Side effects of steroid-sparing agents in patients with bullous pemphigoid and pemphigus: A systematic review

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Background: Systemic glucocorticoids are first-line treatment options for autoimmune blistering diseases; however, their long-term use is associated with significant toxicities.

Objective: To evaluate the side effects of steroid-sparing agents and compare them with those of steroids.

Methods: We searched Cochrane Reviews, Embase, MEDLINE, and Scopus between October 1978 and May 2020 using the keywords "bullous pemphigoid," "pemphigus," "autoimmune blistering diseases," and "side effects." A total of 31 randomized controlled trials and retrospective case series were critically appraised.

Results: This review includes a total of 1685 patients with autoimmune blistering diseases, of whom 781 had bullous pemphigoid and 904 had either pemphigus vulgaris or pemphigus foliaceous.

Limitations: A major limitation is that because adjuvants are generally used in combination with steroids, only 12 of the studies reviewed included a "steroid-only" arm to allow for a direct comparison of side effects. Additionally, there is inadequate literature and lack of standardized grade reporting of specific side effects of each steroid-sparing agent.

Conclusion: In the future, researchers should consider implementing the Common Terminology Criteria for Adverse Events, version 5.0, for reporting of all side effects to allow for consistency and standardization. It would be useful to have an index similar to the Glucocorticoid Toxicity Index to quantify these side effects. (JAAD Int 2022;9:33-43.)

Key words: autoimmune blistering diseases; bullous pemphigoid; CTCAE; glucocorticoids; GTI; immunosuppressants; pemphigus; side effects; steroid-sparing; treatment.

INTRODUCTION

Autoimmune blistering diseases (AIBDs) are a heterogeneous group of skin diseases that are characterized and caused by autoantibodies targeting adhesion molecules on the skin and/or mucous membranes.[1] Systemic steroids are the cornerstone of the management of AIBDs and have considerably improved the survival of patients with these diseases.[2,3] However, long-term and high-dose treatment with systemic glucocorticoids (GCs) carries the risk of significant side effects, which contribute to morbidity and mortality in patients with AIBDs.[4] Therefore, a major goal of the management of AIBDs is to reduce the patient's cumulative exposure to systemic steroids with the use of adjuvant steroid-sparing agents.[1,4,5] This review focuses on the

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treatment of bullous pemphigoid (BP) and pemphigus. Given that pharmacologic side effects are crucial limitations while treating diseases, the objective is to assess the side effect profiles of steroid-sparing adjuvant therapies.

GUIDELINES FOR THERAPEUTIC USE OF STEROID-SPARING ADJUVANT THERAPIES

The primary treatment option for AIBDs is GCs, as mentioned above. Adjuvant agents are primarily used to reduce a patient's total, cumulative GC dosage and are also considered in circumstances in which monotherapy with GCs is inadequate to induce remission of the disease or when there is relapse during a dose-reduction period of GCs.[6,7] The choice of adjuvant treatment is largely dependent on the availability, price, and practical experience of the treating dermatologist as well as the presence of specific contraindications. The use of an immunosuppressive or immunomodulatory agent with potentially GC-sparing ability should be considered, especially when a high, cumulative GC dosage is anticipated or when there are contraindications to oral steroids and comorbidities such as hypertension, diabetes mellitus, osteoporosis, and psychosis.

CAPSULE SUMMARY

- Future researchers should consider implementing the Common Terminology Criteria for Adverse Events, version 5.0, for reporting of all side effects to allow for consistency and standardization.
- The development of a steroid-sparing agents toxicity index, similar to the Glucocorticoid Toxicity Index, would be useful for quantifying the side effects of steroid-sparing agents, especially given their increasing popularity.

Bullous Pemphigoid

The recommendations for the choice of adjuvant drug and its dosage can be classified into 2 groups based on the clinical presentation of BP: extensive BP or localized and mild BP.[6] According to the 2015 consensus by the European Dermatology Forum in collaboration with the European Academy of Dermatology and Venereology, steroids are first-line treatment options, followed by steroids in combination with any 1 of the adjuvant agents listed below as second-line treatment options.[6]

For extensive BP, the adjuvant agents are as follows:

1. Doxycycline alone or in combination with daily oral nicotinamide[8]
2. Azathioprine (AZA) (according to thiopurine methyltransferase [TPMT] activity)[9-11]
3. Mycophenolate mofetil or mycophenolic acid[10,11]
4. Methotrexate[12]
5. Dapsone[13]
6. Cyclosporin[14]

For localized and mild BP, the adjuvant agents include doxycycline and nicotinamide, methotrexate, or dapsone in the same dosages as those for extensive BP.

