REVIEW ARTICLE

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Efficacy of Dapsone in the Treatment of Pemphigus and Pemphigoid

Analysis of Current Data

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Abstract

Dapsone is a chemotherapeutic agent primarily used in treating leprosy, *Pneumocystis jiroveci* (previously *carinii*) pneumonia, and malaria. It is also used as an adjuvant in the treatment of pemphigus and pemphigoid. To assess the role of dapsone in the treatment of pemphigus and pemphigoid, a retrospective review of reports in the English-language literature was conducted. Information on the number of patients treated, their average age, prior therapies, indications for use, protocol (dose and interval) used, concomitant therapies, reported adverse effects, and clinical outcomes were analyzed.

There were 35 case reports/series published describing the use of dapsone in a total of 427 patients. Data on 55 pemphigus patients were obtained from several case reports and some case series and one randomized controlled trial. Of these, 32 patients with pemphigus vulgaris and 14 patients with pemphigus foliaceus responded to dapsone. Data from 13 case series, each including at least five patients, accounted for 372 patients with pemphigoid. The overall response rates to dapsone, when given either alone or in combination with corticosteroids or immunosuppressive agents, were 84% in mucous membrane pemphigoid, and 81% in bullous pemphigoid. Hemolysis was the most common adverse effect observed.

Dapsone is a promising and useful agent in patients with autoimmune mucocutaneous blistering diseases, especially in mucous membrane pemphigoid. It can be used as a corticosteroid-sparing agent. Therefore, its combined use with oral corticosteroids may be useful in pemphigus vulgaris and bullous pemphigoid. Adverse effects of dapsone are dose dependent and usually reversible. Hemolysis and concomitant anemia secondary to hemolysis are expected in most patients. In the opinion of the authors, dapsone is underutilized in the treatment of autoimmune mucocutaneous blistering diseases.

Dapsone is a chemotherapeutic agent primarily used in treating leprosy, *Pneumocystis jiroveci* (previously *carinii*) pneumonia, and malaria.[1] In addition to its antimicrobial effects, it is used as an anti-inflammatory agent in the treatment of several other conditions. It is the drug of choice in dermatitis herpetiformis, with a response rate of 95–97%. It has been used

in many other dermatologic diseases, including pemphigus and pemphigoid.[2]

Pemphigus and pemphigoid are rare autoimmune diseases that have certain common features and are considered potentially fatal. They involve the skin and frequently one or more mucous membranes. The immunopathology of these diseases is well characterized and the target antigens to which the autoantibodies are directed have been studied. Pemphigus is caused by autoantibodies directed against desmogleins. Pemphigoid is caused by autoantibodies directed against several epidermal basement membrane zone proteins. The clinical presentation is highly variable, as is the course and prognosis. The majority of patients respond to conventional therapy, which consists of high-dose systemic corticosteroids and immunosuppressive agents. Patients who are not responsive to conventional immunosuppressive therapy, or in whom it is contraindicated, are treated with intravenous immunoglobulin.[3] Rituximab is another biologic agent that has been recently used.[4] There is evidence in the literature suggesting that patients who have prolonged immunosuppression secondary to corticosteroids, immunosuppressants, and rituximab can die from opportunistic infections.[5,6] Therefore, there is a clear and distinct need to produce less immunosuppression when treating patients with pemphigus and pemphigoid, by the discovery of new drugs and biologic agents, or the use of currently available drugs.

This review is a retrospective analysis of the available literature with the purposes of evaluating (i) the efficacy of dapsone, and (ii) its possible role in drug management strategies for patients with pemphigus and pemphigoid.

1. Materials and Methods

A retrospective review of the English-language literature was conducted for reports on the use of dapsone in the treatment of pemphigus and pemphigoid. PubMed was searched using the following keywords: 'dapsone' and 'pemphigus' or 'pemphigoid.' The search was conducted in January 2008. Thirty-five reports published between October 1969 and August 2008 describing its use in 427 patients were analyzed.

There were 23 case reports/series identified for pemphigus. The studies on pemphigus included in this analysis were based on the following inclusion criteria: (i) English language; (ii) diagnosis based on histology and immunopathology; and (iii) data for efficacy provided. There were 13 case series available for pemphigoid. The clinical studies/reports on pemphigoid included in this analysis were based on the following inclusion criteria: (i) English language; (ii) diagnosis based on histology and immunopathology; (iii) minimum of five patients in each series; and (iii) data for efficacy provided. Since there were fewer patients with pemphigus, case studies were included. However, in pemphigoid, the abundance of patients treated required our limiting the data to series with five patients or more.

The data provided in these 35 reports were critically analyzed to determine what conclusions, if any, could be made. The data from each of these reports is presented under the following categories: numbers of patients treated, average age, prior systemic therapies, indications for use, protocol (dose and interval) used, concomitant systemic therapies, reported adverse effects, and clinical outcomes. Control of disease was defined as having no new lesions and achieving healing of existing lesions.

