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POSITION STATEMENT

Systemic treatment of immune checkpoint inhibitor-induced psoriasis: Inference-based guidance

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Abstract

Background: Immune checkpoint inhibitors (ICIs) are increasingly used to treat various cancers. Their use may result in immune-related adverse events, including psoriasis. When managing psoriasis, induced or exacerbated by an ICI, there are concerns regarding immunosuppression from systemic agents for the treatment of psoriasis (saPs) and the potential impact on ICI efficacy. No direct, high-level evidence exists to address these concerns.

Objective: To address clinically relevant questions regarding the management of ICI-mediated psoriasis (ICI-Ps) with saPs.

Methods: We convened a multidisciplinary panel of 15 international specialists in dermatology, oncology, immunology, and rheumatology. A Delphi process defined clinical concerns related to the systemic treatment of ICI-Ps, focusing on the potential of saPs to impact ICI effectiveness. The saPs considered included biologics targeting tumour necrosis factor, interleukin (IL)-17, IL-12/23 and IL-23, traditional systemic therapies (cyclosporine, methotrexate), small molecules targeting phosphodiesterase-4 or tyrosine kinase 2, systemic retinoids (acitretin), and systemic corticosteroids. A systematic review of the literature was supplemented with evidence supporting an inference-based methodology to derive conclusions on the use of systemic therapies in patients with ICI-Ps. The specialist panel rated the strength of the conclusions using a probabilistic scale.

Results: After reviewing the totality of direct and indirect evidence, we drafted inference-based conclusions and ascribed a level of support, focusing on the potential impact of saPs on ICI efficacy. This work provides a structured framework informing healthcare professional and patient discussions on the risks and benefits of using saPs in patients with cancer who experience ICI-Ps.

Conclusions: Although there is no direct evidence, we support the following conclusions: saPs may be used to treat ICI-Ps without an appreciable loss of ICI effectiveness. Generally, it is not necessary to interrupt ICI therapy. When available, non-steroid saPs are preferred over systemic corticosteroids for the treatment of psoriasis.

Kim A. Papp, Luis Puig and Jennifer Beecker contributed equally to this study.

For affiliations refer to page 1889.

KEYWORDS
atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, guideline, immune checkpoint inhibitors, immune-related adverse events, immunomodulating agents, immunosuppressive agents, ipilimumab, nivolumab, pembrolizumab, psoriasis

INTRODUCTION

The percentage of patients with cancer who are eligible for immune checkpoint inhibitor (ICI) therapy is increasing. Only 1.5% of patients with cancer in the United States were eligible for ICIs in 2011, and 55% were eligible in 2023.[1] Immune checkpoint inhibition permits tumour-resident T-cells to recognize and kill tumour cells. However, ICI blockade is indiscriminate. Individuals susceptible to the indiscriminate activation of T-cells will experience immune-related adverse events (irAEs). Cutaneous toxicities are among the most prevalent irAEs, occurring in up to 71% of patients on ICI therapy.[2,3] Psoriasis, a chronic, recurrent, inflammatory skin disease, is one of the more common cutaneous irAEs.[4] It is diagnosed by clinical features consisting of characteristic skin lesions: sharply demarcated, erythematous papules or plaques covered with silvery-white scales. Skin biopsies may aid in confirming a diagnosis of psoriasis occurring as an irAE. Both de novo psoriasis and exacerbations of psoriasis have been reported as cutaneous irAEs in patients receiving ICIs.[5] De novo psoriasis typically occurs within 5–12 weeks of ICI initiation,[6] whereas exacerbation of pre-existing disease occurs earlier[5,7] and is reported to affect more than half of patients with pre-existing psoriasis.[7] The occurrence of cutaneous irAEs, including psoriasis, is associated with improved survival in patients with cancer treated with ICIs, particularly for patients with melanoma.[7–10]

A recent cohort study from Taiwan suggested that ICI use is associated with a twofold increase in the risk of developing psoriasis.[11] Although some types of psoriasis, including ICI-Ps, can be managed with topical therapies, this manuscript addresses psoriasis requiring systemic agents for effective treatment. If an eruption can be managed by topical therapies, that is a preferred option, with consideration of newer non-steroidal agents if chronic treatment is anticipated. Systemic agents for the treatment of psoriasis (saPs) include traditional systemic therapies (cyclosporine [CsA], methotrexate [MTX]), small molecules targeting phosphodiesterase-4 (PDE-4) or Janus kinase (JAK), systemic retinoids (acitretin) and biologics targeting tumour necrosis factor (TNF), interleukin (IL)-17, IL-12/23, and IL-23. About one-third of reported cases of ICI-Ps were managed with systemic agents, with systemic corticosteroids administered in over 75% of these cases.[12] Currently, the European Academy of Dermatology and Venerology (EADV) guidelines are the only guidelines that consider biologics for worsening symptoms of grade 2 or 3 ICI-Ps.[4] However, given the chronic and recalcitrant nature of psoriasis and the duration of ICI treatment required for some cancers, therapies intended for long-term control of psoriasis may be required.

Why was the study undertaken?

- Immune checkpoint inhibitors (ICIs) are increasingly used to treat cancer and often result in immune-mediated adverse events, including psoriasis. This position statement provides guidance on the systemic treatment of ICI-mediated psoriasis. When considering the use of systemic agents for the treatment of psoriasis, clinicians are concerned about the possibility of interfering with ICI effectiveness.

What does this study add?

- Because direct evidence on this topic is lacking, we implemented a novel inference-based approach to review relevant indirect evidence. After reviewing the totality of evidence, experts supported the potential use of systemic agents to treat ICI-mediated psoriasis and concluded that systemic agents may be used without an appreciable loss of ICI effectiveness. When available, targeted systemic agents are preferred over systemic corticosteroids for the treatment of psoriasis.

What are the implications of this study for disease understanding and/or clinical care?

- This work provides a structured framework informing discussions between healthcare professionals and patients on the risks and benefits of using systemic agents to treat ICI-mediated. Our review of the indirect evidence suggests that systemic agents used to treat psoriasis likely have no impact on ICI efficacy, supporting the potential use of systemic agents to treat ICI-mediated psoriasis, where indicated and accessible.

