Dapsone as Second-Line Treatment for Cutaneous Lupus Erythematosus? A Retrospective Analysis of 34 Patients and a Review of the Literature

Martin Klebes\textsuperscript{a, b}, Nora Wutte\textsuperscript{a}, Elisabeth Aberer\textsuperscript{a}

\textsuperscript{a}Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria; \textsuperscript{b}Internal Medicine, Kantonsspital Münsterlingen, Münsterlingen, Switzerland

\section*{Introduction}

Lupus erythematosus (LE) is a chronic autoimmune-mediated disease with recurrent flares, scarring and long-term morbidity. Various subtypes of cutaneous LE (CLE) exist, such as acute CLE, subacute CLE (SCLE), discoid LE (DLE), LE tumidus (LET) and LE profundus (LEP) \cite{1}. Currently, the treatment of CLE consists of sun protection, topical therapy and different systemic agents.

Antimalarials like chloroquine (CHL) or hydroxychloroquine (HCHL) are first-line systemic agents for the treatment of CLE \cite{2, 3}. In chloroquine-resistant CLE patients, treatment with immunosuppressants and combinations with immunomodulators (e.g. mepacrine and retinoids) or treatment with dapsone has been reported \cite{4}.

Dapsone (4,4′-diaminodiphenylsulfone) possesses antibacterial and anti-inflammatory properties. The anti-inflammatory action has been linked to its inhibitory effect on neutrophil-mediated tissue damage by converting myeloperoxidase into an inactive compound, thus suppressing the formation of toxic oxygen intermediates. Due to its anti-inflammatory properties, dapsone is used in various neutrophilic dermatoses \cite{5}.

To our knowledge, the use of dapsone in CLE has been reported in 137 patients, including case reports and retrospective analyses (table 1). Controlled studies have not been performed so far. According to the AWMF (Association of the Scientific Medical Societies in Germany)
<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Patients, n</th>
<th>LE type</th>
<th>Results</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindskov [10]</td>
<td>1986</td>
<td>Case series</td>
<td>33</td>
<td>DLE</td>
<td>Excellent results in 8, some effect in 8, no change in 17</td>
<td>n.a.</td>
</tr>
<tr>
<td>Coburn [11]</td>
<td>1982</td>
<td>Case series</td>
<td>11</td>
<td>DLE</td>
<td>Improvement in 9</td>
<td>100 mg/day for 6–16 weeks</td>
</tr>
<tr>
<td>Yamada [12]</td>
<td>1989</td>
<td>Case report</td>
<td>1</td>
<td>DLE (developed from LEP)</td>
<td>Efficacy in 3/4 DLE and 1/3 SLE; remission of urticarial vasculitis in SLE, discoid lesions and oral ulcers in DLE; no efficacy in disseminated DLE and widespread SLE</td>
<td>n.a.</td>
</tr>
<tr>
<td>Tsutsui [16]</td>
<td>1996</td>
<td>Case report</td>
<td>1</td>
<td>SCLE</td>
<td>Good disease control with dapsone combined with prednisolone; no response to prednisolone, CHL, cyclosporine or gold</td>
<td>75 mg/day</td>
</tr>
<tr>
<td>Fenton [17]</td>
<td>1986</td>
<td>Case report</td>
<td>1</td>
<td>SCLE</td>
<td>Remission after 3 weeks; no response to steroids or mepacrine</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Böhm [18]</td>
<td>1998</td>
<td>Case report</td>
<td>1</td>
<td>LEP</td>
<td>Immediate improvement, no response to CHL</td>
<td>50–75 mg/week</td>
</tr>
<tr>
<td>Ujiie [19]</td>
<td>2006</td>
<td>Review</td>
<td>10</td>
<td>LEP</td>
<td>Remission within the first 1–8 weeks in all cases; no documentation of long-term effects</td>
<td>25 and 75 mg/day</td>
</tr>
<tr>
<td>Ludgate [8]</td>
<td>2008</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Dramatic improvement</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>Pinto-Almeida [20]</td>
<td>2012</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Dapsone 100 mg/day, combined with HCHL 400 mg/day, hydroxyzine 25 mg t.i.d. and sun protection; no new lesions after 5 days; improvement after 3 weeks</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Yung [22]</td>
<td>2000</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Rapid sustained remission; no response to prednisolone</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Hall [23]</td>
<td>1982</td>
<td>Case series</td>
<td>4</td>
<td>Bullous SLE</td>
<td>Efficacy in all 4 within 24 h, no response to corticoids</td>
<td>n.a.</td>
</tr>
<tr>
<td>Grover [24]</td>
<td>2013</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Remission</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td>Liu [25]</td>
<td>2014</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Reduction in vesiculobullous lesions after 3 days with 200 mg/day, healing with 100 mg/day</td>
<td>n.a.</td>
</tr>
<tr>
<td>Tay [26]</td>
<td>1995</td>
<td>Case report</td>
<td>1</td>
<td>Bullous SLE</td>
<td>Dramatic improvement</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Neri [27]</td>
<td>1999</td>
<td>Case report</td>
<td>1</td>
<td>SLE</td>
<td>Dramatic improvement after 1 month; no response to chloroquine, steroids, steroid pulses, retinoids and cyclophosphamide</td>
<td>n.a.</td>
</tr>
<tr>
<td>Seo [28]</td>
<td>2012</td>
<td>Case report</td>
<td>1</td>
<td>Methimazole-induced bullous SLE</td>
<td>Bullous skin lesions, which were refractory to prednisolone, were partially relieved with the introduction of dapsone</td>
<td>125 mg twice/day</td>
</tr>
<tr>
<td>Chan [29]</td>
<td>2011</td>
<td>Case report</td>
<td>1</td>
<td>SLE with erythema elevatum diutinum</td>
<td>Improvement in erythema elevatum diutinum after a few weeks, no recurrence within 5 years</td>
<td>50 mg/day/2 years</td>
</tr>
</tbody>
</table>

