tive anti-thyroid microsomal antibodies. Antibodies to the extractable nuclear antigens (ENA) were negative. Liver biopsy showed features compatible with chronic active hepatitis. SLE with the associated hepatitis was diagnosed and she was prescribed prednisolone 15 mg daily, which was gradually reduced over two years as her liver function and platelet count stabilised. Over the next four years, she developed recurrent deep venous thrombosis in her left popliteal, left femoral and hepatic veins. She had three spontaneous abortions, all early in the second trimester. Subsequent investigations showed a positive lupus anticoagulant (LAC) and IgG anti-cardiolipin antibody (ACA). She was treated with warfarin. She was diagnosed with migranous headache, fever and polyarthralgia and was diagnosed as having a flare of her underlying lupus and secondary APLS.

She was given corticosteroids with satisfactory response and she was later maintained on azathioprine while the oral prednisolone dose was gradually brought down to 10 mg daily. She was also given diprydamole, an anti-platelet agent, and atenolol for hypertension that was diagnosed during subsequent follow ups but there was no other evidence of renal involvement. Calcium supplements and vitamin D were started for prophylaxis against osteoporosis. She had another flare of her SLE in October 1988 when she presented with polyarthralgia and significant thrombocytopenia. Her warfarin was stopped in view of the potential increase risk in bleeding tendency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was performed, after which her platelet count stabilised. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with prednisolone (9–10 mg/day) and azathioprine until April 1998 when she complained of constant and severe back pain, which was aggravated by movement. A plain radiograph showed no obvious abnormality but magnetic resonance imaging of the thoracolumbar spine showed features suggestive of bone infarction of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AVN. Figure 1 shows the plain radiograph of the lumbar spine. Figure 2 shows the T2 weighted magnetic resonance sagittal image of the thoracolumbar spine of the patient.

Secondly, the pathogenesis of AVN is complex. AVN is a known complication of various systemic conditions including sickle cell disease, prolonged corticosteroid treatment, alcohol abuse and Gaucher’s disease. When occurring in the hip, it is commonly seen in elderly patients after fracture neck of femur, as a result of disturbance to its blood supply. Previous studies in patients with SLE have suggested high dose and prolonged use of corticosteroids causes AVN. Active disease and the presence of APL antibodies may also have important roles in the development of AVN in these patients. It is interesting that our patient had features of secondary APLS with previous venous thrombosis and recurrent abdominal. Additionally, she had a relapsing and remitting disease that required the prolonged use of corticosteroids for disease control. Whether the presence of APL antibodies, active disease, or the prolonged use of corticosteroids, or all three, led to AVN of her L2 vertebral body is unclear. In view of this, we have recently performed a case-control study to evaluate the role of each of these individual potential risk factors.

**Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for RA**

The limiting factor in low dose pulse methotrexate treatment for rheumatoid arthritis (RA) has been its toxicity. We recently treated a female patient with RA, in whom pneumonitis and granulocytopenia developed during methotrexate treatment; her white blood cell count was 1.10×10^9/l and Pao, was 37 mm Hg. Before treatment, at the time of development of adverse reactions, and after recovery after methotrexate was withdrawn, her IgG levels were 17.99, 10.15, 16.75 g/l, IgA 5.14, 3.69, 4.33 g/l, IgM 1.73, 1.08, 3.66 g/l, and lymphocyte 1.96, 0.42, 1.56×10^9/l, respectively. We then investigated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate treatment develop.

One hundred consecutive patients with RA (80 women and 20 men, mean (SD) age 57.5 (9.2) years) receiving between 2.5 and 15 mg of methotrexate weekly in Tokyo Metropolitan Komagome Hospital were followed up from 1991 to 1998. When the patients did not respond and had no adverse reactions, the dose was increased by 1.25 to 2.5 mg/week. Response to treatment, assessed by the patient’s impression of improvement, a decrease in swelling and pain of more than two joints, a decrease of >20 mg/l in the C reactive protein (CRP) level, adverse reactions, lymphocyte and eosinophil counts, serum concentrations of immunoglobulins, fraction, rheumatoid factor, and albumin were studied.

Sixteen adverse reactions occurred in 15 patients; the reactions affected the liver (six patients), the lung (three), the skin (three), the bone marrow (three), and the oral mucosa (one). They recovered after methotrexate was discontinued or reduced, without steroid treatment. Thirty of these 15 patients showed a mean SLD decrease in
CRP from 63 (36) to 32 (55) mg/l, whereas all 22 non-responders who had no adverse events showed a decrease in CRP from 46 (39) to 41 (34) mg/l. A significant relation was found between a good response to treatment and the appearance of adverse reactions. The patients with adverse reactions had a higher creatinine level, and more frequent use of steroid at high dose (7.9 (7.8) vs 3.5) mg/day prednisolone. The patients with the higher creatinine level were older. The albumin level increased more in responders. The rheumatoid factor titre decreased in responders and in patients without adverse reactions. The eosinophil count did not correlate either with response or adverse reactions.

