IN-DEPTH REVIEW

Dapsone and Sulfasalazine as Adjuvant Therapies in Pemphigus Vulgaris: A Systematic Review

Kevin H. Nguyen MS[1], Thomas Norman BA[2], Scott Worswick MD[3]

[1] Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, Pomona, CA
[2] Keck School of Medicine, University of Southern California, Los Angeles, CA
[3] Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, CA

ABSTRACT

Background: Adjuvant treatments are often employed in pemphigus vulgaris (PV) to reduce dependence on corticosteroids. When first-line adjuvants are ineffective, considering alternative adjuvant therapies may be necessary. Dapsone and sulfasalazine represent two options.
Objective: To evaluate the use of dapsone and sulfasalazine in the treatment of PV.
Methods: A PubMed search identified patients with PV treated with dapsone or sulfasalazine. We included all studies with ≥3 patients published in English between 1980 and December 2022. Clinical improvement was defined as disease control or complete remission (when adjuvant therapy was initiated in uncontrolled disease) and as a reduction of corticosteroids to ≤7.5 mg per day (when adjuvant therapy was initiated in controlled disease).
Results: Eleven studies were identified representing 75 patients treated with dapsone and 66 patients treated with sulfasalazine. Six patients received dapsone monotherapy, and all had clinical improvement. Sixty-nine received adjuvant dapsone, leading to clinical improvement in 40 (58%). Fifty-seven patients received sulfasalazine as an adjuvant to intravenous corticosteroids, leading to clinical improvement in 49 (86%). The remaining 9 patients received sulfasalazine following rituximab, and all had clinical improvement.
Conclusions: Dapsone and sulfasalazine have evidence supporting their efficacy and can be considered when first-line adjuvant therapies are unsuccessful.

INTRODUCTION

Pemphigus vulgaris (PV) is life-threatening autoimmune disease characterized by flaccid bullae and erosions affecting the skin and mucosal surfaces, often presenting between the ages of 50 and 60.[1,2] Broadly, PV management involves controlling disease activity and then decreasing medication dose if possible.[3,4] While systemic corticosteroids remain a cornerstone of treatment in controlling initial disease activity, they have many potential side-effects[5] and discontinuation of therapy is not always possible. In some studies, less than half of patients are able to completely discontinue corticosteroids even after three years on treatment.[7-8]

To reduce dependency of corticosteroids, other medications are frequently used in conjunction. Azathioprine, mycophenolate,

and rituximab are the most used adjuvants.[3,4] However, they are not always effective, and each has contraindications and potential side effects.[9-11] When first-line adjuvant medications are ineffective or not viable options, clinicians may need to choose an alternative agent. Two potential options with evidence supporting their efficacy are dapsone, first reported as a treatment of PV in 1960,[12] and sulfasalazine. The purpose of this review is to systematically evaluate the literature for recent evidence of dapsone and sulfasalazine in the management of PV.

METHODS

A PubMed search was conducted for all-peer reviewed articles in English from 1980 to December 2022 using the terms: "pemphigus," "pemphigus vulgaris," "pemphigus treatment," "dapsone," and "sulfasalazine." We included studies of all designs with ≥3 patients. For inclusion, the diagnosis of PV required at least two of the following: clinical, histopathologic, or immunofluorescent evidence. KN and TN conducted an independent review of titles and abstracts. Any disagreement was settled by SW.

Data extracted by KN and TN included age, extent of disease, previously failed therapies, dapsone and sulfasalazine dosing, and whether patients had clinical improvement. When adjuvant therapy was started in uncontrolled disease or at an unclear point in the disease course, clinical improvement was defined as either disease control or complete remission (on or off therapy). Based on consensus guidelines, disease control is the point at which new lesions cease to form and existing lesions begin to heal. Complete remission is the absence of new or established lesions for at least 2 months.[12] Descriptions such as "clearance,"

"cessation," or "control" were considered clinical improvement. In contrast, ongoing or non-specific decreases in lesion formation and partial remission were not included in our definition of clinical improvement. When dapsone was initiated in the setting of controlled but steroid dependent disease, clinical improvement was defined as a reduction of corticosteroids to ≤7.5 mg per day.

