Intraepithelial autoimmune bullous dermatoses disease activity assessment and therapy

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Intraepithelial autoimmune blistering dermatoses are a rare group of skin disorders characterized by disruptions of inter-keratinocyte connections within the epidermis through the action of autoantibodies. The second article in this continuing medical education series presents validated disease activity scoring systems, serologic parameters of disease, treatments, and clinical trials for pemphigus and its subtypes. (J Am Acad Dermatol 2021;84:1523-37.)

Key words: azathioprine; dapsone; intraepithelial autoimmune bullous dermatoses; IVIG; mycophenolate mofetil; pemphigus erythematosus; pemphigus foliaceus; pemphigus herpetiformis; paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome; Pemphigus Disease Activity Index; pemphigus vulgaris; rituximab.

CLINICAL PARAMETERS AND VALIDATED DISEASE ACTIVITY SCORES

Key point

- Several scoring systems, including the Pemphigus Disease Activity Index scoring system, have been developed to monitor disease activity in patients with pemphigus

Several scoring systems for the assessment of pemphigus have been developed and validated.[1]

The most widely used disease activity scoring system is the Pemphigus Disease Activity Index (PDAI).[2] This tool was developed by the International Blistering Diseases Consensus Group after a Cochrane review revealed there were neither consensus definitions nor outcome measures for pemphigus. Its development involved 3 years of international consensus meetings and a validation study conducted at the University of Pennsylvania.[2-4] The PDAI score is a 1-page sheet that can be used easily in clinics to follow patient progress.

The PDAI is purely objective, with equal weighting for skin and different mucosal sites and extra weighting for the scalp, a site commonly affected in pemphigus. The PDAI score ranges from 0 to 263, with moderate disease being defined by a PDAI score of 14 or lower, significant disease being defined by a PDAI score between 15 and 44, and extensive disease being defined by a PDAI score of 45 or greater.[5]

Another frequently employed scoring tool is the Autoimmune Blistering Disease Severity Index System (ABSIS), designed to be applicable to all autoimmune blistering diseases.[6] This index combines objective and subjective measures based on oral symptoms caused by eating or drinking various

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Abbreviations used:

ABSIS:	Autoimmune Blistering Disease Severity Index System
ELISA:	Enzyme-linked immunosorbent assays
IVIG:	Intravenous immunoglobulin
MMF:	Mycophenolate mofetil
PAMS:	Paraneoplastic autoimmune multiorgan syndrome
PDAI:	Pemphigus disease activity index
PE:	Pemphigus erythematosus
PF:	Pemphigus foliaceus
PH:	pemphigus herpetiformis
PCP:	*Pneumocystis jirovecii* pneumonia
PNP:	Paraneoplastic pemphigus
PV:	Pemphigus vulgaris
PVAS:	Pemphigus Vulgaris Activity Score
RA:	Rheumatoid arthritis

foods. A third system called the Pemphigus Vulgaris Activity Score (PVAS), takes into account the extent of mucocutaneous involvement, the type of lesions, and the presence of Nikolsky's sign.[7] A comparison of each of these systems is shown in Table I.

In a validation study comparing the interrater reliability of these scoring systems, the PDAI outperformed both the PVAS and ABSIS.[7,8] Specifically, while the intrarater reliability was excellent for PDAI, PVAS, and ABSIS, the interrater reliability was much better for the PDAI.

The PDAI has an advantage over other scoring systems in that it allows better sensitivity for a low number of lesions, since percentages of body surface area as used in the ABSIS score are unreliable below 1%.[8] The PDAI scores disease activity (i.e., blisters, erosions, and new/recent erythema) separately from damage (i.e., dyspigmentation, resolving erythema from faded lesions), whereas these features are combined in the ABSIS.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) analysis system, which requires set criteria to be satisfied before a disease activity assessment tool is fully validated, shows better validation for the PDAI and PVAS than for many other commonly used scores in dermatology, such as the Psoriasis Area and Severity Index (PASI) and the Eczema Area and Severity Index (EASI).[9] Responsiveness to change, an important component in outcome tools according to the COSMIN, is better when nonspecific damage elements are excluded from monitoring disease activity in the skin. The PDAI score has been shown to correlate with desmoglein 1 and 3 antibody levels by enzyme-linked immunosorbent assays (ELISA) in pemphigus, as detailed below.[10,11] The PDAI is an accepted outcome measure in clinical trials for pemphigus.[8]

Although the PDAI was studied for use in pemphigus foliaceus (PF) and pemphigus vulgaris (PV), it is reasonable to apply it to pemphigus erythematosus (PE), as it is a variant of PF, and to the Neuman subtype of pemphigus vegetans (PVe), as this is a variant of PV. Although the Hallopeau subtype of PVe, pemphigus herpetiformis (PH), and IgA pemphigus require a slightly different approach to treatment (detailed later), the PDAI may still be used as a scoring system for disease activity and response to therapy.

The Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire was developed and validated as a patient-reported outcomes tool. Another index that records the impairment of quality of life related to the treatments given for pemphigus is called the Treatment ABQOL, or TABQOL.[12,13] Patients can be followed as part of clinical practice using these patient-reported outcomes, which correlate better than the Dermatology Life Quality Index (DLQI) with clinical severity scores.

SEROLOGIC PARAMETERS

Key point

- ELISA for desmoglein 1 and 3 autoantibodies have a high level of diagnostic accuracy for the diagnosis of pemphigus

ELISA for autoantibodies directed against desmoglein 1 or 3 are a useful tool for the diagnosis of pemphigus, with an estimated sensitivity of greater than 90% and estimated specificity of 95%.[14,15] In addition to aiding diagnosis, antibody levels against desmogleins 1 and 3 as detected by ELISA are correlated with PDAI skin and ABSIS skin subscores at baseline.[16-18] Anti-desmoglein 1 antibody levels closely follow disease course, with a 79% positive predictive value and an 84% negative predictive value.[19] In contrast, anti-desmoglein 3 antibody levels have been found to have a weaker correlation with disease activity.[19,20] The US Food and Drug Administration has approved the 2 most widely used commercial ELISA kits for desmoglein 1 and 3 (MBL and Euroimmun) for their use as a diagnostic aid only and not for their use in monitoring disease activity.

Identification of circulating anti-desmoglein antibodies may predict disease relapse even if commercial ELISA assays are detecting nonpathogenic autoantibodies, as their detection may serve as a proxy for the presence of pathogenic autoantibodies. It remains to be determined whether to administer rituximab maintenance infusions based on clinical features, laboratory evidence of

Table I. Comparison of validated disease/activity scoring systems

Validated disease/Activity scoring system	Criteria	Advantages	Disadvantages	References
PDAI	Activity (erosions/blisters or new erythema) and damage (post-inflammatory hyperpigmentation or erythema from resolving lesions), each scored separately at 12 anatomic locations typical for pemphigus and scalp separately; activity (erosions/blisters) is scored for 12 mucous membrane locations	Sensitivity to small number of lesions (increases interrater reliability); does not rely on body surface area or lesion type; excellent intra- and interrater reliability for patients with both mild/moderate and extensive disease; investigators generally consider it easier to use compared to ABSIS; takes approximately 3 minutes to complete		2,9,20
ABSIS	Skin involvement (based on body surface area and type of lesion), oral involvement, severity (discomfort during eating/drinking based on type of food and pain/bleeding)	Excellent intra and interrater reliability for patients with extensive disease; takes approximately 5 minutes to complete	Interrater reliability has been found to be lower in patients with mild/moderate extent of disease (likely due to difficulties with estimates of body surface area); only assesses oral mucous membrane; food types only relevant to western diet	6,20
PVAS	Type of skin lesions, number of skin lesions, distribution of skin lesions, presence of Nikolsky sign, type of mucosal lesions, number of mucosal lesions	Fastest instrument to complete (takes an average of 1 minute)	Using Nikolsky sign as a factor may lead to variability in score based on rates' expertise; lower interrater reliability compared to PDAI and ABSIS	7-9

ABSIS, Autoimmune Blistering Disease Severity Index System; *PASI,* Psoriasis Area and Severity Index; *PDAI,* Pemphigus Disease Activity Index; *PVAS,* Pemphigus Vulgaris Activity Score.

circulating anti-desmoglein antibodies, or a combination of both.

TREATMENT OF PEMPHIGUS VULGARIS AND PEMPHIGUS FOLIACEUS

Key point

- First-line treatment for extensive pemphigus is rituximab, and systemic corticosteroids remain another mainstay of treatment

General approach

A wide range of therapeutic modalities have been reported in the treatment of the various forms of pemphigus (Table II). Several factors need to be considered prior to starting any specific treatments for pemphigus, including the subtype of pemphigus, the disease activity as determined by a clinical scoring system such as the PDAI, evaluation for any possible medications that are known to induce pemphigus, determination of any contraindications to various treatments, evaluation for any current active infections or malignancy, and vaccine status. Fig 1, *A* and *B* show a suggested therapeutic algorithm for the management of pemphigus.

