

Canadian Rheumatology Association/Canadian Research Group of Rheumatology in Immuno-Oncology Living Guidelines for Baseline Immunosuppression in Individuals With Preexisting Rheumatic Diseases Initiating Immune Checkpoint Inhibitors. Part 2: Preexisting Systemic Autoimmune Rheumatic Diseases

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ABSTRACT. *Objective.* Although immune checkpoint inhibitors (ICIs) are increasingly used in patients with preexisting systemic autoimmune rheumatic diseases (SARDs), a key concern is whether baseline immunosuppression at the start of ICI treatment might negatively affect cancer outcomes. This risk must be carefully weighed against the potential for a SARD flare. The objective of this study was to develop a living guideline that will provide up-to-date guidance on the management of baseline immunosuppression for preexisting SARDs when initiating cancer immunotherapy with ICIs.

Methods. The Canadian Research Group of Rheumatology in Immuno-Oncology (CanRIO) formed a multidisciplinary panel composed of rheumatologists, oncologists, researchers, and a patient representative, with methodological support from the Canadian Rheumatology Association (CRA). We completed a systematic literature review to inform this first installment of our living guideline. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, the panel developed recommendations for the management of baseline immunosuppression in individuals with preexisting SARDs.

Results. We identified 67 publications that reported on immunosuppression and cancer outcomes by specific preexisting rheumatic diseases, including 36 on preexisting SARD. Eight best practice statements were developed, highlighting the importance of shared decision making between patients and their care team and careful consideration of risk of SARD flare, risk of organ- or life-threatening manifestations, and potential effect of immunosuppression on cancer outcomes. Seven specific recommendations were made, 1 each for preexisting systemic lupus erythematosus, systemic sclerosis, Sjögren disease, myositis, sarcoidosis, vasculitis, and Behçet disease, considering both the available evidence and expert consensus. The general recommendation for preexisting SARDs was to continue baseline immunosuppression, particularly if there are organ- or life-threatening manifestations.

Conclusion. This living guideline will provide contemporary baseline immunosuppression recommendations for individuals with cancer and preexisting SARDs when initiating ICI therapy. New recommendations will be added over time and updated, with the latest recommendations, evidence summaries, and Evidence to Decision summaries available through the CRA and CanRIO websites (www.rheum.ca, www.canrio.ca). (PROSPERO registration: CRD42023461024)

Key Indexing Terms: cancer, immune checkpoint inhibitors, immunosuppression, immunotherapy, inflammatory arthritis, rheumatic diseases

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Immune checkpoint inhibitors (ICIs), although offering improved survival outcomes in individuals with advanced malignancies, can also lead to immune-related adverse events (irAEs), including flare of preexisting rheumatic diseases (RDs).^{1,2} Whereas irAEs have been associated with favorable oncologic outcomes, flares of preexisting systemic autoimmune RDs (SARDs), such as myositis, glomerulonephritis, and interstitial lung disease (ILD), can be severe and even life-threatening.³ However, the risk of SARD flare needs to be balanced with growing concerns that concomitant baseline immunosuppression at the time of ICI initiation may worsen cancer outcomes. Optimal management of baseline immunosuppression in this unique population remains an area of clinical uncertainty, underscoring the need for evidence-based guidelines. Existing guidelines do not provide recommendations for the management of immunosuppression for specific SARDs.^{4,5} Instead, they provide a blanket recommendation for the management of baseline immunosuppression for all preexisting RDs, which limits their clinical utility given the heterogeneity of RDs, which differ significantly in their clinical manifestations, management, and flare risk with ICI exposure.⁶

To address this gap, the Canadian Research Group of Rheumatology in Immuno-Oncology (CanRIO), a network of rheumatologists across Canada with expertise in this area, in collaboration with the Canadian Rheumatology Association (CRA), undertook the development of consensus guidelines using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. By combining the best available evidence with expert opinion, we aim to provide specific and actionable recommendations for each type of preexisting RD. Further, these guidelines were created on MAGICapp, a digital authoring and publication platform for the evidence ecosystem, facilitating updates as significant new research is published.⁷

These preexisting RD consensus guidelines are split into 2 parts. This part, part 2, focuses on preexisting SARDs, which are likely to cause organ- or life-threatening disease. Preexisting inflammatory arthritides (IAs), which cause predominantly musculoskeletal manifestations, are covered in part 1.⁸

The target audience of this set of guidelines is rheumatologists, oncologists, and other healthcare providers involved in the

care of patients with SARD and cancer. The target population includes individuals with cancer and SARD being considered for ICI therapy. These recommendations are intended to help patients and their healthcare team make decisions regarding baseline (ie, at the time of ICI initiation) immunosuppression treatment of SARD but are not meant to replace clinical judgment. The management of rheumatic irAEs (Rh-irAEs), including SARD flares, is outside the scope of this guideline.

METHODS

This living guideline was developed after undertaking a systematic literature review (SLR) and employing the GRADE approach (Table 1).⁹ Guideline work began in June 2019 and consensus meetings were completed in October 2024. These guidelines will be maintained over time. New recommendations will be added, and existing recommendations may be modified in the setting of new evidence. Additional journal articles may be published to supplement the online living version and aid in knowledge translation. Readers should consult the online version available (www.canrio.ca or www.cra.ca) for the latest version.