This group aimed to address an important clinical question: "In patients with psoriasis induced or worsened by ICIs, what are the risks and benefits of treating with saPs?" The scope of work was focused on addressing the potential of saPs to impact ICI effectiveness. While all psoriasis treatments affect immune pathways in a dose-dependent manner, biologic agents target specific pathways, whereas small molecules such as corticosteroids impact multiple pathways, which may increase the risk of broader immunosuppression, especially at high doses. Despite these differences in specificity of immune modulation, biologic saPs are often categorized as immunosuppressants, raising concerns about their potential interference with

the mechanism of action (MoA) of ICIs. Published literature reviews on ICI-Ps conclude that further research is required to provide guidance on treatment options.[3,5,13–17] In the context of ICI therapy, there are no comparative studies of efficacy of different saPs. The low frequency of patients with ICI-Ps treated with saPs and variations in the clinical scenarios make it impossible to derive clinically or statistically meaningful results. Nonetheless, treatment decisions must be made despite the limited evidence. The present initiative utilized a targeted, comprehensive review of indirect evidence and expert elicitation to infer the potential risks associated with treating ICI-Ps with saPs. The authors relied on methodical processes to categorize the primary clinical question into addressable components and sub-components. The totality of evidence was considered in making informed inferences regarding treatment options for ICI-Ps.

METHODS

A panel of 15 medical doctors, specializing in dermatology (10), oncology (4), dermato-oncology (3), immunology (1) and rheumatology (2), was convened following the framework of the New Psoriasis Guidelines group (Box S1, Appendix S1).[18] The detailed methods are outlined in Appendix S1.

INFERENCE-BASED GUIDANCE STATEMENTS AND SUPPORTING EVIDENCE

Framing the conclusions

The limited direct evidence reviewed revealed no major signals for worsening or recurrence of cancers in patients with ICI-Ps treated with saPs.[7,19–25] However, short follow-up times and low numbers of enrolled patients limit the strength of the direct evidence. Our inference-based statements and ratings, summarized in Table 1, supplement the direct evidence in assessing the risk of attenuating ICI response in patients treated with saPs. We have organized our findings into a decision framework to assist in clinical decision making (Figure 1). To assess the impact of saPs in patients with ICI-Ps, we reviewed psoriasis pathogenesis, evidence from populations other than patients with psoriasis, drug MoAs and responses to vaccination while receiving saPs. The resulting statements are not proscriptive, nor are they hierarchical. The statements are intended as advisements with levels of support and estimates of confidence reflecting expert belief based on the best available data. There is no preferred first-line agent presented herein, as all treatment decisions should be made on a case-by-case basis after an informed discussion between the treating physicians (dermatologist and oncologist) and the patient, considering cancer type and prognosis, response to ICI therapy, time since ICI initiation, psoriasis severity, comorbid disease and previous psoriasis therapy received.

The considerations supporting the statements are summarized in the subsequent sections.

Pathogenesis of psoriasis and MoA of saPs and ICIs

Psoriasis is the result of an aberrant inflammatory response mediated by complex interactions between intracellular signalling molecules and extracellular cytokine pathways, mainly in the IL-23/Th17 pathway and driven by T cells.[26] Systemic therapies for psoriasis often target inflammatory cytokines involved in psoriasis pathogenesis: IL-17, IL-12/23, IL-23 and TNF. Neither psoriasis nor its treatments are causally associated with an increased risk of malignancies, though there is weak evidence suggesting a slightly increased incidence of lymphomas and non-melanoma skin cancer in patients with psoriasis.[27]

ICIs are monoclonal antibodies that target co-inhibitory immune checkpoints including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which regulates T-cell activation,[28,29] and programmed cell death protein 1 (PD-1), which inhibits the activation and function of several immunocytes.[30–32] Checkpoints regulate immune response to self-proteins that are broadly expressed on many immune cells. Though the treatment effect occurs by blocking immune checkpoints of tumour-resident T-cells, ICIs act indiscriminately thereby allowing activation of T-cells in other tissues. The efficacy of ICIs is most pronounced in solid tumours characterised by high tumour mutational burden, the presence of tertiary lymphoid structures, the expression of PD-1 protein on cell surfaces and an inflamed microenvironment that includes a greater density of B-cells.[33–36] Tumours responding to ICI therapy may show continued response or loss of response over time while some tumours never respond.[30,37,38] ICI failure may be a result of insufficient expansion of T-cells, inadequate function of T-cells, impaired T-cell memory,[39–41] inadequate levels of ICI in tumour tissue, or ICI effects negated by other processes inhibiting T-cell response. These differential responses are based on the tumour microenvironment and other factors affecting T-cell function.

The indiscriminate action of ICIs results in the de novo expression or exacerbation of immune-mediated disease in susceptible patients,[21] with toxicities being more common in patients on combination ICI therapy.[3] While the specific mechanisms underlying ICI-induced psoriasis remain controversial, the overexpression of Th1/Th17-specific cytokines, such as IL-17, following blockade of PD-1 may be involved.[42]

Vaccine response as a surrogate for T-cell response

As there is a concern that saPs may inhibit T-cell activation, we propose the use of cellular vaccine response be used as

TABLE 1 Inference-based statements.

