Objective: To compare the effectiveness and the adverse effects of 2 different regimens for the treatment of pemphigus: corticosteroids alone compared with a combination of corticosteroids and cyclosporine.

Design: Concurrently randomized trial.

Setting: Tertiary care medical center.

Patients and Methods: We studied 33 sequential hospitalized patients with newly diagnosed pemphigus vulgaris (n=29) or pemphigus foliaceous (n=4) based on clinical, histological, and immunofluorescence criteria who had not previously been treated with systemic corticosteroids or immunosuppressive drugs. Patients were randomly assigned to treatment with methylprednisolone or prednisolone plus cyclosporine.

Intervention: Both groups were treated with similar initial doses of prednisolone (prednisone equivalent, 1 mg/kg), which were increased 50% every 5 to 10 days based on persistence of disease activity. One group was treated in addition with cyclosporine (5 mg/kg).

Main Outcome Measures: Patients were followed up closely for clinical outcome based on time required to control active manifestations of the disease, induction of partial and complete remissions, total amount of corticosteroids administered, frequency of relapses, and development of complications.

Results: The 2 groups were similar in terms of demographics and baseline disease severity. There was no difference between groups in any of the variables used to measure response to treatment or total amount of corticosteroids administered. Complications were more common in patients who received combination therapy.

Conclusion: Combination treatment with corticosteroids and cyclosporine, 5 mg/kg, offers no advantage over treatment with corticosteroids alone in patients with pemphigus.

PATIENTS AND METHODS

PATIENTS

This study was conducted in 33 sequential patients with pemphigus based on clinical, histological, and immunofluorescence criteria who satisfied the following criteria: newly diagnosed disease and no previous systemic therapy with corticosteroids or immunosuppressive agents. All patients were treated at the Department of Dermatology, Aristotle University School of Medicine, Thessaloniki, Greece. Twenty-nine patients had pemphigus vulgaris and 4 had pemphigus foliaceous. There were 14 men and 19 women. All patients had skin lesions. Fifteen patients also had oral lesions, genital lesions, or both. Disease severity was graded in each patient using the criteria listed in Table 1.

RANDOMIZATION AND TREATMENT

All patients were initially hospitalized for at least 2 weeks and were randomly assigned to treatment with prednisolone with or without cyclosporine using a computerized program that allocated every consecutive group of 4 patients to 2 patients in each group. Patients in both groups were treated similarly with oral methylprednisolone (Medrol; Upjohn, Kalamazoo, Mich) using an escalation and maintenance schedule that has been described previously.1,6 The initial dose in all cases was 1 mg/kg of prednisone equivalent daily. One group was treated with methylprednisolone alone and the other group in addition was given cyclosporine (Novartis; R.P. Scherer GMBH, Eberbach, Baden, Germany), 5 mg/kg per day. In both groups, the dose of methylprednisolone was increased in 50% increments every 5 to 10 days until disease activity was controlled, as evidenced by the appearance of no more than 2 new lesions during the previous 3 days.1,6 The dose of methylprednisolone that controlled disease activity, and that of cyclosporine, were maintained until most (80%-90%) lesions cleared. If activity persisted with daily doses of corticosteroids greater than 240 mg of prednisone equivalent, pulse therapy with intravenous methylprednisolone (1 g/d for 5 days) or plasmapheresis was initiated.

When lesions were 80% to 90% cleared, the dose of methylprednisolone was gradually tapered 50% every 2 weeks, as described elsewhere.1,6 The dose of cyclosporine was reduced to 3 mg/kg per day when the corticosteroid dose was decreased to 50% of the maximum dose required to control disease activity. Once the dose of methylprednisolone was reduced to the equivalent of 10 mg of prednisone daily, it was maintained at that level for 1 month. The doses of corticosteroids and cyclosporine were then again gradually reduced, and use of both was discontinued within the next month.

Flares in disease activity (defined as the appearance of >2 lesions during the previous 3 days), whether or not the patient was being treated at the time this occurred, while tapering medications were treated by doubling the dose of corticosteroid administered at the time; if that was insufficient to control disease activity, the dose was further increased in 50% increments every 10 days. After controlling the activity of the disease, medications were again tapered as described above.

EVALUATION OF RESPONSE TO TREATMENT AND TOXIC EFFECTS

Patients were examined at least once a week while disease was active and every 1 to 2 weeks thereafter. Disease severity was graded on a scale from 0 to 8 based on the extent and activity of disease, as described in Table 1. Partial remission was defined as the absence of lesions in patients requiring treatment with prednisone equivalents, 15 mg/d or less, with or without cyclosporine. Complete remission was defined as the absence of lesions in patients requiring no systemic therapy for pemphigus.

