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LETTERS

Long-term followup of patients receiving combined therapy with cyclosporine and methotrexate

To the Editor:

Combined therapy with various disease-modifying antirheumatic drugs (DMARDs) has been shown to be effective and relatively safe for the treatment of refractory rheumatoid arthritis (RA) (1). Methotrexate (MTX) plus cyclosporine (CSA) has proven to be useful in the treatment of severe RA with partial response to MTX (2,3). However, this combination therapy has been analyzed only through short-term periods. Recently, Stein et al have reported that the clinical improvement observed in patients treated with CSA plus MTX for 24 weeks was maintained for another 24 weeks without serious side effects (4). We would like to report our experience using this combined therapy in a group of RA patients treated with CSA plus MTX for at least 3 years.

Between July 1994 and January 1995, 11 patients in our units started combined therapy with MTX plus CSA. There were 8 women and 3 men, with a median age of 48 years (mean ± SD 49.3 ± 9.1 years, range 35–64) and a median disease duration of 6 years (mean ± SD 6.7 ± 4.6 years). Ten of the patients were rheumatoid factor positive. All but 1 of the patients were being treated with prednisone due to severe disease. All met the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) revised criteria for RA (5). In all patients, several DMARDs had been tried without success. Other combined therapies had been prescribed in 5 patients (MTX plus azathioprine in 2, MTX plus chloroquine in 3).

All patients were receiving treatment with MTX, and CSA was added under the following conditions: (a) only partial response to MTX in spite of receiving a maximal dosage (15 mg/week) for at least 3 months, or (b) persistent active synovitis, defined as ≥6 swollen joints, ≥9 tender joints, and morning stiffness ≥60 minutes. In all patients, treatment with CSA at an initial dosage of 2.5 mg/kg/day was added to MTX given at a dosage of 7.5 mg/week. In some patients, both drugs were gradually increased based on RA activity, to a maximum dosage of 5 mg/kg/day and 15 mg/week, respectively. The steroid dosage was not modified during the first 3 months of combined CSA/MTX therapy. Afterwards, the prednisone dosage was reduced in the patients in whom clinical improvement was observed.

A comparative study of clinical and laboratory parameters between baseline and 6, 12, 24, and 36 months was performed. The following standardized parameters were evaluated: (a) morning stiffness, (b) tender joint count (the number of joints with pain on passive movement and tenderness on pressure), (c) swollen joint count, and (d) an acute-phase reactant (erythrocyte sedimentation rate, by the Westergren method). Improvement was defined according to the ACR preliminary core set of disease activity measures for RA clinical trials (6); however, a visual analog pain scale was not used. Functional class was established, according to the Steinbrocker criteria (7), at the beginning of the study and after 36 months of therapy. A nonparametric analysis of variance for related samples (Friedman's test) was applied. P values less than 0.05 were considered significant.

Apart from 1 patient whose RA began to improve after 9 months of combined therapy, all patients had important improvement within the first 6 months of treatment. At baseline, 5 of the 11 patients were in functional class III and 6 in functional class II. Interestingly, after 36 months of combined therapy, none of the patients were in functional class III, and 3 were in remission.

Clinical and laboratory data on the 11 patients are shown in Table 1. The median dosage of CSA after 36 months of combined therapy was 2.5 mg/kg/day (range 2.0–3.0) and that of MTX was 10 mg/week (range 7.5–12.5). There was a slight increase in blood pressure in 3 of the 11 patients. This side effect occurred within the first 9 months of combined therapy. However, the increase in blood pressure was transient and easily controlled by reducing the CSA dosage in 1 patient and initiating oral nifedipine treatment in the other 2. The median serum creatinine concentration after 36 months of treatment increased from 0.92 mg/dl to 1.15 mg/dl. No other severe side effects were observed during the study.

Cyclosporine single therapy has proven to be effective in RA (8), and promising results following short-term clinical trials of combination therapy with CSA and MTX have recently been described (2–4). In patients with refractory RA, we have observed severe side effects following other combined therapies (9). However, in our limited experience, long-term

Table 1. Rheumatoid arthritis severity parameters at baseline and after 6, 12, 24, and 36 months of treatment in 11 patients receiving combined therapy with methotrexate and cyclosporin A*

	Baseline	6 months	12 months	24 months	36 months	P†
Morning stiffness, hours	4.6 ± 7.3	1.8 ± 2.3	0.5 ± 0.4	0.4 ± 0.3	0.3 ± 0.3	<0.001
No. of tender joints	12.5 ± 3.2	6.6 ± 4.1	6.7 ± 7.2	2.5 ± 2.2	2.5 ± 2.3	<0.001
No. of swollen joints	10.1 ± 1.8	5.8 ± 4.0	4.8 ± 7.3	2.3 ± 2.0	2.4 ± 2.2	<0.001
ESR, mm/hour‡	55.5 ± 24.5	50.2 ± 32.1	42.5 ± 28.4	33.2 ± 25.8	35.3 ± 25.7	<0.05
Prednisone dosage, mg/day	12.7 ± 7.9	8.6 ± 4.5	5.8 ± 3.1	5.4 ± 2.9	4.8 ± 3.1	<0.001

* Values are the mean ± SD.
† Baseline versus 36 months.
‡ ESR = erythrocyte sedimentation rate.

combined therapy with CSA and MTX seems to be effective and to have few side effects. The promising results we have observed with this combination therapy indicate that long-term, full-scale prospective studies of MTX plus CSA in RA should be considered.