Inference-based Statements	Level of Support 1-99% Mean support (0.025, 0.975 confidence intervals)	Bayes support (0.025, 0.975 credibility intervals)
Preamble to statement 1: Published clinical studies, case reports, and retrospective cohorts do not provide sufficient evidence to assess the impact of saPs on ICI effectiveness. Hence, we systematically collated indirect evidence that could support or refute the use of saPs in patients with ICI-induced or exacerbated psoriasis. The primary site of tumoricidal action of ICIs are tumour resident T-cells. Assessing the impact of saPs on ICI effectiveness can be recast: what evidence suggests saPs significantly impair T-cell activation? All effects of saPs are dependent on dose and potency (exposure).		
1. In patients treated with saPs, response to vaccination (particularly T-cell-mediated response) can be used as a proxy to assess the impact of saPs on T-cell activation and thereby, the potential effect on ICI action.	**71.8 (62.5, 80.0)**	**71.7 (69.4, 73.9)**
Preamble to statements 2-4: Currently available clinical data on the impact of SCS initiated prior to initiating ICI are equivocal. Some studies suggest antecedent use of SCS reduces ICI response while other studies suggest there is no impact on ICI response. Studies suggesting a significant impact of SCS do not correct for possible confounders including the dose of SCS, tumour burden, and SCS administered for palliative purposes versus SCS administered to treat irAEs. The MoA of SCS suggests exposure-dependent impairment of T-cell activation. Impaired T-cell activation may attenuate ICI-related, tumoricidal pathways.		
2. Lower doses of **prednisone** (<20mg/day) used at the time of initiating or prior to initiating ICI therapy have a low risk of impacting ICI effectiveness.	**76.8 (67.9, 84.4)**	**76.7 (74.5, 78.8)**
3. Lower doses of **prednisone** (<20mg/day) after initiating ICI therapy, have a negligible to low risk of impacting ICI effectiveness.	**80.5 (72.0, 87.5)**	**80.3 (78.3, 82.3)**
4. For the treatment of ICI-induced psoriasis, **high-dose SCS** should be avoided, and targeted systemic therapies should be considered when indicated and accessible.	**90.1 (83.2, 94.9)**	**89.8 (88.2, 91.3)**
Preamble to statement 5: Response to retinoids is dose-dependent. At therapeutic doses, the impact on immune response is modest based on a modest effect size in the treatment of psoriasis and hand dermatitis as surrogate indicators of immunosuppression.		
5. **Acitretin**, when used at therapeutic doses for psoriasis, has a negligible to low risk of impacting ICI effectiveness.	**92.3 (86.1, 96.5)**	**92.1 (90.6, 93.4)**
6. **Apremilast**, when used at therapeutic doses for psoriasis, has a negligible to low risk of impacting ICI effectiveness.	**87.1 (79.6, 92.7)**	**86.9 (85.1, 88.5)**
Preamble to statement 7: Based on MoA, B-cell and T-cell activity will be modified by methotrexate; however, when reviewing vaccine response, there is modest attenuation of B-cells, while T-cell activation remains relatively unaffected. Note recommended dosing for treating psoriasis: weekly single oral dosing (5–25 mg/weekly), lowered to the lowest possible effective dose and longest rest period after optimal clinical response is achieved.		
7. Based on B-cell and T-cell responses seen in patients receiving vaccinations while on methotrexate, **low-dose methotrexate**, when used at therapeutic doses for psoriasis, has minimal to no effect on ICI pathways.	**77.1 (68.2, 84.6)**	**76.9 (74.8, 79.0)**
7. a. **Low-dose methotrexate**, when used at therapeutic doses for psoriasis, has a negligible to low risk of impacting ICI effectiveness.	**81.8 (73.5, 88.5)**	**81.6 (79.6, 83.5)**
8. Based on limited clinical data and response to vaccination, the risk of attenuating ICI-related tumoricidal pathways with **TNF inhibitor** treatment for psoriasis is low.	**77.8 (69.0, 85.2)**	**77.6 (75.5, 79.7)**
8.a. **TNF inhibitors**, when used at therapeutic doses for psoriasis, have a low risk of impairing ICI effectiveness.	**79.8 (71.2, 86.9)**	**79.6 (77.5, 81.6)**
Preamble to statement 9: The increased incidence of IBD with IL-17 inhibitors may limit their use in patients treated with ICIs based on potential to exacerbate ICI-related colitis.		
9. Based on response to vaccination, the risk of attenuating ICI-related tumoricidal pathways with **IL-17 inhibitor** treatment for psoriasis is low.	**80.9 (72.4, 87.8)**	**80.7 (78.6, 82.6)**
9.a. **IL-17 inhibitors**, when used at therapeutic doses for psoriasis, have a low risk of impairing ICI effectiveness.	**82.9 (74.7, 89.4)**	**82.7 (80.7, 84.5)**
10. Based on response to vaccination, the risk of attenuating ICI-related tumoricidal pathways with **IL-23 inhibitor** treatment for psoriasis is low.	**84.8 (76.9, 90.9)**	**84.6 (82.7, 86.4)**
10. a. **IL-23 inhibitors**, when used at therapeutic doses for psoriasis, have a low risk of impairing ICI effectiveness.	**89.2 (82.1, 94.3)**	**89.0 (87.3, 90.5)**
11. Based on response to vaccination, the risk of attenuating ICI-related tumoricidal pathways with **IL-12/23 inhibitor** treatment for psoriasis is low.	**83.8 (75.8, 90.2)**	**83.6 (81.7, 85.4)**
11.a. **IL-12/23 inhibitors**, when used at therapeutic doses for psoriasis, have a low risk of impairing ICI effectiveness.	**87.2 (79.7, 92.8)**	**86.9 (85.2, 88.6)**
Preamble to statement 12: Clinical data is lacking for JAK inhibitors and their potential effects on ICI-related pathways. The impact of intentionally interrupting ICI therapy has not been examined.		
12. Based on the drug's MoA, the risk of attenuating ICI-related tumoricidal pathways with **TYK2 inhibitor** treatment is low.	**71.1 (61.8, 79.4)**	**71.0 (68.7, 73.3)**
12. a. **TYK2 inhibitors**, when used at therapeutic doses for psoriasis, have a low risk of impairing ICI effectiveness.	**68.1 (58.6, 76.7)**	**68.0 (65.6, 70.3)**
13. With the exception of TNF inhibitors, the use of biologic agents for the treatment of ICI-induced or exacerbated psoriasis does not increase the risk of serious infections.	**85.7 (78.0, 91.6)**	**85.5 (83.6, 87.2)**
13. a. Short-term interruption of ICI treatment (i.e., 1-2 dose cycles) in response to severe ICI-induced or exacerbated psoriasis has a low to negligible risk of impairing ICI effectiveness.	**83.1 (74.9, 89.6)**	**82.9 (80.9, 84.7)**
14. A. Short-term interruption of ICI treatment (i.e., 1-2 dose cycles) is unlikely to improve ICI-Ps.	**83.4 (75.2, 89.8)**	**83.1 (81.2, 85.0)**

Note: Statements were drafted after an evidence review of indirect and limited direct evidence to support or refute the use of saPs in patients with ICI-induced or exacerbated psoriasis.