Rituximab

Most data on the treatment of pemphigus are based on studies of the most common types of pemphigus: PV and PF. Unless contraindicated, the first-line treatment for significant (PDAI of 15 to 44) and extensive (PDAI of > 45) PV and PF is now generally considered to be intravenous rituximab (anti-CD20 therapy) with a tapering course of prednisone (starting at 0.5 mg/kg daily over 3 months for significant disease and starting at 1.0 mg/kg daily over 6 months for extensive disease). In comparison to chronic corticosteroid monotherapy, rituximab with corticosteroids has been found to be more effective with a decrease in relapse rate and with a more favorable safety profile.[18,21]

In terms of rituximab dosing, both the rheumatoid arthritis (RA) protocol (2 doses of 1000 grams

Table II. Various treatment modalities for pemphigus subtypes

Treatment modality	Dose	Disease(s)	Side effects	References
Systemic corticosteroid therapy (prednisone or prednisolone)	0.5-1 mg/kg/day	PV, PF, FS, PH, PE, PVe, IgA pemphigus, PNP	Hyperglycemia, weight gain, hypertension, congestive heart failure, hypokalemia, cushingoid changes, osteoporosis, osteonecrosis, peptic ulcer disease, cataracts, glaucoma, psychosis, personality change, depression, pseudotumor cerebri, tuberculosis reactivation, opportunistic infections, myopathy	86,87,93,95,112-117
Rituximab	2 doses of 1 g 2 weeks apart or 4 weekly doses of 375 mg/m^2	PV, PF, FS, PE, PVe, PNP	Infusion reactions, severe mucocutaneous reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatitis B reactivation, progressive multifocal leukoencephalopathy, infections, cytopenias, cardiovascular adverse reactions (especially in patients with history of arrythmias or angina)	21,87,99,116-119
Tetracycline	2 g/day for 1 month, followed by 1 g/day for 1 month	PV, PF, PE	Gastrointestinal adverse effects (e.g., nausea, abdominal discomfort), acute vestibular side effects, pseuedotumor cerebri, photosensitivity, dyspigmentation, vaginal candidiasis, gram-negative acne or folliculitis	49,117,120,121
Niacinamide	1.5 g/day	PV, PF, PVe, PE	Headache, gastrointestinal side effects, hepatotoxicity (rare)	117,120,121
Azathioprine	1-3 mg/kg/day	PV, PF, FS, PH, PE, PVe, IgA pemphigus, PNP	Immunosuppression carcinogenesis (e.g., lymphoproliferative malignancies, cutaneous squamous cell carcinoma), myelosuppression, infection, gastrointestinal symptoms (nausea, vomiting, diarrhea), pancreatitis (rare), hepatic damage	29,89,93,107,114-117,119
Mycophenolate	30-45 mg/kg/day	PV, PF, FS, PVe, PNP	Carcinogenicity (e.g., lymphoproliferative malignancies, nonmelanoma skin cancer), gastrointestinal symptoms, hematologic abnormalities (e.g., neutropenia, thrombocytopenia, anemia), infection, teratogenicity	29,87,106,117,122-124
Methotrexate	15 mg weekly	PV, PF, FS, PH	Hepatotoxitiy, pulmonary toxicity, pancytopenia, malignancy induction, gastrointestinal symptoms, teratogen, alopecia, headaches, fatigue, dizziness	59,87,117,125-127
IVIG	2 g/kg over 2-5 days per month	PV, PF, FS, PH, PE, PNP	Fatigue, nausea, vomiting, chills, infusion-related adverse effects, anaphylactic reactions, fluid overload, acute renal failure, transient neutropenia, hemolysis (rare), headaches, aseptic meningitis, thromboembolic events	87,115,117,119,128-131
Immunoadsorption	2 consecutive days every 2 weeks or 4 consecutive days every 4 weeks	PV, PF	Increased risk of infections, catheter-associated infections, hypotension, bradycardia, anaphylactic reactions	129,131-133
Cyclophosphamide	15 mg/kg monthly	PV, PF, PVe, PNP	Hemorrhagic cystitis, bladder cancer, non-Hodgkin lymphoma, leukemia, squamous cell carcinoma, gastrointestinal adverse effects (nausea, vomiting), myelosuppression, amenorrhea, premature ovarian failure, azoospermia, anagen effluvium	29,105,117,134-136