Details on organization and panel compositions, funding and management of conflicts of interest, development of recommendations, including the generation of PICO (patient/population – intervention – comparison/comparator – outcome) questions, definitions, SLR, and consensus process, are briefly summarized in this paper and further details can be found in part 1 of this living guideline.⁸ Recommendations for the management of baseline immunosuppression for individuals with preexisting SARD including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjögren disease (SjD), myositis, sarcoidosis, vasculitis, and Behçet disease (BD) are outlined in this second part of the living guidelines. Recommendations for the management of baseline immunosuppression for individuals with preexisting IAs, including rheumatoid arthritis, polymyalgia rheumatica (PMR), psoriatic arthritis (PsA), and spondyloarthritis, can be found in part 1 of this living guideline.⁸ All recommendations and Evidence to Decision (EtD) tables can be

Table 1. GRADE levels of evidence and strength of recommendations.⁷⁷

Level of Evidence	
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect
Strength of Recommendation	
Strong	All or almost all persons would choose that intervention
Weak	There is likely to be an important variation in the decision that informed persons are likely to make

This table is derivative of Table 1 in BMJ Best Practice EBM toolkit, “What is GRADE?”⁷² licensed under CC-BY-NC-4.0. GRADE: Grading of Recommendations Assessment, Development, and Evaluation.

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found on MAGICapp (<https://app.magicapp.org/#/guideline/jMKQ9n>).

Organization and panel composition. The ICI–preexisting RD working group, which included clinicians and trainees in rheumatology and oncology, evaluated evidence from the SLR and synthesized it into EtD tables. The working group was separate from the CanRIO consensus panel, which included rheumatologists, oncologists, researchers, methodologists, and a patient representative living with preexisting RD and cancer who had undergone treatment with ICI.

Management of conflicts of interest. Declarations of potential conflicts of interest (COI) were collected from all panelists and those with perceived COI were not eligible to vote.

Development of recommendations.

- **PICO questions.** The list of preexisting SARDs of interest was generated by the CanRIO Guideline Committee. In total, 7 preexisting SARDs were selected, including SSx, SLE, SjD, myositis, sarcoidosis, vasculitis, and BD. The PICO question format for each preexisting SARD was “Should immunosuppression be continued vs discontinued in individuals with preexisting [specific preexisting SARD] initiating ICIs for their cancer?”

The population of interest was people with any cancer and each specific preexisting SARD undergoing ICI therapy. The intervention was baseline immunosuppression, which was defined as the use of any systemic glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs) at the time of ICI initiation. Hydroxychloroquine (HCQ), apremilast, and colchicine were not considered to be immunosuppressive drugs. The comparison was no baseline immunosuppression. The outcomes of interest were preexisting SARD flare, severe preexisting SARD flare, de novo irAE, severe de novo irAE, ICI interruption or cessation, progression-free survival, overall survival, and overall response rate. Severity of preexisting SARD flare and de novo irAEs was based on Common Terminology Criteria for Adverse Events (CTCAE) grading, with grade 1 and 2 considered mild and grades 3 or higher considered severe.⁴

- **Systematic literature review.** The study was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with International Prospective Register of Systematic Reviews (PROSPERO; CRD42023461024).¹⁰ A comprehensive search strategy was developed in collaboration with an experienced librarian (U. Ellis). PubMed/Medline and Embase were searched for all applicable studies published between database inception and May 15, 2023 (full search strategy in Supplementary Table S1, available with the online version for this article). Each study at each stage was independently screened by 2 members of the ICI–preexisting RD working group and disagreements were resolved by a third person (CY, RPAN, MC, AVFM, JG, LJO, AK, KCKL). The following was extracted from each included study: study methods, population, preexisting SARD type, severity, activity and manifestations, baseline immunosuppression, and outcome details.

- **Development of recommendations and good practice statements.** The ICI–preexisting RD working group prepared summaries and created EtD profiles for each preexisting SARD on MAGICapp to outline the evidence and rationale for drafting each recommendation. These were presented to the full CanRIO consensus panel for discussion and voting. Major ICI–preexisting RD papers that did not stratify outcomes by specific preexisting SARD (and were thus not necessarily included in the EtD tables for any preexisting SARD), but included important information on baseline immunosuppression and outcomes, were also summarized for the panel.^{2,3,6,11,12}

The ICI–preexisting RD working group prepared an initial draft of good practice statements (GPS), which were further refined during the consensus process. GPS are distinct from recommendations, as they are actions where the benefits are highly likely to outweigh any potential harms, even if there is not direct evidence to support the recommendation. They are often based on a combination of indirect evidence, logical reasoning, and established norms within a field.

- **Consensus process.** The consensus panel included the ICI–preexisting RD working group (n = 8, including 3 trainee members), other CanRIO active members (n = 10), and the patient representative (n = 1). Two 4-hour meetings were held virtually, during which discussion ensued until consensus was apparent or unlikely, at which point a final vote was taken on each recommendation and each GPS. The direction (to recommend or not) and strength of a final recommendation, which were voted on separately, were determined if > 80% of the panel agreed.

RESULTS

Systematic literature review. The results and flow of information through the different phases of the SLR were previously described in part 1 of this living guideline.⁸ Briefly, in total 9514 titles and abstracts were screened. Two-hundred thirty-six were identified for full text review, of which 67 studies were included for data extraction for any preexisting RD (Figure). Thirty-six studies included data on preexisting SARD and the data extracted for each SARD discussed in this second part of this living guideline are summarized below under each disease-specific recommendation. Evidence on baseline immunosuppression that are not specific to a particular preexisting RD in the setting of ICI are summarized in part 1 of the living guidelines.⁸ In summary, there is evidence that baseline immunosuppression at the time of ICI initiation may have worse cancer outcomes, whereas there are conflicting data regarding the association of baseline immunosuppression and the development of preexisting RD flare or de novo irAEs.^{6,11–16}

Although not specifically sought out in our SLR, the consensus panel also considered several papers that demonstrated that early immunosuppression for the treatment of irAEs, started around the time of ICI initiation, showed more detrimental effects on progression-free survival and overall survival as compared with immunosuppression started later after ICI initiation.^{17–21}

Good practice statements. The consensus committee developed a list of GPS for the management of baseline immunosuppression

