Dapsone as a Glucocorticoid-Sparing Agent in Maintenance-Phase Pemphigus Vulgaris

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Objective: To determine the effect of dapsone on glucocorticoid-dependent patients with active or maintenance-phase pemphigus vulgaris.

Design: Retrospective study of consecutive patients treated with dapsone.

Setting: University of Pennsylvania, Philadelphia (a tertiary referral hospital).

Patients: We observed 9 consecutive adult patients with pemphigus vulgaris being treated with immunosuppressants who were unable to taper prednisone use without abrupt worsening of their disease.

Interventions: Dapsone treatment added to prednisone and other immunosuppressive therapy.

Main Outcome Measure: Steroid dosage.

Results: All patients were unable to taper their steroid dose during the 3 months prior to the initiation of dapsone therapy or had active disease that was not well controlled by prednisone prior to dapsone treatment. With the exception of 1 patient with uncontrolled disease, all 9 patients were able to taper their steroid dose below the adrenal replacement level during dapsone treatment. Maintenance-phase patients taking 15 mg/d or more of prednisone (n = 5) experienced a mean ± SEM drop of 67% ± 7.1% in prednisone dose by 4 months of maximal dapsone treatment and an 84% ± 3.5% drop in prednisone dose after 8 months of dapsone treatment.

Conclusions: These retrospective study findings suggest that dapsone reduces steroid dependence in patients with pemphigus vulgaris, provided they are in the maintenance phase of their disease. These data support the need for a prospective, randomized trial to confirm these findings.

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Pemphigus vulgaris (PV) is an autoimmune vesiculobullous disorder characterized by the presence of autoantibodies to desmoglein 3, which cause intraepidermal acantholysis. The disease typically affects adults. Clinically, PV is characterized by flaccid vesicles and bullae on the face, scalp, neck, chest, groin, and intertriginous areas, usually in a symmetric distribution. Intact blisters may be sparse owing to their inherent fragility, and patients often present with numerous erosions, ulcers, and crusts. The condition is frequently debilitating, and prior to the advent of glucocorticoid therapy, it was often fatal.

To characterize the therapy and clinical course of PV, Bystryn1 suggests 3 therapeutic phases. Phase 1 (control) achieves initial control of the acute disease activity by high-dose glucocorticoid treatment. In phase 2 (consolidation), medication type and dose are kept constant until most lesions are healed and itching ceases. In phase 3 (maintenance), the dose of glucocorticoid is gradually tapered.

Often patients with PV have a protracted phase 3, which leads to a substantial cumulative glucocorticoid dose and considerable morbidity. Immunosuppressants such as azathioprine,2 mycophenolate mofetil,3 and cyclophosphamide are frequently used as glucocorticoid-sparing agents.4 While these regimens have been successful in controlling the disease, a significant subgroup of patients become dependent on glucocorticoid, which ultimately leads to complications such as osteoporosis, adrenal suppression, and predisposition to infection, cataracts, and diabetes mellitus, among other illnesses. Attempts to taper prednisone often lead to flares of the disease. All patients in this series had a protracted phase 3 and needed an alternate therapy to safely control the disease process while they were weaned from the glucocorticoid treatment.

The use of dapsone as therapy for PV was first reported by Winkelmann and Roth5 in 1960 and over the following years has been reported anecdotally to be effective in controlling the disease.1,6-12 However, without a scientific rationale or published clinical
studies, dapsone has not become generally accepted as an effective treatment for pemphigus. The present report is a retrospective evaluation of the efficacy of dapsone in patients with PV to determine whether this medication is effective as a glucocorticoid-sparing agent and, if so, which patients might benefit from this intervention.

**METHODS**

**PATIENTS**

Patients were eligible for analysis if they were unable to fully taper their prednisone dose, which occurred in 8 of 9 cases in spite of concurrent treatment with immunosuppressants, and were able to sustain dapsone treatment for more than 30 days. All patients had PV, and the diagnosis was made clinically and confirmed histologically and by immunofluorescence.