Pemphigus

An international panel of experts has recommended GCs as a first-line treatment option for pemphigus and anti-CD20 monoclonal antibodies, such as rituximab, as a first-line treatment option for new-onset, moderate-to-severe pemphigus and/or in patients who fail to achieve clinical remission with systemic GCs and/or immunosuppressive agents.[15] A course of rituximab is given intravenously, either 1000 mg twice (2 weeks apart) or 375 mg/m^2 4 times (1 week apart).[15] The first-line, corticosteroid-sparing agents are AZA and mycophenolate mofetil. The recommended AZA dosage varies with TPMT activity: patients with high TPMT activity are given a normal AZA dosage of up to 2.5 mg/kg daily, whereas patients with intermediate or low TPMT activity should receive between 0.5 and 1.5 mg/kg/d (patients with no TPMT activity should not be given AZA). The suggested dosage for mycophenolate mofetil is 30 to 45 mg/kg daily,1440 mg daily for mycophenolic acid.

The International Blistering Diseases Consensus Group has listed intravenous immunoglobulin (2 g/kg over 2-5 days each month), immunoadsorption, and cyclophosphamide as "other" alternative adjuvant agents, which likely collectively refer to second-line treatment and so forth. The latter 2 do not have recommended dosages. Generally, these agents are not favored either because of their poor side effect profile or associated high costs.

METHODS

The OVID MEDLINE, OVID Embase, Cochrane Reviews, and Scopus databases were searched between October 1978 and May 2020 for "bullous pemphigoid," "pemphigus," "autoimmune blistering diseases," and "side effects." Retrospective case series (RCS) with a minimum of 5 cases and randomized controlled trials (RCTs) with a minimum population size of 9 patients were screened by 2

Abbreviations used:

AE:	adverse event
AIBD:	autoimmune blistering disease
AZA:	azathioprine
BP:	bullous pemphigoid
CsA:	cyclosporin
CTCAE:	Common Terminology Criteria for Adverse Events
GC:	glucocorticoid
RCS:	retrospective case series
RCT:	randomized controlled trial
TPMT:	thiopurine methyltransferase

investigators (FAPZ, TS). A single reviewer (FAPZ) independently evaluated each retrieved report. A total of 31 RCTs and RCSs were critically evaluated. The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for abstracts and systematic reviews was used (Supplementary Materials 1 and 2, available via Mendeley at https://data.mendeley.com/datasets/hn4hn9yx4g/1). A flowchart outlining the steps taken, according to Preferred Reporting Items for Systematic Reviews

