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Methotrexate and Cyclosporin Combined Therapy in Severe Psoriatic Arthritis. A pilot study

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Methotrexate (MTX) and cyclosporyn-A (Cy-A) are two effective agents in the treatment of psoriatic arthritis (PA), though some patients are resistant to these drugs when they are administered separately.

There is increasing interest, however, in combining two or more disease-modifying antirheumatic drugs (DMARD).

Clinical studies have evaluated several combinations of DMARD and have shown improved efficacy – but typically at the expense of increased toxicity, – compared with single agents. The combination of MTX and Cy-A has been used with encouraging results as prophylactic therapy for graft-versus-host disease (GVHD) in bone marrow transplant recipients (1, 2) and for suppression of collagen-induced arthritis in rats (3).

We present here the results of an open study on the efficacy and safety of MTX and Cy-A given in association, in patients with severe psoriatic arthritis.

MATERIALS AND METHODS

Eight patients (4 male, 4 female; average age 53 years) were entered into the study. All patients were in the 3rd functional class. The disease pattern was peripheral, with axial involvement in 6 cases, asymmetric peripheral involvement in 2. All were unresponsive to antimalarials, gold sodium thiomalate and 5 patients also to MTX or Cy-A when given separately. The above-mentioned drugs were discontinued at least 6 months before the study commenced. Non-steroidal anti-inflammatory drugs were allowed during the study. The dosages of MTX Cy-A were 10–15 mg/week and 3–5 mg/kg/die, respectively. Each patient was examined before starting treatment and monthly thereafter. The following clinical variables were evaluated at each visit:

- overall joint tenderness, expressed as Ritchie articular index modified for distal interphalangeal joints;
- duration of morning stiffness;
- patient's assessment of pain graded on a visual analogue scale.

The following tests were carried out at each visit: complete blood and differential count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine and urine analysis. Serum potassium and sodium, uric acid, albumin, total bilirubin, liver transaminase, alkaline phosphatase were also measured.

RESULTS

General characteristics of the patients studied are shown in Table I.

All patients showed a rapid and significant improvement after the first month of therapy. All patients but one showed clinical improvement after 6 months of therapy (Fig. 1). In fact, one of them discontinued the drugs during the fourth month of treatment due to a mild increase in blood creatinine, which returned spontaneously to normal levels after 2 weeks.

Two patients suffered from a recurrence of the disease process after 21 and 19 months respectively; in one of them, reversible arterial hypertension also ensued. The remaining 5 patients are showing a marked and stable improvement after 32, 24, 19, 13 and 9 months of therapy, respectively. All but one patient showed a significant decrease in erythrocyte sedimentation rate and c-reactive protein level.

DISCUSSION

MTX is a folate antagonist which binds to dihydrofolate reductase. It inhibits purine synthesis and interferes with DNA and protein synthesis. Moreover, MTX has a strong anti-inflammatory and immunomodulatory activity by inhibiting interleukin 1 (IL-1). Cy-A is an immunosuppressive agent; it inhibits IL-2, IL-3 and interferon γ, with subsequent inhibition of T helper/inducer cell proliferation.

The association of low dose MTX + Cy-A (10–15 mg/week and 3–5 mg/kg/die respectively) was rapidly and persistently effective in our cases of severe PA. A close correlation was found between improvement in clinical and laboratory assessment. The therapeutic benefit of this drug combination appears to be additive or synergistic, since the drugs were ineffectual as single agents. Unwanted side effects were all mild and reversible.

In conclusion, this pilot study indicates that the combination MTX + Cy-A may be successfully employed in the management

Table I. *General characteristics of 8 patients with severe psoriatic arthritis*

Patient	Sex	Age	Disease duration (years)	Disease pattern
B.M.	F	57	18	P
C.S.	M	59	23	A + P
D.P.R.	M	54	1	A + P
F.M.S.	F	64	10	A + P
S.S.	F	45	22	A + P
R.G.	M	46	6	A + P
B.M.	M	52	8	A + P
C.C.	F	49	5	P