Cyclosporine	5 mg/kg	PV, PF, PE, PVe, IgA pemphigus, PNP	Renal dysfunction, hypertension, tremor, headache, paresthesia, hyperesthesia, hypertrichosis, gingival hyperplasia, nausea, abdominal discomfort, diarrhea, myalgia, arthralgia, laboratory abnormalities (hyperkalemia, hyperuricemia, hypomagnesemia, hyperlipidemia)	93,111,117,129,137-139
Dapsone	50 mg daily	PV, PF, FS, PH, PE, PVe, IgA pemphigus	Hemolytic anemia, methemoglobinemia, leukopenia, agranulocytosis, hepatitis, dapsone hypersensitivity syndrome/DRESS, morbilliform eruption, exfoliative erythroderma, toxic epidermal necrolysis, nausea, anorexia, psychosis, peripheral neuropathy	52,85,87,93,115,117,140,141
Etanercept	50 mg daily	PV, PF	Malignancy risk (lymphoma), increased risk of nonmelanoma skin cancer, increased risk of infections, reactivation of latent tuberculosis, reactivation of latent hepatitis B	117,142,143
Infliximab	5 mg/kg at weeks 0, 2, 6, 14	PV, PF	Malignancy risk (lymphoma), increased risk of nonmelanoma skin cancer, increased risk of infections, reactivation of latent tuberculosis, reactivation of latent hepatitis B	117,126,144
Sulfasalazine	500 mg 3 times daily	PV, PH	Nausea, vomiting, dizziness, abdominal pain, diarrhea, mood disturbance, mucocutaneous reactions, leukopenia, megaloblastic anemia, thrombocytopenia, abnormal liver function tests	115,145,146
Pentoxyfylline	400 mg 3 times daily	PV, PH	Nausea, gastrointestinal disturbances, dizziness, headache	115,117,145
Acyclovir	1200 mg daily for 2 weeks	PV	Nausea, vomiting, diarrhea, headache, reversible renal impairments caused by crystalline nephropathy	117,147
Colchicine	0.5—2 g/day	IgA pemphigus	Diarrhea, myelosuppression, avoid use with CYP3A4 or P-glycoprotein inhibitors	93,117
Acitretin	30 mg/day	IgA pemphigus	Teratogenicity, dry mucous membranes, cutaneous xerosis, elevation in serum lipids, blepharoconjunctivitis, elevated transaminases, telogen effluvium, nail fragility	93,117
Adalimumab	40 mg bi-weekly	IgA pemphigus	Malignancy risk (lymphoma), increased risk of nonmelanoma skin cancer, increased risk of infections, reactivation of latent tuberculosis, reactivation of latent hepatitis B	93,117
Alemtuzumab	30 mg IV 3 times weekly for 12 weeks	PNP	Infusion reactions, increased risk of infections	117,148
Therapeutic plasma exchange	3 therapeutic plasma exchanges per week for 1-3 months	PV, PF, PVe, PNP	Hypotension, hematoma, access-related infections	66,93,101,129,149-152

DRESS, Drug reaction with eosinophilia and systemic symptoms; *FS,* fogo selvagem; *PE,* pemphigus erythematosus; *PF,* pemphigus foliaceus; *PH,* pemphigus herpetiformis; *PNP,* paraneoplastic pemphigus; *PV,* pemphigus vulgaris; *PVe,* pemphigus vegetans.

