doi.org/10.58931/cdt.2026.72162

ABOUT THE AUTHOR

Nicola Gray, MD, FRCPC

Dr. Nicola Gray is a Fellow of the Royal College of Physicians of Canada in Dermatology and a Clinical Instructor in the Department of Dermatology and Skin Science at the University of British Columbia. She practices community-based medical dermatology at Kelowna Health and Memory Centre in British Columbia. Dr. Gray holds a PhD from the University of Cape Town and completed her specialist dermatology training at Stellenbosch University in South Africa.

Affiliations: Clinical Instructor, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, British Columbia

Treatment of Psoriasiform Drug Eruptions in Patients on Immune Checkpoint Inhibitors

Nicola Gray, MD, FRCPC

Introduction

Immune checkpoint inhibitors are increasingly used in oncology, including in Canada.[1] Pembrolizumab alone is Health Canada-approved for at least 15 distinct cancer types.[2] Cutaneous immune-related adverse events (irAEs) are the most common toxicities associated with immune checkpoint inhibitors, occurring in more than 30% of patients. These reactions impair quality of life and can lead to temporary interruption or permanent cessation of these potentially lifesaving therapies.[3] With their increasing use, dermatologists in community practice, not only those in tertiary centres, are likely to encounter affected patients, and are well placed to improve both quality of life and treatment outcomes. The goal of this article is to review practical, community-based management strategies, with a focus on systemic therapy selection and oncologic safety.

Cutaneous irAEs comprise a wide range of clinical presentations, including maculopapular rash, pruritus, blistering disorders, lichenoid diseases, psoriasiform diseases, inflammation of the oral mucosa, and sicca syndrome/oral dysesthesia. Psoriasiform diseases account for approximately 23% of cutaneous irAEs, and are most strongly associated with programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor monotherapy.[4,5] Notably, psoriasiform irAEs are unique in that systemic steroids are not part of the latest National Comprehensive Cancer Network (NCCN) treatment algorithm, given concerns about the risk of pustular rebound flares.[6] In clinical practice, patients with moderate-to-severe disease are referred to dermatology for assistance with non-steroid systemic treatments.

Brief Review of Pathogenesis and Clinical Features

Psoriasis is a complex immune-mediated disorder, driven by T cells and increased interleukin (IL)-23/Th17 signalling. The mechanism in the setting of immune checkpoint inhibitor therapy remains incompletely understood.[7] Psoriasiform irAEs include both de novo psoriasis, typically occurring within the first 5 to 12 weeks of therapy, and flares of pre-existing psoriasis, which tend to occur earlier in the treatment course.[7] Clinical findings mirror those of idiopathic psoriasis, including, but not limited to, plaque, guttate, inverse, palmoplantar, and pustular subtypes.[4,8-11] In one retrospective case series of 115 patients with immune checkpoint-mediated psoriasis, nail psoriasis occurred in 32.7% of cases, and psoriatic arthritis in 8.1%.[11] Skin biopsy findings are also consistent with idiopathic psoriasis, typically demonstrating a thickened stratum corneum with parakeratosis, psoriasiform epidermal hyperplasia, and a lymphocytic infiltrate.[4]

Treatment Principles

The aims of treatment are to achieve control of skin disease, thereby improving quality of life and avoiding interruption of immunotherapy where possible. Treatment is stratified according to the severity of the psoriasiform eruption. The most recent NCCN guidelines on the management of immune checkpoint inhibitor-related toxicities define psoriasis and psoriasiform disorders as mild if body surface area (BSA) <10%, moderate if BSA is 10–30% or when disease is not responsive to high-potency topical steroids, and severe if BSA is >30%.[6]

Mild Disease

Fortunately, most cases (85.9%) of psoriasiform irAEs are mild and can be managed with topical therapies, most commonly ultrapotent topical corticosteroids. In our setting, a topical combination gel or ointment containing calcipotriol 50 mcg/g and betamethasone dipropionate 0.5mg/g is most often used. For facial, inverse, or genital involvement, lower-potency topical steroids, or off-label tacrolimus 0.1% ointment are used. Alternative options include topical calcipotriol monotherapy, as well as newer on-label agents, such as topical roflumilast 0.3% or topical tapinarof 1%. In clinical practice, topical treatment selection is additionally influenced by costs and availability through provincial drug formulary listings.

Moderate and Severe Disease

The decision to interrupt potentially lifesaving immunotherapy is not clear-cut, particularly regarding moderate disease. NCCN guidelines recommend holding immunotherapy in moderate disease, whereas others recommend continuing immunotherapy with concurrent dermatologic consultation.[4,6] Management requires multidisciplinary decision-making involving the oncologist, dermatologist, and patient. Patient preferences for symptom control versus maintenance of immunotherapy should be carefully considered. For severe disease, guidelines unanimously recommend that therapy should be withheld.