Abbreviations: IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitors; ICI-Ps, ICI-mediated psoriasis; IL, interleukin; irAE, immune-related adverse event; JAK, Janus kinase; MoA, mechanism of action; saPs, systemic agents for the treatment of psoriasis; SCS, systemic corticosteroids; TNF, tumour necrosis factor; TYK2, tyrosine kinase 2.

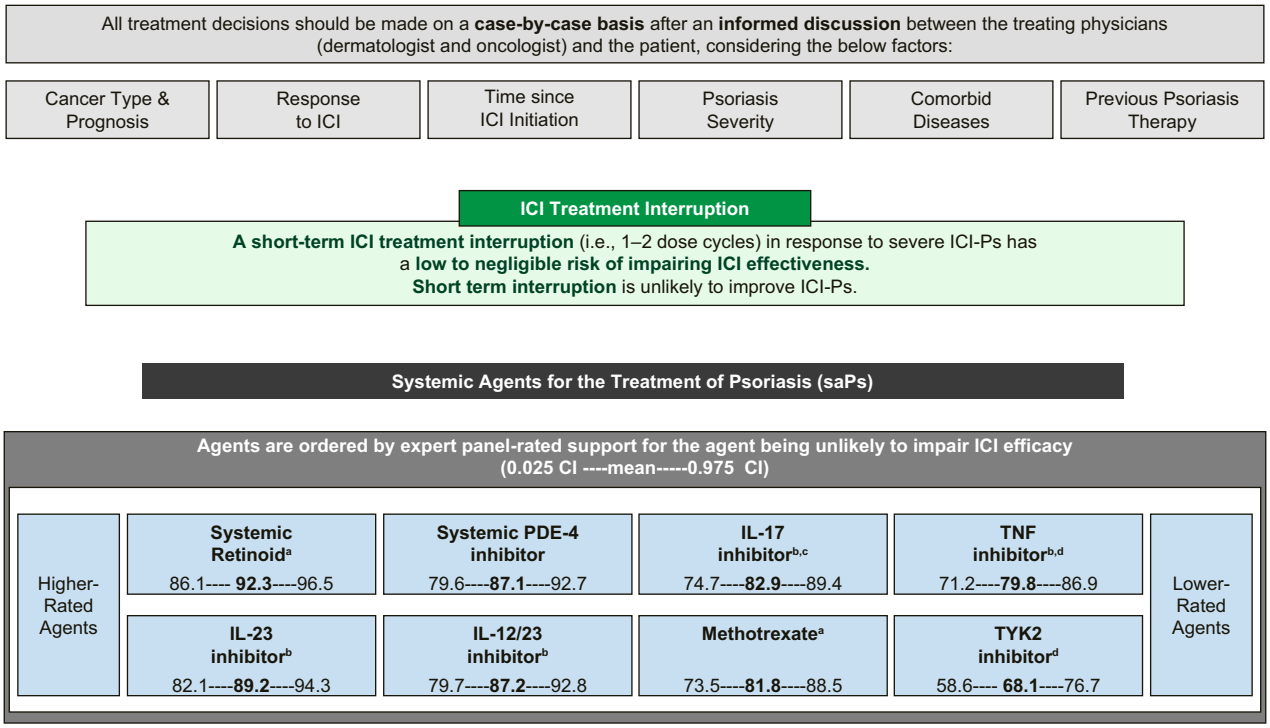

FIGURE 1 Decision framework for treating ICI-Ps with systemic therapies. This decision framework intends to assist in clinical decision-making. Statements are not meant to be hierarchical or proscriptive. The statements are intended as advisements with levels of support and estimates of confidence reflecting expert belief based on the best available data. For details, refer to the text of this manuscript. Although systemic corticosteroids are often used by oncologists for the treatment of ICI-Ps, use of high-dose systemic corticosteroids should be minimized and low-dose systemic corticosteroids are not preferred for long-term use. [a]Traditional systemic agents including cyclosporine, methotrexate and retinoids are slow to act and less well tolerated than newer small molecules and biologic agents. The group did not agree on a statement for the use of cyclosporine A in ICI-Ps. [b]Biologic agents have a higher efficacy, faster onset of action (2–11 weeks), target specificity and may improve ICI efficacy as per pre-clinical studies. They are not widely used in cancer patients, and there is minimal direct evidence to support their use. [c]Caution for exacerbation of new onset inflammatory bowel disease and colitis. [d]Caution for tuberculosis reactivation. CI, confidence interval; ICI, immune checkpoint inhibitor; ICI-Ps, ICI-mediated psoriasis; IL, interleukin; PDE-4, phosphodiesterase-4; saPs, systemic agents for the treatment of psoriasis; TNF, tumour necrosis factor; TYK2, tyrosine kinase 2.

a surrogate for potential interference of saPs with ICI efficacy. Vaccines stimulate cellular and humoral immunity. Although the immunologic goals of vaccination and ICIs differ, both depend upon the ability to mount an effective T-cell response. The impact of saPs on vaccine-associated T-cell activation provides insight into the potential impact of saPs on ICI function. Recent studies on COVID-19 vaccines directly assess T-cell response.[43] Vaccine response studies in patients with psoriasis or psoriatic arthritis treated with MTX, TNF inhibitors (TNFi), IL-17 inhibitors (IL-17i) and IL-23 inhibitors (IL-23i) found that cellular immune responses were not attenuated in most patients after receiving a single[44] or second dose[45,46] of the COVID-19 vaccine. A study of 92 patients with inflammatory arthritis receiving MTX, Janus kinase inhibitors (JAKis), or biologics, including TNFi and IL-17i, concluded that T-cell immunity was preserved in patients receiving vaccination against COVID-19.[47] Response to tetanus toxoid vaccination was used to assess T-cell response in patients receiving JAKi (tofacitinib or baricitinib).[48,49] Vaccine response studies in patients on ICI therapy suggest that cellular and humoral responses to vaccines are increased for cancer patients on ICI therapy.[50]

