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Chronicity of Immune Checkpoint Inhibitor–Associated Inflammatory Arthritis After Immunotherapy Discontinuation: Results From the Canadian Research Group of Rheumatology in Immuno-Oncology Database

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Objective. Immune checkpoint inhibitors (ICIs) improve overall survival (OS) and progression-free survival (PFS) in many types of malignancies but can result in off-target immune-related adverse events including inflammatory arthritis (ICI-associated inflammatory arthritis [ICI-IA]), which can persist even after ICI cessation. We aimed to examine the proportion of patients with ICI-IA who develop chronic ICI-IA and describe characteristics and outcomes associated with chronic ICI-IA.

Methods. We identified patients from the Canadian Research Group of Rheumatology in Immuno-Oncology retrospective cohort who developed de novo ICI-IA with at least three months of follow-up after ICI cessation. Chronic ICI-IA was defined as symptoms or ongoing immunosuppression lasting beyond three months after ICI discontinuation. Acute ICI-IA was defined as resolution of ICI-IA symptoms and discontinuation of immunosuppression within three months of ICI discontinuation. OS and PFS were assessed with Kaplan–Meier curves. Landmark multivariable Cox proportional hazard models for OS and PFS were conducted.

Results. The study cohort included 119 patients. A total of 15 patients (13%) had acute ICI-IA, whereas 104 (87%) had chronic ICI-IA. Patients with chronic ICI-IA were more likely to be White and to have polyarthritis at presentation. After adjusting for age, sex, tumor type, stage of cancer, ICI-IA treatment, and time from ICI initiation to ICI-IA onset, patients with chronic ICI-IA had greater PFS from ICI initiation (adjusted hazard ratio 0.27, 95% confidence interval 0.08–0.98; $P = 0.046$). Adjusted hazard ratio for OS was similar between those with acute versus chronic ICI-IA.

Conclusion. ICI-IA frequently persists after ICI discontinuation. Chronic ICI-IA is associated with improved PFS, but not OS, as compared to acute ICI-IA.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) improve overall survival (OS) and progression-free survival (PFS) in many types of malignancies and are the new pillar of cancer treatment.[1] It is estimated that over 40% of patients with cancer in the United States are candidates for ICIs as part of their cancer management,[2] and this proportion is expected to increase significantly in the coming years. ICIs target molecules that usually inhibit immune activation, including cytotoxic T lymphocyte–associated protein (CTLA)-4 and/or programmed cell death (PD)-1 or its ligand PD-L1. CTLA-4 and PD-1/PD-L1 pathways dampen the natural antitumor response by inhibiting effector

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lymphocytes.[3] By blocking these pathways, ICIs lead to sustained activation of the immune system and a strong antitumor response.

Unfortunately, ICIs can also lead to off-target immune-related adverse events (irAEs). One of the most disabling irAEs is inflammatory arthritis (ICI-associated inflammatory arthritis [ICI-IA]),[4] affecting ≤7.5% of those treated with ICIs.[5] ICI-IA often worsens with ICI infusions[6] and can lead to ICI discontinuation in 9% of patients,[4,7] which could negatively affect tumor outcomes.[8] Some irAEs such as colitis and pneumonitis tend to resolve quickly after ICI discontinuation.[9,10] However, there is increasing recognition that some irAEs can last a long time and become chronic, persisting despite ICI cessation.[9] A recent publication defined chronic irAEs as symptoms or the need for ongoing immunosuppression lasting beyond three months after ICI discontinuation.[11] The prevalence of chronic ICI-IA per this new definition has not formally been studied, although it has been estimated that between 49% and 86% of patients who develop ICI-IA still have active arthritis at 12 weeks after ICI cessation.[9,12,13] However, these data come from studies of small sample sizes or studies that combined both arthritis and arthralgias.

The relationship between ICI-IA and tumor response is complex. Although the development of ICI-IA has been generally associated with favorable tumor responses,[13,14] in one study, higher Clinical Disease Activity Index (CDAI) at ICI-IA presentation was associated with lower PFS.[15] Furthermore, immunosuppressants (prednisone, disease-modifying antirheumatic drugs [DMARDs]) used to treat ICI-IA have also been associated with reduced tumor response.[15–17] The impact of chronic ICI-IA and chronic DMARD use on tumor outcomes remains largely unknown.[13] In this multicentered retrospective cohort study, we assessed the frequency and the factors associated with chronic ICI-IA and PFS and OS associated with chronicity.

