Methyl prednisolone pulse therapy in the treatment of systemic lupus erythematosus

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SUMMARY Twenty patients with active systemic lupus erythematosus (SLE) were treated with methyl prednisolone pulse therapy (MPPT) and followed up for up to 24 weeks (mean 18 weeks). Beneficial effects of MPPT were observed principally on arthralgia, pleuritic pain, vasculitic skin rash, pyrexia, and lymphadenopathy. The serological tests showing the most improvement were DNA binding and the serum C3 level. MPPT was found to be both safe and easy to administer. It may be of value in treating patients with SLE whose disease is not controlled by moderate doses of corticosteroids and may also enable the dose of maintenance corticosteroids to be reduced appreciably.

A number of studies have been described in which lupus nephritis has been treated with methyl prednisolone pulse therapy (MPPT). The apparent success of this method has prompted an assessment of this form of treatment in a much wider variety of lupus manifestations. Where MPPT has been used before in nonrenal lupus most of the patients treated were severely ill. In this study patients with active disease were selected but not those in acute crisis or terminally ill. Thus it was hoped to establish whether MPPT might have a role in the routine management of active SLE by inducing clinical or serological improvement and in enabling the oral maintenance dose of corticosteroids to be reduced.

Patients, materials, and methods

Twenty patients, all female, with 4 or more of the American Rheumatism Association's criteria for the classification of systemic lupus erythematosus (SLE) were studied (a positive antinuclear factor, >40, was however substituted for a positive LE cell test). Each patient had active disease, and the group as a whole exhibited a wide variety of clinical manifestations. The patients were examined clinically on 3 occasions during the 6 weeks prior to MPPT. At each attendance before and after therapy a questionnaire covering the variety of lupus manifestations was completed. In addition full blood counts, urea and electrolytes, liver function tests, double stranded (ds) DNA binding (Amersham kit), circulating immune complexes (polyethylene glycol precipitation), and serum C3 were measured whenever the patient was examined.

Patients were stabilised so far as possible with regard to treatment during the 6 weeks prior to MPPT so that they could be used as their own controls in the subsequent assessments. Fifteen of the 20 patients were on regular maintenance oral prednisolone before MPPT, the others, all with active disease not controlled by nonsteroidal agents, would otherwise have started on oral corticosteroids. Five of the patients on oral prednisolone were also being treated with azathioprine.

MPPT comprised 1 g methyl prednisolone, given intravenously in 500 ml normal saline over 4 hours on 3 successive days. Patients were admitted to hospital on the day prior to treatment and observed in hospital for 48 hours after treatment and thereafter at regular intervals in the outpatient department. A total of 25 courses of MPPT were given to the 20 patients. However, insufficient information was available for 2 of the repeat courses, and they are not included in the analysis. Follow-up periods varied from 4 to 24 weeks (mean, 18 weeks).

Results

The results of the clinical assessments and serological tests given are the means of 3 values obtained during
the following time periods: (a) before treatment; (b) 0–4 weeks after treatment; (c) 5–12 weeks after treatment; (d) 13–24 weeks after treatment. The comparisons described in the figures and tables are always made between the pretreatment period and a post-treatment period. The only serological results which have not been included in the assessments are those obtained when the oral prednisolone dose was increased by 10 mg or more per day during the follow-up period, as this might have unduly influenced the results. As a consequence of this out of a potential 60 ‘study periods’ 7 have been excluded.

The overall results, as judged clinically, are shown in Table 1. The outcome after 4, 12, and 24 weeks was classified as follows. If after MPPT a patient’s clinical features fully resolved throughout the assessment period, it was considered that complete sustained improvement had occurred. Partial sustained improvement was judged to have taken place when one or more of a patient’s clinical features improved during the whole assessment period but other manifestations showed no change. In several patients improvement in some clinical features occurred, but this was not sustained for the whole of the assessment period. Certain patients showed no alteration in their clinical state. Three patients were judged, overall, to have shown definite clinical deterioration following MPPT even though certain individual features showed improvement.

Physicians’ assessment of the response of individual manifestations to MPPT are shown in Table 2.

Arthralgia, pleuritic pain, and pyrexia were found to be the features most likely to respond. The changes in laboratory tests and visual analogue scale, which applied to the whole group, are analysed in Table 3. Changes in DNA binding and serum C3 level showed the most change. As indicated by the visual analogue results, the majority of patients felt better or showed no adverse response to the treatment (note: decrease in the scale means patients feel better).

Patients were subdivided into those with arthralgia, thrombocytopenia, and marked renal involvement (proteinuria >1 g/24 hours, +/− increased serum creatinine). The results of the changes in relevant tests for each subgroup are shown in Table 4.