2. Results

2.1 Pemphigus Vulgaris

The data for patients with pemphigus vulgaris are presented in table I. There were 37 patients in 13 reports who were treated with dapsone.[7-19] Dapsone was used as monotherapy in six (16%) patients.[7,10-12] All six patients had a clinical response that resulted in clinical remission with a dosage of 100–200 mg/day. Nonetheless, all six were receiving maintenance therapy at the time of reporting.

In 16 (43%) patients, dapsone in dosages of 50–200 mg/day was added to prednisone.[8,9,11,14-16,18] In three patients, prednisone was discontinued; in seven patients, the dose of prednisone prior to initiation of dapsone was reduced. It was not possible to reduce prednisone dose in three patients. In a further three patients, addition of dapsone improved symptoms but had to be discontinued or replaced with immunosuppressants because of adverse effects.

In 15 (41%) patients, dapsone was used in combination with prednisone and immunosuppressants.[13,17,19] Of these, 11 patients had a clinical response. In one patient, dapsone had to be discontinued because of adverse effects. Three of these 11 patients did not meet the criteria for response to dapsone specified in the randomized controlled trial.[19]

Overall, 32 of 37 (86%) patients responded to dapsone at dosages varying between 50 and 200 mg/day when used either alone or in combination with prednisone and/or immunosuppressants. Five (14%) patients did not respond. A total of nine (24%) patients developed adverse effects. However, dapsone was discontinued in only four (11%) of these patients.[7-18]

Table I. Data on patients (pt[s]) with pemphigus vulgaris (PV) treated with dapsone (Dap)

Case reports/series	No. of pts	Age; y (sex)	Previous systemic Rx	Indications for Dap	Dosage of Dap, mg/d (max)	Duration of Dap Rx	Concomitant systemic Rx	Adverse effects of Dap (no. of pts)	Clinical outcome
DeMento and Grover[7]	1	45 (F)	None	DH + PV	200	14 mo	None	NR	Control of disease within 1 wk, pt asymptomatic at 14 mo with maintenance Rx
Piamphongsant[8]	1	28 (M)	Pred	Infection and post-surgical	100	7 mo	Pred	NR	Control of disease, no active lesions at 7 mo with maintenance Rx
Haim and Friedman-Birnbaum[9]	2	35 (M)	Pred + Mtx	Previous Rx ineffective	100	4 mo	Pred	NR	Completely clear of symptoms after 1 wk, able to taper Pred, in remission at 4 wk follow-up
		29 (F)	Pred + Mtx	Previous Rx ineffective	100	1 mo	Pred	NR	Marked improvement of symptoms after initiation of Dap, able to taper Pred, pt discharged free of symptoms after 1 mo of Rx
Pearson et al.[10]	3	45 (F)	Pred	Relapse at tapering	100	NR	None	NR	Lesions controlled within 3 wk, control of disease with maintenance Rx
		57 (M)	Pred + gold	Previous Rx ineffective	200	NR	None	NR	Disease initially cleared, failure after lowering dose, controlled by maintenance Rx
		59 (F)	Pred	Previous Rx ineffective	100	NR	None	NR	No new lesions at 1 wk, control of disease with maintenance Rx
Ahmed and Salm[11]	2	16 (F)	Pred	Previous Rx ineffective	200	NR	Pred	Hemolysis	Pt stopped developing new blisters, able to taper Pred, Dap discontinued due to hemolysis, no relapse on Pred maintenance Rx
		17 (M)	Pred + Dap	Previous Rx ineffective	200	NR	None	NR	Pred was gradually tapered, disease controlled with maintenance Rx
Rodan et al.[12]	1	NR	None	PV	200	NR	None	NR	Skin clearing achieved in 4 wk
Ahmed and Hombal[13]	3	23 (F)	Pred + Aza + gold	Previous Rx ineffective	200	11 mo	Pred + Cyc	NR	Improvement at 2 mo, pt off Dap at 11 mo, disease free on maintenance Rx with Cyc

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Table I. Contd

Case reports/series	No. of pts	Age; y (sex)	Previous systemic Rx	Indications for Dap	Dosage of Dap, mg/d (max)	Duration of Dap Rx	Concomitant systemic Rx	Adverse effects of Dap (no. of pts)	Clinical outcome
		33 (M)	Pred + Aza	Previous Rx ineffective	100	7 mo	Pred + Cyc	NR	Pt off Dap at 7 mo, off all systemic Rx at 11 mo, disease free at 20 mo follow-up
		70 (M)	Pred	Previous Rx ineffective	100	5 mo	Pred + Cyc + Aza	Hemolysis	Skin lesions decreased, Dap discontinued at 5 mo due to hemolysis
Barnard et al.[14]	1	66 (M)	None	PV	200	3 wk	Pred	Sulfone syndrome	Oral lesions improved, Dap discontinued due to sulfone syndrome, Rx continued with Pred
Bjarnason et al.[15]	1	5 (M)	None	PV	100	30 mo	Pred	NR	All lesions disappeared in 3 wk. Pt in remission 19 mo after discontinuation of systemic Rx
Tan and Tay[16]	1	60 (M)	None	PV	100	6 mo	Pred	NR	Improvement within 3 d, able to taper Pred, control of disease with maintenance Rx at 6 mo follow-up
Chiang et al.[17]	1	54 (F)	Pred	Previous Rx ineffective	100	NR	Pred, IV Pred, Aza, Mycp	Hemolysis	Pt improved, Dap discontinued due to hemolysis, Rx continued with Aza
Heaphy et al.[18]	9	Mean 58 [range 42–72]	Pred + ISA	Previous Rx ineffective/ corticosteroid dependent	50–150	8 mo	Pred	Hemolysis (3)	67% decrease at 4 mo, 84% decrease at 8 mo in Pred doses in 5 pts Pred discontinued in 2 pts Unable to taper Pred in 2 pts
Werth et al.[19]	11	Mean 44 [range 19–64]	Pred + ISA	Attempt to reduce dose of Pred during maintenance phase of Rx	50–200	119 d	Pred + ISA	Methmg (1) Paresthesias (1)	Pred dose lowered to <7.5 mg/d in 8 of 11 pts (73%) receiving Dap Response to Dap ranged from 44.4% (strict ITT), to 71.4% (per protocol, no crossover) to 72.7% (per protocol analysis including pts who switched groups)

