MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER (MASCC) 2020 CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF SEVERE DERMATOLOGICAL TOXICITIES FROM CHECKPOINT INHIBITORS

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Running title: Immune-mediated dermatological toxicities

Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; JC and ML shared sections on dermatological immune-related adverse events equally, while BLR and DBJ provided clinical input and BLR, DBJ and RA editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

Acknowledgments

This work was funded in part by NIH/NIAMS grant U01AR077511 and the NIH/NCI Cancer Center Support Grant P30 CA008748.

Professor BL Rapoport is supported by supported by the Cancer Association of South Africa (CANSA) and the National Research Foundation (NRF) of South Africa.

Dr. I. Glezerman is supported by the NIH/NCI (Cancer Center Support Grant P30 CA008748)

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Abstract

Immune checkpoint inhibitors (ICIs) frequently result in cutaneous immune-related adverse events (IrAEs). Although the majority of these events are mild-to-moderate in severity, up to 5% are severe, which may lead to morbidity and dose interruption or discontinuation of ICI therapy. In addition, up to 25% of dermatologic IrAEs are corticosteroid-refractory or corticosteroid-dependent. These 2020 MASCC recommendations cover the diagnosis and management of cutaneous IrAEs with a focus on moderate-to-severe and corticosteroid-resistant events. Although the usage of immune-suppressive therapy has been advocated in this setting, there is a lack of randomized clinical trial data to provide a compelling level of evidence of its therapeutic benefit.

Keywords: bullous dermatoses, corticosteroids, cutaneous IrAEs, Inflammatory dermatitis, pruritus, skin rash, vitiligo

Introduction

Dermatologic toxicities secondary to anti-CTLA-4 and anti-PD-1/anti-PD-L1 inhibitors are the most common immune-related adverse events among all organ systems. Rash, pruritus, and vitiligo are most frequently observed, while immunobullous reactions and severe cutaneous adverse events are less common, but are important to recognize and treat promptly. Rarer side effects have been reported and continue to emerge daily. Cutaneous side-effects may be a surrogate for clinical benefit; therefore, it is important to recognize these side-effects and appropriately manage them, while trying to avoid discontinuation of immunotherapy if at all possible. With early diagnosis and prompt management, patients may be able to continue treatment with immune checkpoint inhibitors (ICIs), which may ultimately be crucial for overall treatment outcomes. However, it is also important to recognize potentially severe side-effects and to know when to hold or discontinue immunotherapy permanently.

The majority of dermatologic reactions secondary to ICIs are of grade 1-2, with grade 3-4 reactions occurring in <3% during monotherapy with ipilimumab or anti-PD-1 and <5% with the combination [1]. However, it is the grade 3-4 reactions that need prompt recognition and appropriate management in order to prevent potentially fatal outcomes and/or unnecessary permanent discontinuation of life-saving immunotherapy. The pathophysiologic mechanisms of cutaneous immune related adverse events have not been fully elucidated. Yet they appear to be clearly related to enhanced T-cell activation against dermal or epidermal antigens mediated by blockade of PD-1 and CTLA-4 receptors.

Broadly, the skin reactions observed with ICI therapy can be categorized as follows:

- Inflammatory dermatitis, which can be of various clinical presentations and histologic patterns, including eczematous/spongiotic, lichenoid (collective term for conditions that are flat-topped, often scaly in appearance that are associated with infiltration/inflammation between the dermis and epidermis), psoriasiform, and urticarial;
- Immunobullous reactions, including bullous pemphigoid, pemphigus vulgaris, and lichen planus pemphigoides;
- Severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN);
- Pruritus, either in association with, or separate from, visible skin reactions;
- Immune-mediated alteration of melanocytes, including regression of nevi and vitiligo.

Clinical examples of these skin reactions are shown in Fig. 1.