RESULTS

Our initial search yielded 264 non-duplicate articles **(Figure 1)**. After applying inclusion/exclusion criteria, 237 articles were excluded during title/abstract screening and 15 were excluded during full-text screening. One additional article was excluded during data extraction because we were unable to delineate which patients received dapsone versus standard therapy. Ultimately, 11 studies representing 141 patients were included, 75 patients treated with dapsone (8 studies), and 66 patients treated sulfasalazine (3 studies).

Dapsone as Monotherapy

Monotherapy dapsone was reported in 6 patients with uncontrolled disease.[14,15] Two had pemphigus vegetans,[14] and three had PV affecting <10% body surface area (BSA).[15] All cases had clinical improvement,[14,15] but authors of one study recommended against using dapsone as first-line therapy due to a high failure rate in unpublished cases.[15]

Dapsone as Adjuvant Therapy

Dapsone as adjuvant therapy was reported in 69 patients **(Table 1)**.[15-21] When reported, dapsone was initiated between 1 to 49 months after PV diagnosis.[16-18,20-21]
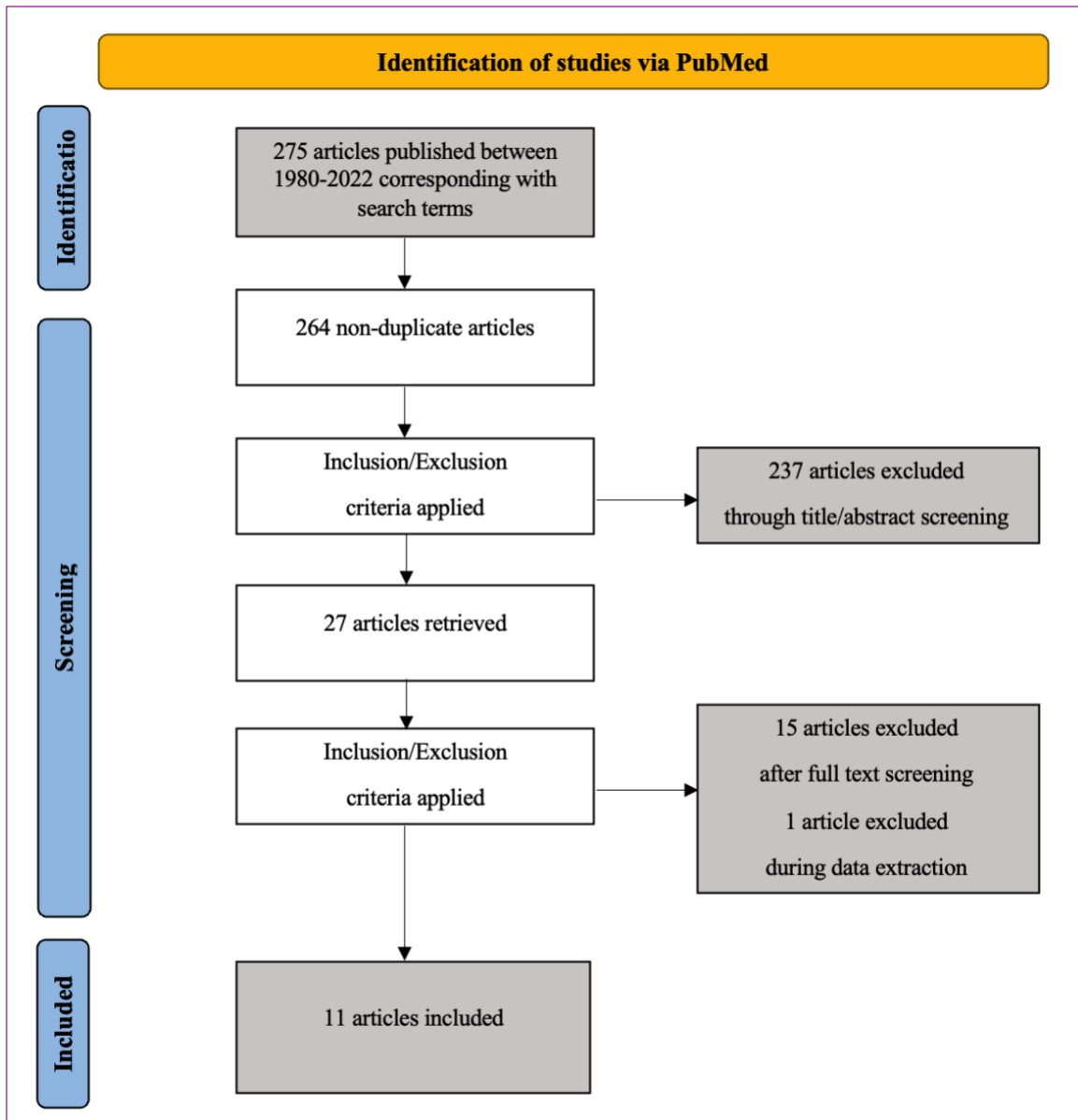
Figure 1. Diagram of the screening and selection of articles in the literature review.

