Dapsone Therapy for Pustular Psoriasis: Case Series and Review of the Literature

Johanna S. Sheu a, b, Sherrie J. Divito a, c, Monica Enamandram e, Joseph F. Merola a, c, d

a Harvard Medical School, b Department of Pediatrics, Massachusetts General Hospital Boston, c Department of Dermatology and d Division of Rheumatology, Department of Medicine, Brigham and Women’s Hospital, Boston, Mass., and e Department of Dermatology, Stanford Medical Center, Palo Alto, Calif., USA

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Pustular psoriasis · Palmoplantar pustular psoriasis · Dapsone · Glucose-6-phosphate dehydrogenase

Abstract

Background: Pustular psoriasis is an uncommon psoriasis variant, clinically characterized as small sterile pustules on an erythematous base. Evidence for therapy is lacking, and many currently employed systemic therapeutics carry risks of significant side effects, without specifically targeting disease etiology which includes the aggregation of neutrophils. Observations: We report therapy with the anti-neutrophil agent dapsone in 5 patients with pustular psoriasis and provide a brief review of the literature. Four patients responded to oral dapsone and 1 to topical dapsone therapy. All 5 patients had previously failed multiple topical and systemic treatments. In 2 cases, oral dapsone allowed for the discontinuation of other systemic agents. One patient stopped oral dapsone due to a side effect of sleep disturbance. Conclusion: Dapsone has a much safer side effect profile and may target the pathophysiology of pustular psoriasis more directly than many other systemic agents. As such, dapsone should be considered for the treatment of patients with pustular psoriasis.

Introduction

Pustular psoriasis is a variant of psoriasis characterized clinically by small sterile pustules surrounded by erythematous skin. It is commonly subtyped into generalized forms (i.e., ‘von Zumbusch’, annular and exanthematic), localized forms [palmoplantar pustular psoriasis (PPPP) and drug-induced pustular psoriasis (table 1)]. PPPP has been associated with smoking, thyroid disease or thyroid hormone laboratory abnormalities and gluten sensitivity [1]. Drug-induced cases have been associated with multiple medications, including anti-tumor necrosis factor alpha (TNFα) agents [2]. However, the overall pathogenesis of pustular psoriasis remains unclear. On histopathological analysis, pustular psoriasis lesions reveal an intraepidermal, neutrophil-dominant infiltrate [3], suggesting that neutrophil inhibition may treat the disease.

There are few randomized controlled trials available to guide therapy and, currently, both topical and systemic agents are employed, the latter including methotrexate, acitretin, anti-TNFα therapies and cyclosporine [3, 4]. With these systemic treatments, side effects are not uncommon and can be dangerous. An alternative agent with fewer side effects would be ideal.

Dapsone is a sulfone antibiotic that also has anti-inflammatory effects. It can be given both orally and topically, and has been utilized for its anti-inflammatory properties in a number of skin conditions including dermatitis herpetiformis, bullous diseases and pyoderma gangrenosum. Its effects include inhibiting the myeloperoxidase system, neutrophil adhesion and neutrophil chemotaxis [5]. Dapsone may also affect cellular adhesion, especially in the setting of TNFα-activated neutrophils [6], suggesting that it may have additional benefit in anti-TNFα therapy-induced disease. As such, it could potentially serve as an effective agent in pustular disorders such as pustular psoriasis. Here, we report 5 cases of pustular psoriasis where the addition of dapsone was effective and did not cause any significant side effects and, in some cases, even allowed for the decreased use or the discontinuation of other systemic medications.

Report of Cases

Five patients were treated with either oral or topical dapsone therapy (table 2). One had generalized pustular psoriasis and the other 4 had PPPP. Of the PPPP cases, 1 had anti-TNFα-drug-induced disease. All 4 patients treated with oral dapsone had previously trialed topical therapies and ≥ 1 systemic medications including methotrexate, adalimumab, etanercept and infliximab. In all 4 cases, the oral dapsone was initiated at

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25 mg daily after glucose-6-phosphate dehydrogenase (G6PD) and complete blood counts were found to be within normal limits. Dapsone doses were escalated according to clinical response. Maximum dose of oral dapsone ranged from 25 to 100 mg daily. All patients demonstrated improvement at these doses. Duration of treatment ranged from 4 to 30 months. In cases 2 and 3, discontinuation of other concurrent systemic medications (methotrexate and adalimumab, respectively) was possible following dapsone addition. One patient treated with topical 5% dapsone gel also noted significant clinical improvement in palmoplantar pustular disease.