**TREATMENT PROTOCOL**

Patients received high-dose prednisone treatment in combination with an immunosuppressant or other anti-inflammatory agents for the acute phase of the disease. The prednisone dose was tapered when the initial flare was controlled and no new blisters appeared. Patients whose prednisone doses could not be tapered without significant PV exacerbation (n=7) or whose disease was uncontrolled in spite of the above treatment (n=2) constituted the study population. All patients began treatment with 50 mg/d of dapsone and titrated up to either 125 or 150 mg/d over the course of approximately 1 month. After therapeutic levels of dapsone were reached, a steroid taper was then reattempted. Prior to initiation of dapsone therapy all patients were tested for glucose-6-phosphate dehydrogenase deficiency and abnormalities in liver function tests and hemoglobin. Met-hemoglobinemia was monitored by close clinical observation.

For each patient, the average daily doses of prednisone at 3 months and at 30 days prior to initiating dapsone treatment are reported, as well as at 4 months after initiation and at 4 and 8 months after reaching 150 mg/d of dapsone. The percentage drop in prednisone dose from 30 days before initiating dapsone treatment to 8 months after reaching 150 mg/d was calculated for each patient and was used as the primary parameter for statistical analysis.

**STATISTICAL ANALYSIS**

To account for the difference in steroid dose and clinical phase we stratified the patients into 3 groups for statistical analysis. Groups 1 and 2 were in maintenance phase, but group 2 received either low or moderate doses of steroids, while group 1 received 15 mg/d or more of prednisone. The patients in group 3 had uncontrolled disease in spite of steroid treatment. For groups of 3 or more patients, the mean±SEM steroid dose was calculated and compared with a 0% drop (ie, no effect) by the t test.

**RESULTS**

Nine patients with PV unable to fully taper their prednisone dose were treated with dapsone (Table 1). Seven of the patients were steroid dependent, but their disease was controlled. It was impossible to taper the glucocorticoid therapy further in these patients without stimulating a flare of their disease activity. Five of our 9 patients required prednisone doses of 15 mg/d or more.

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y/Race</th>
<th>Time Between Diagnosis and Dapsone Treatment, mo</th>
<th>Other Treatments Prior to Dapsone</th>
<th>Prednisone Dose at Start of Dapsone Treatment, mg</th>
<th>Dose-Limiting Adverse Effects of Dapsone Use</th>
<th>Type of PV</th>
<th>Biopsy Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/66/W</td>
<td>13</td>
<td>Cyclophosphamide Azathioprine</td>
<td>30</td>
<td>None</td>
<td>Oral</td>
<td>Spongiotic</td>
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<tr>
<td>2/F/71/W</td>
<td>49</td>
<td>Azathioprine Mycophenolate mofetil Methotrexate</td>
<td>20</td>
<td>None</td>
<td>Oral, minor skin</td>
<td>SA</td>
</tr>
<tr>
<td>3/M/47/W</td>
<td>10</td>
<td>Azathioprine Methotrexate</td>
<td>15</td>
<td>None</td>
<td>Skin, oral</td>
<td>SA</td>
</tr>
<tr>
<td>4/M/60/W</td>
<td>5</td>
<td>Azathioprine</td>
<td>35</td>
<td>None</td>
<td>Oral</td>
<td>SA</td>
</tr>
<tr>
<td>5/M/66/W</td>
<td>10</td>
<td>Cyclophosphamide</td>
<td>30</td>
<td>Decreased hematocrit</td>
<td>Skin, oral</td>
<td>SA</td>
</tr>
<tr>
<td>6/F/42/W</td>
<td>11</td>
<td>Doxycycline</td>
<td>10</td>
<td>Decreased hematocrit</td>
<td>Skin, oral</td>
<td>SA</td>
</tr>
<tr>
<td>7/M/50/W</td>
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<td>Azathioprine</td>
<td>10</td>
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<td>SA</td>
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<tr>
<td>8/F/54/B</td>
<td>32</td>
<td>Gold Azathioprine Cyclophosphamide</td>
<td>20</td>
<td>None</td>
<td>Oral, minor skin</td>
<td>SA</td>
</tr>
<tr>
<td>9/F/72/W</td>
<td>12</td>
<td>Cyclophosphamide</td>
<td>10</td>
<td>Decreased hematocrit</td>
<td>Oral, skin</td>
<td>SA</td>
</tr>
</tbody>
</table>

Abbreviations: B, black; PV, pemphigus vulgaris; SA, suprabasilar acantholysis; W, white.