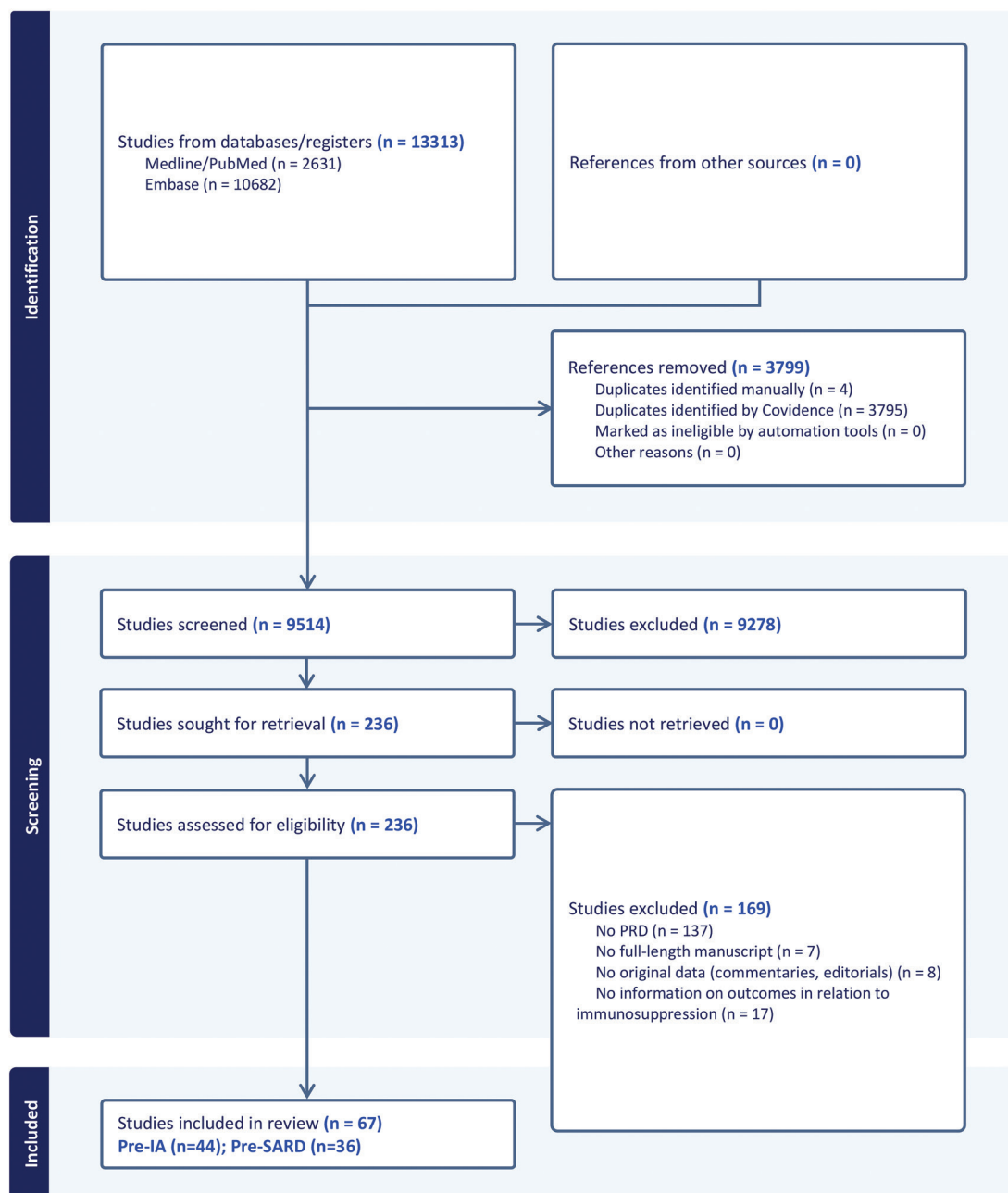


Figure. PRISMA flow diagram of systematic literature review. PRD: preexisting rheumatic disease; Pre-IA: preexisting inflammatory arthritis; Pre-SARD: preexisting systemic autoimmune rheumatic disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

for all individuals with preexisting RD who are being considered for cancer immunotherapy with ICIs. These statements are meant to support the recommendations for each SARD (Table 2). These statements address the importance of advocating for patients with preexisting SARD to have equal access to ICI therapy, of shared decision making and multidisciplinary care, and of minimizing the use of immunosuppression to the least amount needed for preexisting SARD control. The committee provided a guidance of using < 10 mg/day of prednisone when possible, as this is often the cutoff used by oncologists for when

ICI therapy can be started/restarted. We also address the need to discontinue abatacept, a cytotoxic T lymphocyte-associated protein 4 (CTLA-4) analog, in the setting of ICI initiation, as the immunosuppressive mechanism of abatacept directly opposes the immune-activating effects of ICIs, and concurrent use may reduce the efficacy of cancer immunotherapy.²²

Recommendations

The preexisting SARD-specific recommendations were made considering the general evidence on baseline immunosuppression

Table 2. Good practice statements for the management of baseline immunosuppression in individuals with preexisting RD initiating ICIs for cancer.