PATIENTS AND METHODS

Study design and population. We conducted a retrospective cohort study using the Canadian Research Group of Rheumatology in Immuno-Oncology (CanRIO) retrospective database. The CanRIO network is a collaboration of Canadian rheumatologists with interest and experience in the assessment and management of patients with rheumatic irAEs (Rh-irAEs) after exposure to ICIs (www.canrio.ca). The CanRIO retrospective cohort was established in January 2019 and initially included patients seen from January 2013 to January 2019.[4] Updated information from original patients and new patients was added up to December 2022. It includes standardized chart review and data extraction from all adult patients (age >18 years at inclusion) who developed an Rh-irAE after exposure to ICIs (either a CTLA-4, PD-1, or PD-L1 inhibitor alone or in combination for a diagnosis of cancer, either in the context of standard clinical care or as part of a clinical trial) seen at participating CanRIO sites (n = 10). Patients with pre-existing autoimmune disease other than pre-existing IA were included. Data were extracted from charts and entered into a double-encrypted REDCap database, hosted centrally at the University of Alberta. The study has central ethics approval at the research ethics board at McGill University and independent ethics approval at each participating academic institution. Waiver of individual patient consent was granted at all participating CanRIO sites.

For this study, the CanRIO retrospective database was searched between January 2013 to December 2022 for all patients with de novo ICI-IA. ICI-IA was defined as new IA after ICI exposure diagnosed by the treating rheumatologist, which required the presence of new-onset synovitis in at least one joint on physical examination and/or imaging with no alternate explanation. Patients were included if they had at least three months of follow-up after ICI-IA and at least three months of follow-up after ICI cessation. Patients with pre-existing IA (such as rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease–associated arthritis, or connective tissue disease–associated arthritis) were excluded. Patient with pre-existing autoimmune disease other than pre-existing IA were included.

Chronicity definition. Patients were classified as having chronic ICI-IA if they had ongoing ICI-IA symptoms or were on immunosuppressive treatment (prednisone and/or DMARDs) for ICI-IA for three months or longer after ICI treatment discontinuation. Acute ICI-IA was defined as the resolution of ICI-IA symptoms in the absence of all immunosuppressive treatment within three months of ICI cessation.

Outcomes. Best cancer response was defined by the treating oncologist as complete response, partial response, progressive disease, or stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 when available and by clinical judgment of the treating oncologist when RECIST scoring was not available.[18] OS was defined as the number of weeks between ICI initiation and death. PFS was defined as the number of weeks between ICI initiation and the first imaging confirmation of tumor progression or recurrence.

Covariates. Covariates were extracted from the CanRIO retrospective database, including sex, ethnicity, ICI type, ICI duration, comorbidities, and medication use at the time of ICI-IA onset. Age was the age of the patient in years at ICI-IA onset. Pre-existing autoimmune disease included any autoimmune disease that was diagnosed before ICI initiation other than IA. In those with more than one cancer type, tumor type was the cancer for which the ICI was prescribed. Cancer treatment before ICI initiation was defined as any cancer treatment given for the same cancer as the one the ICI was prescribed for before ICI treatment initiation. Cancer stage was defined as the stage when the ICI was initiated according to the American Joint Committee on Cancer.[19] When patients were exposed to more than one ICI therapy regimen

sequentially, ICI type was the ICI or ICI combination that the patient first received. Other irAE was defined as any non-ICI-IA irAE for which the onset occurred after starting ICI. Pattern of joint involvement, symmetry of joint involvement, affected joints, and additional features were defined at the time of first rheumatology assessment. Monoarthritis was defined as synovitis of only one joint, oligoarthritis as synovitis of two to four joints, and polyarthritis as synovitis of five joints or more. Symmetry of joint involvement was defined as symmetric if joint involvement was similar between the right and the left side and palindromic if the arthritis would come and go with complete resolution between the episodes. Inflammatory back pain was defined as pain located in the spine worse toward the end of the night, worse with rest, improved with activity, and associated with early morning stiffness. Polymyalgia rheumatica symptoms were defined as inflammatory involvement predominantly affecting shoulder and/or hip girdle. Tenosynovitis was defined as inflammation affecting the tendon sheets, enthesitis as inflammation of the site of tendon insertion, and bursitis as inflammation of a bursa, diagnosed either with imaging or physical examination.