Previously administered adjuvants were azathioprine, cyclophosphamide, doxycycline, gold, intravenous immunoglobulin, methotrexate, and mycophenolate mofetil.[16,18,21] At dapsone initiation, mean prednisone doses ranged from <7 to 45 mg per day.[15-17, 19-21] The maximum dapsone dose ranged from 50 to 200 mg per day[15-21] with reported durations of treatment ranging from 4 months to 3 years.[16-19]

There were 22 patients that received dapsone in the setting of uncontrolled disease, leading to clinical improvement in 11 (50%).[14,15,19] Seven were from a prospective study that selected for patients with newly diagnosed PV limited to the oral mucosa.[20] The other 4 had relapsing disease: two had disease affecting <10% BSA,[15] and the other two started cyclophosphamide concurrent to dapsone.[16]

Table 1. Evidence supporting dapsone as monotherapy and adjuvant therapy.

Study author (year)	No.	Mean age [range]	Surfaces involved (patient no.)	Patient characteristics	Time from diagnosis to dapsone	Previous adjuvant therapy (patient no.)	Mean [range] prednisone dose at dapsone initiation (mg/day)	Range of maximum dapsone dose (mg/day)	Dapsone duration	Study specific outcomes	Clinical complications attributed to dapsone (patient no.)
Evidence supporting dapsone as monotherapy											
Pearson[14] (1980)	3	N/A [45-57]	oral + skin (2), skin (1)	2 had pemphigus vegetans	0-3 years	AmB (1), gold (1)	N/A	100-200	NR	All with "controlled" lesions. 1 relapsed requiring dapsone 300mg to control disease.	NR
Piamphongsant[15] (1991)	3	NR	NR	<10% BSA involved	NR	NR	N/A	100	NR	All with complete clearance.	NR
Evidence supporting dapsone in adjuvant therapy											
Retrospective studies											
Ahmed[16] (1987)	3	42 [23-70]	oral + skin (2), skin (1)	All with uncontrolled disease; 2 experiencing disease flares	~6-26 months	AZA (2), gold (1)	45 [30-60]	100-200	5-11 months	2 had cessation of blister formation and discontinued steroids after 6 and 7 months. The other patient's "skin lesions decreased," but then developed hemolytic anemia after 5 months	Hemolytic anemia (1)
Piamphongsant[15] (1991)	2	NR	NR	<10% BSA involved; both relapsed when steroids were tapered to 30mg/day	NR	NR	30 [N/A]	100	NR	All with complete clearance.	NR
Heaphy[17] (2005)	9	59 [42-72]	oral (2), oral + skin (7)	7 with controlled disease, unable to taper steroids; 2 with uncontrolled disease	5-49 months	AZA (6), CP (5), doxy (1), gold (1), MFM (1), MTX (2)	20 [10-35]	125-150	8 months	7 with controlled disease tapered steroids to <7.5mg/day (n=5) [mean reduction: 84%] or discontinued steroids entirely (n=2); 2 with uncontrolled disease increased steroid doses	Decreased hematocrit (3)