Good Practice Statement	
A	The presence of preexisting RD should not preclude patients from being considered for ICI therapy, when indicated for the treatment of their cancer.
B	All treatment decisions should be made through shared decision making between patients and their caregivers, rheumatologists, and oncologists, along with other members of the treatment team. - When weighing the risks and benefits of ICI therapy in patients with preexisting RD, the following elements need to be considered: the intention of ICI treatment (ie, adjuvant, curative, or palliative); available alternative cancer treatments; type, severity, activity, and risk of flare of underlying preexisting RD; and patient values and priorities in their health management. - When weighing the risks and benefits of continuing immunosuppression in patients with preexisting RD, the following elements need to be considered: degree of immunosuppression, half-life of immunosuppressive drugs, and potential interactions or risks associated with concurrent immunosuppression and other cancer therapies (eg, chemotherapy and targeted therapy) in addition to ICI(s).
C	The treatment team should be encouraged to reach out to other specialists when there is uncertainty and, when possible, multidisciplinary case rounds are recommended for discussion of complex or unusual cases.
D	The use of new or escalation of immunosuppressive drugs is not recommended solely for the purpose of preventing a flare in patients with preexisting RD starting ICI therapy.
E	For all patients with preexisting RD being considered for ICI therapy, the lowest required amount of immunosuppression should be used to control the preexisting RD.
F	Glucocorticoids should be tapered to the lowest effective dose possible, ideally to < 10 mg prednisone-equivalent daily.
G	In patients on ICI and concurrent chemotherapy, immunosuppression should be discontinued in order to minimize drug toxicities.
H	In patients on abatacept for preexisting RD, abatacept should be stopped or switched to an alternative treatment prior to starting ICI.

ICI: immune checkpoint inhibitor; RD: rheumatic disease.

in the setting of ICIs, the preexisting SARD-specific evidence derived from the SLR, along with expert opinion (Table 3). Data on median overall survival, progression-free survival, and overall response rate were not available at the specific preexisting SARD level, unless specifically discussed below each recommendation. All recommendations had full consensus (16/16 in agreement) unless otherwise specified. The level of evidence was *very low* in support of each preexisting SARD-specific recommendation. Due to the very low certainty of evidence, recommendations relied heavily on expert opinion, which resulted in all recommendations being assigned a strength of *weak*. Due to the sparsity of evidence, the panel did not find it appropriate to make assessments for equity-deserving groups in this guideline.

Recommendation 1. We conditionally recommend continuing baseline immunosuppression in patients with preexisting SSc, particularly if they are at high risk of severe SSc manifestations. This decision needs to be made considering SSc disease phenotype, duration, and activity.

Subgroup considerations.

- (1) Those with preexisting SSc and anti-RNA polymerase III antibodies (ARA) may be at particular risk of flare after ICI initiation and should be closely monitored.
 - (2) Consider paraneoplastic SSc if onset of SSc symptoms occurs close to cancer diagnosis.
- Summary of evidence linked to recommendation.** There were a total of 9 studies, including 28 individuals with preexisting SSc,^{13,23-30} but only 4 studies, including 21 individuals, had information on ≥ 1 outcome of interest associated with baseline immunosuppression status.^{23,26,28,29} Three of these studies included 20 individuals with preexisting SSc who were not on baseline immunosuppression at the time of ICI initiation.^{23,26,28}

One study included 1 individual with preexisting SSc who was maintained on baseline immunosuppression at the time of ICI initiation.²⁹ The largest case series described by Panhaleux et al included 17 individuals with preexisting SSc, 8 of whom had limited SSc and 9 had diffuse SSc.²³ SSc manifestations before starting ICI included Raynaud phenomenon (RP; 14/17, 82%), cutaneous symptoms (12/17, 71%), digestive symptoms (10/17, 59%), joint involvement (5/17, 29%), ILD (5/17, 29%), and pulmonary hypertension (PH; 2/17, 12%). Two individuals had positive ARA. Whereas none (0/17) of these individuals were on baseline immunosuppression at the time of ICI initiation, 6/17 were previously treated with glucocorticoids (35%) and 6/17 were previously treated with nonglucocorticoid immunosuppression (35%). All individuals in this cohort were considered to have quiescent or inactive disease. Of the remaining 3 individuals not on baseline immunosuppression who were not part of the larger case series, 2 had limited cutaneous SSc, 1 of whom had ARA; the third had diffuse SSc.^{26,28}

Of the 20 individuals who were not on baseline immunosuppression, 3 had a mild SSc flare (2 skin, 1 other) and 4 had severe SSc flare (2 skin, 1 ILD, 1 scleroderma renal crisis). All 3 cases with positive ARA had an SSc flare. Of the 5 patients with ILD, only one had a flare. Of the 2 cases of PH, none had worsening of PH during ICI despite no baseline immunosuppression. Eleven of the 20 patients with SSc without baseline immunosuppression developed a de novo irAE, of which 2 were severe.

The individual with preexisting SSc maintained on immunosuppression had a prior diagnosis of SLE and SSc, with manifestations including malar rash, photosensitivity, RP, puffy digits, and high antientromere antibody titers.²⁹ She was maintained on prednisolone 2.5 mg daily throughout ICI therapy and did not experience SSc flare or de novo irAE. The median

Table 3. Recommendations for the management of baseline immunosuppression in individuals with preexisting SARD initiating ICIs for cancer.