Systemic corticosteroids (SCS)

SCS are commonly used in oncology to control early stages of irAEs. However, SCS are not typically used by dermatologists to treat psoriasis because of long-term risks and the potential for disease flares upon SCS cessation. A systematic review of case reports concluded that patients with psoriasis who received SCS therapy frequently had permanent ICI discontinuation.[5] Confounders complicating the rationale for ICI discontinuation include psoriasis severity and cancer stage. Although steroid avoidance or steroid sparing agents may be preferred, prescription of many saPs requires assessment by a dermatologist, which may delay treatment. Rapid access to SCS may be favoured over delayed access to targeted systemic therapies. As SCS are permitted for the treatment of irAEs in clinical trials, SCS use in this setting is more extensively studied compared to other systemic therapies.[51,52] Some studies have suggested that steroids may be detrimental to tumour response when used at initiation of ICI therapy (at doses of more than 10 mg/day of prednisone),[53] in response to severe irAEs (at doses of more than 7.5 mg/day of prednisone,[54] or for more than 30 days[55]);

while other studies have found no statistically significant effect on survival or response to immunotherapy with concurrent SCS use when adjusting for confounders.[56,57] In a small study of healthy volunteers, a single dose of 0.2 mg/kg of prednisone did not profoundly impact cytokine production.[58] Physiologically, based on the volume of distribution of prednisolone and drug half-life, significant effects on T-cell function are unlikely at doses of less than 20 mg of prednisone daily.[59] Clinical trials of ICIs have typically excluded patients who received baseline corticosteroids at doses greater than 10 mg of prednisone daily. Low-dose steroids, approximately 10 mg/day of prednisone or equivalent at baseline, do not appear to compromise the anti-tumour efficacy of ICIs, particularly when given for inflammatory reasons.[57] A dose of less than 20 mg prednisone daily was considered for rating by authors in the statements (Table 1) as this dose is not generally considered to be moderately or severely immunocompromising.

Traditional systemic therapies

Methotrexate (MTX)

Methotrexate (MTX) is an antimetabolite, originally used at high doses for its cytotoxic effects targeting faster replicating cells with high metabolic rates. At lower doses, antimetabolites are known to interfere with pathways and cell types involved with inflammatory conditions such as psoriasis and inflammatory arthritis. As a treatment for psoriasis, MTX is given in a weekly single oral dose of 5–25 mg/week. Despite some studies showing normal T-cell response to COVID-19 vaccination,[44–46] one study showed that activated $CD8^+$ T-cells were not induced after COVID-19 vaccination in patients with immune-mediated inflammatory diseases treated with MTX[60]; however, senior age (>60 years) may be a confounding factor for the reduced immunogenicity observed.[43] In patients where glucocorticoids cannot be tapered successfully, MTX has been used in the treatment of ICI-related arthritis, without increasing cancer progression.[61]

Cyclosporine A (CsA)

Cyclosporine A (CsA) suppresses synthesis of interleukins, predominantly IL-2, thereby inhibiting T lymphocyte activation.[62] As a potent inhibitor of T-cell activation, CsA may impair the expansion of T-cells required for adequate ICI response, negating ICI efficacy. Response to tetanus vaccination in 11 patients receiving CsA for chronic uveitis was normal.[63] Slight attenuation of cellular response to COVID-19 vaccination was noted in liver transplant recipients receiving CsA.[64] Based on these two vaccine response studies, the magnitude of the effect of clinically relevant doses of CsA on T-cells is likely modest. The group did not agree on a statement for the use of Csa in ICI-Ps.

Retinoids

Acitretin, an oral vitamin A analogue, is modestly effective in treating psoriasis.[65,66] Maximal response and drug intolerance to retinoids are dose dependent, with maximal response occurring at 3–6 months of treatment while intolerance is often experienced within the first few weeks of treatment initiation.[67] Retinoids significantly affect T cells, antigen-presenting cells, dendritic cells, B cells, and immune cell trafficking.[68] At therapeutic doses for psoriasis, the impact of acitretin on immune response is likely minimal, given the modest effect on psoriasis. As such, systemic retinoids are not thought to impair ICI activity at therapeutic doses.

Biologics

A common precaution in clinical practice is the avoidance of biologics for the treatment of psoriasis for a period of 5 years following remission of a cancer. A previous analysis[27] and a small retrospective cohort[69] suggest that a wait time may not be warranted for patients with solid organ tumours.

Tumour necrosis factor inhibitors (TNFi)

TNF is involved in various physiological and pathological processes, including inflammation, immune regulation, and apoptosis.[70–72] In cancer, TNF is thought to have context-dependent, tumour-promoting and tumour-suppressive effects, depending on the cancer type and microenvironment.[70,73] Historically, TNF was initially thought to be a serum factor that induced tumour necrosis. More recent studies have identified an oncogenic role for TNF in inflammation-related cancer.[73] Retrospective studies suggest that infliximab was effective in resolving gastrointestinal irAEs with no evidence of cancer progression.[74–77] Vaccine studies in patients with inflammatory bowel disease (IBD) treated with TNFi showed sustained or increased cellular response following vaccination.[78,79] These observations suggest that at therapeutic doses, TNFis (adalimumab, certolizumab, etanercept, golimumab, infliximab) are unlikely to impair ICI effectiveness. Furthermore, murine studies suggest TNFi may improve the anti-tumour therapeutic activity of ICIs.[80–82] An ongoing clinical trial (NCT05867004) is exploring the use of concurrent TNFis and ICI therapy to boost the anti-tumour response. One consideration when using TNFi is the potential for tuberculosis (TB) reactivation, necessitating assessment of TB risk before starting therapy.[83] A systematic review of 35 cases of TB in patients with PD-1/PD-L1 blockade suggested a significant increase in the risk of TB associated with ICIs,[84] though this study did not control for confounders such as chemotherapy use. The authors agreed that baseline risk of TB should be established for each patient, noting that malignancy may increase the risk of false negative TB tests.[85]