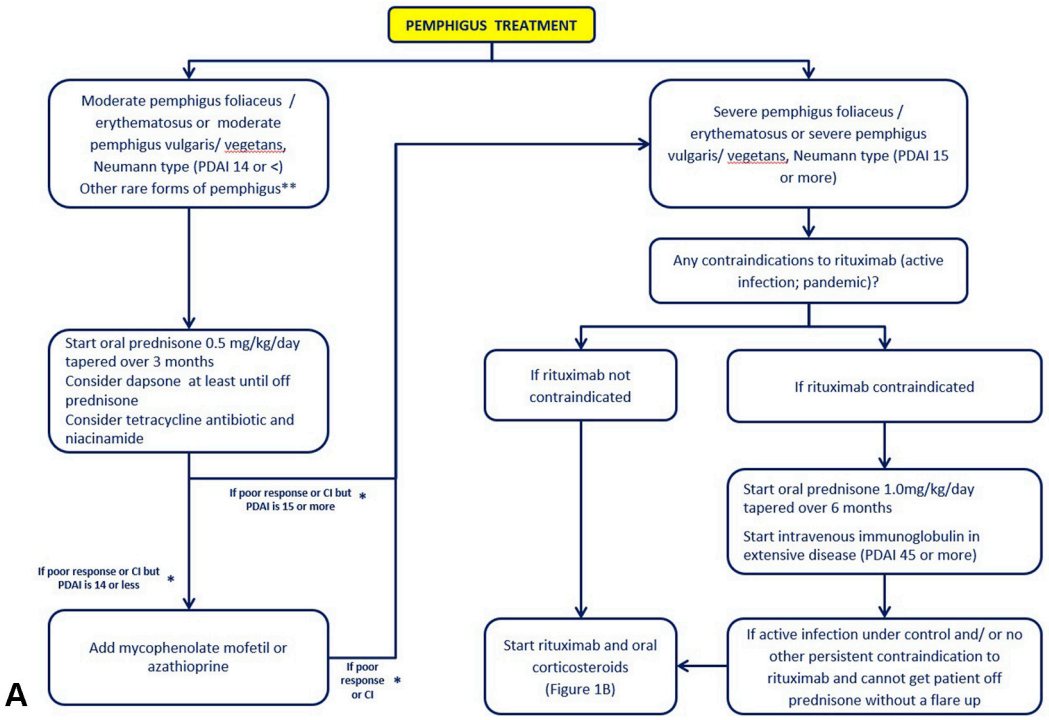

Fig 1. Suggested therapeutic algorithm guide in the management of pemphigus. **A**, Pemphigus treatment. **B**, Rituximab and oral corticosteroids for pemphigus. *Any secondary infection should be excluded prior to starting the next treatment in the therapeutic level. **Rare foms of pemphigus include pemphigus herpetiformis, pemphigus vegetans Hallopeau subtype and IgA pemphigus. *CI*, Contraindications.

intravenously administered 2 weeks apart) and the lymphoma protocol (375 mg/m^2 intravenous rituximab administered weekly for 4 weeks) have been studied in PV and PF and have been found to have comparable response rates. The US Food and Drug Administration approved the RA protocol for treatment of pemphigus in 2018.[22] A recent retrospective study showed that patients treated with the lymphoma protocol were 2.7 times more likely to achieve complete remission off therapy compared to patients treated with the RA protocol.[22] This study also found that older patient age and BMI less than 35 were associated with higher odds of achieving complete remission off therapy, independent of dosing regimen.[22]

Relapse of pemphigus is defined as the development of 3 or more new lesions within 1 month that do not heal within 1 week.[23] The majority of relapses after this regimen occur early (between 6 and 12 months) and the main predictors for relapse are a high pretreatment PDAI score (≥45) or persistently elevated desmoglein 1 and/or 3 autoantibodies 3 months after the first cycle of rituximab.[23] In this subset of patients, an additional single infusion of low-dose intravenous rituximab 500 mg administered around 6 months after the first cycle or when circulating CD20-positive B cells are detectable at normal levels is recommended to decrease the early relapse rate.[23] Insufficient data exist on the benefit of further scheduled cycles of rituximab in patients with pemphigus who are in clinical remission following an initial cycle and a follow-up single low-dose (500 mg) infusion 6 months later.

There is scant evidence available on the safety and efficacy of the continued use of oral immunosuppressive agents or corticosteroids when starting rituximab. In general, the therapeutic aim is to taper to the lowest possible doses of oral immunosuppressive agents and systemic steroids while rituximab takes full effect. The decision on whether to stop or taper other immunosuppressive agents once starting rituximab should be determined on a case-by-case basis.

Systemic corticosteroids

Because it reliably offers rapid disease control, systemic corticosteroid therapy remains a mainstay of treatment, particularly when rituximab cannot be obtained or is contraindicated. Given the chronicity of pemphigus, immunosuppressive adjuvant therapy is usually added to help decrease the corticosteroid dose and reduce flares. Frequently employed