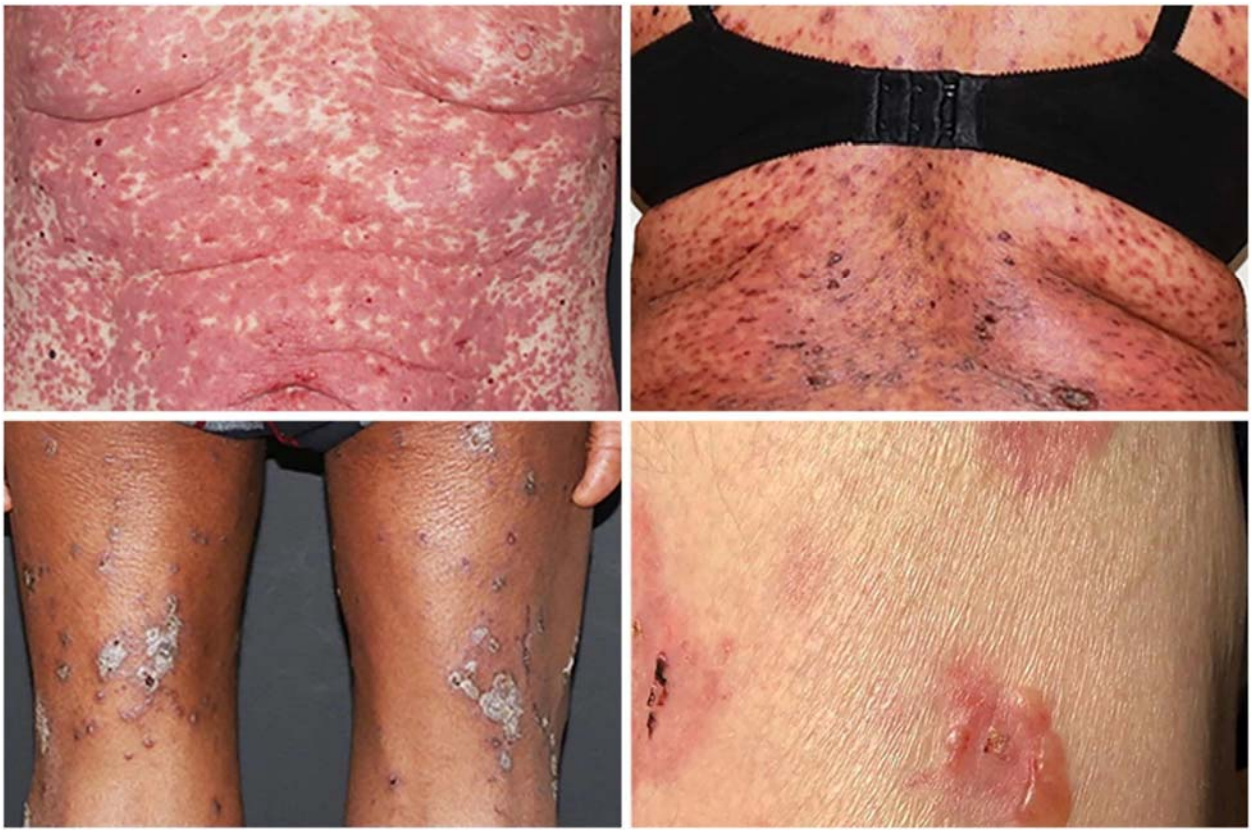

Fig 1. Clinical phenotype of dermatologic immune-related adverse events (IrAEs): maculopapular rash (left upper), lichenoid rash (right upper), eczematous (left lower), and bullous pemphigoid (right lower)

Aside from these categories, there are case reports of other more rare types of cutaneous reactions, including autoimmune skin diseases such as dermatomyositis, scleroderma, subacute cutaneous lupus erythematosus, granulomatous disease, and alopecia areata, which will not be discussed at length in this manuscript.

Literature Review and Recommendations

A systematic literature search was conducted for papers from 1960 to May 2019. The MEDLINE (via PubMed) and Thomson-Reuters' Web of Science databases were searched using the following generic drug names and synonyms as search terms: ipilimumab (Yervoy®), pembrolizumab (MK-3475, SCH900475, lambrolizumab Keytruda®), nivolumab (BMS-936558, MDX-1106, ONO-4538, Opdivo®), atezolizumab (MPDL-3280A, RG-7446, R05541267, Tecentriq®), avelumab (MSB-0010718C,

Bavencio®), durvalumab (MEDI-4736, Imfinzi®), and cemiplumab (REGN2810, Libtayo®). Primary case reports, case series, and data from clinical trials were included. All published peer-reviewed literature from the search was reviewed (limited to the English language only, with inclusion of selected non-English reports with abstracts in English). The evidence used for these guidelines consists mainly of systematic reviews of observational data, consensus guidelines [2,3,4,5,6], case series, and case reports guided by dermatologist authors (J.C. and M.E.L.).