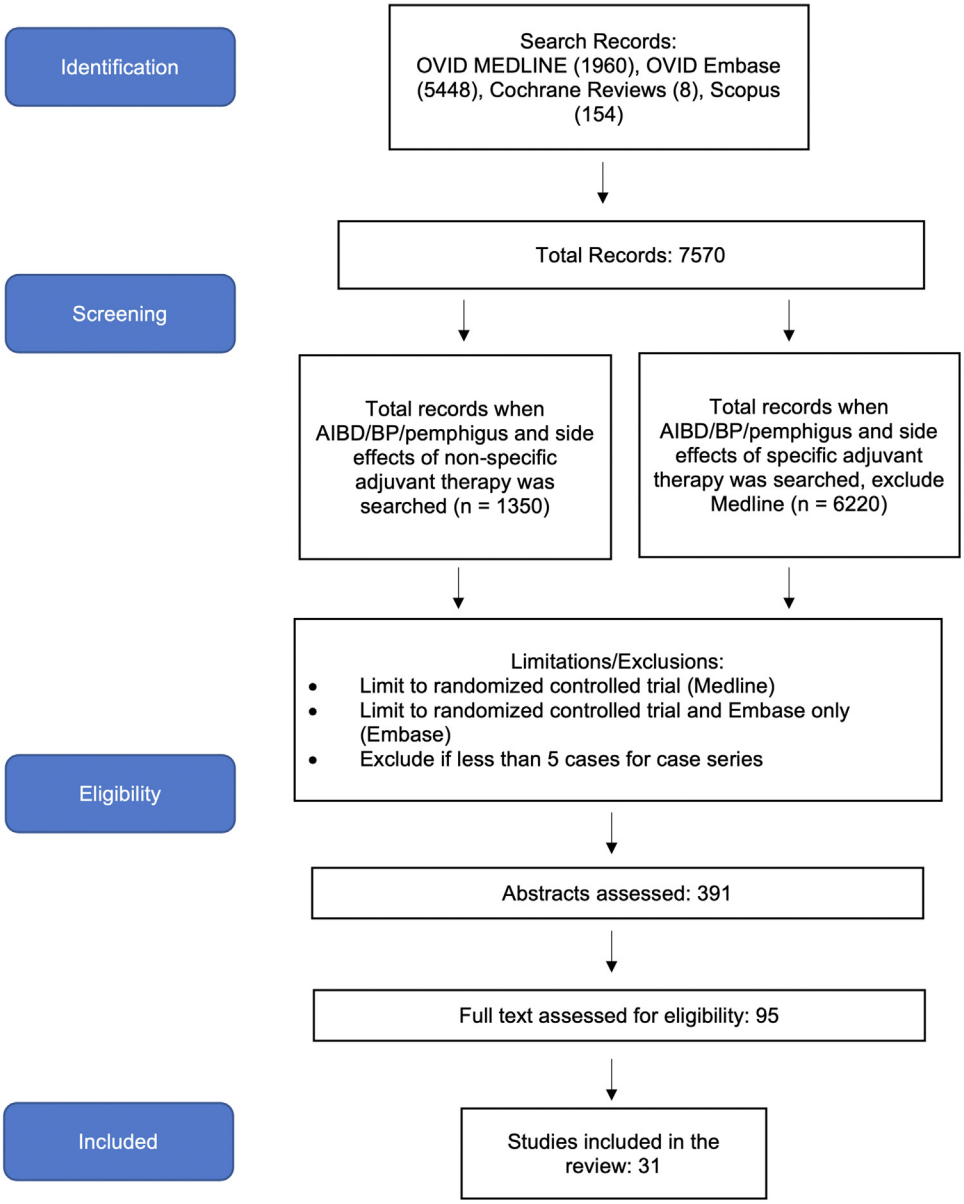

Fig 1. Flowchart illustrating the results of the search strategy. *AIBD*, Autoimmune blistering disease; *BP*, bullous pemphigoid.

Table I. Summary of randomized controlled trials and retrospective case studies evaluating adjuvant therapy in bullous pemphigoids