In our practice, following G6PD screening, doses of 25–50 mg once daily are initiated with dose titrated to response of 100–150 mg/day as tolerated. Patients had complete blood count testing 1–2 weeks after the initial dose and then every 1–2 weeks until a stable dose was achieved. Periodic liver function and renal function tests are...
Table 2. Characteristics of patients with pustular psoriasis on dapsone treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Characteristics</th>
<th>Psoriasis arthritis</th>
<th>Comorbid diseases</th>
<th>Previous therapies</th>
<th>Time on previous therapies, months</th>
<th>Maximum daily dose of dapsone, mg</th>
<th>Interval from start of dapsone to improvements noted by the dermatologist, months</th>
<th>Total duration of dapsone treatment, months</th>
<th>Concurrent medications</th>
<th>Medication discontinued due to dapsone efficacy</th>
<th>Outcome</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 M/68 Plantar</td>
<td>Yes</td>
<td>None</td>
<td>Topical steroids and calcipotriol, MTX, etanercept, infliximab</td>
<td>2</td>
<td>50</td>
<td>1</td>
<td>12</td>
<td>Topical steroids, topical calcipotriol</td>
<td>None</td>
<td>Stopped dapsone due to excellent disease control; 3 months with no disease recurrence</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2 F/65 Generalized: elbows, thighs, flanks</td>
<td>No Aortic valve stenosis, OA, endometrial cancer, s/p hysterectomy</td>
<td>Topical steroids and calcipotriol, acitretin, MTX</td>
<td>10</td>
<td>75</td>
<td>1</td>
<td>30</td>
<td>MTX 22.5 mg weekly, acitretin 25 mg 3x weekly, topical steroids</td>
<td>MTX</td>
<td>Continues on dapsone 25 mg/day with disease control</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 F/55 Palmoplantar</td>
<td>No Smoker, HC, gout</td>
<td>Topical steroids, intralesional steroids, NB-UVB, acitretin, MTX, adalimumab</td>
<td>8.5</td>
<td>25</td>
<td>2</td>
<td>30</td>
<td>Adalimumab 40 mg every other week</td>
<td>None</td>
<td>Continues on dapsone 25 mg/day with disease control</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 F/34 TNFα-induced palmpoplantar</td>
<td>Yes</td>
<td>None</td>
<td>Topical steroids, adalimumab, etanercept, MTX</td>
<td>5</td>
<td>100</td>
<td>1</td>
<td>2.5</td>
<td>Etanercept 50 mg 2x weekly, MTX 25 mg 1x weekly</td>
<td>None</td>
<td>Stopped dapsone due to a side effect</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>5</td>
<td>5 F/69 Palmoplantar</td>
<td>No Ex-smoker, HTN, HC</td>
<td>Topical steroids and roxithromycin, NB-UVB</td>
<td>3</td>
<td>5% topical</td>
<td>5</td>
<td>18</td>
<td>Topical tazarotene 0.1% cream, weekly NB-UVB, topical steroids</td>
<td>None</td>
<td>Continues on 5% topical dapsone with disease control</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

HC = Hypercholesterolemia; HTN = hypertension; MTX = methotrexate; NB-UVB = narrow-band UVB light therapy; OA = osteoarthritis; s/p = status post.
sole and subsequently developed tender, erythematous nodules on the trunk and limbs, indicative of Sweet’s syndrome [11]; the palmoplantar pustules were responsive to oral and topical steroids combined with oral dapsone 100 mg daily. The second patient was treated successfully with oral dapsone 50 mg daily for 5 weeks, but then reportedly developed dapsone hypersensitivity syndrome [12].

Discussion

In generalized pustular psoriasis in adults, first-line treatment includes acitretin, cyclosporine, methotrexate, infliximab or topical agents (steroids, calcipotriene and tacrolimus). Second-line treatment includes adalimumab, etanercept, alefacept or combination therapy [3]. Small studies and single case studies have also reported other systemic medications such as anakinra and ustekinumab to be effective [3, 4, 13–15, 39].

In localized PPPP, first-line treatment includes topical agents (steroids and calcipotriene) under occlusion or light therapy. For recalcitrant disease, oral retinoids, cyclosporine, methotrexate, biological agents and anakinra have been found to be useful [3, 13, 15, 16]. Recent recommendations suggest the use of biologics only in patients with concurrent psoriatic arthritis results of the use of such agents for PPPP are conflicting, and these medications confer significant side effects including immunosuppression, bone marrow suppression and liver damage [16, 17]. Dapsone is an antibacterial agent used for the treatment of leprosy and prophylaxis against pneumocystis pneumonia. Its anti-inflammatory properties have proven useful in the treatment of dermatological diseases such as dermatitis herpetiformis, bullous diseases and pyoderma gangrenosum.