Aza = azathioprine; **Cyc** = cyclophosphamide; **DH** = dermatitis herpetiformis; **F** = female; **ISA** = immunosuppressive agent; **ITT** = intent-to-treat; **IV** = intravenous; **M** = male; **max** = maximum; **Methmg** = methemoglobinemia; **Mtx** = methotrexate; **Mycp** = mycophenolate mofetil; **NR** = not reported; **Pred** = prednisone; **Rx** = therapy.

2.2 Pemphigus Foliaceus

The data for patients with pemphigus foliaceus are presented in table II. There were 18 patients with pemphigus foliaceus reported to be treated with dapsone.[8,20-28] Dapsone was used as monotherapy in 14 (78%) patients.[8,20-23,26] Of these, nine patients had a clinical response that resulted in clinical remission with a dosage of 100–300 mg/day. Two of these patients continued to remain in remission after the discontinuation of dapsone, while seven required maintenance therapy at the time of reporting. One patient initially responded, but dapsone was discontinued because of adverse effects. Four of 14 patients did not respond.

Dapsone was given with prednisone in the remaining four (22%) patients, resulting in clinical remission with a dosage of 25–75 mg/day.[24,25,27,28] Two patients had remission after discontinuation of dapsone, and two required maintenance therapy. In three patients, use of dapsone resulted in discontinuation of prednisone. In one patient, use of dapsone allowed the tapering of prednisone; however, dapsone had to be discontinued because of adverse effects.

Overall, 14 of 18 (78%) patients responded to dapsone when given at dosages between 25 and 300 mg/day, alone or in combination with prednisone. Four (22%) patients did not respond. A total of six (33%) patients developed adverse effects, and in two (11%) patients, dapsone had to be discontinued.[8,20-28]

2.3 Mucous Membrane Pemphigoid

The data for patients with mucous membrane pemphigoid (MMP) are presented in table III. There are at least 202 MMP patients in seven reports who were treated with dapsone.[29-35] Dapsone was used as monotherapy in 91 patients and in combination with corticosteroids and/or immunosuppressants in 111 patients. Dapsone alone or in combination with corticosteroids and/or immunosuppressants was the initial treatment choice in 187 of 202 patients. Overall, 170 (84%) of 202 patients showed clinical improvement with dapsone when given at dosages between 25 and 200 mg/day. Thirty-two patients did not respond, providing a failure rate of 16%. A total of 76 (37%) patients developed adverse effects, but discontinuation was warranted in only 20 (10%) patients.[29-35]

In the largest series, dapsone as initial therapy controlled disease and inhibited progression in 31 of 69 patients.[33] The addition or substitution of cyclophosphamide or addition of azathioprine provided control of disease in an additional 29 patients. Thus, 60 of 69 patients had their disease controlled with dapsone alone or in combination with cyclophosphamide or azathioprine. In the same study, it was reported that 10 of 11 MMP patients who had not responded to initial use of cyclophosphamide/azathioprine had their disease controlled when dapsone was added.[33]

2.4 Bullous Pemphigoid

The data for patients with bullous pemphigoid are presented in table IV. There are at least 170 bullous pemphigoid patients who were treated with dapsone reported in six studies.[36-41] Dapsone was used in combination with corticosteroids and/or immunosuppressants in 88 patients and as monotherapy in 82 patients. Dapsone alone or in combination with corticosteroids and/or immunosuppressants was the initial treatment choice in 142 of 170 patients. Overall, 139 of 170 (81%) patients showed clinical improvement when dapsone was given at varying dosages of 50–300 mg/day. 31 (18%) patients did not respond to dapsone. A total of 63 (37%) patients developed adverse effects, but dapsone was discontinued in only nine (5%) patients.[36-41]

In the largest series with 62 patients, dapsone was given at a dosage of 1–1.5 mg/kg/day in combination with methylprednisolone and topical corticosteroids. At 6 months, 100% of patients demonstrated clearing of all skin lesions. At 3 months, 20% of the patients had discontinued systemic therapy; at 6 months, 30%; and at 12 months, 53% of the 62 patients had discontinued systemic therapy. Unfortunately, follow-up of patients receiving systemic therapy beyond 12 months was not provided.[41] Since the patients received combination therapy, the contribution of each of the two drugs to the induction and sustained clinical remission cannot be determined.