Author; year; country*	Type	Steroid (GC); adjuvant†	Study arms	Study population and indication	CTCAE grading of AEs
Burton et al[18]; 1978; England	RCT, nonblinded	Prednisone; AZA	GC only; GC, AZA	25 patients with newly diagnosed BP	Grade 2: 2/12 patients (17%)
Beissert et al[10]; 2007; Germany	RCT, multicenter, nonblinded	Methylprednisolone; AZA/MMF	GC, AZA; GC, MMF	73 patients with newly diagnosed mild-to-severe BP	AZA Grade 3: 8/36 patients (22%) Grade 4: 3/36 patients (8%) MMF Grade 3: 11/34 patients (32%) Grade 4: 2/34 patients (6%)
Sticherling et al[19]; 2017; Germany	RCT, multicenter, nonblinded	Methylprednisolone; AZA/dapsone	GC, AZA; GC, dapsone	54 patients with newly diagnosed BP	AZA >Grade 1: 18/27 patients (67%) Dapsone >Grade 1: 13/27 patients (48%)
Gual et al[20]; 2014; Spain	Retrospective case series	Prednisone; CTX	GC, CTX	20 patients with moderate-to-severe BP, initially treated with STS or systemic GCs and with CsA as first-, second-, or third-line adjuvant	Grade 2: 3/20 patients (15%)
Schmidt et al[21]; 2005; Austria and Germany	Retrospective case series	Methylprednisolone; dapsone	GC, dapsone	62 patients with untreated or refractory BP	Grade 1: 10/62 patients (16%) Grade 2: 9/62 patients (15%) Grade 5: 5/62 patients (8%)
Amagai et al[22]; 2017; Japan	RCT, multicenter, double-blinded	Prednisone; IVIg	GC only; GC, IVIg	56 patients with BP were on a stable regimen, which included GCs	AEs were recorded as the number of events per AE and not all AEs experienced per patient
Kjellman et al[23]; 2008; Sweden	Retrospective case series	Prednisone; MTX	GC, MTX; MTX only	98 patients with newly diagnosed mild-to-severe BP	Grade 2: 5/98 patients (5%)
Du-Thanh et al[12]; 2011; France	Retrospective case series	STS, bethamethasone propionate, or clobetasol proprionate; MTX	GC, MTX	70 patients initially treated with short-term STS and low-dose MTX, followed by long-term, low-dose MTX	Grade 1: 2/70 patients (3%) Grade 2: 3/70 patients (4%) Grade 3: 2/70 patients (3%) Grade 4: 8/70 patients (11%) Grade 5: 1/70 patients (3%)
Delaumenie et al[24]; 2019; France	Retrospective case series	TPC; MTX	GC, MTX	51 patients with moderate-to-severe BP, initially treated with TPC as first line	Grade 1 and 2: NA (48%) Grade 3: NA (22%)
Polansky et al[25]; 2019; US	Retrospective case series	Prednisone; RTX	GC, RTX	20 patients with untreated severe or refractory BP	AEs could not be graded because of inadequate information
Williams et al[26]; 2017; UK and Germany	RCT, multicenter	Prednisone; tetracycline	GC only; tetracycline only	234 patients with newly diagnosed BP	Grade 0/1/2: 99/121 patients (81%) Grade 3: 14/121 patients (12%) Grade 4: 5/121 patients (4%) Grade 5: 3/121 patients (3%)

Fivenson et al[8]; 1994; US	Randomized, open-label trial	Prednisone; TCN	GC only; TCN only	18 patients with BP with no systemic GC therapy within 2 wk of enrollment	Grade 2: 2/12 patients (17%) Grade 3 or 4: 1/12 (possibly treatment related) (8%)

AE, Adverse event; *AZA*, azathioprine; *BP*, bullous pemphigoid; *CsA*, Cyclosporin; *CTCAE*, Common Terminology Criteria for Adverse Events; *CTX*, cyclophosphamide; *GC*, glucocorticoid; *IVIg*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *NA*, not available; *RCT*, randomized control trial; *RTX*, rituximab; *STS*, superpotent topical steroid; *TCN*, tetracycline and nicotinamide; *UK*, United Kingdom; *US*, United States.
*The corresponding studies for each drug are arranged in chronologic order, ie, most recent to least recent.
†The drugs are presented in alphabetical order by steroid-sparing adjuvant agent.

and Meta-Analyses guidelines, to identify studies for review in this article is shown in Fig 1.

The Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, was used to grade adverse events (AEs) recorded in the studies when possible (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/hn4hn9yx4g/1).[16] The common side effects of steroids were referenced using the Glucocorticoid Toxicity Index.[17]

Tables I[8,10,12,18-25] and II[26-45] illustrate summarized compilations of the RCTs and RCSs carried out to evaluate the adjuvant therapies used in patients with BP and pemphigus, respectively. The confidence of the data presented in this systematic review is ensured based on clear inclusion and exclusion criteria; the search was comprehensive, in that, appropriate databases were used, and there was neither a language bias (no restriction of inclusion based on language) nor restriction of inclusion based on publication status. The included data are recent and up to date.

RESULTS

A total of 781 participants with BP were included in the selected RCTs and RCSs (Table I).[8,10,12,18-25] Of those whose side effects could be assigned a single grade classification according to the CTCAE definitions, 12 participants (1.5%) experienced grade 1 AEs, 24 participants (3.1%) experienced grade 2 AEs, 35 participants (4.5%) experienced grade 3 AEs, 18 participants (2.3%) experienced grade 4 AEs, and 9 participants (1.2%) experienced grade 5 AEs. For pemphigus, there were a total of 904 participants from the selected RCTs and RCSs (Table II).[26-45] Of those whose side effects could be assigned a single grade classification according to the CTCAE definitions, 13 participants (1.4%) experienced grade 1 AEs, 155 participants (17%) experienced grade 2 AEs, 17 participants (1.9%) experienced grade 3 AEs, 17 participants (1.9%) experienced grade 4 AEs, and no participant experienced grade 5 AEs.