The mechanism of utility of dapsone in treating pustular psoriasis is likely due to its inhibitory effects on neutrophil recruitment/adherence and myeloperoxidase. It is thought that dapsone interferes with integrin-mediated neutrophil adherence and G protein-mediated signal transduction for neutrophil recruitment [18–20]. The antioxidant properties of dapsone are likely exerted through the inhibition of myeloperoxidase, resulting in reduced reactive oxygen species. At sites of inflammation, neutrophils generate superoxide anions which dismutate to hydrogen peroxide. This is then converted by myeloperoxidase to hypochlorous acid, a potent cytotoxic molecule which can cause significant tissue damage. Through direct myeloperoxidase inhibition, dapsone prevents local tissue injury [21, 22]. Dapsone’s metabolites, dapsonehydroxylamine and monoacetyl dapsone, have also been studied in vitro and in vivo and found to have anti-inflammatory effects. Topical application of dapsonehydroxylamine has been found to inhibit polymorphonuclear leukocytes in human skin [23, 24]. The exact mechanism of dapsone in neutrophil-mediated disease is unknown and further studies on the effects of its metabolites on neutrophils, especially in the skin, are needed. These studies will help inform physicians as to which disease states dapsone may be the most useful.

The side effect profile of dapsone includes methemoglobinemia, dose-related hemolysis and agranulocytosis as well as the more rare hypersensitivity syndrome, peripheral motor neuropathy, insomnia and hepatitis/gastrointestinal or renal toxicity [12, 18]. Patients deficient in G6PD should not be given oral dapsone due to the risk of severe hemolysis. Despite a sulfone moiety, patients with sulfia allergies may tolerate dapsone, but previous allergic reactions must be considered, as demonstrated by Strom et al. [25]. Agranulocytosis has been found to develop at a higher rate in patients receiving dapsone for dermatitis herpetiformis compared to patients treated for leprosy [19]. It is hypothesized that the development of agranulocytosis is dependent on many risk factors, possibly including immune status, drug dosage and ethnic origin [20]. Studies investigating the coadministration of medications to try and increase dapsone tolerance have produced varying results, and there is a lack of large, randomized controlled trials to confirm the findings. Studies on vitamin E have found no effect [26] or a partial protective effect when 800 units were administered for 4 weeks [27]. Studies on vitamin C doses that are >1 mmol (attainable by intravenous administration) have found methemoglobinemia reduction; however, oral administration cannot exceed 200 μmol because of the gastrointestinal absorption [28–30]. Studies on the cytochrome P450 inhibitor cimetidine in rats and small studies on humans have found that concurrent administration reduces levels of methemoglobinemia [31, 32]. In humans, this reduction was demonstrated with a dose of cimetidine 8-hourly, with 800 mg/h prior to the dapsone dose and 2 subsequent doses of 400 mg each, administered for 3 weeks (but not longer than 12 weeks) [33]. Other than dose-related hemolysis, the above side effects are fairly uncommon, and patients are easily monitored by means of laboratory exams for hemolysis via hemoglobin/ hematocrit, reticulocyte count, and haptoglobin. The FDA Dermatology Advisory Committee recommends that G6PD levels are checked prior to initiation and complete blood counts should be performed weekly for the first month, monthly for 6 months and twice annually thereafter [34]. We recommend weekly or biweekly laboratory exams for the first month, then monthly checks for an additional 3–5 months on a stable dose. If a patient remains on a stable dose with no laboratory abnormalities, tests can be performed every 3 months thereafter. Patients should be advised to call their physician if they develop shortness of breath, dark urine or increased fatigue. To assess for symptoms of peripheral motor neuropathy, patients should be asked about foot drop or difficulty buttoning their shirt and similar tasks, and their physical strength should be tested. Overall, oral dapsone has fewer significant side effects and is not nearly as immunosuppressive as many other systemic agents. Moreover, it is a once-daily pill, and not as expensive as many of the other agents described.

Topical dapsone 5% gel has a safe side effect profile due to its very low systemic absorption. The most common non-application-site side effect noted is headache in 20% of patients, but with no significant changes in laboratory values [35].

Conclusion

The above 5 cases demonstrate that a clinical benefit was obtained by the administration of either oral or topical dapsone for pustular psoriasis and, overall, the drug was well-tolerated. The mechanism of dapsone in anti-inflammatory skin diseases is complex; however, its effectiveness in treating these clinically heterogeneous cases of pustular psoriasis suggests a common underlying pathophysiological mechanism. Based on this case series, previous case reports and small series, and its known anti-neutrophil effects, dapsone is a viable treatment choice for patients with pustular psoriasis.
Disclosures Statement

Dr. Merola serves as an investigator for Amgen, Pfizer and Biogen IDEC, a consultant to Biogen IDEC, receives research funding from Biogen IDEC, has served on a Scientific Advisory Board for Amgen, Eli Lilly and Novartis and is a speaker for Abbvie. Ms. Sheu, Dr. Divito and Dr. Enamandram have no financial disclosures. This study was not supported by any outside funding sources.

References