After treatment the levels of IgG, IgA, and IgM, γ fractions, and lymphocyte count in the 15 patients who had adverse reactions were significantly reduced compared with the values before treatment. The reductions and reduction ratios compared with pretreatment values were significantly greater in patients with adverse reactions than in those without. Table 1 gives the results obtained and the threshold values that could differentiate between patients with and without adverse reactions.

The authors thank Dr Victoria Elegant and Ms Keiko Miyahara for their help.

SHIGEGO INOKUMA

HAJIME KONO

HISANORI NAKAYAMA

JUN'ICHI MIYAHARA

Department of Allergy and Immunological Diseases,
Tokyo Metropolitan Komagome Hospital,
Tokyo, Japan

Dr Shigeko Inokuma, Tokyo Metropolitan Komagome Hospital, 3-18-2 Honkomagome, Bunkyo-ku, Tokyo, 113–8677, Japan

Email: inokuma-k@komagome-hospital.bunkyo.tokyo.jp


Table 1 Pretreatment value, decrease, decrease ratio, and threshold value of immunoglobulin levels and lymphocyte count in patients used to differentiate between patients with and without adverse reactions. Values are shown as mean (SD).

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<thead>
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<tbody>
<tr>
<td>IgG†</td>
<td>With adverse reaction (n)</td>
<td>Without adverse reaction (n)</td>
<td>p Value‡</td>
<td>Threshold value</td>
<td>p Value¶</td>
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<tr>
<td>IgA†</td>
<td>Pre</td>
<td>Post-pre (g/l)</td>
<td>Post-pre/pre −0.30 (0.13)(15)</td>
<td>−0.06 (0.10)(81)</td>
<td>0.171 ***</td>
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<td></td>
<td></td>
<td>−2.3 (3.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>**** 4.62 ***</td>
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<tr>
<td>IgM†</td>
<td>Pre</td>
<td>Post-pre (g/l)</td>
<td>Post-pre/pre −0.31 (0.14)(15)</td>
<td>−0.03 (0.18)(81)</td>
<td>0.189 ***</td>
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<td></td>
<td></td>
<td>−2.15 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>**** 0.83 ***</td>
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<td></td>
<td></td>
<td>−2.35 (0.60)(15)</td>
<td>−0.15 (0.44)(81)</td>
<td>**** 0.26 ***</td>
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<tr>
<td>γ Globulin</td>
<td>Pre</td>
<td>Post-pre (g/l)</td>
<td>Post-pre/pre −0.35 (0.17)(15)</td>
<td>−0.17 (0.17)(81)</td>
<td>0.257 ***</td>
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<td>−5.07 (3.61)(15)</td>
<td>−1.30 (3.22)(67)</td>
<td>**** 2.38 ***</td>
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<td></td>
<td></td>
<td>−6.23 (3.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>**** 4.62 ***</td>
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<tr>
<td></td>
<td></td>
<td>−3.65 (2.17)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>**** 4.62 ***</td>
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<tr>
<td>Lymphocyte</td>
<td>Pre</td>
<td>Post-pre (10⁶/l)</td>
<td>Post-pre/10⁶/l</td>
<td>−0.35 (0.31)(14)</td>
<td>0.12 (0.71)(80)</td>
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<td></td>
<td></td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>**** 0.18 ***</td>
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<tr>
<td></td>
<td></td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>**** 0.18 ***</td>
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NS = p<0.05; *p<0.05; ***p<0.005; ****p<0.0001.
‡Comparison of patients with and without adverse reactions.
†To differentiate between patients with and without adverse reactions.

There is the encouraging phenomenon. Is the encouraging possibility that monitoring the immunoglobulin level and the lymphocyte count might disclose life threatening reactions and enable the doctor to know when to reduce the dosage or to stop the drug entirely.

The authors thank Dr Victoria Elegant and Ms Keiko Miyahara for their help.

SHIGEGO INOKUMA

HAJIME KONO

HISANORI NAKAYAMA

JUN'ICHI MIYAHARA

Department of Allergy and Immunological Diseases,
Tokyo Metropolitan Komagome Hospital,
Tokyo, Japan

Dr Shigeko Inokuma, Tokyo Metropolitan Komagome Hospital, 3-18-2 Honkomagome, Bunkyo-ku, Tokyo, 113–8677, Japan

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