Interleukin (IL)-23i and IL-12/23i

Murine studies have demonstrated that IL-12 and IL-23 may have roles in both tumour immunity and promotion, respectively.[86] Based on vaccine studies, there is no evidence of attenuated T-cell responses with IL-23 inhibition. One study, conducted in a group of patients with Crohn's disease who were treated with ustekinumab or adalimumab, showed that T-cell responses following influenza vaccination were similar to healthy controls.[87] There are numerous non-case controlled case series demonstrating mixed results with the use of IL-12/IL-23i (ustekinumab) and IL-23i (guselkumab, risankizumab, tildrakizumab) to treat ICI-Ps.[5,20,21,88]

IL-17i

IL-17A is a proinflammatory cytokine produced primarily by T helper (Th) 17 cells and plays a critical role in the innate immune response, including the activation and recruitment of neutrophils.[89] Autoimmune diseases and cancer are associated with an increased expression of IL-17A.[90] Studies in murine models have produced conflicting evidence for the role of IL-17A in tumour promotion[91] and suppression.[92–96] Ongoing studies are evaluating the benefits of IL-17A blockade as an adjuvant to overcome ICI resistance in 'immunologically cold' cancers, including colorectal cancer, since increased IL-17 expression observed in these cancers has been associated with poor response to ICIs.[97] Vaccination studies of secukinumab and ixekizumab do not demonstrate attenuation of cellular response to the COVID-19 vaccine, suggesting IL-17 blockade may not impact ICI response.[45] A cautionary case from the literature describes a patient whose psoriasis cleared but suffered a loss of tumour response to pembrolizumab upon treatment with secukinumab.[98] A causal relationship was not established.

Small molecules

PDE-4i

Apremilast inhibits PDE-4, resulting in broad reduction of pro-inflammatory cytokines. No information regarding the impact of apremilast therapy on response to vaccination is currently available.[99] Despite having an inhibitory effect on Th1, Th2, and Th17 cytokine production, T-cell expansion or antibody response in vivo is unaffected by apremilast.[100] Apremilast is moderately effective in treating psoriasis: drug failure rates of 49% to 65% were observed after a median treatment period of 146–200 days.[101]

JAKi

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling pathway mediates IFN-gamma expression by NK cells. IFN-gamma upregulates PD-L1 expression on tumour cells.[102] Acquired resistance to PD-1 blockade immunotherapy has been associated with mutations in JAK2.[103] In pre-clinical models of non-small cell lung cancer (NSCLC), JAK1/2-STAT1/3 inhibition displayed strong synergistic activity with ICIs, presumably overcoming ICI treatment resistance.[102] Interferon signalling modulation through JAK1 inhibition may help prevent resistance to anti-PD-1 therapy. Ongoing clinical trials are exploring targeted JAK/STAT inhibition combined with anti-PD-1/PD-L1 therapy.[104] Encouraging results were noted in a Phase 2 trial of pembrolizumab plus a brief course of itacitinib in NSCLC.[105] Differences in risk between different JAKis are expected based on JAK member selectivity (JAK1, JAK2, JAK3 and tyrosine kinase 2 [TYK2]). TYK2 inhibitors block interferon gamma but show limited effects on interferon alpha signalling[106] and may thus have varying effects on tumour response compared to JAK1 inhibitors. Deucravacitinib, a TYK2 inhibitor, is the only JAKi indicated for the treatment of plaque psoriasis—although other JAKis, including upadacitinib,[107] tofacitinib[108] and baricitinib,[109] have demonstrated effectiveness in treating plaque psoriasis, and some are approved to treat psoriatic arthritis. No studies were identified that studied TYK2i and ICI therapy.

While appropriately designed studies are needed to understand the clinical impact of JAKi on anti-tumour immune surveillance, ICI efficacy and adverse events, one study of patients with psoriasis receiving tofacitinib suggests that these patients are able to mount satisfactory B-cell and T-cell-dependent responses to 13-serotype pneumococcal conjugate vaccine (PCV-13) and tetanus toxoid vaccines.[48] The potential for TB reactivation may be a concern with the use of JAKis.

Infections and cancer

Serious adverse events, including severe infections and malignancy, are rarely seen in non-cancer patients treated with saPs.[110] Although some pre-clinical studies have raised concerns that immune checkpoint blockade is associated with increased susceptibility to certain infections, including TB[111] and listeriosis,[112,113] infections that occur with ICI treatment are thought to be related to immunosuppressive therapy for irAEs.[114] Multiple case reports have highlighted instances of opportunistic infection following irAEs and treatment with agents such as corticosteroids and TNFi[115,116]; however, many studies suggest that corticosteroids and other therapies classified as immunosuppressants are not the drivers for infection in patients receiving ICI therapy.[117–120] Clinicians should have a low threshold of investigation for opportunistic infection following irAE treatment. Additional caution is warranted when ICIs are combined with chemotherapy.[121,122] Clinicians should also be aware of neutropenia as a rare side effect of ICIs.[123]

ICI treatment interruptions

The real risks of ICI continuation, discontinuation or interruption in the response to ICI-Ps are unknown and depend on multiple factors, including treatment setting: adjuvant,

neoadjuvant, metastatic, complete remission; and the tumour microenvironment. As such, the decision to interrupt ICI treatment to manage psoriasis may pose a risk to the patient. Case reports of ICI-Ps suggest most psoriasis events are manageable while 13.6%–22.9% result in ICI discontinuation.[5,13,124] A retrospective study of 76 patients with pre-existing psoriasis reported an ICI discontinuation rate of 7%.[7] When a patient experiences de novo or exacerbated psoriasis due to ICI therapy, there is a risk of worsening psoriasis with ongoing ICI therapy. Patient-centred decision making is important in weighing risks and benefits. Maintaining tumour response is likely more important than the discomfort of a psoriasis flare. Risks related to psoriasis flares are thought to be lower than other irAEs like pneumonitis; however, other co-presenting irAEs and comorbidities should be taken into consideration.