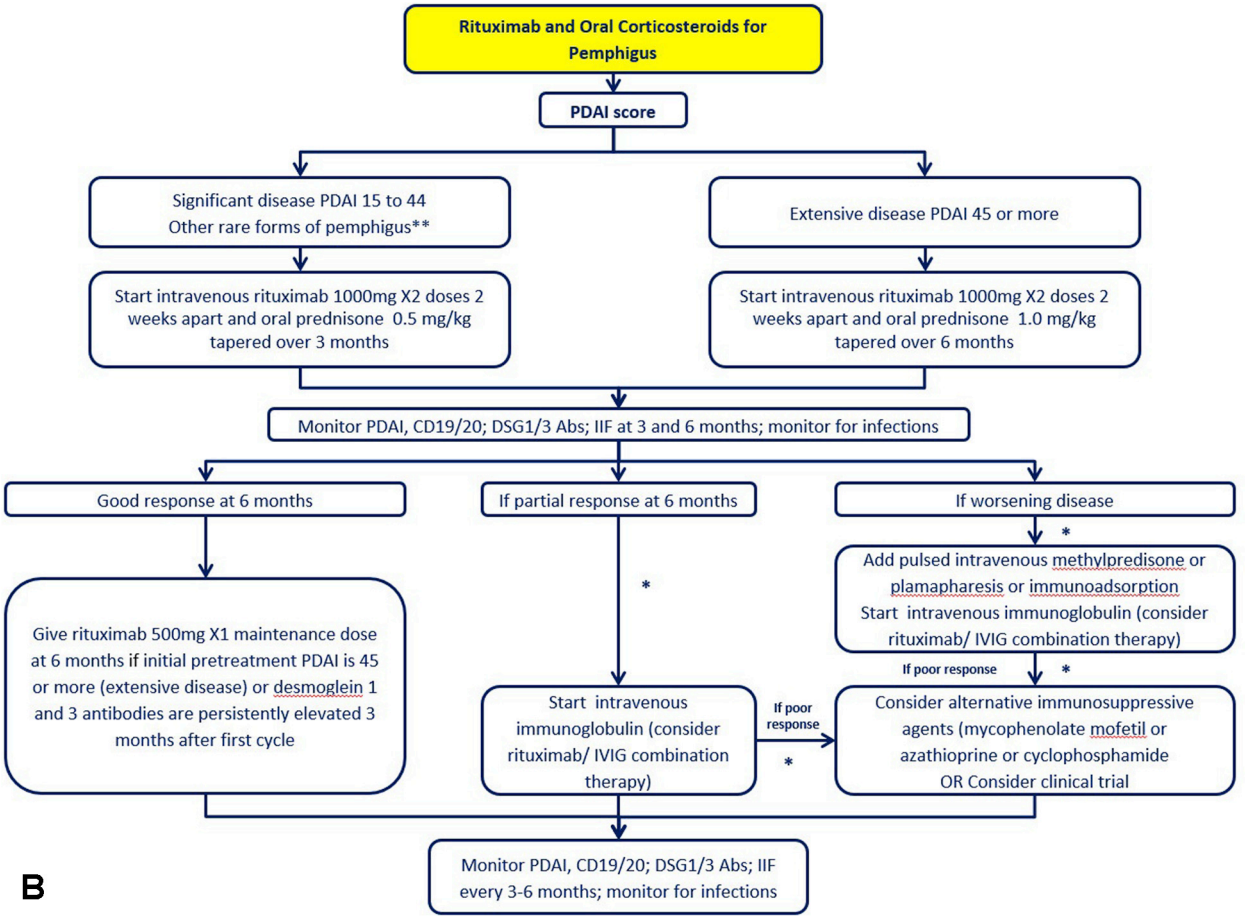

Fig 1. (*continued*).

corticosteroid-sparing agents include azathioprine and mycophenolate mofetil (MMF).[24-31] Other corticosteroid-sparing therapeutic interventions include intravenous immunoglobulin (IVIG), which is usually used in combination with an oral immunosuppressive agent; immunoadsorption; or oral or pulsed intravenous cyclophosphamide.[18,32-44] The use of IVIG, plasmapheresis, and immunoadsorption results in relatively rapid improvement of pemphigus and therefore may be particularly good initial short-term alternative treatments to high-dose corticosteroids, especially in those individuals in whom the latter is contraindicated.

Patients on greater than or equal to 20 mg prednisone-equivalent per day, or prednisone in addition to a cytotoxic agent, for 4 weeks or longer, should be considered for Pneumocystis jirovecii pneumonia (PCP) prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) double strength by mouth daily or 3 times per week.[45-47] Additional risk factors that may further prompt PCP prophylaxis include patients with T- or B cell immunodeficiencies, prior organ transplantation, pulmonary fibrosis, or lymphopenia.[47] If a patient happens to be treated with dapsone for pemphigus, this medication serves as a PCP prophylaxis, and the addition of Trimethoprim-sulfamethoxazole is not required.

Other treatment modalities

Other treatment modalities reported to be potentially helpful in the management of pemphigus include tetracycline antibiotics (tetracycline, doxycycline, and minocycline), niacinamide, dapsone, cholinergic agonists, methotrexate, oral calcineurin inhibitors (cyclosporin and tacroloimus), and plasmapheresis.[48-71]

In addition to its positive adjuvant effect on disease activity, dapsone is also an effective agent used for PCP prophylaxis, as above.[51-55,72]

Tetracycline antibiotics, cyclosporine, niacinamide, and cholinergic agonists (pyridostigmine) also have been found to control disease activity.[48-50,56,61] These agents are thought to inhibit the keratinocyte apoptolysis of pemphigus pathogenesis by mitigating mitochondrial injury

from antimitochondrial antibodies (including antibodies to the nicotinic acetylcholine receptor) that may be present in patients with pemphigus.[73,74] Adding 1 or more of these mitochondria-protective agents, such as minocycline and niacinamide, to the treatment regimen of pemphigus may potentially decrease the relapse rate.[75]

Recalcitrant cases

In cases of PV and PF that are not completely responsive to the above treatments, or remain recalcitrant or worsen, alternative and combination treatments should be considered. These include the addition of IVIG in combination with repeated rituximab infusions, pulsed intravenous cyclophosphamide with or without pulsed intravenous methylprednisolone or dexamethasone or plasmapheresis; the addition of an immunosuppressive agent (MMF or azathioprine or methotrexate); or the addition of plasmapheresis or immunoadsorption, where available.[24-44,57-71,76-79] Cyclosporine and tacrolimus also can be considered as other treatment modalities.[61-65] Enrolling patients in a clinical trial is an excellent option, when logistically feasible. Table III provides a list of current clinical trials.

