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Dapsone in the management of the autoimmune bullous diseases

Evan W. Piette and

Department of Dermatology, University of Pennsylvania, 2 Rhodes Pavilion, 3600 Spruce St, Philadelphia, PA 19119

Victoria P. Werth, MD[Professor]

Department of Dermatology, University of Pennsylvania, 2 Rhodes Pavilion, 3600 Spruce St, Philadelphia, PA 19119, Phone: 215-823-4298, Fax: 215-573-2143

Evan W. Piette: epiette@mail.med.upenn.edu; Victoria P. Werth: werth@mail.med.upenn.edu

Synopsis

Dapsone is occasionally used in the treatment of the autoimmune bullous diseases, a group of disorders resulting from autoimmunity directed against basement membrane and/or intercellular adhesion molecules on cutaneous and mucosal surfaces. This review will summarize the limited published data evaluating dapsone as a therapy for the AIBD.

Keywords

Dapsone; autoimmune bullous disease; review

Introduction

Dapsone is a sulfone-derived medication that was first used in humans to treat leprosy in the 1940s.¹ Since then, it has been used as an antimicrobial agent and has been found to have anti-inflammatory properties. It is used in a number of dermatologic conditions, particularly those with neutrophil predominance as it inhibits neutrophil activation and recruitment through a number of different pathways.¹ Dapsone has also been used in the treatment of the autoimmune bullous diseases (AIBD), a group of disorders resulting from autoimmunity directed against basement membrane and/or intercellular adhesion molecules on cutaneous and mucosal surfaces.² This review will summarize the published data evaluating dapsone as a therapy for the AIBD. Common adverse effects of this medication include methemoglobinemia and anemia, particularly in patients who are G6PD deficient. There are also a number of additional rare adverse effects associated with dapsone use, most notably agranulocytosis and a hypersensitivity reaction known as the “dapsone-syndrome.”^{1, 2}

Pemphigus

Pemphigus is an antibody mediated blistering disease that primarily affects the elderly and is associated with high morbidity and, when untreated, mortality. Two subtypes of pemphigus

Correspondence to: Victoria P. Werth, werth@mail.med.upenn.edu.

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will reviewed here, pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Immunosuppressives are the mainstay of treatment for PV, and dapsone was first reported as an adjunct to therapy in the 1960s.³ There has been one randomized, double blind, placebo controlled trial evaluating the use of dapsone for PV.^{4, 5} In this study by Werth *et al*, 19 patients receiving systemic immunosuppressive therapy for PV were randomized to two groups treated with the addition of either dapsone or placebo. Success was defined by the ability to taper systemic glucocorticoids to at least 7.5 mg/d within one year of reaching the maximum dose of dapsone (200 mg/d). Of the 9 patients receiving dapsone, 5 (56%) were successfully treated, 3 failed treatment, and 1 dropped out of the study. Of the 10 patients receiving placebo, 3 (30%) were successfully treated, and 7 failed treatment. Though the difference between groups was not significant ($p = 0.37$), the trend favored the dapsone treated group. Additionally, four patients in the placebo group failed treatment and were switched to treatment with dapsone. Of these, 3 (75%) were successfully treated after initiating dapsone. Overall, 8 of 11 patients (73%) receiving dapsone versus 3 of 10 (30%) receiving placebo reached the primary outcome measure of 7.5 mg/d or less of prednisone. No adverse events requiring the discontinuation of dapsone were noted.⁴

The remaining published data on dapsone for pemphigus stems from case reports and series, nicely summarized in a 2009 review by Gürcan *et al*.⁶ In their review, the authors found 12 reports, in addition to the Werth *et al* trial discussed above, describing an additional 26 patients who received dapsone for treatment of their PV. In these additional cases, at dosages varying between 50 and 200 mg/day, 24 of the 26 (92%) patients responded to dapsone alone or in addition to other systemic immunomodulators.⁶ In 16 of these reported cases, dapsone was added to prednisone presumably as a steroid sparing agent, though this was not explicitly stated in every paper. In 10 of these 16 patients (63%), prednisone doses were reduced after initiation of dapsone. In 6 of 16 patients (38%), prednisone dosages could not be decreased due to either continued disease or adverse events associated with dapsone. Overall, dapsone was discontinued due to adverse effects in only 4 of the 26 (15%) patients; three secondary to hemolysis and one secondary to dapsone-syndrome.⁶

Pemphigus foliaceus (PF) causes disease similar to PV, with the key clinical difference being that mucosal surfaces are spared in PF. Of the ten published reports summarized by Gürcan *et al*, nine are reports of its use in only a single patient.⁶ Basset *et al* reported nine additional PF patients treated with dapsone in a case series published in 1987.⁷ Of the 18 total reported patients in the literature, 14 (78%) responded to dapsone at doses of 25 to 300 mg/d alone or in combination with systemic prednisone.⁶ Six of the 18 patients had adverse events (33%), and two (11%) required discontinuation of dapsone therapy (one patient due to peripheral neuropathy, and the second patient because of dapsone induced hypersensitivity).⁶

Pemphigoid

Bullous pemphigoid (BP) affects both mucosal and cutaneous surfaces. In contrast to PV, BP may remit spontaneously and can often be treated with lower doses of immunosuppressives.² A Cochrane review published in 2010 did not identify any randomized controlled trials evaluating dapsone as a therapy for BP.⁸ The 2009 review by Gürcan *et al* summarized the available case series, and concluded that there are at least six published studies encompassing 170 patients with BP who received dapsone.⁶ 139 (81%) of these patients showed clinical improvement with 50 to 300 mg/d of dapsone alone, or in combination with immunosuppressives. 63 (37%) developed adverse effects and nine (5%) required discontinuation of the drug.⁶