n.a. = Not available.
guidelines, dapsone is recommended in CLE and LEP, especially in therapy-resistant cases or in the presence of intolerance to antimalarials [6]. The efficacy of dapsone was reported in SCLE, LEP, urticarial vasculitis, oral ulcerations and bullous eruptions complicating systemic LE (SLE) [7, 8].

We found dapsone to be effective in various subtypes of LE. To confirm our subjective impressions, we performed a retrospective study to evaluate the efficacy and safety of dapsone in treatment-resistant CLE.

**Patients and Methods**

We reviewed the records of 34 patients who had been treated with dapsone in the Department of Dermatology and Venereology at the Medical University of Graz from January 2005 to December 2012. The medical document database at our Department was searched using the key word 'dapsone'. All patient records identified by this key word were analyzed. Patients with the following diagnoses were selected: lupus, LE, CLE, DLE, SCLE, SLE, LEP and LET. The patients' data were documented in an Excel table.

LE was classified according to the Düsseldorfer classification [1]. At the time of analysis, 17 patients were undergoing treatment with CHL/HCHL. The majority of the patients had received CHL/HCHL in the past; their exact number could not be determined from the records. We analyzed the duration of disease, the dosage of dapsone, treatment duration, previous treatment, additional therapies with CHL or HCHL, the course of the disease and side effects of treatment.

The efficacy of dapsone was assessed semiquantitatively according to the registered course of the disease in the patients' records. Results were divided into the following categories: cured, improved, constant and drug discontinuation. Information on adverse clinical events and the reasons for discontinuation of dapsone was obtained from medical records.

A review of the published literature was performed. We searched for combinations of the terms 'dapsone', 'dapsone treatment' and 'CLE, lupus, lupus erythematosus, LE, SCLE, LET, LEP, SLE and DLE' in Medline (1950–2014) and the Cochrane Database of Systematic Reviews, without restriction for language.

**Statistics**

Owing to the exploratory nature of our analysis, the results of statistical tests are presented in descriptive form. Data are shown as means and medians. The efficacy of dapsone was measured semiquantitatively. Further statistical analysis was performed with the software program SPSS® 20.