Considerations and contraindications to immunosuppressive therapy

When initiating immunosuppressive therapy, the patient's individual risk for infection is an important consideration and is of particular importance during the COVID-19 pandemic.[80-82] Two recent studies conducted in France and Iran have found an increased risk of death from COVID-19 among pemphigus patients treated with rituximab compared to other therapies (P. Joly, MD, presentation to the European Academy of Dermatology and Venerology Blistering Disease Task Force, 2020; M. Daneshpazhooh, MD, PhD, personal communication, November 2020, virtual EADV congress, 2020). The decision of whether to initiate or continue immunosuppressive medications should be determined on a case-by-case basis, depending on factors that include the severity of a patient's autoimmune blistering disease, underlying comorbidities that may place the patient at higher risk for severe COVID-19 infection, patient goals, the ability of the patient to adhere to measures to reduce infection risk, including social distancing, mask use, and regular hand washing, and local infection rates for COVID-19.[80-82] Prior to initiating immunosuppressive medications in patients with pemphigus, testing for active COVID-19 infection might be considered to further assess the risks of immunosuppression, particularly if local infection rates are high.[80-82]

If the use of rituximab is contraindicated for reasons related to a patient's increased risk for infection or malignancy, then the treatment approach for severe pemphigus should be focused on utilizing non-immunosuppressing treatments, such as IVIG, dapsone, or a tetracycline antibiotic and niacinamide.[32-37,48-55] A tapering dose of prednisone using the lowest possible doses over a shorter period of time or plasmapheresis or immunoadsorption (if systemic corticosteroids are completely contraindicated) can also be considered, especially if IVIG is not controlling the disease rapidly enough.

Treatment of moderate cases of pemphigus foliaceus and pemphigus vulgaris

In PF and PV with a PDAI score of 14 or less, the treatment includes a more conservative approach, starting with a tapering dose of prednisone (starting at 0.5 mg/kg daily), a tetracycline antibiotic with niacinamide, or dapsone.[48-55] If patients do not respond and/or require continued prednisone with this regimen, then addition of an immunosuppressive agent such as MMF or azathioprine could be considered.[24-31] If the patient has progressive and severe disease with a PDAI>14, then rituximab and oral corticosteroids should be considered, as above. Although treatment of patients with mild disease with rituximab has not been evaluated in a randomized clinical trial, this treatment modality could be a potential future treatment option for these patients. In addition, new therapies which have action against pathways for B cells and other cells active in pemphigus are emerging and may be an option for patients with mild disease.

Clinical course

Pemphigus is a chronic disorder and the clinical course following treatment is variable. With rituximab, complete remission of the disease occurs in about 89% of patients at 24 months, though relapse rates are variable.[21] We have treated many patients who have not relapsed for several years after a single cycle of treatment with rituximab and who, at the time of relapse, responded completely to another cycle of rituximab (personal observations, MJC, JSL).

TREATMENT OF OTHER INTRAEPITHELIAL AUTOIMMUNE BULLOUS DERMATOSES

Key point

- Patients with PE should avoid exposure to ultraviolet radiation to prevent exacerbations
- Patient with PH generally respond well to oral dapsone

Table III. Treatment modalities currently undergoing clinical trials for the treatment of pemphigus

Drug	Route of administration	Mechanism of action	Current status
Ofatumumab	Subcutaneous	Fully human anti-CD20 monoclonal antibody	Efficacy in pemphigus was being studied in a phase 3 clinical trial (NCT02613910, clinicaltrials.gov).[153] The study was terminated early due to factors unrelated to patient safety or efficacy
Mycophenolate mofetil	Oral	Inhibits *de novo* purine synthesis specific to lymphocytes	Studied in a phase 3 clinical trial for treatment of pemphigus compared to rituximab (NCT02383589; clinicaltrials.gov).[31,153] Data have been posted to clinicaltrials.gov, and a publication is likely forthcoming.
Ianalumab (VAY736)	Intravenous	Human monoclonal antibody that targets BAFF-R, blocking the binding of BAFF to BAFF-R, which normally signals for B cell differentiation, proliferation, and survival.[153]	A Phase 2 trial investigating use of ianalumab to treat pemphigus has been completed and results have yet to be published (NCT01930175; clinicaltrials.gov).[153]
Rilzabrutnib (PRN-1008)	Oral	Reversible covalent BTK inhibitor, which can inhibit both the innate rapid onset and adaptive immune response which generates autoantibodies	Two phase-2 studies, 1 in pemphigus patients (NCT02704429; clinicaltrials.gov) and 1 in dogs who have pemphigus. Both have been completed and presented at EADV and AAD but not yet published. A phase-3 randomized controlled trial for rilzabrutinib vs placebo in addition to steroid tapering is currently underway (phase 3; NCT03762265; clinicaltrials.gov).
Efgartigimod (ARGX-113)	Intravenous	Human IgG1-derived Fc fragment that binds to human neonatal Fc receptor	Phase 2; NCT03334058; clinicaltrials.gov.[153]
Regulatory T-cell Adoptive Therapy	Intravenous	Autologous polyclonal expanded T regulatory cells	Phase 1; NCT03239470; clinicaltrials.gov).[153]