Rash/Inflammatory Dermatitis

An inflammatory dermatitis described to be of several different clinical and histologic variants, including non-specific maculopapular or morbilliform rash, eczematous/spongiotic, lichenoid, and psoriasiform [7,8,9,10]. The non-specific morbilliform eruption typically occurs in the first 3–6 weeks or sooner primarily with anti-CTLA-4 therapy [11, 12], though delayed onset of months has been reported [13]. Other reactions are more common with PD(L)1 inhibitors as single agents or when combined with anti-CTLA-4; eczematous eruptions clinically present with pruritic, ill-defined, erythematous, and scaly papules and plaques, most commonly on the trunk and extremities. Lichenoid eruptions are seen particularly with anti-PD-1 and anti-PD-L1 agents [10, 14,15,16] that are characterized by an infiltrate of inflammatory cells in the dermis and epidermis, with the lesions having polygonal shapes and a violaceous color, reminiscent of naturally occurring lichen. Onset of lichenoid cutaneous reactions tends to be delayed, with a mean of 4 months, but may occur up to over a year later [10, 17]. Psoriasiform eruptions secondary to anti-PD-1/anti-PD-L1 therapy have been well-established, either as new onset or as exacerbations of pre-existing psoriasis [18, 19]. Plaque psoriasis is the most common clinical presentation, while guttate, pustular, or inverse variants of psoriasis are possible, albeit less common [19]. Concomitant psoriatic arthritis can also develop, which may require systemic therapy for control [11].

Bullous dermatoses

Though several types of cutaneous eruptions in the setting of immune checkpoint blockade can present as bullous, including lichenoid reactions, autoimmune blistering disease-like reactions are distinct mucocutaneous manifestations. More specifically, bullous pemphigoid is an autoimmune antibody-mediated disorder that can develop de novo, or as an exacerbation of pre-existing bullous pemphigoid secondary to PD-1 and PD-L1 inhibitor-targeted therapy [20,21,22,23]. These are rare with CTLA-4 inhibition. Pruritus is a predominant feature that can sometimes precede onset of visible bullae by months. Bullae develop approximately 6 to 8 months after initiation of immune checkpoint blockade as part of bullous pemphigoid, pemphigus vulgaris, or lichen planus pemphigoides, though a subset of reported cases demonstrate delayed onset up of to one and a half years. Oral mucosa can be involved in approximately 30% of patients [24, 25]. In approximately 75% of patients who develop autoimmune blistering disorders, discontinuation of immunotherapy may be necessary, though cases of successful treatment while continuing immunotherapy have been reported.

Severe Cutaneous Adverse Reactions (SCARs)

Rare cases of SCARs, including SJS, TEN, acute generalized exanthematous pustulosis (AGEP), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with both CTLA-4 and PD-1/PD-L1 inhibitors; some resulting in death [26,27,28,29,30,31,32]. It is notable that these reactions may occur without the classic clinical morphology or time course, which is typically within a few days to 4 weeks after initiation of the offending drug. These reactions can occur in a delayed or progressive fashion after several cycles of treatment [26, 32]. Although two cases of pembrolizumab-induced SJS have been successfully treated with cyclosporine, additional studies are required to improve the level of evidence [32].

Pruritus

Grade 3 incidence secondary to PD-1 inhibitor therapy ranges from 5% to 10% [13, 33]. Pruritus can occur either with or without rash, most commonly on the trunk and extremities, and can be associated with a significantly decreased quality of life [11].

In the case of severe or unremitting pruritus, an occult diagnosis of bullous pemphigoid should be considered, as pruritus can be the presenting symptom in the absence of bullae for many weeks to months before typical changes of bullous pemphigoid present.

I. Rash/inflammatory dermatitis

Diagnostic Work-up:

For any inflammatory dermatitis, each patient should undergo the following evaluations:

- Pertinent history and physical examination;
- Rule out any other cause for the skin condition, including infection, other drug side-effect, or unrelated primary skin disorder;
- Blood laboratory values, including complete blood cell count, as well as liver and kidney function tests;
- Specific serologic studies if an autoimmune condition is suspected, such as dermatomyositis or lupus: screening for antinuclear (ANA), SS-A/anti-Ro, SS-B/anti-La, autoantibodies and/or other serologic tests;
- Skin biopsy.

Grade 3: Macules/papules covering > 30% body surface area (BSA) with or without associated symptoms; limiting self-care ADLs; or grade 2 not responding to therapy.