Study	N	Age	Location	Severity/Notes	Prior steroid duration	Other therapies	Dapsone dose (other)	Dapsone dose	Follow-up	Outcome	Adverse effects
Baum[18] (2016)	26	44 [20-67]	mucosa (3), mucosa + skin (18), skin (5)	Unspecified severity. Steroid dose before dapsone ranged from 0-90 (mean 57±24) mg/day	~0-2 years	AZA (1), IVIG (1), MTX (1)	NR	50-150	4-69 months	11 in complete remission, and 5 in partial remission. Mean dose reduction since dapsone initiation was 68%.	Headache (1), neutropenia (1)[a]
Alkereye[19] (2020)	3	30 [24-33]	NR	Unspecified severity, but excluded patients treated with steroids >7mg/day	NR	NR	<7mg/day [N/A]	50-100	18 months - 3 years	All had disease remission off treatment	NR
Prospective studies											
Azizi[20] (2008)	15	53[b] [34-68]	oral (15)	"Moderate-severe disease" limited to oral mucosa; uncontrolled after prednisone 40mg/day for 4 weeks	1 month	NR	40 [N/A]	100	NR	7 with complete clearance of lesions; 3 >75% improvement; 5 with <50% improvement	NR
Werth[21] (2008)	9[c] Treatment vs 10 Control	48 [31-64] vs 41 [19-53]	oral (4), oral + skin (2), skin (3) vs oral (5), oral + skin (3), skin (2)	dbRCT of steroid-dependent maintenance phase. Prior therapy continued. Treatment group received dapsone. Groups cross-over allowed if steroids not tapered by >25% at 4 months. Primary outcome: tapering steroids to ≤7.5mg/day	3-39 months vs 5-180 months	AZA (3), MFM (1) vs AZA (3), MFM (1), gold (1)	26 [15-30] vs 29 [20-40]	125-200	NR	5 treatment vs 3 placebo tapered steroids to <7.5mg/day (ITT: 55.6% vs 30%) 2 treatment failures were non-adherent (PP, no crossover: 71.4%) 4 placebo failures started dapsone; 3 tapered steroids to <7.5mg/day (PP, crossover: 72.7%)	MH (1), paresthesia (1)

[A]99 patients were excluded from study due to dapsone adverse effects: methemoglobinemia (n=2), hemoglobin reduction ≥1.5g/dl or symptomatic anemia (n=94), and elevated liver function tests (n=3)
[b]Values are that for all 20 reported by Azizi et al, although only 15 went on to receive dapsone adjuvant therapy.
[c]For our study's overall count, we included the 11 that received dapsone [excluding non-adherent patients and including those who switched groups to receive dapsone]

AmB, amphotericin B; AZA, azathioprine; BSA, body surface area; CP, cyclophosphamide; dbRCT, double-blind randomized controlled trial; Doxy, doxycycline; IVIG, intravenous immunoglobulin; ITT, intention to treat; LFT, liver function tests; MTX, methotrexate; MFM, mycophenolate mofetil; MH, methemoglobinemia; N/A, not applicable; NR, none reported; PP, per protocol

In 18 patients, dapsone was used in controlled but steroid-dependent disease, leading to clinical improvement in 15 (83%).[17,21] Eight patients were from a double-

blind, randomized, placebo-controlled trial.[21] In the trial, all patients continued previous therapeutic regimens, and those randomized to the treatment group also received dapsone. Two patients in the treatment group were non-adherent. Four patients randomized to placebo group switched to the treatment group after failing to adequately taper corticosteroids. Excluding non-adherent patients and including those who crossed over to the treatment group (per protocol, crossover analysis), 8 (72.7%) of the 11 patients who received dapsone tapered corticosteroids to less than 7.5 mg per day.

There were 29 patients in which it was unclear at what point in the clinical course dapsone was initiated.[18,19] Most had disease affecting the skin and mucosa. Prior to dapsone initiation, steroid doses ranged from 0 to 90 mg per day. Following treatment, 14 (48%) patients had clinical improvement, with 8 in complete remission on therapy and 6 in complete remission off therapy.

Overall, 40 (58%) of the 69 patients treated with adjuvant dapsone experienced clinical improvement.[15-21] There were 52 patients in which corticosteroid doses following initiation of dapsone were reported.[16-19,21] A reduction to at least 10 mg per day was observed in 37 (71%). When reported, mean reductions in steroid dose ranged from 68-84%.[17,18] There were 26 patients with adequately described follow-up. Ten (38%) discontinued corticosteroids entirely[16,17,19,21] at approximately 6 to 14 months after starting dapsone.[16,17,21] Clinical complications attributed to dapsone were reported in 8 patients.[16-18,21] However, multiple studies required that patients tolerate dapsone prior to inclusion.[17,18,21] Baum et al excluded 99 patients that were unable to tolerate dapsone for at least 3 months. The most common reason for exclusion was a reduction in hemoglobin >1.5mg/dl or symptoms of anemia.[18]