Discontinuing ICI treatment may theoretically increase the risk of cancer progression; however, complete and partial responses were maintained in a large subset of patients after discontinuing ICI therapy.[125] In addition, some patients treated for lung cancer and melanoma show durable responses despite shorter treatment times.[126–128] The optimal duration of ICI treatment has yet to be defined. For many cancers, the maximal benefit of ICI therapy is generally seen in the first 6 months of treatment.[125] Expectedly, the onset of ICI-induced off-target inflammatory reactions also most often occurs within weeks to months of initiating ICI treatment.[129] The foregoing, supported by ICI pharmacokinetic profiles, suggests that interrupting ICI therapy for short periods of time (i.e. 1–2 cycles) is unlikely to substantially impact the effectiveness of ICI therapy, but interruption of ICI therapy may not alter the severity of the ICI-induced inflammatory reaction. A prospective study of 60 patients with ICI-induced inflammatory arthritis noted that more than half of these patients experienced active inflammatory arthritis after a median of 9 months post-ICI cessation.[130] Although some guidelines suggest that ICI therapy should be stopped if more than 30% of the body surface area is affected by a cutaneous irAE, this panel suggests otherwise given the importance of maintaining ICI therapy and the availability of targeted psoriasis therapies. A pharmacovigilance cohort study of ICI rechallenge following discontinuation due to toxicities observed that of 16 patients whose ICI therapy was interrupted due to skin toxicity, six patients experienced recurrence of skin reactions upon ICI rechallenge.[131] The ongoing STOP-GAP study aims to compare the effects on patients with metastatic melanoma taking a PD-1 inhibitor intermittently versus taking the same type of agent continuously.[132]

Considering the totality of the available data, most ICI-Ps reactions do not warrant ICI interruption. If ICI treatment is interrupted, a short-term interruption (i.e. 1–2 cycles) and rechallenge while controlling psoriasis is appropriate. In the groups' experience and based on our understanding of the pathogenesis of psoriasis, ICI-Ps is unlikely to resolve with short-term ICI interruption. Decisions to stop or proceed with immune checkpoint inhibition are based on the depth and duration of response to ICI, the expected magnitude of long-term benefit of ICI, the severity of the irAE, the therapeutic index of treatment and importantly—patient comfort level.

DISCUSSION/LIMITATIONS

A major limitation of the conclusions made in this work is that all evidence considered is low-level or indirect. The numerical ratings in Table 1 reflect the level of confidence in the conclusions as rated by the authors. Generalizations made herein may not be relevant for all tumour types and should be considered on a case-by-case basis. A team-based approach including oncologists, dermatologists, and the patient is recommended, where possible. The ICIs considered herein do not include those in development and other classes already in use (e.g. Lymphocyte-activation gene 3, [LAG-3], T-cell immunoreceptor with immunoglobulin and ITIM domain [TIGIT]), which were beyond the scope of our review; however, this consensus could likely be applied to those therapies as well. One goal of this work was to avoid categorical terms like 'immunosuppression'. In many studies and review articles, targeted biologic agents are referred to as immunosuppressants without regard to target relevance, target specificity or dose—precisely the reasons for our avoidance of the term.

Other groups have published guidance on the treatment of ICI-Ps. Our group's initiative is unique as it considers indirect evidence, with the authors assigning a likelihood to statements based on an extensive review of the totality of evidence. An EADV position statement[4] recommended IL-23 inhibitors for the treatment of higher-grade psoriasis-like rash associated with ICI therapy. The Canadian skin management in oncology (CaSMO) project[133] recommended phototherapy, acitretin or apremilast for patients with ICI-Ps who failed topical therapies, followed by MTX or biologics—especially IL-23i. Based on the cases published in the literature prior to 2020, Nadelman et al.[3] recommend apremilast or phototherapy for the treatment of grade 2 psoriasiform rashes, and other therapies, including acitretin, CsA, MTX and TNFi, upon systemic corticosteroid failure for grade 3 rashes. The treatment algorithm by Nikolaou et al.[21] indicates a preference for phototherapy, acitretin, MTX and apremilast before biologics, with TNFi as a first-line biologic after non-response to other saPs. Although phototherapy is another treatment option for psoriasis not considered as part of this work, access and coordinating appointments may be a limitation for its use, especially for patients with cancer who already have multiple appointments to coordinate. Based on the high efficacy and fast onset of action of biologics compared to other saPs, they may be preferred as an early treatment for ICI-Ps in some patients with severe psoriasis, or psoriasis that has a high impact on quality of life.

Biologics are not often recommended for ICI-Ps due to theoretical concerns of interference with ICI action and possible cancer progression. These concerns have resulted in a

low number of published case studies and cohorts of cancer patients treated with biologics. Our review suggests that biologics are not likely to interfere with ICI MoA and can be used in patients with moderate to severe psoriasis when indicated and accessible.

CONCLUSIONS

We reviewed indirect evidence supporting inferences on additional risks and benefits imposed on patients with cancer who require systemic therapies for the treatment of psoriasis that has been induced or exacerbated by ICIs. The focus was on addressing the potential of saPs to impact ICI effectiveness. Based on our review of the totality of direct and indirect evidence, authors rated inference-based conclusion statements and drafted a decision framework that considers the complexity of the topic. All treatment decisions should be made on a case-by-case basis after an informed discussion between the treating physician, patient and oncologist.