3. Discussion

The lack of randomized controlled trials to evaluate the efficacy of dapsone in the treatment of pemphigus or pemphigoid is a limitation of the available data. The rarity and the potential fatality of these diseases may be some of the many reasons why studies that provide definitive objective and comparative data are largely unavailable. Analysis of the data in this review would indicate that, among several drugs used to treat patients with pemphigus and pemphigoid, dapsone is a useful agent in certain patients and under certain circumstances.

In MMP, the overall response rate to dapsone when used either alone or in combination with corticosteroids or immunosuppressants was 84%. The clinical response was seen as early as 2 weeks in many patients. Ocular lesions require longer to demonstrate maximal benefit, while gingival lesions respond more rapidly.[29] Patients with localized mucosal disease activity

Table II. Data on patients (pt[s]) with pemphigus foliaceus (PF) treated with dapsone (Dap)

Case reports/series	No. of pts	Age; y (sex)	Previous systemic Rx	Indications for Dap	Dosage of Dap, mg/d (max)	Duration of Dap Rx	Concomitant systemic Rx	Adverse effects of Dap (no. of pts)	Clinical outcome
Connor[20]	1	58 (M)	None	Topical therapy ineffective	100	3 y	None	NR	Marked clearing of lesions in 1 wk, controlled with maintenance Rx for 3 y
Piamphongsant[8]	1	30 (M)	None	PF	100	2 wk	None	NR	Response in 2 wk, Dap gradually tapered, no new lesions
Basset et al.[21]	9	Mean 53 [range 28–82]	None	PF/PE	200–300	22 mo	None	Anemia and toxic hepatitis (1) Methmg (2)	5 of 9 pts responded to Rx in 2 wks: 1 pt off all Rx and in remission, 4 pts on maintenance Rx 4 of 9 pts did not respond; Rx continued with Pred and/or Cyc
Leibowitz and Voss[22]	1	12 (F)	None	Topical therapy ineffective	100	6 wk	None	NR	Improved at 2 wk, off Rx at 6 wk, disease free at 12 mo follow-up
Rhodes et al.[23]	1	35 (F)	None	Topical therapy ineffective	200	4 wk	None	Peripheral neuropathy	Good response in 1 wk, failed to taper dose. Dap discontinued at 4 wk due to peripheral neuropathy; Rx continued with topical CS
Galambrun et al.[24]	1	8 (M)	Pred	Failed Pred tapering/ adverse effects of Rx	25–50	NR	Pred	Methmg	Complete remission in 4 wk, Pred withdrawn, Dap withdrawn at 9 mo, disease free off all Rx after another 9 mo follow-up
Mehravaran et al.[25]	1	7 (F)	Pred	Inadequate response to previous Rx	25	3 y	Pred	NR	Rapid improvement in a few days, complete recovery in 1 mo, Pred withdrawn, in remission with maintenance Rx for 3 y
Cianchini et al.[26]	1	70 (F)	None	PF	100	6 mo	None	NR	Complete clearing of lesions at 8 wk, controlled with maintenance Rx, clinical condition stable at 6 mo
Khachemoune et al.[27]	1	58 (F)	Pred	Previous Rx ineffective	50	6 mo	Pred	NR	Pt improved and Dap discontinued at 6 mo, Pred discontinued at 18 mo, disease free at 3 mo follow-up
Takahashi et al.[28]	1	37 (M)	Pred	Previous Rx ineffective	75	1 mo	Pred	Dap-induced hypersensitivity	Pt improved, Pred tapered by 33% at 1 mo, Dap discontinued at 1 mo due to Dap-induced hypersensitivity

CS = corticosteroids; **Cyc** = cyclophosphamide; **F** = female; **M** = male; **max** = maximum; **Methmg** = methemoglobinemia; **NR** = not reported; **PE** = pemphigus erythematosus; **Pred** = prednisone; **Rx** = therapy.

are more responsive to dapsone.[30] Dapsone is the most effective agent for modestly active ocular cicatricial pemphigoid (OCP) when compared with cyclophosphamide and azathioprine.[33] Dapsone is recommended as the initial drug of choice for patients with MMP who have mild to moderate disease that is not rapidly progressive.[30,31,33,34] Serious adverse effects usually occurred when the dosage exceeded 100 mg/day.[31,34,35] In one study, when dapsone was given at 25–75 mg/day for 3 months, no anemia was reported.[32] Dr Rogers[42] has reported on his experience of treating 129 patients with MMP at the Mayo Clinic (Rochester, MN, USA). His observations indicate that dapsone is valuable in mild or localized MMP as the drug of first choice. In patients with extensive or rapidly progressive disease, it can be a valuable adjuvant to corticosteroids, with or without immunosuppressants.[42]