**Results**

Thirty-four patients (7 males and 27 females) with the different CLE subtypes [DLE (56%), SCLE (23%), LET (12%) and SLE (9%)] were treated with dapsone (table 2). The majority of the patients (79%) were female with an average of 49 years (SD ±16, range 27–80). The mean duration of disease was 124 months (SD ±94, range 10–504). In 17 patients, dapsone treatment was combined with CHL/HCHL. Dapsone was given at a median dose of 100 mg/day for a mean duration of 16 months (1–82 months). Six (18%) patients showed complete remission. All of their skin lesions were cured after a mean treatment period of 7 months. Improvement was noted in 14 (41%) patients after an average period of 2 months, while the disease remained constant in 5 (15%) patients. Dapsone was discontinued in 9 (27%) patients after a mean period of 3 months due to adverse effects in 4 cases (12%) and exacerbation of skin lesions in 3 patients. In 1 case, the treatment was discontinued on the patient’s request while another patient discontinued treatment on her own. The effect of the treatment differed in the various subtypes of LE as listed in table 2. The best effect was seen in SCLE patients with either disease remission or improvement in 6/8 patients.

| LE subtypes | Patients, n | Sex F/M | Age, years | Duration of disease, months | Duration of dapsone treatment, months | Dose, mg | ANA+/-dsDNA Ab, n | Course of the disease, n | Course of the disease, n%
|-------------|------------|---------|------------|-----------------------------|--------------------------------------|----------|-------------------|-------------------------|-------------------------|
| DLE         | 19         | 74/26   | 49         | 154±108 (17–504)            | 16±22 (1–82)                         | 100 (50–125) | 8/1               | 2 (11)                  | 9 (47)                  | 3 (16)                  | 5 (26)
| SCLE        | 8          | 100/0   | 52         | 73±39 (24–120)              | 20±13 (2–40)                         | 100 (25–100) | 6/1               | 2 (25)                  | 4 (50)                  | 0 (0)                   | 2 (25)
| LET         | 4          | 75/25   | 41         | 66±42 (10–108)              | 8±5 (1–14)                           | 100 (100–125) | 0/0               | 1 (25)                  | 1 (25)                  | 1 (25)                  | 1 (25)
| SLE         | 3          | 66/33   | 50         | 144±68 (96–192)             | 13±15 (1–30)                         | 100 (75–100) | 3/1               | 1 (33)                  | 0 (0)                   | 1 (33)                  | 1 (33)
| Total       | 34         | 79/21   | 49         | 124±94 (10–504)             | 16±18 (1–82)                         | 100 (25–125) | 17/3              | 6 (18)                  | 14 (41)                 | 5 (15)                  | 9 (27)

* Means ± SD with ranges. b Medians with ranges. c Numbers of patients with percentages.
The median dose of dapsone was 100 mg in 26/34 patients. Three patients received a median dose of 75 mg, 2 patients a median dose of 50 mg and likewise 2 patients a median dose of 125 mg. One patient with a median dose of just 25 mg showed improvement. A median dose of 50 mg resulted in cure and improvement in 1 patient each. The same effects were observed with a median dose of 125 mg, which also led to cure and improvement in 1 patient each.

Seventeen of the 34 (50%) patients received dapsone monotherapy, while in 17 (50%) patients dapsone was given additionally to the current CHL/HCHL therapy (fig. 1). Skin lesions were cured or improved in 9/17 patients after combined treatment with CHL/HCHL and after monotherapy in 11/17 patients. Drug eruption was observed in 2 patients in the 1st month of treatment. The same effects were observed with a median dose of 125 mg, which also led to cure and improvement in 1 patient each.

In a study by Ruzicka and Goerz [13] on the effects of dapsone in 7 patients (4 with DLE and 3 with a widespread rash of SLE), SLE patients had remission of discoid lesions, oral lesions and urticarial vasculitis. However, 2 patients with SLE and widespread cutaneous lesions as well as 1 patient with disseminated chronic LE remained unresponsive to dapsone.

In our study, the best effect was seen in SCLE patients: disease remission or improvement was noted in 75% of the patients similarly to other reports [14–17]. No patient in our study had LEP. However, Ujiie et al. [19] reported a case of LEP successfully treated with dapsone and reviewed 10 previously reported Japanese patients with LEP. Disease remission was noted in all patients between 1 and 8 weeks (mean, 4.6 weeks). Yamada et al. [12] and Böhm et al. [18] also described positive effects in LEP patients treated with dapsone.