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Paradoxical immunologic effects of 2-CdA therapy: comment on the article by Davis et al

To the Editor:

We read with great interest the article by Davis et al, reporting on their pilot study of 2-chloro-2′-deoxyadenosine (2-CdA) in the treatment of systemic lupus erythematosus (SLE)–associated glomerulonephritis (GN) (Davis JC Jr, Austin H III, Boumpas D, Fleisher TA, Yarboro C, Larson A, et al. A pilot study of 2-chloro-2′-deoxyadenosine in the treatment of systemic lupus erythematosus–associated glomerulonephritis. Arthritis Rheum 1998;41:335–43). We wish to report some paradoxical immunologic effects of 2-CdA therapy observed in 1 patient with SLE-associated GN, who experienced a severe lupus flare during therapy despite profound drug-induced lymphopenia, and in 3 patients with chronic lymphoid leukemia (CLL), who developed Coombs-positive hemolytic anemia (2 patients) or inflammatory polyarthritis with antinuclear antibodies (ANA) (1 patient). These unexpected side effects of 2-CdA might be related to the observation by Davis et al of persistent type 2 cytokine expression in peripheral blood mononuclear cells (PBMC) from 2-CdA–treated patients.

The first patient was a 47-year-old woman with SLE treated with prednisolone (10 mg/day) and azathioprine (100 mg/day) who developed microscopic hematuria (30–40 red blood cells/high power field [RBC/HPF]) and proteinuria (1.0 gm/day), together with high-titer anti-DNA antibody (1,004 units/ml by Farr assay; normal <8) and severe hypocomplementemia (C3 36 mg/dl; normal ≥60). Kidney biopsy showed World Health Organization class III GN. Azathioprine was withdrawn, the prednisolone dosage increased (to 20 mg/day), and 2-CdA prescribed (0.15 mg/kg/day given intravenously [IV] on 2 consecutive days every 2 weeks). Two weeks after the third 2-CdA course (i.e., 6 weeks after the first injection and after the increase in steroid dosage), she developed high-grade fever, splinter hemorrhages, overt polysynovitis, and angioedema. Her anti-DNA antibody level rose to 3,080 units/ml, and urinalysis indicated the persistence of hematuria (80–100 RBC/HPF) and proteinuria (1.4 gm/day). Interestingly, her white blood cell, neutrophil, lymphocyte, and CD4-positive cell counts dropped from 4,410/μl to 800/μl, 4,010/μl to 650/μl, 150/μl to 80/μl, and 100/μl to 30/μl, before and after 2-CdA therapy, respectively. Therapy with 2-CdA was discontinued, and the patient was treated successfully with IV pulse methylprednisolone and cyclophosphamide.

We also observed 2 CLL patients given 2-CdA as first-line chemotherapy (5.6 mg/m^2/day for 5 consecutive days in monthly intervals) who developed Coombs-positive hemolytic anemia during treatment. The first patient, age 60, with a negative Coombs test result before treatment, had a decrease in his hemoglobin (Hgb) level from 11.4 gm/dl to 8.3 gm/dl after 2 courses of 2-CdA, and his Coombs test result became positive. He recovered with glucocorticoid therapy. The second patient, age 64, with a positive Coombs test result but a normal Hgb level and no signs of hemolysis before treatment, developed hemolytic anemia after 6 courses of 2-CdA (Hgb level dropped from 11.2 gm/dl to 8.2 gm/dl). He recovered partially (Hgb 10.1 gm/dl) after withdrawal of 2-CdA, without glucocorticoid therapy.

Finally, a third CLL patient, age 54, was treated with a similar 2-CdA regimen after failure of glucocorticoid and chlorambucil treatment. Four months after the sixth and last course of 2-CdA, he developed symmetric polyarthritis, associated with ANA (titer 1:2,650), which responded to nonsteroidal antiinflammatory drugs and 2-CdA withdrawal.

In conclusion, our observations, together with 4 other cases of autoimmune hemolysis reported in CLL patients given 2-CdA (Chasty RC, Myint H, Oscier DG, Orchard JA, Busuttil DP, Hamon MD, et al. Autoimmune haemolysis in patients with B-CLL treated with chlorodeoxyadenosine [CDA] [abstract]. Br J Haematol 1996;93 Suppl I:71), indicate that 2-CdA therapy might be associated with various paradoxical humoral-