In patients with bullous pemphigoid, the overall response rate to dapsone was 81% when given either alone or in combination with corticosteroids or immunosuppressants. Dapsone was less effective as monotherapy than when combined with topical corticosteroids.[39] It is recommended that in widespread, recurrent, recalcitrant bullous pemphigoid, when adequate control is not achieved with prednisone and azathioprine, before increasing the prednisone dose, a brief course of dapsone be included in the overall treatment strategy.[38] The effectiveness of dapsone when combined with oral prednisone alone or with azathioprine was 92% in one study.[38] In a more recent study of 62 patients, the combination of dapsone and oral methylprednisolone achieved control of disease in 100% of patients.[41] Patients who respond to a sulfone will also respond to sulfonamides. A trial of dapsone therapy prior to resorting to corticosteroids is recommended, especially if there is a preexisting contraindication to corticosteroids.[37] All of the nonresponders and partial responders in the study by Venning et al.[37] were subsequently controlled relatively easily with prednisone alone or in combination with dapsone or azathioprine. Among patients <60 years of age, those who were middle aged and had pure vesicular, vesiculobullous or mixed bullous disease responded well to dapsone.[36] However, in two other studies, this was not confirmed.[37,39] Adverse effects were reversible when dapsone was stopped.[40]

The analysis of the data demonstrated that 32 of 37 (86%) patients with pemphigus vulgaris[7-19] and 14 of 18 (78%) patients with pemphigus foliaceus[8,20-28] responded to dapsone. In most of these reports, dapsone was used as an adjuvant because of inadequate responses or contraindications to corticosteroids and immunosuppressants.[8,9,11-18,23-28] It has been demonstrated that the addition of dapsone decreases the dose of corticosteroid required to control the disease.[18,19,24,28] Similarly, use of dapsone allows a safer taper of prednisone, reducing the possibility of recurrence. Recently, a randomized controlled trial was conducted by Werth et al.[19] The 19 patients in this study were in the maintenance phase of their treatment and therefore did not have acute disease. All the patients continued to receive immunosuppressive therapies during the entire trial. The purpose of the trial was to determine if the use of dapsone facilitated the reduction of oral prednisone, compared with placebo. Not surprisingly, patients in the placebo group improved, because they were still being treated with immunosuppressive agents. The statistical analysis did not demonstrate a clear superiority of dapsone over placebo, but there was a definite trend to efficacy of dapsone as a corticosteroid-sparing agent in the maintenance phase of pemphigus vulgaris.[19]

Dapsone acts against microorganisms by inhibiting the synthesis of dihydrofolic acid through competition with para-aminobenzoate for the active site of dihydropteroate synthetase.[43] Dapsone has an outstanding therapeutic efficacy against many skin diseases characterized by neutrophil-rich infiltrates. Inflammatory diseases that respond to dapsone are almost invariably associated with the infiltration of large numbers of polymorphonuclear leukocytes into the affected tissues.[1] Dapsone has been shown to suppress human neutrophil migration.[44-51] A more recent study has shown that the anti-inflammatory action of dapsone is via inhibition of calcium-dependent functions of neutrophils, including release of tissue-damaging oxidants and proteases in the affected skin.[52] Dapsone also reduces the release of prostaglandins and leukotrienes, and blocks their inflammatory effects.[53-58] In antibody-mediated diseases such as pemphigus vulgaris, pemphigus foliaceus, MMP and bullous pemphigoid, very little is known about the mechanism of action of dapsone. In one study, it has been shown that dapsone inhibits neutrophil adherence to pathogenic IgG in bullous pemphigoid and to IgA in patients with IgA dermatoses in a dose-response manner.[59] It also inhibits the bullous pemphigoid IgG-induced interleukin-8 release from cultured normal human epidermal keratinocytes by mechanisms that act at the post-transcriptional level.[60]

3.1 Adverse Effects

Adverse effects were observed in 24–37% of the patients in this analysis. However, in only 5–11% of patients, were their consequences serious enough to require discontinuation of the drug. The overall incidence of adverse effects appears to be unusually high. However, the adverse effects associated with prolonged administration of the high doses of corticosteroids that

Table III. Data on patients (pt[s]) with mucous membrane pemphigoid (MMP) treated with dapsone (Dap)