In SLE, 1 of 3 patients who had pulmonary involvement, leukopenia, cutaneous lesions and a butterfly rash responded dramatically to dapsone after 2 weeks of treatment. Its efficacy in SLE, especially in the bullous forms of the disease, has been described in some case reports [8, 20–26]. One case of bullous SLE with signs of SLE was reported in 2013 by Grover et al. [24]. After initial treat-

**Discussion**

Dapsone, given as monotherapy or in combination with antimalarials, resulted in remission or improvement in more than 50% of patients. In 17 patients, dapsone was added to chloroquine because of inefficacy of the former; cure was observed in 2 and improvement in 7 of them. The efficacy of dapsone differed in the various subtypes of LE. Dapsone led to remission or improvement in nearly 60% of DLE patients. Similar results were reported by Lindskov and Reymann [10], who treated 33 patients with discoid LE in 1986, and achieved excellent results in 8 (24%) patients, some effect in 8 (24%) patients, and no response in 17 (52%) patients. Of 6 patients who received a combination of dapsone and HCHL, 2 responded well while no effect was seen in 1 patient with hypertrophic lesions. Coburn and Shuster [11] treated 11 patients with DLE; the authors noted a moderate effect in 4 patients and appreciable improvement in a further 4 patients.

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ment with corticosteroids and HCHL, new lesions developed. With dapsone treatment, the lesions healed and corticosteroids could be withdrawn. The combination of dapsone/HCHL was continued for 1 year, with continued remission of SLE. One patient with bullous SLE, with lesions induced by UVB photosensitivity, responded dramatically to dapsone [21]. Bullous skin lesions, refractory to prednisolone, were partially relieved with the introduction of dapsone in 1 patient with methimazole-induced bullous SLE [28]. Chan et al. [29] reported successful treatment with 50 mg of dapsone for erythema elevatum diutinum in connection with SLE; the skin lesions were markedly improved after a few weeks.

We registered no correlation between the dose of dapsone and its efficacy. With a dapsone dose of 25 mg in combination with 500 mg vitamin C, Ruzicka and Goerz [13] observed healing of DLE. This leads to the hypothesis that individual aspects such as genetic disposition are more closely related to the patient’s response to dapsone than the dosage of the substance.

Overall, the risk of dapsone-dependent side effects is very low. Dapsone has been used for more than 60 years, even in children. In the present study, it was tolerated well and had to be discontinued due to side effects in just 4 patients. Three of these patients received additional treatment with antimalarials. Lindskov and Reymann [10] observed side effects in 9 of 33 patients, and 6 of the 9 patients with side effects discontinued dapsone because of its side effects, such as dyspepsia, exanthema, fever, methemoglobinemia or vertigo [10].

One of our patients developed the DRESS syndrome. This syndrome is an idiosyncratic dose-independent reaction, with serious concomitant symptoms such as fever, generalized lymphadenopathy, hepatitis, hepatosplenomegaly and maculopapular exanthema. The latter may also indicate exacerbation of the disease, calling for further histological investigation to confirm the diagnosis. The DRESS syndrome was noted in 1.4% of patients [30]. Another patient in our study developed peripheral neuropathy after 7 months of treatment. Neurological symptoms caused by dapsone are rare [5, 31]; their duration varies between a few weeks and several years. Our patient’s peripheral neuropathy resolved after discontinuation of dapsone.

One patient developed hemolytic anemia. This side effect is well known and has been reported frequently in connection with other diseases as well [31–33]. In a retrospective study, Deps et al. [34] reported that nearly half of their patients with leprosy developed hemolytic anemia during treatment with dapsone. Methemoglobin levels were increased in nearly all (31 of 34) patients without clinical symptoms.

The present investigation showed that dapsone is an effective and safe medication for patients with CLE. It appears to be as effective as antimalarials, which are given as first-line treatment, and achieve a treatment response of 50–95% [35–38]. In our study, the best response to dapsone was seen in patients with SCLE.

Limitations of the study were the subjective clinical interpretation of improvement due to the retrospective nature of the study, the small sample size and the variable dosages of dapsone.

Since 50% of our patients received dapsone in combination with antimalarials, which is also a limitation of our study, we do not know whether monotherapy would have been as effective in these patients. Moreover, additional dapsone was given to those patients who did not respond to CHL/HCHL alone. The beneficial effects of dapsone treatment, associated with rare and reversible side effects, lead to the hypothesis that dapsone might be an effective treatment option for CLE patients and could be used as second-line therapy. However, well-designed, prospective studies dividing subtypes of CLE would be needed to make a better statement on the efficacy of dapsone.

Acknowledgments

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Statement of Ethics

This study was approved by the Ethics Committee of the Medical University of Graz, Austria (No. 25-100 ex 12/13).

Disclosure Statement

The authors have no financial or any other conflict of interest. There was no funding.

References