Mucous membrane pemphigoid (MMP) differs from BP in that it is limited to mucosal surfaces. A randomized, double-blind, non-placebo controlled trial published in 1986 compared 40 patients with ocular MMP treated for 6 months with either dapsone (2 mg/kg/day) or cyclophosphamide (2 mg/kg/day).^{9, 10} Cyclophosphamide was found to be superior to dapsone in this group of patients, as 20/20 (100%) responded to cyclophosphamide versus 14/20 (70%) in the dapsone group.^{9, 10} The remaining data investigating dapsone for MMP are from non-randomized studies and reports. In the Gürcan review, six additional publications encompassing 182 patients with MMP treated with dapsone are discussed.⁶ Of the 182 patients, 156 (86%) showed improvement with dapsone therapy. 20 patients (11%) developed adverse effects that required discontinuation of dapsone.⁶

Bullous lupus erythematosus

Bullous lupus erythematosus is a subtype of acute cutaneous lupus erythematosus (ACLE) characterized by subepidermal vesiculobullous skin lesions. Dapsone is occasionally used as an adjunctive treatment for CLE, and is thought to be particularly useful in patients with bullous disease.¹¹ However, there is a dearth of studies in the literature evaluating its use and published data are largely anecdotal. There are at least 19 bullous ACLE patients reported in 12 case reports and series, and 17/19 (89%) showed improvement of their bullous lesions within days to weeks of initiation of 50 to 100 mg/d of dapsone therapy.^{12–23} One of the two patients reported as a non-responder had progression of disease after a week of dapsone 50 mg/day, but developed abnormal liver enzymes when the dose was increased to 100 mg/day requiring discontinuation of therapy.¹⁸ As such, it is difficult to determine whether dapsone may have been effective in this patient at a higher dose. Out of the 17 patients reported as improving with dapsone, at least 8 (42%) had failed systemic glucocorticoid therapy, which prompted the addition of dapsone.^{12, 15, 16, 21, 23}

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is an autoimmune blistering disease characterized by IgG autoantibodies that target type VII collagen. It is a rare disease without sex or racial predilection, and has a prevalence of approximately 0.2/million people.²⁴ EBA is a notoriously difficult disease to treat, and typically requires therapy with glucocorticoids and additional immunosuppressives such as methotrexate, mycophenolate, or azathioprine.²⁴ Dapsone is occasionally used as an adjunctive treatment, though similar to bullous ACLE, published reports regarding its effectiveness in adults are sparse.¹⁰ Hughes and Callen reported a patient who responded to dapsone 150 mg/day after failing treatment with niacinamide, tetracycline, and systemic prednisone.²⁵ Two single-patient case reports note improvement with the use of dapsone in combination with systemic steroids.^{26, 27} A report published out of Vienna in 1988 noted improvement with dapsone and corticosteroids in two of three patients,²⁸ and a German study from 1994 reported a patient successfully treated with colchicine after failing to respond to dapsone.²⁹ Cunningham *et al* reported a patient partially treated with colchicine who showed complete improvement after the addition of dapsone 50 mg/day.³⁰ Overall, 6 of the 8 (75%) reported EBA patients treated with dapsone responded to the medication.

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is an inflammatory skin condition associated with celiac disease. It is primarily a disease of Caucasians, with a multifactorial etiology involving both genetics and environmental triggers.³¹ Due to the association with celiac disease, the definitive treatment of DH is a gluten free diet,³² with pharmacological therapy used as an adjunct until the diet becomes effective. Dapsone has long been used as the first line therapy in this capacity.^{31, 33, 34} Like most of the blistering diseases discussed in this review,

randomized controlled trials evaluating the efficacy of dapsone in DH are lacking, and currently published data are limited to small case series.^{33–35} Nonetheless, there is strong expert consensus that dapsone is highly efficacious for the treatment of DH, and it remains the only medication approved by the Food and Drug Administration for use in this disease.^{31, 36}

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is an immunobullous disease that has been recognized as a unique entity since the 1980s.³⁷ Classically, LABD has features similar to BP and DH, and can be distinguished by linear IgA deposition on direct immunofluorescence. Dapsone is regarded as the first line therapy for LABD, but as with dermatitis herpetiformis, the evidence in adults is largely based on small case reports, case series, and anecdotal evidence.^{37–41} Treatment is generally started at low doses, and is slowly titrated to a maintenance dose of 100–200 mg/day in adults.^{37, 41}

Conclusions

While dapsone is regularly used in the treatment of the AIBD, large studies evaluating its effectiveness and safety are lacking. Smaller studies and isolated reports do indicate that dapsone is effective, but in order to truly determine the benefits and risks of using this medication larger studies are needed. The best data available seems to be in MMP and PV, as evidence from RCTs have been published. Additionally, there seems to be wide consensus that dapsone should be first-line pharmacological therapy for DH and LABD. When used, the lowest effective dose should be prescribed up to a maximum of 200 mg/day, though doses up to 300 mg/d have been reported.⁶ Prior to initiation of dapsone therapy, patients should be screened for glucose-6-phosphate dehydrogenase deficiency, as patients with decreased activity of this enzyme show an approximately two-fold increased sensitivity toward development of hemolysis.¹ Additionally, a complete blood count with reticulocyte count should be checked weekly during the initial titration of dapsone dose, then every two weeks for the first three months, then every three months after that for the development of hemolytic anemia and agranulocytosis. Liver enzymes, electrolytes, and urinalysis should also be monitored when using dapsone. Peripheral neuropathy, while rare, is a well described adverse effect of dapsone, and periodic screening for both motor and sensory neuropathy is warranted.¹

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