Case series	No. of pts	Mean age; y (range)	Previous systemic Rx (no. of pts)	Indications for Dap	Dosage of Dap	Duration of Dap/follow-up period	Concomitant systemic Rx	Adverse effects of Dap (no. of pts)	Clinical outcome
Rogers et al.[29]	24	60 (28–79)	Pred (4) Pred + Aza (4) Sul (3) Pred + Cyc (1) Dap (1) Aza (1) None (10)	Inadequate response to previous Rx Adverse effects of systemic Rx OCP/OP/MMP	75–200 mg/d	NR	Gradually discontinued in 4 pts	Hemolysis (7) Rash (2)	20 of 24 pts had mild to no inflammatory activity after 2–12 wks' Rx 16 pts required maintenance Rx 2 pts went into prolonged remission, 1 recurred at 1.5 y, treated with Pred + Aza 4 pts had no beneficial effect, responded to Pred + Aza Dap discontinued in 4 pts due to adverse effects
Rogers[30]	55	60 (26–87)	None	OCP/OP/MMP	25–150 mg/d	Rx assessed at 12 wk	None	Hemolysis (8) Fatigue (5) DHS (1)	47 of 55 pts had suppression and prevention of progressive disease with Dap, Sul, or a combination of both 6 pts in remission off Rx at a 4 y follow-up Dap discontinued in 9 pts due to adverse effects
Foster[31]	20	62 (NR)	None	OCP	≥2 mg/kg/d	Rx assessed at 12 wk	Pred	Hemolysis (19) Nausea (4) Hepatitis (1) Abdominal pain (2) Peripheral neuropathy (1)	14 of 20 pts responded to Dap, with abolition of conjunctival inflammation and no evidence of scarring 4 of 20 pts had incomplete response, pts responded to Cyc 2 pts did not respond after 12 wk, pts responded to Cyc

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Table III. Contd

Case series	No. of pts	Mean age; y (range)	Previous systemic Rx (no. of pts)	Indications for Dap	Dosage of Dap	Duration of Dap/follow-up period	Concomitant systemic Rx	Adverse effects of Dap (no. of pts)	Clinical outcome
Matthews et al.[32]	7	51 (20–74)	None	Inadequate response to local Rx	25–75 mg/d	Rx assessed at 12 wk	None	Headaches and dizziness (2)	3 of 5 pts had benefit but not complete recovery 2 pts did not respond Dap discontinued in 2 pts due to adverse effects
Tauber et al.[33]	80	68 (23–95)	None	OCP/MMP	≥2 mg/kg/d	17 mo/1–60 mo	Pred (NR) Cyc/Aza (6)	Hemolysis (9) Gastrointestinal complications (12) Rash (2) Renal dysfunction (1) Liver dysfunction (1)	Dap as initial Rx controlled progression of conjunctival cicatrization in 31 of 69 pts Addition or substitution of Cyc, or addition of Aza achieved control in 60 of 69 pts Addition of Dap to failure of initial Cyc/Aza controlled 10 of 11 pts Dap discontinued in 3 pts due to adverse effects
Fern et al.[34]	5	60 (40–72)	None	OCP	50–100 mg/d	NR	Pred (1)	Jaundice (1) Cyanosis and hemolysis (1)	5 of 5 pts had acute conjunctival inflammation controlled at 1–4 wk Length of asymptomatic remissions off all Rx ranged from 1 to 8 mo, but all patients required maintenance Rx
Ciarrocca and Greenberg[35]	11	63 (17–86)	None	OP/OCP/MMP Inadequate response to local Rx	25–175 mg/d	>6 mo/NR	None	Hemolysis (11) Methmg (2)	7 of 11 pts had complete clearance of all lesions and absence of clinical disease 4 of 11 pts had >75% improvement Dap discontinued in 2 pts due to adverse effects

Aza = azathioprine; **Cyc** = cyclophosphamide; **DHS** = dapsone hypersensitivity syndrome; **Methmg** = methemoglobinemia; **NR** = not reported; **OCP** = ocular cicatricial pemphigoid; **OP** = oral pemphigoid; **Pred** = prednisone; **Rx** = therapy; **Sul** = sulfapyridine.

Table IV. Data on patients (pt[s]) with bullous pemphigoid (BP) treated with dapsone (Dap)

Case series	No. of pts	Mean age; y (range)	Previous systemic Rx (no. of pts)	Indications for Dap	Dosage of Dap	Duration of Dap/follow-up period	Concomitant systemic Rx (no. of pts)	Adverse effects of Dap (no. of pts)	Clinical outcome
Piamphongsant[36]	21	49 (6–80)	None	BP	100–200 mg/d	NR	None (18) Pred (3)	NR	12 of 21 pts controlled by Dap alone in 2–3 wk 3 of 21 pts responded with added Pred, in 1 pt Pred could be discontinued All responsive pts on maintenance Rx 6 of 21 pts had no response, response to Pred
Venning et al.[37]	18	73 (49–89)	None (15) Pred (3)	BP	50–100 mg/d	Mean total follow-up period 30 mo (1.5–143)	None (15) Pred (3)	Anemia (2) Hemolysis (2) Agranulocytosis (1) Rash (1)	8 of 18 pts had complete abolition of fresh blisters in 2–4 wk; 4 pts in remission for 9–28 mo after discontinuation of Rx 6 of 18 pts had reduction in the number of fresh lesions, and response with substitution or addition of Pred 4 pts had no response, response to Pred/Pred + Aza Dap discontinued in 4 pts due to anemia
Jeffes and Ahmed[38]	13	62 (20–77)	Pred (7) Pred + Aza (6)	Recurrent BP Adverse effects of previous Rx	100–300 mg/d	Dap given for 5 mo (2–21)	Pred (11) Pred + Aza (2)	Nausea (2) Rash (2) Peripheral neuropathy (2) Methmg (1) Anemia (1) Hepatitis (1)	12 of 13 pts had rapid clearing of lesions at 10–15 d, and healing of previous lesions Addition of Dap allowed 50% reduction in maintenance dose of Pred
Bouscarat et al.[39]	36	73 (38–95)	None	BP	50–200 mg/d	Rx assessed at 1 mo	None (34) CS (2)	Anemia Methmg Cyanosis Hemolysis Neutropenia (total 21)	10 of 36 pts had complete regression of blisters at 1 mo 6 of 36 pts showed regression of >50% of blisters 20 of 36 pts had no response, response to Pred Dap alone was less effective than when combined with topical CS