DISCUSSION

The CTCAE (versions 5.0, 4.0, and 3.0) and its predecessor, the Common Toxicity Criteria (versions 2.0 and 1.0), were developed under the direction of the Cancer Therapy Evaluation Program of the National Cancer Institute in an effort to provide a standard language for reporting AEs that occur in sponsored clinical trials.[47] However, this limits the use of the CTCAE in National Cancer Institute-sponsored trials and creates a disparity between National Cancer Institute-sponsored and nonsponsored trials. The authors recommend that researchers

Table II. Summary of randomized controlled trials and retrospective case studies evaluating adjuvant therapy in patients with pemphigus

Author; year; country*	Type	Steroid; adjuvant	Study arms	Study population and indication	CTCAE grading of AEs
Rose et al[27]; 2005; Germany	RCT, multicenter, nonblinded	Methylprednisolone/ dexamethasone; AZA/CTX	Methylprednisolone, AZA; dexamethasone, CTX	22 patients with newly diagnosed PV/PF	AEs were recorded as the number of events per AE and not all AEs experienced per patient
Kakuta et al[28]; 2018; Japan	Retrospective case series	None; AZA	AZA only	8 patients with newly diagnosed PV/PF	Grade 2: 2/8 patients (25%)
Dastgheib et al[29]; 2015; Iran	RCT	Prednisone; AZA/ tacrolimus	GC, AZA; GC, tacrolimus	41 patients with PV	AZA Grade 2: 3/21 patients (14%) Grade 3: 1/21 patients (5%) Tacrolimus Grade 1: 1/20 patients (5%) Grade 2: 1/20 patients (5%)
Chams-Davatchi et al[30]; 2007; Iran	RCT, nonblinded	Prednisone; AZA/ MMF/CsA	GC only; GC, AZA; GC, MMF; GC, CTX	90 patients with newly diagnosed PV	AEs were not described for each treatment arm; it was noted just that there was no significant difference in AE profiles across the 4 groups
Olszewska et al[31]; 2007; Poland	Retrospective case series	Prednisone; AZA/CTX/ CsA	GC only; GC, AZA; GC, CTX; GC, CsA	101 patients with moderate-to-severe PV	AEs were recorded as the number of events per AE and not all AEs experienced per patient
Cummins et al[32]; 2003; US	RCT, nonblinded	Prednisone; CTX	GC, CTX	A total of 23 with refractory PV/PF	Grade 2: 11/23 patients (47%) Grade 3: 3/23 patients (13%)
Sharma and Khandpur[33]; 2013; India	RCT, nonblinded	Prednisone; CTX IV pulse therapy	GC only; GC, CTX	60 patients with mild-to-moderate PV	AEs were recorded as the percentage difference compared with control arm
Khandpur et al[34]; 2017; India	Cross-sectional, prospective, clinical, laboratory investigational	Dexamethasone; CTX IV pulse therapy	GC, CTX	44 patients with PV/PF who have been on CsA for at least 1 y	Grade 2: 23/44 patients (52%)
Ioannides et al[35]; 2000; Greece	RCT	Prednisone; CsA	GC only; GC, CsA	33 patients with newly diagnosed PV/PF	AEs were recorded as the number of events per AE and not all AEs experienced per patient