Arthritis activity at ICI-IA onset was assessed with the CDAI, a validated tool to measure rheumatoid arthritis disease activity using clinical data retrieved from the charts.[20] Variables included in the CDAI calculation are on a scale from 0 to 10 for physician global assessment and patient global assessment and 0 to 28 for total tender joints and total swollen joints. Time from ICI initiation to ICI-IA was defined as the time between the first ICI administration and the time of first symptom occurrence of ICI-IA symptoms. Time from ICI-IA onset to ICI-IA treatment was defined as the time from the date of ICI-IA symptom onset to the date of treatment initiation. Treatment was all ICI-IA treatments used during the follow-up period (nonsteroidal anti-inflammatory drugs, prednisone, intra-articular glucocorticoids, and/or DMARDs). Maximal dosage of prednisone in milligrams per day was defined as the maximal daily dose received for the treatment of ICI-IA between ICI-IA onset and data collection. Duration of prednisone was defined as total duration of prednisone prescribed for ICI-IA from ICI-IA onset until the end of the course or data collection. Duration of DMARDs was defined as the total duration in weeks that a patient received DMARDs either in monotherapy, combination, or sequential. ICI management relative to ICI-IA was defined as continued if ICI treatment was maintained, temporarily held if doses of ICI were held, and discontinued if ICI treatment was indefinitely stopped because of ICI-IA.

Statistical analyses. Summary statistics were used to describe baseline demographics and clinical characteristics, and these were stratified by ICI-IA chronicity (acute vs chronic). Descriptive data are presented as frequency and percentage, mean ± SD, or median and interquartile range. Continuous variables were compared using nonparametric Mann–Whitney test. Categorical variables were analyzed using chi-square test (sex, pattern of joint involvement, progression) or Fisher's exact test for low cell counts (ethnicity, comorbidities, medication at time of ICI-IA, pre-existing autoimmune disease, family history of rheumatic disease, tumor type, stage of cancer, type of ICI, treatment, best cancer response, death). Two-sided P <0.05 was considered statistically significant.

OS and PFS were summarized with Kaplan–Meier curves and compared between those with chronic ICI-IA and those with acute ICI-IA using log-rank tests. As per convention, time from ICI initiation was the landmark used to calculate OS and PFS, but for the Cox proportional hazards models, landmark analysis was performed for events that occurred after ICI-IA onset.[21,22] Patients who progressed before ICI-IA were excluded from the PFS analyses. Patients were censored at their last follow-up date. Competing risk of death was considered in the models for PFS. Assumption of proportional hazards was confirmed using Schoenfeld residual methods. Multivariable Cox proportional hazard models (hazard ratios and 95% confidence intervals [CIs]) for outcomes OS and PFS, controlling for age, sex, tumor type, stage of cancer, ICI-IA treatment, and time from ICI initiation to ICI-IA onset were conducted. Sensitivity analysis of the PFS Cox proportional hazard model was conducted, only examining progression events that occur at least three months after ICI discontinuation (after chronicity of ICI-IA is established). Effect modification by sex was assessed using interaction terms sex*-chronicity for the outcomes of PFS and OS. Analyses were performed using the software STATA/SE 13.1 (StataCorp). Data collected for this study, including deidentified individual participant data, data dictionary, and study protocol will be made available to others upon reasonable request after the publication date of the manuscript.

RESULTS

The CanRIO retrospective cohort included 367 patients, of which 172 patients had de novo ICI-IA. ICI was discontinued in 128 patients at the time of last follow-up, including 119 who had three months or more of follow-up after ICI cessation. A total of 104 of the 119 patients (87%) had chronic ICI-IA and 15 (13%) had acute ICI-IA (Figure 1). A total of 57 patients (58.8%) were men, with a mean age (±SD) of 66 (±13) years.