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Table IV. Contd

Case series	No. of pts	Mean age; y (range)	Previous systemic Rx (no. of pts)	Indications for Dap	Dosage of Dap	Duration of Dap/follow-up period	Concomitant systemic Rx (no. of pts)	Adverse effects of Dap (no. of pts)	Clinical outcome
Singalavanija and Limpongsanurak[40]	20	3 (0–11)	None	BP	1–2 mg/kg/d	Dap given for 3 mo (1–24)	Pred (4) None (16)	Hepatitis (2)	18 of 20 pts stopped developing new lesions, most cases responded by 1–2 mo 2 of 20 pts responded with the addition of Pred
Schmidt et al.[41]	62	76 (NR)	Tetracycline + nicotinamide (11) Aza (1)	Inadequate control	1–1.5 mg/kg/d	Rx assessed at 3, 6, 12 mo intervals	MPred (62)	Anemia (4) Methmg (2) Gastrointestinal complications (5) Elevated serum creatinine (4) Nausea (2) Dyspnea (4) Dizziness (3) Exanthema (1)	100% of patients' skin lesions cleared at 6 mo After 3, 6, and 12 mo, no further Rx was required in 20%, 30%, and 53% of pts, respectively 5 of 62 pts discontinued dapsone due to adverse effects 5 of 62 pts died due to non-Dap-related causes

Aza = azathioprine; **CS** = corticosteroid; **Methmg** = methemoglobinemia; **MPred** = methylprednisolone; **NR** = not reported; **Pred** = prednisone; **Rx** = therapy.

are often needed to achieve control of the diseases are significant, catastrophic, and potentially fatal.[5] There are many possible explanations for the high incidence of adverse effects observed in these patients treated with dapsone. First, the majority of patients were older. Such patients often have multiple medical problems and are frequently receiving multiple medications that compound and complicate drug metabolism. Second, in order to be effective, dapsone causes an unavoidable hemolytic anemia. Third, glucose 6-phosphate dehydrogenase (G6PD) levels are critical for metabolism of the drug. If G6PD screening is not carried out, the rate of adverse effects may be higher. It is critical to highlight that, compared with corticosteroids, the adverse-effect profile of dapsone is far less serious and in most instances the adverse effects are reversible.[5]

Adverse effects associated with dapsone at daily doses below 100 mg are mostly not serious. They can be categorized as pharmacologic/toxic and allergic/idiosyncratic (table V).[1,61] The most common pharmacologic/toxic adverse effects are mainly hematologic and include methemoglobinemia, hemolysis, and anemia.[1,2,43,61] Absorption of dapsone is virtually complete within 3 hours of administration, and a high proportion of the drug is converted to hydroxylamine, which is the metabolite that causes these hematologic adverse effects. Methemoglobinemia occurs to a variable extent in all patients. It becomes less pronounced as treatment is continued because of adaptive mechanisms. It may increase dramatically in patients with methemoglobin reductase enzyme deficiency.[43] Long-term administration of dapsone at dosages of 100 mg/day in relatively healthy patients usually results in methemoglobinemia that is not clinically significant. At methemoglobinemia levels of 30% or higher, dyspnea, nausea, and tachycardia occur. Lethargy, stupor, and deteriorating consciousness occur at methemoglobinemia levels of around 55%, and a level of 70% is usually fatal.[1]

Hemolysis induced by dapsone occurs in healthy individuals in a dose-dependent manner, and a reduction in hemoglobin will be detectable at dapsone dosages >50 mg/day.[43] In one study of 100 leprosy patients receiving an average dosage of dapsone 100 mg/day, an average fall in hemoglobin levels of 2 g/dL was seen.[62] Patients with G6PD deficiency are more susceptible to developing hemolysis. To minimize hemolysis, the daily dapsone dose should not exceed 1.5 mg/kg bodyweight or 100 mg in healthy people with normal G6PD levels, and 50 mg in G6PD-deficient people.[2]

Agranulocytosis is reported mostly in patients with dermatitis herpetiformis, and its cause is not known.[63] Most cases of agranulocytosis due to dapsone develop within the first 8–12 weeks of therapy.[43]

Table V. Adverse effects of dapsone

Pharmacologic/toxic
Methemoglobinemia
Hemolysis
Anemia
Nausea
Vomiting
Fatigue
Anorexia
Headache
Dizziness
Allergic/idiosyncratic
Dapsone hypersensitivity syndrome
Agranulocytosis
Exanthematous eruption
Stevens-Johnson syndrome/toxic epidermal necrolysis
Photosensitivity
Peripheral neuropathy
Hepatitis
Nephritis and renal failure
Hypoalbuminemia
Psychosis
Hypothyroidism
Drug-induced lupus erythematosus