Sulfasalazine as Adjuvant Therapy

Adjuvant sulfasalazine was used in 66 patients with uncontrolled disease **(Table 2)**.[22-24] In 57 patients, sulfasalazine was administered with intravenous corticosteroids. Sulfasalazine was given at 500 mg three times a day and co-administered with pentoxifylline 400 mg three times a day.[22,23] Fifteen of these patients were from a non-blinded study, and 13 of them achieved complete remission.[23] The other 42 patients were from a double-blind, placebo-controlled trial.[22] At this study's endpoint, disease control was noted in 36 (86%) patients in the treatment group (those receiving sulfasalazine and pentoxifylline) versus 4 (18%) in the control group. While the difference between groups was statistically significant, this study was not randomized, and baseline differences between groups may have impacted results. A greater percentage of patients in the treatment group had less extensive disease at study initiation.

In the remaining 9 patients, sulfasalazine was used after rituximab due to persistent oral lesions.[24] Patients first received rituximab 1000 mg at day 1 and 14, and prednisone was given at doses ranging from 10 to 30 mg daily. One month after rituximab initiation, sulfasalazine was started (doses ranged from 500 to 1500 mg twice daily). All patients achieved remission at 3 months. However, this was not placebo-controlled, so it is

Table 2. Evidence supporting sulfasalazine as adjuvant therapy.

Study author (year)	Patient number	Mean age [range]	Extent of disease at sulfasalazine initiation	Previous systemic therapies (patient no.)	Treatment regimen received in addition to sulfasalazine	Sulfasalazine dose (mg)	Study specific outcomes	Clinical complications (patients no.)
Evidence supporting sulfasalazine as an adjuvant in steroid-based treatment regimens								
El-Darouti[2] (2009)	42 treatment Vs. 22 control	43 [22-65] Vs. 39 [24-50]	30-60% BSA (14), >60% BSA (28) Vs. 30-60% BSA (4), >60% BSA (18)	NR	14-day cycle: D1: 500 mg IV CP D1-5: 500 mg IV steroids D6-14: 100 mg oral CP D8+9: oral 60 mg steroid Cycle repeated until no new lesions formed. Then, IV steroids and CP pulses were tapered to monthly. Between pulses, patients received oral CP 100 mg daily and oral steroids 60 mg 2 days per week. Oral steroids were gradually discontinued and then, IV pulses were continued for 6 months. After that, oral CP was continued for another year.	500 tid + PTX 400 tid [Started at beginning of treatment regimen continued thereafter]	36 (86%) in treatment group versus 4 (18%) in the control group achieved an absence new lesions and complete healing of existing ones.	Treatment group: gastric pain (12), nausea (4), and headache (5) Control group: headache (3)
Dogra[23] (2015)	15[a]	25 [12-40]	>30% BSA and/or extensive oral erosions (11), 11-30% BSA (4)	Dexamethasone + CP (2)	28-day cycle D1-3: 100 mg IV dexamethasone Unspecified oral & IV corticosteroids Cycle repeated until no new lesions formed. Thereafter, the cycle was continued but without oral steroids for 9 months.	500 tid + PTX 400 tid [Initiated with IV dexamethasone and continued until 9 months after dexamethasone was discontinued]	13 in remission and 2 lost to follow-up. Of those in remission, 7 were not receiving any medication, 4 were receiving sulfasalazine and PTX alone.	Nausea, vomiting, headache, and fatigue (7), acneiform eruptions (5), elevated liver enzymes (2), plane warts (1)
Evidence supporting sulfasalazine as an adjuvant following rituximab								
Navarro-Navarro[24] (2021)	9	51 [25-78]	Persistent oral lesions 1 month after Rituximab	AZA (3), doxycycline (1), IVIG (3), MTX (2), methylprednisolone (2), metronidazole (1), minocycline (1), nicotinamide (1), MMF (1), prednisone (6)	D1-14: Rituximab 1000 mg* D1-onward: Prednisone 10-30 mg per day *6 cases were pre-treated with methylprednisolone 125 or 250 mg over 3-5 days	500-1500 bid [Started 1 month after the first dose of rituximab]	All achieved remission in 3 months. Sulfasalazine and prednisone (2.5-5mg per day) were then continued for another 3-6 months.	Reversible neutropenia (1), diarrhea (1)

[a]One unspecified patient had pemphigus foliaceous. They are included in our study.
AZA, azathioprine; BID, twice a day; BSA, body surface area; CP, cyclophosphamide; D, day; IV, intravenous; IVIG, intravenous immunoglobulin; MTX, methotrexate; MMF, mycophenolate mofetil; PTX, pentoxifylline; TID, three times a day.

unclear whether the effect may have been achieved had sulfasalazine not been initiated at all.

