2% to 15.0%, and from 23.5% to 20.5%, respectively). There seem to be no consistent changes in CD8 positivity (from...