RESULTS

PATIENT CHARACTERISTICS

The baseline demographic and clinical characteristics of the patients are summarized in Table 2. A total of 33 patients participated in the study: 17 were randomized to treatment with methylprednisolone only and 16 to treatment with methylprednisolone and cyclosporine. Corticosteroid-only treated patients vs those treated with corticosteroids and cyclosporine were similar with respect to baseline clinical characteristics and disease severity: mean age, 51 vs 49 years; 7 (41%) vs 7 (44%) men; mean disease duration before randomization, 3.0 vs 3.2 months; mean baseline pemphigus antibody titers, 503 vs 545; and mean baseline disease severity score, 4.7 vs 5.2.

CLINICAL RESPONSES

Multiple end points were used to evaluate clinical response to treatment, including time to heal 80% of lesions, flare in disease activity while tapering medication, percentage of patients in partial and complete remissions at fixed intervals after randomization, mean time to reach these end points, and total dose of corticosteroids required to control disease activity and induce partial and complete remissions (Table 3). Based on these criteria, response to treatment was similar in both groups for all end points studied. None of the small differences present between treatment groups were statistically significant.

Mean ± SD duration of treatment required to heal approximately 80% of lesions was 16.7 ± 5.2 days (range, 11-32 days) in patients treated with corticosteroids alone compared with 17.1 ± 5.2 days (range, 13-29) for those treated with the combination of corticosteroids plus cyclosporine. Disease activity in 3 patients, 2 treated with corticosteroids only and 1 treated with corticosteroids plus cyclosporine, could not be controlled with corticosteroid therapy (doses of 240 mg/d of prednisone equivalent). Disease activity was controlled with plasmapheresis in 2 of these patients and with pulse therapy with megadose methylprednisolone in the third.

A flare in disease activity while tapering medications occurred in 3 patients, 2 treated with corticosteroids alone and 1 also treated with cyclosporine. The flares

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were controlled by doubling the corticosteroid dose administered.

Partial remission, as defined in the “Patients and Methods” section, was induced 6 months after randomization in 6 patients (35%) treated with corticosteroids only and in 5 (31%) treated with combination therapy. One year after randomization, partial remissions were induced in 12 patients (71%) treated with corticosteroids only and in 12 (75%) treated with combination therapy. Mean ± SD time to induction of partial remission was 50.6 ± 12.4 days (range, 35–85 days) in the corticosteroid-only group vs 48.2 ± 12.2 days (range, 33–82 days) in the combination therapy group. These minor differences are not statistically significant.

Complete remission, defined as the absence of lesions and no systemic therapy for pemphigus, was induced in 5 patients (29%) receiving methylprednisolone only and 4 (25%) receiving methylprednisolone and cyclosporine 1 year after randomization; mean ± SD time to induction of complete remission was 124.0 ± 12.6 days (range, 109–160 days) vs 122.0 ± 11.9 days (range, 105–155 days), respectively.

The mean total dose of corticosteroids required to heal 80% of lesions, to reach partial remission, and to reach complete remission was similar in both groups.

Four to 6 years after randomization, 10 patients (5 in each group) remain in complete remission. All other patients are in partial remission, receiving an average of 2.5 mg of prednisone equivalent daily.

**ADVERSE EFFECTS**

There was no mortality. The overall incidence of adverse effects was higher in the group treated with corticosteroids plus cyclosporine, as shown in Table 4, predominantly because of the presence of cyclosporine adverse effects in patients receiving this drug, as evidenced by a higher frequency of hypertrichosis, hypertension, elevated serum urea and creatinine levels, and decreased creatinine clearance. The incidence of other adverse effects was similar between the 2 groups.

**Comment**

The most important result of this randomized clinical trial is that adjuvant therapy of pemphigus with cyclosporine did not seem to be effective. Patients treated with a combination of systemic corticosteroids and cyclosporine did not respond to therapy more rapidly, did not require lower amounts of corticosteroids to control their disease, and did not enter into remission more often or more rapidly than those treated with corticosteroids only. However, patients taking combination therapy had more adverse effects.

This study was designed as a randomized and concurrently controlled trial to circumvent the major difficulty in the interpretation of previous studies of cyclosporine in the treatment of pemphigus, which are for the most part uncontrolled. In our trial, 33 patients were randomly assigned to treatment with methylprednisolone alone or in combination with cyclosporine at a dose of 5 mg/d. Standardized and defined protocols were used to grade disease severity, to escalate and taper medication doses, and to evaluate responses to therapy. The 2 treatment groups were similar with respect to demographic characteristics and baseline disease severity.