Management:

-Withhold ICI therapy;

-Dermatology referral for guidance in management;

-Consider skin biopsy and clinical photography to aid in monitoring;

-Initiate oral prednisone or intravenous methylprednisolone (or equivalent) 1 mg/kg daily, tapering over 4 weeks or longer if needed;
-If there is a quick response to steroid treatment, can consider shorter taper over 2 weeks;
-If there is no improvement in rash at 1 mg/kg daily dosing within 5 days, then consider increasing steroid dosing to 2 mg/kg daily (or 1 mg/kg twice daily);
-May consider resuming ICI if rash reverts to grade 1 or mild grade 2 with close monitoring;
-If rash recurs with steroid taper or discontinuation, consider either maintenance low-dose oral prednisone (e.g. 10 mg daily), while resuming ICI therapy or adjunctive dermatologic treatments with co-management by Dermatology (*e.g.* narrowband ultraviolet B phototherapy 2-3 times a week for several weeks to months and discontinue phototherapy after rash has resolved);
- For psoriasiform eruptions, consider steroid-sparing therapies, such as phototherapy, acitretin (e.g., 10–25 mg daily), apremilast (e.g., 30 mg twice daily), or methotrexate (e.g., 15 mg weekly), in order to avoid long-term treatment with systemic corticosteroids [19, 34,35,36,37]. However, the level of evidence for such recommendations is very low, largely based on case reports. TNF-alpha inhibitors, such as etanercept, adalimumab, or infliximab, and interleukin inhibitors, such as ustekinumab (IL-12/23 inhibitor), secukinumab (IL-17 inhibitor), ixekizumab (IL-17 inhibitor), brodalumab (IL-17RA inhibitor), tildrakizumab (IL-23 inhibitor), risankizumab (IL-23 inhibitor), and guselkumab (IL-23 inhibitor), can be considered in severe cases, but must be used with caution and careful monitoring as potential impact on tumor control by immune checkpoint blockade is not yet known. It should be emphasized, however, that these recommendations are based largely on case series or case reports and compelling supporting evidence is awaited [38,39,40,41,42,43].

Grade 4: Macules/papules covering >30% BSA with associated symptoms, unresponsive to prior interventions, rapidly progressing, and/or intolerable.

Management:

- Discontinue ICI
- Urgent dermatology referral for skin biopsy and guidance in management
- Initiate high-dose intravenous methylprednisolone (or equivalent) 1–2 mg/kg daily until toxicity improves, tapering over at least 4 weeks or longer if needed
- Monitor closely for possible progression to SCAR
- Admit patient to hospital with co-management between oncology and dermatology
- Determine appropriateness with dermatology of resuming ICI once skin toxicity resolves and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg daily
- If rash does not resolve to grade 1 or less, discontinue ICI permanently and consider alternative antineoplastic therapy

II. Bullous dermatoses

Diagnostic Work-up:

For any bullous dermatosis, each patient should undergo the following evaluations:

- Pertinent history and physical examination;
- Rule out any other cause for the skin condition, including infection, other drug side-effect, or unrelated primary skin disorder;
- Consult Dermatology to rule out other causes for blisters of the skin, including herpes simplex, herpes zoster, bullous impetigo;
- Blood laboratory values, including complete blood cell count, as well as liver and kidney function tests, may be performed if needed;
- Specific serologic studies if bullous pemphigoid is suspected, including anti-BP180 and anti-BP230 IgG antibody levels, or under the guidance of Dermatology, other serologic studies and sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering conditions;

- Skin biopsy if the diagnosis of bullous pemphigoid is suspected (lesional biopsy for hematoxylin and eosin evaluation and perilesional biopsy for direct immunofluorescence evaluation).

Grade 3: Blisters >30% BSA with skin sloughing with associated pain or pruritus and limiting self-care ADLs

Management:

- Withhold ICI therapy;
- Urgent Dermatology referral for work-up and guidance in management;
- Consider admission to hospital for initial management and supportive wound care;
- Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg daily until improvement is achieved, then transition to prednisone (or equivalent) 0.5-1 mg/kg daily, tapering over at least 4 weeks;
- For diagnosis of bullous pemphigoid, after initial treatment with high-dose corticosteroids, consider treatment with steroid-sparing therapies, such as rituximab (e.g., 500 mg IV weekly for 4 weeks) or omalizumab (e.g., 300 mg every 4 weeks) in order to avoid long-term treatment with systemic corticosteroids [39,40,41];
- Treat skin with ointment emollient, such as petrolatum, with non-stick bandages over any open erosions, changed once to twice daily; use of oral antibiotic such as doxycycline at a dose of 50 to 100 mg twice daily may be useful if any signs of bacterial superinfection are evident [44];
- If any concern for overlying infection (*e.g.* purulent drainage, significant edema or induration, fever), obtain cultures of skin and/or blood and consult infectious diseases specialist for guidance in management.