A rare but serious adverse effect is dapsone hypersensitivity syndrome. The syndrome consists of fever, rash, lymphadenopathy, and different degrees of organ involvement. This entity is also termed drug reaction with eosinophilia and systemic symptoms (DRESS). Dapsone hypersensitivity syndrome may be considered a manifestation of DRESS syndrome.[64] Only a few cases have been reported in patients taking dosages of <100 mg/day. The incidence is less than 0.5% and it occurs, on average, 27 days after the initiation of therapy.[2] It is generally self-limiting and most patients recover following cessation of dapsone therapy. However, deaths have been reported.[64]

Peripheral neuropathy is less commonly reported in autoimmune mucocutaneous blistering diseases, but is more common in leprosy patients and is also reported in patients with dapsone hypersensitivity syndrome. It frequently only involves the motor neurons, or mixed sensorimotor neurons, and may affect upper, lower, or both extremities. It occurs with dosages over 100 mg/day with a variable onset, which can be within weeks to years of beginning therapy. It is reversible and usually resolves within 1 year after discontinuation of dapsone, but may persist longer.[23]

Other less commonly reported adverse effects include exanthematous eruption, fever, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, hepatitis, nephritis and renal failure, hypoalbuminemia, psychosis, hypothyroidism, and minor gastrointestinal complaints.[1,2,43,61]

Sulfapyridine has been reported to be a good alternative to dapsone in OCP patients with reduced tolerance to dapsone.[30,65,66] It has also been used in bullous pemphigoid.[37,67] The efficacy has been shown to be similar to dapsone in patients with OCP.[66] Sulfasalazine, an oral precursor of sulfapyridine, which is used mainly in the treatment of rheumatoid arthritis and ulcerative colitis, has also been reported to be effective and a good alternative to dapsone in patients with OCP.[68,69] Sulfasalazine has multiple immunomodulatory properties: (i) it normalizes lymphocyte activity by inhibiting T-lymphocyte proliferation and reducing the production of immunoglobulins and several cytokines; (ii) it inhibits the chemotactic response of neutrophils, the release of enzymes and superoxide anions, the metabolism of prostaglandins by leukocytes, and folate-dependent enzyme activity; and (iii) it has antibacterial properties.[69] Gastrointestinal and CNS symptoms (headache, dizziness) are the most frequent adverse effects of sulfasalazine. Other rare adverse effects include hypersensitivity reactions, hepatotoxicity, pulmonary disease, immune disorders, and lupus-like syndromes.[69] In one study, allergic reactions presenting as skin rash have been reported with an incidence of 15% in OCP patients treated with sulfapyridine.[65]

Rifampin (rifampicin) lowers dapsone concentrations 7- to 10-fold by accelerating plasma clearance. Folic acid antagonists such as pyrimethamine may increase the likelihood of hematologic reactions. There is a mutual interaction between dapsone and trimethoprim in which each raises the concentration of the other about 1.5-fold.[70]

Because of several potentially harmful adverse effects, dapsone therapy needs careful monitoring. Prior to starting dapsone, a complete blood count, reticulocyte count, G6PD, liver function studies, urine analysis, and renal function tests should be performed. During therapy, blood count, reticulocyte count, platelet count, and leukocyte count should be obtained weekly for the first month, then twice per month during the next 2 months and every 3 months thereafter. Liver and renal function should be tested every 3 months. Methemoglobin levels should be obtained in patients who become symptomatic for methemoglobinemia.[71] The use of cimetidine, a metabolic inhibitor that reduces hepatic oxidation of dapsone to the hydroxylamine, may reduce the anemia associated with dapsone.[72-74]

4. Conclusions

Despite the limitations of our analysis, certain important preliminary conclusions can be drawn from the existing data. Dapsone is a promising agent in patients with autoimmune mucocutaneous blistering diseases. It appears that dapsone can be used as an adjuvant when patients are not responsive to corticosteroids, or in younger patients to avoid long-term adverse effects of corticosteroids. Larger case series or randomized controlled trials need to be conducted to evaluate the efficacy of dapsone in the treatment of pemphigus. In pemphigoid, despite the fact that randomized controlled trials are not available, the efficacy of dapsone is better established, and it is often preferred as initial treatment, either alone or in combination with prednisone or immunosuppressants. The majority of patients with MMP and bullous pemphigoid are responsive to dapsone. Adverse effects are dose dependent and usually not clinically significant when the dosage is ≤100 mg/day. In the opinion of the authors, dapsone is a valuable and useful agent that is underutilized. One of the reasons for this underutilization may simply be the lack of information available. The ease of using rapidly effective systemic corticosteroids may not stimulate physicians to look for alternative drugs. As the population ages in North America, Europe and Japan, it is likely that drugs other than corticosteroids will gain more favor, simply because they are effective, but less toxic.

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