SARD	Recommendation	Subgroup Considerations	Level of Evidence	Strength of Recommendation
1. Systemic sclerosis (SSc)	We conditionally recommend continuing baseline immunosuppression in patients with preexisting SSc, particularly if they are at high risk of severe SSc manifestations. This decision needs to be made considering SSc disease phenotype, duration, and activity.	(1) Those with preexisting SSc and anti-RNA polymerase III antibodies may be at particular risk of flare after ICI initiation and should be closely monitored. (2) Consider paraneoplastic SSc if onset of SSc symptoms occurs close to cancer diagnosis.	Very low	Weak
2. Systemic lupus erythematosus (SLE)	We conditionally recommend continuing baseline immunosuppression in patients with preexisting SLE. This decision needs to be made considering SLE disease phenotype, severity, and activity. We conditionally recommend continuing hydroxychloroquine in patients with SLE initiating ICI.	–	Very low	Weak
3. Sjögren disease (SjD)	We conditionally recommend continuing baseline immunosuppression in patients with preexisting extraglandular SjD.	In those with sicca-limited SjD, there is currently no clear evidence to support the use of immunosuppression.	Very low	Weak
4. Myositis	We conditionally recommend continuing baseline immunosuppression in patients with preexisting myositis, particularly if they are at high risk of severe flare. This decision needs to be made considering myositis disease phenotype, duration, and activity.	(1) Consider paraneoplastic myositis, including full myositis antibody panel, if symptom onset occurs in close timing with cancer diagnosis. (2) In those with severe organ involvement (ie, lung and cardiac), we recommend ensuring optimal baseline control is established.	Very low	Weak
5. Sarcoidosis	We conditionally recommend considering reducing or discontinuing baseline immunosuppression in patients with preexisting sarcoidosis, unless they have organ-threatening disease. This decision needs to be made considering sarcoidosis disease phenotype, duration, and activity.	In those with severe organ involvement (eg, parenchymal lung disease, heart, brain and nervous system, eye involvement), we recommend ensuring optimal baseline control is established.	Very low	Weak
6. Vasculitis	We conditionally recommend continuing baseline immunosuppression in patients with preexisting vasculitis.	Those with EGPA may be at particular risk of de novo ICI-associated colitis despite baseline immunosuppression and should be closely monitored.	Very low	Weak
7. Behçet disease (BD)	We conditionally recommend continuing baseline immunosuppression in patients with preexisting BD, particularly if they are at high risk of severe BD manifestations. This decision needs to be made considering BD phenotype, duration, and activity.	In patients with mucocutaneous-predominant BD, consider optimizing colchicine in order to deescalate immunosuppression.	Very low	Weak

EGPA: eosinophilic granulomatosis with polyangiitis; ICI: immune checkpoint inhibitor; SARD: systemic autoimmune rheumatic disease.

overall survival for the 17 individuals described by Panhaleux et al was 15.8 months, and the median progression-free survival was 6.2 months.²³ Nine of the 20 individuals not on baseline immunosuppression had a positive tumor response, as did the 1 individual maintained on baseline immunosuppression with prednisolone 2.5 mg daily.

- *Other considerations for the recommendation.* SSc can have life-threatening manifestations, for which effective treatment is limited. SSc has also been reported to occur as a paraneoplastic manifestation, particularly among individuals positive for ARA.³¹⁻³⁵
- *Rationale for the recommendation.* Despite evidence of significant selection and/or reporting bias of individuals with mild

or quiescent preexisting SSc, there was still a large proportion of individuals who had SSc flares, including 20% with severe flares. There was insufficient evidence to compare the outcomes of those with or without baseline immunosuppression. However, the committee felt that the risk of organ- and life-threatening SSc flares were too great to consider stopping baseline immunosuppression. Given that all 3 individuals with ARA developed severe SSc flares, these individuals warrant especially close monitoring. The committee also recommended considering and testing for paraneoplastic SSc if the timing of onset of symptoms occurs in close timing of cancer diagnosis, as management of paraneoplastic SSc is different from management of preexisting SSc.

Recommendation 2. We conditionally recommend continuing baseline immunosuppression in patients with preexisting SLE. This decision needs to be made considering SLE disease phenotype, severity, and activity. We conditionally recommend continuing HCQ in patients with SLE initiating ICI.

- *Summary of evidence linked to recommendation.* There were a total of 18 studies that included 36 individuals with preexisting SLE.^{13,15,24,25,29,30,36-47} Four individuals from 3 studies had specific information on baseline immunosuppression associated with ≥ 1 outcome of interest (peripheral arterial disease [PAD] flare or de novo irAE).^{37,44,45} One was a case report of an individual chronically maintained on only a low-dose glucocorticoid (not HCQ) for mild disease activity (arthritis).³⁷ This individual developed severe SLE reactivation with secondary immune thrombocytopenic purpura, nephritic syndrome with acute renal injury, and programmed cell death protein 1 (PD-1)-blocked related inflammatory enterocolitis that resulted in the cessation of their ICI. The other 2 individuals were from a single-center study.⁴⁴ None of these individuals were on immunosuppressive therapy or HCQ. These individuals did not experience a flare or de novo irAE. The latter study additionally included an individual with discoid lupus without SLE on monotherapy HCQ, who did not develop SLE symptoms.⁴⁴ There was also a case report of pembrolizumab-related Guillain-Barré syndrome in an individual with inactive SLE on a csDMARD and HCQ that resulted in discontinuation of the ICI.⁴⁵

A French multicenter cohort study of different PADs reported on 7 patients with preexisting SLE, but unfortunately, outcomes were not reported by baseline immunosuppression status.⁴³ Of the 7 individuals, 2 were on csDMARDs at ICI initiation, and 3 had a mild/moderate SLE flare and/or de novo irAE. None of these individuals discontinued ICIs. One other study reported an individual with SLE with a moderate flare of arthritis and rash requiring topical steroids and prednisone, resulting in a temporary interruption of ICI.¹³ This study also included an individual with discoid lupus without SLE, who developed severe central diabetes insipidus that resulted in the temporary cessation of their ICI. Unfortunately, the study did not specifically comment on whether these 2 patients were on immunosuppression at baseline.

- *Other considerations for the recommendation.* Flares of SLE, in general, can range from mild to severe, including life-threatening organ failure. Severe SLE is associated with high morbidity and mortality.

- *Rationale for the recommendation.* The evidence available on use of immunosuppression in patients with SLE receiving ICI is limited, without detailed information on SLE phenotype, baseline immunosuppression therapy, and tumor outcomes, and is likely confounded by reporting bias. This recommendation was based on clinical experience and hypothetical risk. SLE flares in reported cases were frequent and ranged from mild to severe, including in those with lupus nephritis. De novo irAEs were also frequent and in some cases, resulted in temporary or permanent ICI cessation.