III. SCARs (Severe Cutaneous Adverse Reactions), including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS/DIHS (drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome)

Diagnostic Work-up:

For any potential severe cutaneous adverse reaction, each patient should undergo the following evaluations:

- Pertinent history, complete review of systems, and physical examination;
- Skin examination should include examination of all areas, including all mucous membranes (eyes, nares, oropharynx, genitals, perianal area);
- Rule out any other cause for the skin condition, including infection, other drug side-effect, or unrelated primary skin disorder;
- Blood laboratory values, including complete blood cell count with differential, liver, and kidney function tests, including urinalysis; if patient is febrile, include blood cultures and urine cultures;
- Skin biopsy is indicated to assess for full-thickness epidermal necrosis, as seen in SJS/TEN;
- For significant involvement of mucous membranes or blistering of skin, consider admission to the hospital for monitoring and management, and to the intensive care unit or burn unit if needed;
- Pay special attention to the following symptoms on review of symptoms as concerning signs: skin pain, fevers, ocular pain or photophobia, sores of discomfort in the nares, sores or discomfort in the oropharynx, pain with swallowing, hoarseness, sores or discomfort in vaginal area for women or meatus of penis in men, sores or discomfort in the perianal area, pain with bowel movements, dysuria, abdominal pain, myalgias, arthralgias, malaise;

- Physical examination should include assessment for lymphadenopathy, facial swelling, or distal extremity swelling (can be signs of DIHS/DRESS); pustules, vesicles, bullae, or erosions; targetoid lesions with central dusky erythema (as can be seen in SJS/TEN).

Grade 3: Skin sloughing covering <10% BSA with associated signs (e.g. erythema, purpura, epidermal detachment, mucous membrane detachment)

Management:
-Withhold ICI therapy;
-Dermatology referral for work-up and guidance in management;
-Consider admission to hospital for initial management and supportive wound care
-Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg daily until improvement is achieved, then transition to prednisone (or equivalent) 0.5-1 mg/kg daily, tapering over at least 4 weeks when toxicity resolves;
-Treat skin with ointment emollient, such as petrolatum, with non-stick bandages over any open erosions, changed once to twice daily; use of topical antibiotic ointment may be useful if any signs of bacterial superinfection;
-For mucous membrane involvement of SJS or TEN, offer appropriate consulting services to help prevent sequelae from scarring (*e.g.* ophthalmology, ear, nose, and throat, gynecology, urology).

Grade 4: Skin sloughing covering 10-30% BSA with associated signs (e.g. erythema, purpura, epidermal detachment, mucous membrane detachment) or skin erythema ≥30% BSA with systemic symptoms (e.g. fever) and concerning laboratory work-up abnormalities suggestive of DRESS/DIHS (e.g. elevated liver function tests, elevated creatinine, atypical lymphocytes); skin sloughing covering ≥30% BSA with associated symptoms (e.g. erythema, purpura, epidermal detachment) defines toxic epidermal necrolysis.

Management:

-Permanently discontinue ICI therapy;

-Urgent Dermatology referral for work-up and guidance in management;

-Admit patient immediately to intensive care unit or burn unit for supportive care in wound care and fluid/electrolyte management;

-For mucous membrane involvement of SJS or TEN, offer appropriate consulting services to help prevent sequelae from scarring (*e.g.* ophthalmology, ear, nose, and throat, gynecology, urology);

-Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg daily until improvement is achieved, then transition to prednisone (or equivalent) 0.5-1 mg/kg daily, tapering over at least 4 weeks when toxicity resolves;

-If no response or resolution with systemic corticosteroids, consider IVIG (e.g. 1 gm/kg/day x 3 days) or cyclosporine (e.g. 3-6 mg/kg/day) with slow taper over 4-6 weeks after toxicity has resolved;