*Patients in maintenance phase undergoing high-dose steroid therapy (≥15 mg/d of prednisone) when dapsone treatment was begun.
†Patients without disease activity undergoing moderate-dose steroid treatment (<15 mg/d of prednisone).
‡Patients with active disease.
to achieve disease control (ie, no development of new lesions); 2 of the 9 patients achieved control with less than 15 mg/d (group 2). The last 2 of the 9 patients had poor disease control even with substantial doses of glucocorticoid (maximum previous dose, 80 and 200 mg/d, respectively) (group 3).

Based on their steroid dose, group 1 patients with steroid-dependent controlled disease had a mean ± SEM stable prednisone dose during the 90 days before starting dapsone therapy of 27.2 ± 6.0 mg/d. Four months after reaching a dapsone dose of 150 mg/d, the mean ± SEM daily prednisone dose had fallen by 67.2% ± 7.1% to 10.1 ± 2.4 mg/d (n = 5; *P* < .001). By 8 months it had fallen by 84.0% ± 3.5% to 3.8 ± 0.7 mg/d (n = 5; *P* < .001). There was no statistical difference in the predapsone average daily glucocorticoid dose during the 1-month period vs the 3-month period prior to dapsone use, which suggests that these patients did not tolerate a decrease in glucocorticoid dose during the 3 months prior to the start of dapsone therapy (Table 2).

During dapsone therapy, however, the prednisone doses for all patients could be tapered to below 7.5 mg/d (Figure). The 2 patients in group 2 also experienced a significant drop in their mean prednisone dose, from 10.3 mg/d 1 month before dapsone therapy to 0 mg/d 8 months after reaching 150 mg/d of dapsone. The 2 patients in group 3 with uncontrolled glucocorticoid-unresponsive disease were unable to lower their glucocorticoid dose after dapsone treatment was started.

Three of the patients had a drop in hemoglobin levels, which made dose adjustments of dapsone necessary, but in none of the patients in this series was this drop clinically significant. We did not observe a case of dapsone-induced sulfone hypersensitivity syndrome or methemoglobinemia that became clinically noticeable.

### Table 2. Analysis of Prednisone Doses Before and During Dapsone Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>3 mo, avg</th>
<th>30 d, avg</th>
<th>4 mo</th>
<th>4 mo After 100 mg/d Reached</th>
<th>4 mo After 150 mg/d Reached</th>
<th>8 mo After 150 mg/d Reached</th>
<th>Drop in Prednisone Dose by 8 mo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>90.9</td>
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<tr>
<td>2</td>
<td>36</td>
<td>32</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>5</td>
<td>83.4</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>29</td>
<td>20</td>
<td>17</td>
<td>10</td>
<td>5</td>
<td>82.4</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>15</td>
<td>7</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>73.3</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>30</td>
<td>13</td>
<td>15</td>
<td>15</td>
<td>3</td>
<td>90.0</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>27.2 ± 6.0</td>
<td>25.2 ± 3.6</td>
<td>14.3 ± 2.4</td>
<td>12.5 ± 2.3</td>
<td>10.1 ± 2.4</td>
<td>3.8 ± 0.7</td>
<td>84.0 ± 3.5</td>
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<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinued</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>11</td>
<td>2</td>
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<tr>
<td>7</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Mean</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>41</td>
<td>NA</td>
</tr>
<tr>
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<td>25</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>201</td>
<td>NA</td>
</tr>
<tr>
<td>Mean</td>
<td>22</td>
<td>17.5</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>121</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: avg, on average; NA, not applicable.