AAD, American Academy of Dermatology; *anti-CD20,* anti-cluster of differentiation 20; *BAFF*, B-cell activating factor; *BAFF-R*, B cell activating receptor; *BTK,* Bruton's tyrosine kinase; IgG1, Immunoglobulin G1; *EADV,* European Academy of Dermatology and Venerology.

Data on treatment of the other variants of pemphigus, including drug-induced pemphigus, PE, fogo selvagem, PVe, PH, IgG/IgA pemphigus, IgA pemphigus, and paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS), are limited to case series and reports and consensus recommendations.

Drug-induced pemphigus should be managed by discontinuing the suspected causative medication, where feasible. In addition, immunosuppressive medications including systemic steroids as described above for pemphigus, may be required.[83,84] Cases of drug-induced pemphigus that are associated with a thiol-containing drug tend to remit once the drug is discontinued, while a subset of cases associated with a non-thiol drug tend to have a chronic course despite discontinuing the inciting drug.[84] These latter cases will require more prolonged therapy and should be treated like PV and PF.

The treatment of PE is similar to that of PF, being a variant of this subtype of pemphigus (Fig 1, *A* and *B*).[85,86] Patients with PE should avoid exposure to UV radiation to prevent exacerbations. Antimalarials have been reported to be helpful.[85,86]

The treatment modalities used for FS are similar to those used for PF.[87] Factors that determine the initial treatment of choice of FS depends on the extent of the disease and cost and availability of the medication.[87] For localized disease, first-line treatment includes topical and intralesional corticosteroids, topical calcineurin inhibitors, and oral dapsone or low-dose prednisone (0.25 mg/kg daily).[87] Prednisone at a dose of 0.5 mg/kg daily is used for refractory localized disease or moderate disease involving more than 10% of body surface area.[87] When the disease is widespread and covers > 10% of body surface area, high-dose prednisone (1 mg/kg daily) is used in combination with an additional steroid-sparing immunosuppressive agent, such as methotrexate, azathioprine, or MMF.[87] When feasible, rituximab and oral corticosteroid therapy are used as first-line therapy, especially in severe extensive disease.[87] Rituximab and IVIG are considered for refractory cases.[87] Cyclophosphamide is another consideration for refractory disease but should be used with caution given its serious side effects profile.[87] Additionally, photoprotection, strongyloidiasis prophylaxis, and treatment of superinfection are important aspects of treatment of FS.[87]

PH is unique in that it generally has a less-severe clinical course and usually responds wells to dapsone at 100-300 mg by mouth per day, with or without low-dose systemic corticosteroids.[88,89] Anecdotally, dapsone and possibly a combination of tetracycline and niacinamide (personal observations, MJC) are particularly helpful in PH, which is pathologically characterized by a brisk inflammatory infiltrate of eosinophils and neutrophils.[89]

The treatment of PVe depends on the subtype and extent of the disease. The Hallopeau subtype, which is more mild, can generally be controlled with low-dose systemic corticosteroids to achieve disease remission.[90,91] On the other hand, the Neumann subtype tends to follow a more severe course similar to pemphigus vulgaris, with relapses and remissions, and therefore should be treated like PV (Fig 1, *A* and *B*).[90,91]

IgA pemphigus is typically treated with oral dapsone.[92] In cases with a partial response, a tapering course of oral corticosteroids may be added.[92] For patients who cannot tolerate dapsone or who have recalcitrant disease, additional reported therapies include colchicine, adalimumab (tumor necrosis-alpha inhibitor), acitretin, cyclophosphamide, MMF, azathioprine, IVIG, rituximab, and plasmapheresis.[92-94]

Treatment of PNP/PAMS includes addressing the underlying malignancy, as well as the initiation of systemic corticosteroids, rituximab (especially when associated with underlying hematologic malignancies of B cell origin), IVIG, or other immunosuppressive agents, such as cyclophosphamide, MMF, azathioprine, cyclosporine, tacrolimus, or alemtuzumab.[95-111] Care must be taken to balance the treatment of PNP/PAMS with the risk of suppressing cancer surveillance via immunosuppression. PNP/PAMS has a poor prognosis and often is difficult to treat.

Conflicts of interest

None disclosed.

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