The baseline use of HCQ was discussed at length with the panel. HCQ is a mainstay therapy of SLE treatment, known to prevent flares⁴⁸ and improve survival.⁴⁹ Although it has immunomodulatory properties, it is not immunosuppressive. Murine studies have raised concerns that HCQ alone or in combination with azithromycin could reduce the efficacy of anti-PD-1 therapy.^{50,51} However, the doses of HCQ used in murine studies were much higher, similar to those used in SARS-CoV-2 trials, than those traditionally used in SLE. All members (16/16) of our panel recommended continuation of HCQ for SLE with ICI therapy: 13/16 as a conditional recommendation and 3/16 as a strong recommendation.

Recommendation 3. We conditionally recommend continuing baseline immunosuppression in patients with preexisting extraglandular SjD.

Subgroup considerations.

In those with sicca-limited SjD, there is currently no clear evidence to support the use of immunosuppression.

- *Summary of evidence linked to recommendation.* There were a total of 8 studies and 14 individuals with SjD.^{13,14,25,36,42-44,52} Only 1 of these, reporting on 2 individuals with SjD, had information on baseline immunosuppression status associated with ≥ 1 outcome of interest: 1 not on baseline immunosuppression and the other on baseline methotrexate and rituximab.⁴⁴ Neither of these cases had a SjD flare or de novo irAE. Cancer outcomes were not reported.

Of the remaining 12 individuals for whom baseline immunosuppression status was not reported,^{13,14,25,36,42,43,52} 1 developed severe interstitial pneumonitis requiring high-dose prednisone and discontinuation of ICI,⁴² 3 had a flare of their underlying SjD with ≥ 1 of the patients stopping ICI (unclear for 2/3 patients),^{14,25} and 5 were treated with ICI without SjD flare or de novo irAE.^{13,42,43} For 3 patients, outcomes were not reported.^{14,25} Cancer outcomes were not reported.

- *Other considerations for the recommendation.* Immunosuppression is generally only used to treat extraglandular SjD. As such, the panel reasoned that if a patient with SjD requires baseline immunosuppression, it is likely for the treatment of extraglandular disease, which can be organ- or life-threatening.⁵³ Whereas ICI-induced sicca syndrome may be responsive to immunosuppression,⁵⁴ there is no evidence to support the use of baseline immunosuppression for preventing glandular flares in patients with preexisting SjD.

- *Rationale for the recommendation.* There is insufficient evidence to make definitive recommendations regarding the use

of baseline immunosuppression in individuals with preexisting SjD. However, given that extraglandular SjD can be severe (eg, neurological, cardiopulmonary, renal, hematological, or gastrointestinal involvement; vasculitis), the committee felt that individuals who required immunosuppression for management of extraglandular SjD should continue immunosuppression treatment at the lowest effective dose.

Recommendation 4. We conditionally recommend continuing baseline immunosuppression in patients with preexisting myositis, particularly if they are at high risk of severe flare. This decision needs to be made considering myositis disease phenotype, duration, and activity.

Subgroup considerations.

(1) Consider paraneoplastic myositis, including full myositis antibody panel, if symptom onset occurs in close timing with cancer diagnosis.

(2) In those with severe organ involvement (ie, lung and cardiac), we recommend ensuring optimal baseline disease control is established prior to ICI initiation.

- *Summary of evidence linked to recommendation.* There were a total of 7 studies including a total of 7 individuals with information on preexisting myositis treated with ICI therapy.^{43,46,55-59} Of these, only 5 of the studies included data on baseline immunosuppression status and ≥ 1 outcome of interest.⁵⁵⁻⁵⁹ Four of the 5 individuals were not on baseline immunosuppression, and 1/5 (with preexisting antisynthetase syndrome) was on baseline immunosuppression with prednisone.⁵⁵ While on baseline immunosuppression with prednisone, the patient with antisynthetase syndrome experienced a severe flare of ILD leading to death, despite stopping ICI and the administration of high-dose glucocorticoids. Of the 4 without baseline immunosuppression, 3 had myositis flares, and 1 had severe de novo irAE (grade 4 neutropenia). The irAE event occurred in the patient who did not have flare of underlying myositis. Three of 4 without baseline immunosuppression required early cessation of ICI. Tumor outcomes were not reported.

- *Other considerations for the recommendation.* There is likely significant selection bias in the individuals with preexisting myositis who were offered ICI therapy, as only 1 of the 5 individuals was on baseline immunosuppression, which is unusual for individuals with inflammatory myositis. Despite this, all but one had a flare of their myositis, suggesting that the risk of flare for preexisting myositis is high. Myositis is often associated with underlying cancer and could represent a paraneoplastic manifestation, which is managed differently than noncancer-associated myositis.^{60,61}

- *Rationale for the recommendation.* Individuals with preexisting myositis remain at high risk for both flares and de novo irAEs when starting ICI therapy, even while on baseline immunosuppression. This includes the possibility for severe, life-threatening disease flares. Although the patient on baseline immunosuppression developed ILD leading to death, there is insufficient evidence to say that baseline immunosuppression does not prevent myositis flare. The panel felt that the potential

for severe harm related to myositis flare warranted the continuation of baseline immunosuppression. Cancer-associated myositis is defined as cancer that is diagnosed within 3 years of myositis onset, and thus it is important in these individuals to look for signs of paraneoplastic myositis, which can improve with cancer therapy.⁶¹ Further, the committee felt that given the potentially life-threatening nature of severe organ manifestations of myositis, it was important to ensure the disease was well controlled prior to starting ICI therapy. Given the lack of data on cancer outcomes, the effect of immunosuppression on ICI effectiveness in patients with myositis remains uncertain.

Recommendation 5. We conditionally recommend considering reducing or discontinuing baseline immunosuppression in patients with preexisting sarcoidosis, unless they have organ-threatening disease. This decision needs to be made considering sarcoidosis disease phenotype, duration, and activity.

Subgroup considerations.