Patients were also divided into those on and off corticosteroid therapy immediately prior to MPPT. Fig. 1 shows the outcome, as judged by the alteration in daily oral prednisolone requirement. In 2 patients it proved possible to stop oral prednisolone and in 5

Table 1 Overall assessment of 20 patients (given 23 courses of MPPT) as judged clinically

<table>
<thead>
<tr>
<th>Weeks</th>
<th>4</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete sustained improvement</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Partial sustained improvement</td>
<td>10</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Some improvement, not sustained</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Worse</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Fig. 1 Changes in oral steroid requirements in patients given MPPT.
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Table 2  Breakdown of the response of individual clinical features to MPPT

<table>
<thead>
<tr>
<th>Physicians' assessment of response of individual features</th>
<th>A</th>
<th>B</th>
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</thead>
<tbody>
<tr>
<td>(A) Features which commonly responded:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15/16</td>
<td></td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>7/8</td>
<td></td>
</tr>
<tr>
<td>Vasculitic skin rash</td>
<td>5/8</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6/6</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>(B) Features which occasionally responded:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3/6</td>
<td></td>
</tr>
<tr>
<td>Improved renal function tests</td>
<td>3/8</td>
<td></td>
</tr>
</tbody>
</table>

patients, followed-up for the full 24 weeks, a marked reduction in daily corticosteroid requirement was noted. Conversely 5 patients were not on steroids at the beginning of the study (though they were candidates for this type of therapy). However, 4 of these were subsequently treated with oral prednisolone, though not for a minimum of 6 weeks after MPPT.

No major side effects were observed following MPPT. Three patients developed upper respiratory tract infections within 3 days of treatment. A further 3 patients noticed transient facial swelling and 2 had
migraine headaches within 24 hours of the last infusion. Two patients developed mild indigestion, and as a precaution the majority were given concomitant cimetidine (1 g per day for 1 week, beginning on the first day of MPPT).

Three patients on oral prednisolone were given repeat courses of MPPT a minimum of 3 months after initial treatment which had had no effect. In two cases azathioprine was added to their therapy prior to the second course. Interestingly, 2 of these repeat courses were followed by clinical improvement. Insufficient data were available to judge the outcome of the 2 other patients given repeat MPPT (one on oral prednisolone, one not).

Of the 3 patients who deteriorated following MPPT one developed marked abdominal serositis 6 weeks after treatment, one developed marked thrombocytopenia and hypertension 7 weeks after treatment, and one with mild cerebral involvement became grossly psychotic within 2 weeks of MPPT.

Fig. 2 shows the response of a 46-year-old patient with arthralgia, vasculitic skin rash, and serological abnormalities typical of SLE.

**Discussion**

MPPT has previously been used in the treatment of lupus nephritis, nonrenal lupus, rapidly progressive glomerulonephritis, minimal change nephrotic syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis, and polyarteritis nodosa. The previous studies on patients with SLE, without significant nephritis, have been confined to relatively small numbers of extremely ill subjects. We have studied the effects of MPPT on 20 patients with active SLE and found it to be both effective and safe. The majority of patients gained some benefit, no major side effects were observed and the administration of the drug is straightforward. Future courses of treatment may be given on an outpatient basis. In comparison with plasmapheresis, another form of treatment we have used for our SLE patients, MPPT is considerably cheaper. Although we have made no formal comparison the benefits of MPPT seem to be at least as good as those following plasma exchange.

Overall 16 of the 23 courses of treatment were followed by some improvement in clinical state and even at 24 weeks after MPPT, approximately one-third of the patients continued to show partial, sustained improvement. Interestingly arthralgia was the individual symptom showing the most improvement in contrast to some earlier reports of this symptom commencing after MPPT. Again in contrast to
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Earlier literature\(^1\) to 3 little benefit was observed in patients with lupus nephritis as assessed by a fall in the plasma urea, plasma creatinine or 24 h urinary protein. In common with some of the case reports described by Dosa et al.,\(^4\) Eyanson et al.,\(^4\) and Fessel\(^5\) a rise in serum C3 levels and fall in anti-DNA antibody was seen. Little change was observed in circulating immune complex levels, lymphocyte counts, and ESR.

The mechanism by which such large pulses of corticosteroids act is unclear. It is known that these agents can cause transient lymphocytopenia with a selective effect on T cells.\(^1\)\(^,\)\(^9\)\(^,\)\(^1\) The result of such action may be to block helper or cytotoxic T cells involved in the autoimmune process. It is also possible that MPPT may suppress inflammation by impeding the access of neutrophils and macrophages to the inflammatory site.\(^11\)

In conclusion, despite the empirical nature of this study, it seems reasonable to suggest that MPPT may have a role in the treatment of patients with a variety of forms of SLE.

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References