Overall, sulfasalazine was used in 57 patients concurrent to intravenous corticosteroids, leading to clinical improvement in 49 (86%).[22,23] In 9 patients sulfasalazine was used following rituximab, leading to clinical improvement in all nine.[24] There were 38 side effects reported, most commonly gastric pain.[22-24] Sulfasalazine

was only discontinued in two patients, one had diarrhea and the other had reversible neutropenia.[24]

DISCUSSION

Since literature demonstrating the efficacy of dapsone and sulfasalazine in the management of PV is largely retrospective and non-controlled, it is difficult to make strong conclusions about their effectiveness. Data synthesis was limited by the non-uniformity of study designs and initiation of adjuvant dapsone or sulfasalazine at varying points in the disease course. Despite these limitations, we observed that both adjuvant dapsone and sulfasalazine can be effective in the management of PV.

Although dapsone monotherapy was observed to have high efficacy, there were only a few patients in this review and high rates of failure in unpublished cases.[15] Therefore, we would not recommend this therapeutic option as first-line in PV treatment; instead, dapsone monotherapy may be effective in mild disease if other therapies fail.

Regarding dapsone as adjuvant therapy, 58% of patients overall experienced clinical improvement.[15-21]In 2009, Gürcan et al published a review of dapsone in PV treatment.[25] Of the 37 patients included in their review, clinical improvement was observed in 32 (86%). Our lower value could be explained by excluding case reports and including more recent literature that has lower rates of reported success.[18] Regardless, both of our reviews support the use of adjuvant dapsone in specific circumstances. For instance, we observed the greatest percentage of clinical improvement in cases when dapsone was introduced in the setting of controlled but steroid-dependent disease,[17,21] highlighting a potential therapeutic niche for this agent.

Adjuvant sulfasalazine was used exclusively in patients with active disease leading to clinical remission in most instances. While this could lead to the conclusion that sulfasalazine is highly efficacious in PV management, it is important to interpret these results with a degree of caution. In the two studies where adjuvant sulfasalazine was used with intravenous corticosteroids, pentoxifylline was co-administered. Sulfasalazine and pentoxifylline have been theorized to act in synergy to reduce TNF-α-mediated acantholysis.[22] Additional research would be required to determine whether sulfasalazine alone is beneficial. In the other study, patients were treated with rituximab one month prior to sulfasalazine introduction. As rituximab alone has a high efficacy in controlling PV,[9] it is unclear whether sulfasalazine had any role in causing improvement.

The exact mechanisms by which dapsone or sulfasalazine aid in PV treatment are not well understood. However, dapsone and sulfasalazine have a range of documented mechanism for decreasing inflammation which include downregulating neutrophil activity and decreasing inflammatory cytokines and reactive oxygen species.[26,27] Mechanistically, it might then be expected that colchicine could be efficacious in PV. As such, colchicine was included in our initial study design. However, there were no published studies describing its use in PV, although colchicine has unsuccessfully been used in the management of IgA pemphigus.[28]

CONCLUSION

In reviewing literature from 1980 to 2022, adjuvant dapsone led to clinical improvement

in 58% of cases with greatest efficacy observed when administered in patients with controlled disease. Sulfasalazine use was only reported in patients with uncontrolled disease but led to clinical improvement in most instances. Although our conclusions are limited by the largely retrospective nature of studies included, our review synthesizes existing evidence for dapsone and sulfasalazine—two potentially underutilized adjuvant therapies that clinicians can add to their arsenal when managing PV.

Corresponding Author:
Kevin Nguyen,
200 W 3rd St, Pomona, CA 91766
Email: kevin.nguyen2@westernu.edu

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