In those with severe organ involvement (eg, parenchymal lung disease, heart, brain and nervous system, eye involvement), we recommend ensuring optimal baseline control is established.

- *Summary of evidence linked to recommendation.* There were a total of 14 studies including 57 individuals with preexisting sarcoidosis,^{24-26,36,39,41,42,44,46,47,52,58,62,63} but only 5 studies comprising 42 individuals had information on both baseline immunosuppression status associated with ≥ 1 outcome of interest.^{26,44,52,58,62} Among these, only 1 patient was on baseline immunosuppression (low-dose glucocorticoid and HCQ).⁶² This individual developed grade 1 arthralgia and grade 2 pneumonitis managed with 60 mg of oral prednisone.

Among the 41 cases of preexisting sarcoidosis with no baseline immunosuppression, 3 experienced flares of sarcoidosis, all of which responded to systemic glucocorticoids. One individual developed de novo immune-related colitis followed by sarcoidosis flare characterized by constitutional symptoms, hilar lymphadenopathy, panniculitis, subcutaneous nodules, arthritis, and uveitis, and was successfully treated with prednisone, methotrexate, and ICI discontinuation.⁶² The second individual developed a grade 3 sarcoidosis flare, characterized with dyspnea, thoracic pain, and hilar lesions, and was effectively treated with prednisone and temporary (1 dose) cessation of ICI.⁵⁸ The third individual developed a grade 4 sarcoidosis flare and responded to glucocorticoid and ICI discontinuation.⁵² Three studies with a total of 36 cases of preexisting sarcoidosis reported de novo irAE.^{26,58,62} Of these, only 1 was on baseline immunosuppression and 35 were not on baseline immunosuppression. Among the 35 not on baseline immunosuppression, 18 developed mild de novo irAEs and none experienced severe de novo irAEs. The patient on baseline immunosuppression developed de novo grade 1 arthralgia and grade 2 pneumonitis that was managed with oral prednisone with no severe irAEs.^{26,58,62} There were minimal reports of tumor outcomes. One study reported that 15 of 31 cases remained alive at the end of follow-up, and that there was no difference based on baseline immunosuppression.⁶²

- *Other considerations for the recommendation.* Sarcoidosis can

range from asymptomatic mild disease to severe life-threatening disease with severe multiorgan involvement (lung, heart, brain, nervous system, and ocular). In cases of mild asymptomatic disease, immunosuppression is often not indicated.⁶⁴

- *Rationale for the recommendation.* The evidence suggests a low risk of sarcoidosis flare, even in cases without baseline immunosuppression. With only 1 reported case with baseline immunosuppression for sarcoidosis, there is insufficient evidence to determine if baseline immunosuppression prevents flares or de novo irAE. Further, all cases of sarcoidosis flares responded to systemic treatment. Given that nonorgan-threatening sarcoid is often managed without immunosuppression, the risk of sarcoidosis flare was low and treatable in the published cases, and baseline immunosuppression could potentially worsen cancer outcomes,^{11,16,43} the panel conditionally recommended reducing or discontinuing immunosuppression in patients with sarcoidosis without organ-threatening disease. In those with organ-threatening disease, the panel agreed that the potential risk of harm from reducing immunosuppression may outweigh the theoretical benefit of tapering or stopping immunosuppression and therefore recommended continuing immunosuppression at the lowest effective dose.

Recommendation 6. We conditionally recommend continuing baseline immunosuppression in patients with preexisting vasculitis.

Subgroup considerations.

Those with eosinophilic granulomatosis with polyangiitis (EGPA) may be at particular risk of de novo ICI-associated colitis despite baseline immunosuppression and should be closely monitored.

- *Summary of evidence linked to recommendation.* There were of total of 12 studies including 16 individuals with preexisting vasculitis,^{13,24,26,30,39,42,44,58,65-68} but only 7 studies reporting on 7 individuals with preexisting vasculitis had information on baseline immunosuppression and ≥ 1 outcome of interest.^{26,44,58,65-68} All 7 individuals had antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including 3 with EGPA,^{26,58,65} 1 with microscopic polyangiitis (MPA),⁶⁶ and 3 with granulomatosis with polyangiitis (GPA).^{44,67,68} Five of these 7 individuals were on immunosuppression and in remission at the time of ICI initiation, including 3 with EGPA on glucocorticoids, 1 with GPA on methotrexate (4 mg weekly) and prednisone (0.5 mg daily), and 1 with MPA on rituximab maintenance therapy. None of the 5 on baseline immunosuppression had a vasculitis flare. Of the 2 with GPA who were not on baseline immunosuppression, 1 had a severe flare requiring treatment with rituximab⁶⁷ and cessation of ICI, and the other had no flare.⁶⁸ All 3 with EGPA developed de novo colitis, despite being on baseline glucocorticoids at the time of irAE. None of the other individuals developed de novo irAE.

There were minimal data on survival based on baseline immunosuppression. One patient with MPA on baseline immunosuppression had cancer progression leading to death.⁶⁶ The other 4 on baseline immunosuppression had partial/mixed tumor

responses. There were no survival or cancer outcomes reported on the 2 patients who were not on baseline immunosuppression.

There were case reports of individuals with baseline giant cell arteritis (GCA), aortitis, and IgA vasculitis treated with ICI. These did not describe baseline immunosuppression associated with outcomes of interest and therefore could not be used to make specific recommendations. One retrospective study⁴¹ reported 2 patients with GCA, 1 patient with aortitis and 1 patient with urticarial vasculitis. Baseline immunosuppression status was unknown. One patient with GCA/PMR had a flare of GCA after 1 dose of ICI therapy. The patient with aortitis developed grade 3 hypophysitis. The patient with urticarial vasculitis had no flare or de novo irAE. Another case series¹³ reported 1 patient with GCA with unknown immunosuppression status who developed nephritis requiring cessation of ICI. One study³⁰ included 1 patient with IgA vasculitis not on immunosuppression but did not report the outcome of flare or de novo irAE.