Treatment options beyond topical therapies include narrowband ultraviolet B (UVB) phototherapy, if available and practicable for the patient. Systemic therapies include acitretin, apremilast, traditional immunomodulators such as methotrexate and cyclosporine, and biologic therapies.[4,6]

Acitretin and apremilast demonstrate relatively modest efficacy but are useful components of the psoriasis treatment toolkit as they are not immunosuppressive. Acitretin is useful for hyperkeratotic palmoplantar disease, and can be used in combination with phototherapy, although it lacks efficacy for treating psoriatic arthritis.[12] By contrast, apremilast can be used for psoriatic arthritis. The potential for phosphodiesterase-4 inhibitor-associated diarrhea needs to be kept in mind for patients started on apremilast (and to some extent, topical roflumilast), to avoid

confusion with symptoms of immune checkpoint inhibitor-induced colitis. In our setting, these agents are infrequently used, as we find alternative systemic agents are more effective.

There is concern that immunosuppressive treatments may reduce the efficacy of immune checkpoint inhibitors, with limited data available to assess this risk. This issue is of particular concern for cyclosporine, despite its inclusion in the NCCN guidelines as a potential treatment option for severe psoriasiform irAEs.[7,13] Specifically, cyclosporine downregulates CD8+ T-cell activation, while immune checkpoint inhibitors aim to promote CD8+ tumour reactive T-cell responses.[13] Real-world data evaluating the impact of cyclosporine on immune checkpoint inhibitor survival outcomes are lacking. Moreover, such studies addressing this question may not be ethical to pursue given the availability of alternative systemic immunomodulators, including more cost-effective options (methotrexate) and more targeted options with less global immunosuppression (biologics).

The Role of Biologics

Biologic agents approved for treating psoriasis, such as tumour necrosis factor (TNF), IL-17, and IL-23 inhibitors, are recommended for moderate-to-severe psoriasiform irAEs.[6] While TNF inhibitors demonstrate lower efficacy for psoriasis compared with other approved biologics, they may be appropriate in select cases, such as those with concomitant psoriatic axial spondyloarthritis or multi-system toxicity. It is reassuring to note that, despite their relatively upstream immunosuppressive effects, TNF inhibitors have been studied in the management of immune checkpoint inhibitor-associated colitis, with no association found between TNF inhibitor use and adverse disease outcomes.[14,15]

IL-17 inhibitors are an attractive option, particularly in cases where disease severity requires immune checkpoint inhibitor interruption, given their rapid response rates. In a network meta-analysis, the time for 50% of patients to achieve Psoriasis Area and Severity Index (PASI)75 is 3.4 weeks for bimekizumab, compared to 5.7 weeks for risankizumab, and 11 weeks for methotrexate.[16] Interestingly, IL-17 may play a role in immune checkpoint inhibitor resistance; accordingly, IL-17 inhibitors in combination with anti-PD-1 therapy are being studied for the treatment of microsatellite-stable colorectal cancers.[17] When considering IL-17 inhibition, the risk of inflammatory bowel disease needs to be considered and differentiated from immune checkpoint inhibitor-related colitis. In addition, patients need to be monitored for mucocutaneous candidiasis, particularly if they are receiving other chemotherapies that increase risk.

IL-23 inhibitors are highly effective, demonstrate a reasonably rapid onset, and have an excellent safety profile. Retrospective data shows no increased risk of cancer recurrence, progression, or development in patients with a history of cancer treated with IL-23i.[18] Furthermore, a 2025 Delphi consensus consisting of 15 specialists across multiple disciplines rated IL-23 inhibitors and systemic retinoids most favourably in terms of risk of impairing immune checkpoint inhibitor efficacy.[7]

Knowledge Gaps and Future Directions

The glaring gap in the literature is the lack of direct real-world evidence assessing whether immunosuppressive psoriasis treatments, particularly methotrexate, cyclosporine, and biologics, impact tumour response, progression-free survival, and overall survival. The development of registries and prospective cohort studies would be immensely helpful in this regard.

Furthermore, the relative efficacy and rate of onset of disease control is extrapolated from studies of idiopathic psoriasis; validation of these outcomes in the setting of immune checkpoint inhibitor-related disease would be highly informative.

Lastly, a better understanding of the pathogenesis of psoriasis as distinct from other cutaneous irAEs could help develop biomarkers to predict which patients are at highest risk of these reactions. Such biomarkers could assist with pre-emptive referral to dermatology and closer disease monitoring, allowing earlier detection

and treatment, and reducing the risk of treatment interruption. Implementing this approach would require close collaboration between oncology and dermatology, as well as measures to address long wait times for dermatology services. Other factors relevant in the Canadian setting include differences in provincial criteria for biologic access across provinces, and travel burden associated with accessing specialist care.

Conclusion

Psoriasiform eruptions are a relatively common and clinically distinct subset of cutaneous irAEs and are increasingly encountered in community dermatology practice. While mild disease can be managed with topical therapies, moderate and severe disease requires phototherapy and/or systemic agents. We are fortunate to have a broad range of systemic treatment options, including acitretin, apremilast, traditional immunosuppressants, and biologic therapies. However, in clinical practice, treatment options need to balance effective psoriasis control with preservation of anti-tumour immunity. In the absence of high-quality data, a patient-centred multidisciplinary approach is recommended to optimize quality of life and treatment outcomes.

Correspondence

Nicola Gray, MD, FRCPC
Email: nicolagrayemail@gmail.com

Financial Disclosures

N.G.: None declared.

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