We found no significant difference between the 2 groups in their response to therapy as evaluated by multiple variables, including proportion of patients responding to therapy, time required to control disease activity, proportion of patients experiencing a flare in disease activity during maintenance therapy, proportion of patients achieving partial or complete remission, and

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**Table 1. Severity Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Extent of Disease</th>
<th>Activity of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesions</td>
<td>No lesions</td>
</tr>
<tr>
<td>1</td>
<td>1-5 Lesions</td>
<td>Healing lesions only; no pruritus</td>
</tr>
<tr>
<td>2</td>
<td>6-20 Lesions or 3%-10% of the body surface involved</td>
<td>Active lesions, but no new lesions for the past 3 d</td>
</tr>
<tr>
<td>3</td>
<td>21-50 Lesions or 11%-20% of the body surface involved</td>
<td>1-5 new bullae or urticarial plaques in the past 3 d</td>
</tr>
<tr>
<td>4</td>
<td>&gt;50 Lesions or &gt;20% of the body surface involved</td>
<td>&gt;5 New bullae or urticarial plaques in the past 3 d</td>
</tr>
</tbody>
</table>

*Disease severity is graded on a scale of 1 to 8 based on the sum of (1) the extent of disease graded on a scale from 0 to 4 based on the number of lesions or percentage of body area involved (whichever is greater) and (2) the activity of the disease, also graded on a scale from 0 to 4.

**Table 2. Baseline Characteristics of Study Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methylprednisolone Only Group (n = 17)</th>
<th>Methylprednisolone + Cyclosporine Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>51 (28-72)</td>
<td>49 (30-69)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (41)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (59)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Pemphigus vulgaris, No. of patients</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Pemphigus foliaceus, No. of patients</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duration of disease, mean, mo*</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Skin lesions, No. (%) of patients</td>
<td>17 (100)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Oral lesions, No. (%) of patients</td>
<td>8 (47)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Disease severity score, mean†</td>
<td>4.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Total duration of follow-up, mean (range), mo</td>
<td>59.9 (48.0-72.0)</td>
<td>60.5 (48.0-71.0)</td>
</tr>
</tbody>
</table>

*From diagnosis to randomization.
†Calculated as described in Table 1.
time required to reach remission. Cyclosporine did not seem to act as a steroid-sparing agent. The total amount of methylprednisolone administered during the course of the disease until partial or complete remission was reached was similar in the 2 groups. By contrast, the incidence of adverse effects was higher in the group that received cyclosporine as a result of adverse effects to this drug. Adverse effects of corticosteroid treatment were similar in both groups. These results differ from those of most previous studies of the use of cyclosporine to treat pemphigus, which describe the drug as useful. Lapidoth et al reported that cyclosporine at an initial dose 5 mg/kg per day, subsequently adjusted to obtain blood levels of 100 to 150 mg/L, and given in conjunction with prednisone at a dose of 60 to 80 mg/d in 16 patients reduced time to new blister formation, hospitalization, and the total dose of prednisone administered compared with a control group of 15 patients treated with prednisone (120 mg/d) only. However, because the control group was historic, the significance of these differences is uncertain. As in our study, adverse effects were more common in patients treated with cyclosporine. In 2 small studies, 2 patients and 4 patients with pemphigus unresponsive to moderate doses of prednisone (1 mg/kg) improved after addition of 6 to 8 mg/kg of cyclosporine to their regimen. Because the effects of prednisone are time dependent, it is unclear whether the improvement resulted from the addition of cyclosporine, the use of cyclosporine at a higher dose than used in our trial, or the continued administration of corticosteroids. Individual case reports describe the drug as effective in 8 patients and as ineffective in 4.

However, our results are consistent with those of the only other randomized trial of cyclosporine use for pemphigus, which was conducted in 28 patients with pemphigus restricted to the oral cavity. Patients were randomly allocated to treatment with 40 mg of prednisone equivalent daily or to the same dose of corticosteroids given together with cyclophosphamide, 100 mg/d, or cyclosporine, 5 mg/kg per day. There was no significant difference in the duration of treatment required to achieve remission or in the relapse rate among the 3 groups. Again, the incidence of complications was higher with combination treatment.

In summary, the results of this trial, together with those of a previous randomized trial of oral pemphigus, suggest strongly that cyclosporine administered at a dose of 5 mg/kg offers no advantage over the use of systemic corticosteroids only in the treatment of pemphigus. To our knowledge, no adjuvant therapy for pemphigus has been shown to be effective on the basis of randomized studies. Thus, the optimal adjuvant that can best reduce corticosteroid requirements or minimize adverse effects in the treatment of pemphigus remains uncertain. Our personal rec-
ommendations for the use of adjuvants to treat pemphigus have been published elsewhere.1,5

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REFERENCES