-Treat skin with ointment emollient, such as petrolatum, with non-stick bandages over any open erosions, changed once to twice daily; use of topical antibiotic ointment may be useful if any signs of bacterial superinfection;

-If any concern of overlying infection (*e.g.* purulent drainage, significant edema or induration, fever), obtain cultures of skin and/or blood and consult infectious diseases specialist for guidance in management;

-In a patient who has experienced a SCAR, such as SJS/TEN or DIHS/DRESS, it is generally recommended to avoid re-challenge with the offending drug since re-challenge can result in a SCAR of even higher severity or death. For patients who develop DIHS/DRESS, long-term or later side-effects involving other organs, such as the kidney, thyroid, and heart, can occur; therefore, continued monitoring for at least 6 months should be considered.

IV. Pruritus

Diagnostic Work-up:

For patients with pruritus, consider other causes of pruritus with the following evaluations:

- Pertinent history and physical examination;
- Rule out any other cause for the skin condition, including infection (such as scabies), other drug side-effect, or unrelated primary skin disorder;
- Blood laboratory values, including complete blood cell count, as well as differential, liver, kidney, and thyroid function tests, and iron levels;
- Skin biopsy (lesional biopsy for hematoxylin and eosin evaluation and perilesional biopsy for direct immunofluorescence evaluation) can be considered as cases of occult bullous pemphigoid can present as pruritus only without specific skin changes;
- Specific serologic studies if bullous pemphigoid is suspected, including anti-BP180 and anti-BP230 IgG antibody levels, IgE levels, or under the guidance of Dermatology, other serologic studies and sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering conditions.

Grade 3: Widespread and constant, limiting self-care ADLs or sleep; systemic corticosteroid or immunosuppressive therapy indicated.

Management:

- Dermatology referral;
- Initiate oral corticosteroids such as prednisone (or equivalent) 0.5-1 mg/kg/day tapered over 2-4 weeks;
- Initiate addition of an alternative non-steroid agent, such as gabapentin (100–300 mg TID), pregabalin, naltrexone, aprepitant (80 mg daily for 3–5 days or 3-day course of 125 mg, 80 mg, and 80 mg) [45], or oral or topical (5% cream) doxepin

A summary of the management of the dermatological IrAE's is shown in Figure 2.