* Patients in maintenance phase undergoing high-dose steroid therapy (≥15 mg/d of prednisone) when dapsone treatment was begun.

† Patients without disease activity undergoing moderate-dose steroid treatment (<15 mg/d of prednisone).

‡ Patients with active disease.

Pemphigus vulgaris is a potentially life-threatening autoimmune blistering disorder. Aggressive treatment is needed to control the inflammation of the skin and decrease pemphigus antibody production. Many patients with PV treated with standard oral prednisone and cytotoxic regimens achieve control of their disease, but a large subset of patients require long-term prednisone courses at doses that lead to substantial morbidity, with flares of the disease when the steroid doses are tapered.13

Compared with steroids, dapsone has a more benign adverse effect profile during long-term use; dapsone has
been used for decades by patients with leprosy and is the drug of choice for dermatitis herpetiformis. As suggested in other publications and supported by our experience, dapsone has a favorable safety profile compared with most alternative treatments for pemphigus. However, frequent adverse effects include hemolytic anemia and methemoglobinemia, which may necessitate stopping treatment. Other, rare, adverse effects include blood dyscrasias, exfoliative dermatitis, hepatic damage (which may be dose dependent), mood or other mental changes, peripheral neuritis, and “sulfone syndrome,” which has been reported to occur in less than 0.5% to 2% of cases. None of the patients in the present series had to discontinue dapsone therapy owing to an adverse reaction. While we monitored methemoglobinemia clinically, we performed liver function tests and measured levels of hemoglobin regularly and evaluated glucose-6-phosphate dehydrogenase prior to initiation of therapy.

In addition to our series, there have been sporadic reports in the literature about the efficacy of dapsone as an adjuvant and glucocorticoid-sparing drug in the treatment of pemphigus, particularly during the maintenance phase of the disease. In some cases, patients have been reported to improve within 2 to 3 weeks of beginning dapsone treatment, leading to a marked reduction or elimination of glucocorticoid use within 1 to 3 months. The mode of action of dapsone in inducing remission of pemphigus is obscure. Although a favorable clinical response to dapsone has been observed in a number of inflammatory skin disorders characterized by neutrophil-mediated disease, neutrophils are not considered to play a substantial role in the pathogenesis of pemphigus. A possible mechanism that may account for the effectiveness of dapsone during the maintenance phase is inhibition of eosinophilic spongiosis. The concept that ES may be an early marker of pemphigus has been supported by the notion that ES may be an early marker of pemphigus. Dapsone has been shown to be an inhibitor of eosinophilic peroxidase, a mediator of inflammation that may play a role in the spongiotic events observed in pemphigus lesions.

Additional mechanisms have been proposed for the action of dapsone in respect to other pathologic processes. These mechanisms of immune response modification such as stabilization of lysosomal membranes, protection from auto-oxidative tissue damage, and inhibition of specific immunoglobulin production may play a role in altering the initial disease process in PV, but evidence linking these possible modes of action with a demonstrated effect in patients with pemphigus is lacking.

In conclusion, this series presents further clinical evidence that dapsone is effective in treating PV. Dapsone appears to benefit patients requiring maintenance with either low or intermediate doses of prednisone in the maintenance phase of their disease and may allow tapering or discontinuation of steroid doses in these patients. Our experience does not support the use of dapsone in active disease that is not controlled by glucocorticoids; however, we treated only 2 patients with active disease and cannot exclude the possibility that dapsone might be beneficial in some of these patients. Other physicians use dapsone for treatment of early and active pemphigus, but their experience has not been formally presented. Based on our experience, we are conducting a double-blind, placebo-controlled clinical trial of dapsone as a glucocorticoid-sparing agent in patients with chronic PV who are in the maintenance phase but unable to taper steroid doses without experiencing a flare of their disease.

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REFERENCES