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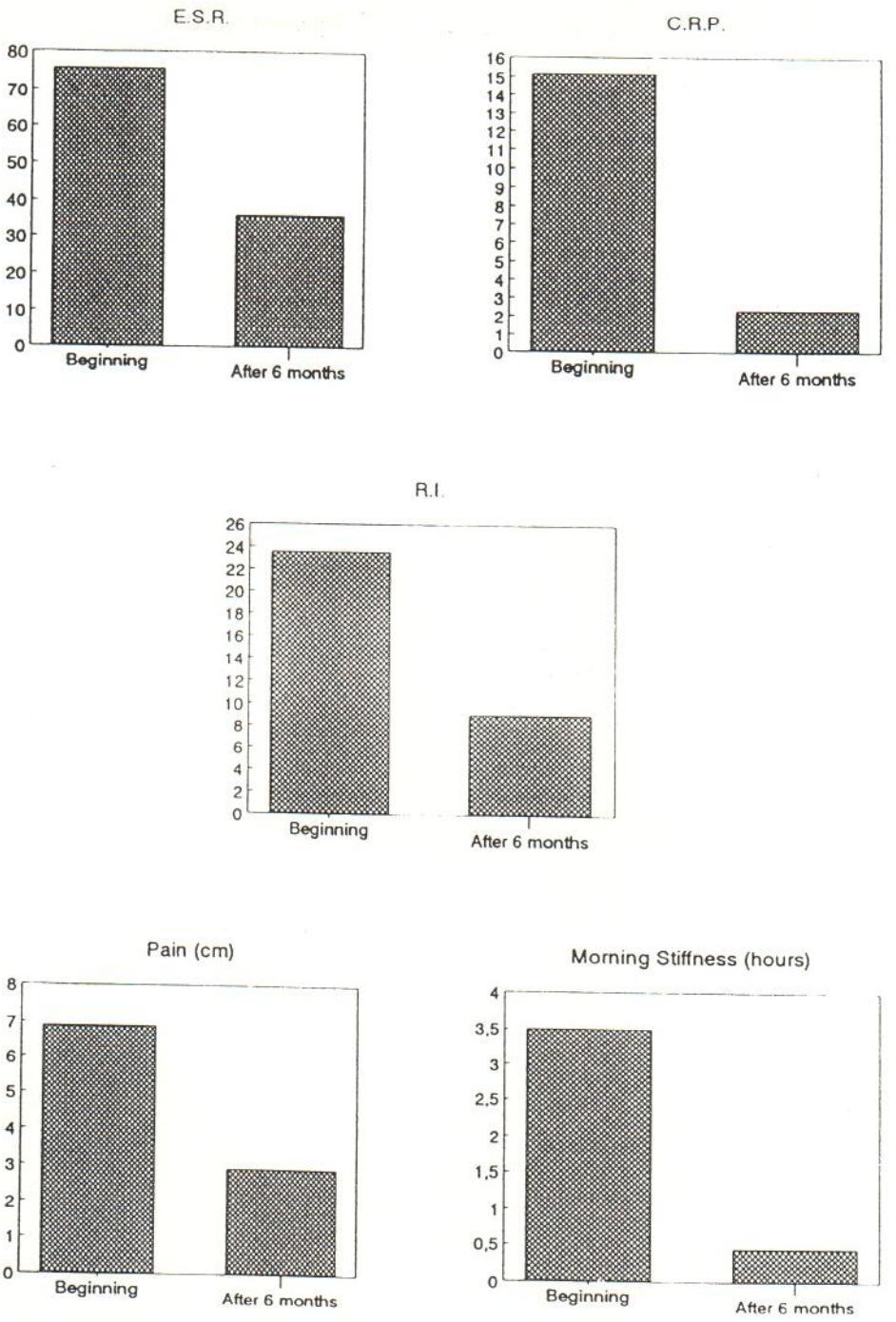

Fig. 1. Mean values of clinical data for 7 patients with psoriatic arthritis before and after 6 months of combined therapy with MTX and Cy-A.

of severe psoriatic arthritis. Further studies will be necessary to define the clinical impact of MTX + Cy-A on larger series of psoriatic arthritis and to assess the role of this association as a first line therapy in problematic cases.

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