Baum et al[36]; 2016; Israel	Retrospective case series	Prednisone; dapsone	GC, dapsone	125 patients who received dapsone between 1984 and 2013; for the purpose of this review, excluded patients will be evaluated as they experienced early AEs and, thus, were not included in the study	Grade 2: 99/125 patients (79%)
Werth et al[37]; 2008; US	RCT, multicenter, double-blind	Prednisone; dapsone	GC only; GC, dapsone	19 patients with chronic PV in the maintenance phase[†]	Grade 1: 1/9 patients (11%) Grade 2: 1/9 patients (11%)
Svecova; 2016[46]; Slovakia	Retrospective case series	Prednisone; IVIg	GC, IVIg	10 patients with PV with at least 3 consecutive courses of IVIg	Grade 2: 8/10 patients (80%)
Beissert et al[39]; 2010; Canada, Germany, India, Israel, Turkey, Ukraine, UK, US	RCT, nonblinded	Prednisone; MMF	GC only; GC, MMF	A total of 94 with existing mild-to-moderate PV	Grade 3: 3/58 patients (5%)
Ioannides et al[40]; 2012; Greece	RCT, nonblinded	Methylprednisolone; MMF	GC only, GC, MMF	47 patients with newly diagnosed PV/PF	Grade 1: 11/24 patients (46%)
Baum et al[41]; 2012; Israel	Retrospective case series	Prednisone; MTX	GC, MTX	30 patients with untreated or refractory PV	Grade 2: 4/30 patients (13%)
Tran et al[42]; 2013; US	Retrospective case series	Prednisone; MTX	GC, MTX	23 patients with PV with refractory PV and subsequently on MTX for at least 3 consecutive mo	Grade 2: 2/23 patients (9%)
Chen et al[43]; 2020; France	RCT, phase 3 open-label	Prednisone; RTX	GC only; GC, RTX	A total of 74 patients with newly diagnosed PV	Grade 1/2: 22/38 patients (58%) all attributed to Infusion-Related Reaction Grade 3: 10/38 patients (29%) from drug itself; 1/38 patients (3%) from IRR Grade 4: 2/38 patients (5%)
Kurihara et al[44]; 2019; Japan	Multicenter, phase 1/2 open-label	Prednisolone; RTX	GC, RTX	9 patients with refractory PV/PF	Grade 3/4: 9/9 patients had at least one AE in this grade
McCarty and Fivenson[45], 2014; US	Retrospective case series	Not specified; TCN	GC, TCN	A total of 51 with/without initial GC therapy and at least 3 mo of TCN	Grade 2: 3/51 patients (6%)

AE, Adverse event; *AZA*, azathioprine; *BP*, bullous pemphigoid; *CTCAE*, Common Terminology Criteria for Adverse Events; *CsA*, cyclosporin; *CTX*, cyclophosphamide; *GC*, glucocorticoid; *IV*, intravenous; *IVIg*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *PF*, pemphigus foliaceous; *PV*, pemphigus vulgaris; *RTX*, rituximab; *RCT*, randomized control trial; *STS*, superpotent topical steroids; *TCN*, tetracycline and nicotinamide; *UK*, United Kingdom; *US*, United States.

*Drugs are presented in alphabetical order of steroid-sparing adjuvant agent and the corresponding studies for each drug is arranged in chronological order, ie, most recent to least recent.

[†]The maintenance phase is defined as disease controlled with steroids and/or stable dosages for at least 2 months on cytotoxic agents, including AZA, MMF, or MTX.[37]

Table III. Common steroid-induced side effects are classified by organ system in alphabetical order[49-61]

Organ system	Side effects
Cardiovascular	Coronary heart disease, heart failure, hypertension, ischemic heart disease
Dermatologic	Acne, delayed wound healing, easy bruising, ecchymosis, erosion, hair loss, hirsutism, purpura, skin atrophy, striae
Endocrine and Metabolic	Adrenal suppression, Cushingoid features, diabetes mellitus, dyslipidemia, hyperglycemia, weight gain
Gastrointestinal	Gastritis, gastrointestinal bleeding, hepatic steatosis, pancreatitis, peptic ulcer disease, visceral perforation
Immunologic	Predisposition to infections, reactivation of latent infections
Musculoskeletal	Myopathy, osteonecrosis, osteoporosis
Neuropsychiatric	Akathisia, anxiety, cognitive impairment, depression, euphoria, mood changes, mood lability
Ophthalmologic	Cataract, glaucoma

Table IV. Classification of adverse events recorded in the reviewed randomized control trials and randomized case series according to how likely they are due to glucocorticosteroids or steroid-sparing adjuvant therapy for pemphigoid and pemphigus