- *Other considerations for the recommendation.* There is likely significant selection bias in the individuals with preexisting vasculitis who were offered ICI therapy. Outside the setting of ICI therapy, vasculitis has a high risk of flaring with the discontinuation of immunosuppression.^{69,70}

- *Rationale for the recommendation.* Although the number of cases is small, the risk of flare appears to be low in individuals with AAV who are in remission and maintained on baseline immunosuppression. Further, 4/5 of these cases had at least partial tumor response despite baseline immunosuppression. The committee felt that discontinuing immunosuppression in patients with preexisting vasculitis could result in severe organ- or life-threatening vasculitis flares. The committee felt that it was important to highlight that whereas there were only 3 cases of EGPA, all 3 developed de novo colitis despite being on glucocorticoids, thus potentially representing a population that is at particularly high risk of developing ICI-colitis.

Recommendation 7. We conditionally recommend continuing baseline immunosuppression in patients with preexisting BD, particularly if they are at high risk of severe BD manifestations. This decision needs to be made considering BD phenotype, duration, and activity.

Subgroup considerations.

In patients with mucocutaneous-predominant BD, consider optimizing colchicine in order to deescalate immunosuppression.

- *Summary of evidence linked to recommendation.* There were a total of 3 studies including 3 individuals with preexisting BD.^{14,71,72} Of these, 2 studies had information on baseline immunosuppression status and ≥ 1 outcome of interest. Neither of the 2 patients in these studies were on baseline immunosuppression.^{71,72} The first individual had previously received methotrexate and HCQ for oral and genital ulcers and deep vein thrombosis, and had stopped immunosuppression 1 year prior to ICI initiation.⁷¹ Despite mildly active BD when starting ICI, the patient did not have a BD flare or de novo irAE. In the second individual, there were no details on BD phenotype, but despite

no baseline immunosuppression at ICI initiation, the patient did not experience a BD flare or de novo irAE.⁷² Of these 2 cases, 1 had cancer progression leading to death whereas the other had no survival or tumor outcomes reported.^{71,72}

- *Other considerations for the recommendation.* BD can have severe organ- and life-threatening manifestations.⁷³ Mucocutaneous BD can be treated without immunosuppression and colchicine is recommended as first-line therapy before the addition of immunosuppression.⁷⁴ Apremilast is also now frequently used to treat mucocutaneous forms of BD. Several studies have reported the safety of apremilast in individuals with cancer and psoriasis⁷⁵ and PsA,⁷⁶ but not specifically in those with BD.

- *Rationale for the recommendation.* Given the evidence suggesting that baseline immunosuppression may worsen cancer outcomes,^{11,16,43} in individuals with milder disease phenotypes (eg, mucocutaneous disease), use of colchicine to facilitate the deescalation of immunosuppression can be considered. The panel did not make specific recommendations on the use of apremilast for BD, as current guidelines do not recommend the use of apremilast over immunosuppression and there is insufficient evidence to support the safety of switching to apremilast in those with preexisting BD starting ICI therapy.⁷⁴

DISCUSSION

These consensus guidelines represent the inaugural CRA/CanRIO living recommendations for the management of immunosuppression in patients with preexisting SARDs who are treated with ICI. By combining the best available evidence with expert opinion, we have provided specific and actionable living recommendations for each type of SARD, which will be updated as significant new research is published.

These consensus guidelines (part 1 and part 2) underscore the importance of addressing the specific challenges in managing preexisting RDs in individuals with cancer initiating ICIs. Our systematic review highlights the dearth of high-quality evidence to guide management, particularly for individual RDs. Similarly, the data supporting specific immunosuppressive agents are lacking, particularly with bDMARD and tsDMARDs, limiting our ability to make specific recommendations regarding specific classes of immunosuppressive medications. In the absence of strong evidence, it is particularly important for stakeholders in this field to contribute their expert opinions to provide guidance on the management of these particularly vulnerable individuals. Expert opinion was particularly important when balancing the potential risk of worse cancer outcomes with continued baseline immunosuppression and the potential risk of organ- or life-threatening flares of SARDs with stopping immunosuppression in the setting of minimal evidence to guide decision making. Despite the limited available evidence, the committee was able to come to consensus on all the recommendations, generally erring on the side of preventing SARD flares by continuing baseline immunosuppression, demonstrating that there is consistency in current practice patterns.

In part 2 of these living guidelines, the general recommendation for preexisting SARDs is to continue baseline immuno-

suppression, particularly if there are organ- or life-threatening manifestations. By fostering collaboration between oncologists, rheumatologists, and researchers, future research should aim to generate the high-quality evidence needed to refine and update these living guidelines. The committee is planning to update our literature review every 2-3 years to assess the need to update these guidelines. This iterative approach will ensure that our recommendations remain responsive to emerging evidence, thereby improving patient care and outcomes in this complex and rapidly evolving field.

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CONTRIBUTIONS

Concept and design: CY, SJ. Acquisition, analysis, or interpretation of data: CY, MC, AVFM, JG, LJO, AK, KCKL, RPAN. Drafting of the manuscript: CY, MC, AVFM, JG, LJO, AK, KCKL, RPAN. Critical review of the manuscript for important intellectual content: all authors. Administrative, technical, or material support: LGA, JPP, GSH. Supervision: CY.

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ETHICS AND PATIENT CONSENT

Patients and/or the public were involved in the design, conduct, reporting, or dissemination plans of this research. Ethics approval was not required for this project.

DATA AVAILABILITY

Results of the systematic literature review and synthesis are available on MAGICapp, a digital authoring and publication platform for the evidence ecosystem, by MAGIC Evidence Ecosystem Foundation.

SUPPLEMENTARY DATA

Supplementary material accompanies the online version of this article.

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