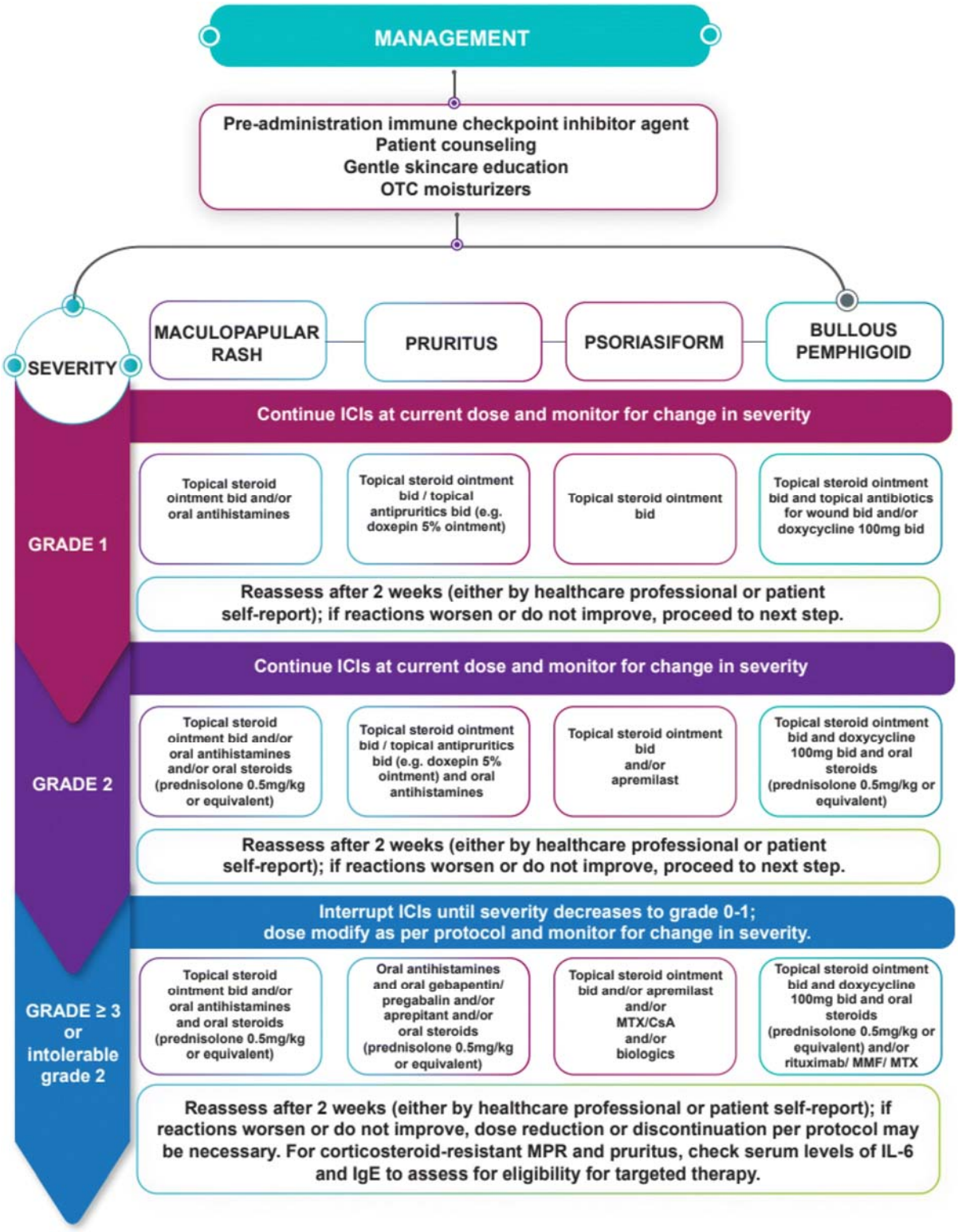

Fig 2. Management of dermatologic immune-related adverse events

Conclusions

Given the various clinical presentations of dermatologic IrAEs, accurate diagnosis is critical in order to enable implementation of effective treatment strategies. In addition, since dermatologic events occur early during immunotherapy, recognition at this stage would allow continuation of anti-cancer therapy, while retaining quality of life. The most common clinical presentations include pruritus, lichenoid rash, psoriasis, atopic dermatitis, and vitiligo. Laboratory investigations are also important in aiding diagnosis and treatment, particularly measurement of autoantibodies, both systemically and in skin biopsies. Targeted biologic therapies should be considered in patients with corticosteroid-resistant/refractory dermatologic IrAEs. However, the level of evidence for the usage of these agents remains largely unconfirmed.

Conflict of interest

AB, RA, JC, TC, PG, DG and VRS have no conflict of interest to declare. MD reports grants from Novartis, other from Neoleukin Therapeutics, personal fees from Partner Therapeutics, personal fees from Tillotts Pharma, grants from Genentech, outside the submitted work. MG reports other from Bristol Myers Squibb (BMS) and from AstraZeneca, outside the submitted work. IG reports stock ownership from Pfizer Inc., personal fees from CytomX Inc, outside the submitted work. DBJ reports other from Array Biopharma, grants and other from BMS, other from Jansen, grants from Incyte, other from Merck, other from Novartis, outside the submitted work. In addition, DBJ has a patent Co-inventor on use of CTLA-4 agonist for IAEs pending. ML reports other (royalties) from Legacy Healthcare Services, from Apricity Health, LLC, from Azitra, Inc., from Deciphera, from Galderma Research and Development, from Johnson and Johnson, from NCODA, from Novocure Inc., from Kyowa Kirin, Inc., from Loxo, from Merck Sharp and Dohme Corporation, from Janssen Research & Development, LLC, from Menlo Therapeutics, from Novartis Pharmaceuticals Corporation, from QED Therapeutics, from F. Hoffmann-La Roche AG, from Amgen Inc., from Astrazeneca Pharmceuticals LP, from Genentech Inc., from Seattle Genetics, from Lutris, from Paxman Coolers, from OnQuality Pharmaceuticals Ltd, and from Takeda Millenium,

outside the submitted work. BLR reports personal fees and other from Merck and Co, grants, personal fees and other from BMS, grants, personal fees and other from Roche South Africa, personal fees and other from AstraZeneca, during the conduct of the study. MSA reports personal fees from Gilead, grants from Pfizer, personal fees from Abbvie, outside the submitted work. All work with these entities has ended.

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