	Adverse event*		
Drug	Likely to be true GCAE	Likely to be true AEs of adjuvant therapy for pemphigoid and pemphigus	Unable to be distinguished
AZA	Amenorrhea, cataract, cerebrovascular accident, Cushingoid features, depression, diabetes mellitus, duodenal ulcer, GI bleeding, GI ulcer, GI discomfort, glaucoma, hot flushes, hyperglycemia, hypertension, hypertrichosis, lumbar stenosis, mood changes, myopathy, edema, osteoporosis, pancreatitis, temporary psychosis, tendonitis, redistribution of fat, weight gain	Diarrhea, liver function test abnormalities, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), pharyngitis, vomiting	Arthralgia/myalgia, dizziness, deep venous thrombosis, drug-related exanthema, effluvium, infection
CTX		Acute myeloid leukemia, bladder symptoms (enuresis, frequency/urgency of urination, hematuria, incontinence, nocturia), myelosuppression (anemia, leukopenia, thrombocytopenia), nausea, vomiting	Acute heart failure, dizziness, infection, headache
CsA		Elevated transaminase, gingival hyperplasia, hyperbilirubinemia, nephrotoxicity (decreased creatinine clearance, increased urea/serum creatinine)	N/A
Dapsone		Anemia, cyanosis, fever, liver function abnormalities, methemoglobinemia, paresthesia	Arthralgia/myalgia, dizziness, drug-related exanthema, infection, renal failure

Continued

Table IV. Cont'd

Drug	Adverse event*		
	Likely to be true GCAE	Likely to be true AEs of adjuvant therapy for pemphigoid and pemphigus	Unable to be distinguished
IVIg		Chest pain, decreased blood alkaline phosphatase, depressed platelet count, elevated blood lactate dehydrogenase, fever, injection site erythema/pain, liver function test abnormalities, malaise	N/A
MMF		Fatigue, hypokalemia, liver function test abnormalities, myelosuppression (lymphopenia, neutropenia)	Arthralgia/myalgia, eye disease, infection
MTX		Alopecia, anemia, interstitial pneumopathy, liver function test abnormalities, myelosuppression (leukopenia, pancytopenia, thrombocytopenia)	Alveolitis, asthenia, GI bleeding, GI ulcer, pulmonary embolism
RTX		Arthralgia/myalgia, hypogammaglobulinemia, hypergamma glutamyltransferase	Cerebrovascular accident, dental carries, headache, infection, nasal septum perforation, peripheral neuropathy, phlebitis, psoriatic arthropathy, pulmonary embolism, venous thrombosis
TCN		Diarrhea, nausea, vomiting	Decubitus ulcers, deep venous thrombosis, erosive gastritis

AE, Adverse event; *AZA*, azathioprine; *CsA*, cyclosporin; *CTX*, cyclophosphamide; *GC*, glucocorticosteroid; *GCAE*, glucocorticoid-induced adverse events; *IVIg*, intravenous immunoglobulin; *GI*, gastrointestinal; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *N/A*, not available; *RTX*, rituximab; *RCT*, randomized control trial; *TCN*, tetracycline and nicotinamide.
*The AEs are listed in alphabetical order.

use the CTCAE, version 5.0, while reporting AEs in future clinical studies.

One major limitation of this analysis is that adjuvant interventions are almost always used in combination with steroids and rarely used as monotherapy. Of the 31 selected studies, only 12 included a "steroid-only" arm, which allowed for a direct comparison of the side effects of steroid-sparing agents with those of steroids. This posed a challenge of identifying the true side effects of the adjuvants from those of steroids. To overcome this, commonly accepted steroid-induced side effects were referenced to exclude side effects that are more likely to be caused by steroids than by the adjuvant drugs.[48] These common steroid-induced side effects according to organ system are presented in Table III.[49-61]

Additionally, the side effects of the adjuvant drugs were extracted from their respective product information, certified by the Food and Drug Administration of the United States, to further guide the distinction between the side effects of the adjuvant drugs and those of steroids (Supplementary Material 3, available via Mendeley at https://data.mendeley.com/datasets/hn4hn9yx4g/1).[62-71] The observed AEs for each steroid-sparing agent were then categorized based on how likely they were to be true side effects of the adjuvant drugs by comparing and contrasting data from the aforementioned datasets (Table IV).

Because of lack of available data on specific side effects of each steroid-sparing agent and the lack of standardized grade reporting of such AEs, we were unable to accurately compare the severity of the side effects of steroid-sparing agents with those of the side effects of steroids.

CONCLUSION

The CTCAE could be used to define terms and could be measured as part of a steroid-sparing agent toxicity index, which could be developed using a similar methodology as that for the Glucocorticoid Toxicity Index. The long-term side effects of medications are otherwise challenging to quantify in patients with chronic autoimmune diseases.

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Conflicts of interest

None disclosed.

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