AUTHOR CONTRIBUTIONS

KAP contributed to the funding acquisition, conceptualization, formal analysis, methodology, supervision and writing—original draft. All authors contributed to the data curation, investigation and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

KAP has served as an advisor/consultant for AbbVie, Akros, Amgen, Anacor, Arcutis Biotherapeutics, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, Leo, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi-aventis, Sanofi Genzyme, Takeda, UCB and Valeant; has received grants/honoraria from AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis Biotherapeutics, Astellas, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Leo Pharma, Medimmune, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi-aventis, Sanofi Genzyme, Takeda, UCB and Valeant; and has served as a speaker for AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Leo Pharma, Merck (MSD), Novartis, Pfizer, Sanofi Genzyme and Valeant. KAP serves as the treasurer of the Dermatology Association of Ontario. LP has received grants and honoraria from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Fresenius Kabi, Horizon Therapeutics, Johnson and Johnson,

Leo Pharma, Novartis, Samsung Bioepis, Sandoz, Stada, Sun Pharma, Takeda and UCB; and has served as an Advisory Board Member for the International Psoriasis Council and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). JB has served as an investigator, speaker, advisor/consultant for and/or received grants/honoraria from AbbVie, Amgen, Arcutis Biotherapeutics, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, Galderma, Eli Lilly, Evelo, Incyte, Janssen, Johnson and Johnson, Leo Pharma, L'Oréal Group, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, Reistone, UCB and Vyne. VC has received grants and honoraria from AbbVie, Bristol-Myers Squibb, Eli Lilly, Fresenius Kabi, Johnson and Johnson, Novartis and UCB, and has served as an Advisory Board Member for AbbVie, Bristol-Myers Squibb, Eli Lilly, Johnson and Johnson, Novartis and UCB. VC participates in a leadership or fiduciary role for the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). His spouse is an employee of AstraZeneca. J. Claveau has served as a consultant/advisory board member and received honoraria from Amgen, AstraZeneca, Briston-Myers Squibb, EMD-Serono, Incyte, Johnson and Johnson, Merck, Novartis, Pfizer, Regeneron and Sanofi. J. Cortes has served as a consultant and received honoraria from AbbVie, ARIAD Pharmaceuticals, AstraZeneca, Bayer, BiOasis Technologies Inc., Biocon, BioInvent, BioNTech, Boehringer Ingelheim, BridgeBio, Circle Pharma Inc., Clovis Oncology, Daiichi Sankyo Inc., Delcath Systems, Eisai Co., Eli Lilly, Ellipses Pharma, ExpreS2ion Biotechnologies, GEMoaB Monoclonals, Gilead, Guardant Health, Hexagon Bio, HiberCell, IQVIA, Jazz Pharmaceuticals, Leuko, Menarini, Merck (MSD), Novartis, Pfizer, PIQUR Therapeutics AG, Queen Mary University of London, Reveal Genomics, Roche, Scorpion Therapeutics, Seagen (formerly Seattle Genetics), Servier, Shire, Steamline Therapeutics and Zymeworks; has served as a speaker for AstraZeneca, Daiichi Sankyo Inc., Eisai Co., Eli Lilly, Gilead, Merck (MSD), Novartis, Pfizer, Roche, Steamline Therapeutics. J. Cortes is involved in patents for 'Pharmaceutical Combinations of a Pi3k Inhibitor and a Microtubule Destabilizing Agent' and 'Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy' and owns stocks or stock options in MAJ3 Capital and Leuko. JD has served as an advisor/consultant for AbbVie, Amgen, Bausch, Celgene, Janssen, Leo Pharma, Lilly, Novartis and Sanofi; has received grants and honoraria from AbbVie, Janssen, Corbis, Lilly; and has served as a speaker for Celgene, Janssen. JD is supported by a Senior Scientist Award of the BC Children's Hospital Research Institute. 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RAJ has received honoraria and/or participated in contracted research from Alkermes, Amgen, Astellas, AstraZeneca, Bayer, Beigene, Bold Therapeutics, Bristol Myers Squibb, Conjupro, EMD Serono, Fusion Pharmaceuticals, Jazz Pharmaceuticals, Janssen Pharmaceuticals, Eli Lilly, Macrogenics, Merck Sharp and Dohme, Mirati, Novartis, Pfizer, Roche, Sanofi, SignalChem and Takeda. RAJ has served as an Advisory Board Member or consultant for Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, EMD Serono, Fusion Pharmaceuticals, Jazz Pharmaceuticals, Janssen Pharmaceuticals, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda. RAJ participates in a leadership or fiduciary role for Lung Cancer Canada. BM has served as an advisory board member for, and/or received honoraria from Roche, Pfizer, Jazz Pharmaceuticals, Novartis, Bristol-Myers Squibb, Merck, BI, Amgen, AZ, Ibsen, Aisai, Lilly and Janssen. ABP has declared no relevant conflicts of interest. MBS has received honoraria from AbbVie, Amgen, Arcutis Biotherapeutics, Bausch Health, Bristol-Myers Squibb, Eli Lilly, Janssen, Leo Pharma, Merck (MSD), Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma and UCB, and has served in a leadership or fiduciary role for the Canadian Dermatology Association and the Dermatology Association of Ontario (DAO). MBS also supports clinical trials for AbbVie, Alumis, Amgen, Bristol-Myers Squibb, Janssen and Takeda. SS has received honoraria from AstraZeneca, Daiichi Sankyo Inc., Eli Lilly, Gilead, Incyte, Juniper Biologics, Knight Therapeutics Inc., Merck (MSD), and Novartis, and has served as an Advisory Board Member for AbbVie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Gilead, Incyte, Merck (MSD), and Novartis. VS has received honoraria from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Merck (MSD), Novartis, and Pierre Fabre, and has served as an Advisory Board Member for Bristol-Myers Squibb. SLS has participated in contracted research with trial funding paid to her institution by Amgen, Arcus, AstraZeneca, Bristol-Myers Squibb, GSK, Merck, Novartis, and Sanofi. SLS has served as an Advisory Board Member or consultant for Amgen, Astellas, AstraZeneca, Beigene, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, GSK, Janssen, Knight, Merck (MSD), Novartis, Pfizer, Roche, Sanofi, Takeda and Taiho. SLS participates in a leadership role for Lung Cancer Canada as president of the board of directors.

DATA AVAILABILITY STATEMENT

Data summaries are available upon request by contacting the corresponding author. Statement rating data are available in Appendices S1 and S2.

ETHICAL APPROVAL

Ethics committee approval was not required per section 2.3b of the TCPS2 since experts who participated in the surveys are published authors on this work and therefore have no expectation of privacy.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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