Dapsone in the Management of Autoimmune Bullous Diseases

Evan W. Piette, MD[a], Victoria P. Werth, MD[a,b,*]

KEYWORDS

• Dapsone • Autoimmune bullous disease • Review

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 antiinflammatory properties. Dapsone is used in several dermatologic conditions, particularly those with neutrophil predominance because it inhibits neutrophil activation and recruitment through several 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 summarizes the published data evaluating dapsone as a therapy for AIBD. Common adverse effects of this medication include methemoglobinemia and anemia, particularly in patients who are glucose-6-phosphate dehydrogenase deficient. There are also several additional rare adverse effects associated with dapsone use, 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 are reviewed here: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Immunosuppressives are the mainstay of treatment of PV, and dapsone was first reported as an adjunct to therapy in the 1960s.[3] There has been 1 randomized, double-blind, placebo-controlled trial evaluating the use of dapsone for PV.[4,5] In this study by Werth and colleagues,[4] 19 patients receiving systemic immunosuppressive therapy for PV were randomized to 2 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 1 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. Although the difference between groups was not significant ($P = .37$), the trend favored the dapsone-treated group. In addition, 4 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 stem from case reports and series,

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[a] Department of Dermatology, Perelman Center for Advanced Medicine, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA

[b] Division of Dermatology, Philadelphia V.A. Medical Center, Philadelphia, PA, USA

* Corresponding author. Department of Dermatology, Perelman Center for Advanced Medicine, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104.

E-mail address: werth@mail.med.upenn.edu

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nicely summarized in a 2009 review by Gürcan and Ahmed.[6] In their review, the investigators found 12 reports, in addition to the trial by Werth and colleagues[4] discussed earlier, describing an additional 26 patients who received dapsone for treatment of their PV.[6] In these additional cases, at dosages varying between 50 and 200 mg/d, 24 of the 26 (92%) patients responded to dapsone alone or in addition to other systemic immunomodulators. In 16 of these reported cases, dapsone was added to prednisone presumably as a steroid-sparing agent, although this was not explicitly stated in every study. 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 because of either continued disease or adverse events associated with dapsone. Overall, dapsone was discontinued because of adverse effects in only 4 of the 26 (15%) patients, 3 secondary to hemolysis and 1 secondary to dapsone syndrome.[6]

PF causes disease similar to PV, with the key clinical difference being that mucosal surfaces are spared in PF. Of the 10 published reports summarized by Gürcan and colleagues,[6] 9 are reports of dapsone use in only a single patient. Basset and colleagues[7] reported 9 additional patients with PF treated with dapsone in a case series published in 1987. Of the total 18 patients reported in the literature, 14 (78%) responded to dapsone at doses of 25 to 300 mg/d alone or in combination with systemic prednisone.[6] Of the 18 patients, 6 had adverse events (33%) and 2 (11%) required discontinuation of dapsone therapy (one patient because of peripheral neuropathy and the other 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 and Ahmed[6] summarized the available case series and concluded that there are at least 6 published studies encompassing 170 patients with BP who received dapsone. Of these patients, 139 (81%) showed clinical improvement with 50 to 300 mg/d of dapsone alone or in combination with immunosuppressives. Adverse effects developed in 63 patients (37%), and 9 (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/d) or cyclophosphamide (2 mg/kg/d).[9,10] Cyclophosphamide was found to be superior to dapsone in this group of patients because all 20 patients (100%) treated with cyclophosphamide responded to the drug compared with 14 of 20 (70%) in the dapsone group.[9,10] The remaining data investigating dapsone for MMP are from nonrandomized studies and reports. In the Gürcan review, 6 additional publications encompassing 182 patients with MMP treated with dapsone are discussed.[6] Of the 182 patients, 156 (86%) showed improvement with dapsone therapy. Twenty 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 of cutaneous lupus erythematosus 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 patients with bullous ACLE reported in 12 case reports and series, and 17 (89%) showed improvement in their bullous lesions within days to weeks of initiation of 50 to 100 mg/d of dapsone therapy.[12–23] One of the 2 patients reported as a nonresponder had progression of disease after a week of dapsone 50 mg/d, but developed abnormal liver enzymes when the dose was increased to 100 mg/d requiring discontinuation of therapy.[18] Thus, it is difficult to determine whether dapsone may have been effective in this patient at a higher dose. 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 ACQUISTA

Epidermolysis bullosa acquista (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 per million people.[24] EBA is a notoriously difficult disease to treat and typically requires therapy