Baseline characteristics of patients with acute and chronic ICI-IA were compared. There was no difference in sex, age, comorbidities, medications at time of ICI-IA onset, pre-existing autoimmune disease, family history of rheumatic disease, tumor type, cancer treatment before ICI initiation, stage of cancer at ICI initiation, or type of ICI (Table 1). No patients were taking steroid-sparing agents at the time of ICI-IA diagnosis. It is unknown whether they were previously treated with steroid-sparing agents for a nonarthritis irAE before ICI-IA onset. White people were more likely to have chronic ICI-IA (P = 0.014). Polyarthritis at presentation compared with mono-/oligoarthritis was associated with

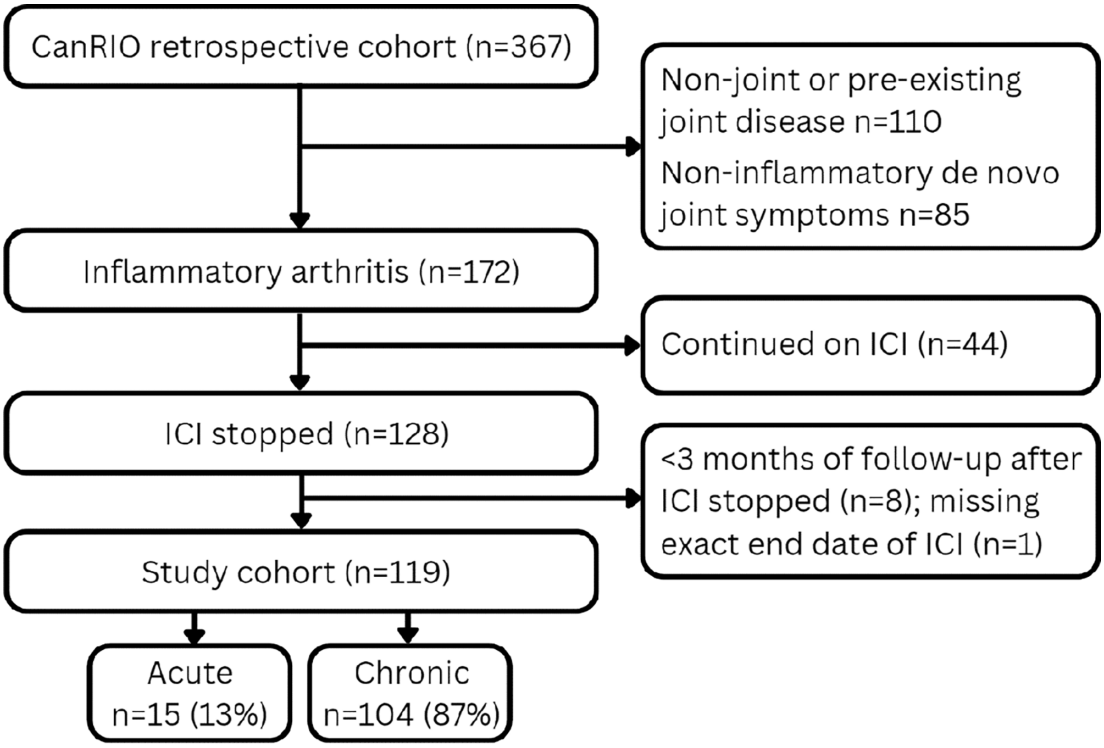

Figure 1. Flowchart of study patients. CanRIO, Canadian Research Group of Rheumatology in Immuno-Oncology; ICI, immune checkpoint inhibitor.

chronicity. Involvement of the wrists and ankles/feet was more frequently seen in those who developed chronic ICI-IA. However, baseline CDAI was not different between acute and chronic ICI-IA. Time from ICI initiation to ICI-IA onset and time from ICI-IA onset to ICI-IA treatment were similar between acute and chronic ICI-IA. Mean ICI-IA duration at the time of ICI discontinuation was longer in those with acute ICI-IA compared with chronic ICI-IA (37.0 vs 12.7 weeks; $P = 0.03$). The percentage of ICI-IA treated with prednisone and DMARDs and maximum daily dose of prednisone were not significantly different between those with acute versus chronic ICI-IA. As expected, duration of prednisone and DMARD use was both significantly longer in patients with chronic ICI-IA. Timing of initiation of prednisone and DMARDs was similar between those with acute ICI-IA and those with chronic ICI-IA. Patients with acute ICI-IA were more likely to have had their ICI delayed due to their ICI-IA, whereas patients with chronic ICI-IA were more likely to have had their ICI treatment stopped permanently due to their ICI-IA. ICI-IA persistence at various timepoints after ICI discontinuation is shown in Table 2. Best cancer response was similar between acute and chronic ICI-IA (Table 3). Total duration of ICI treatment and duration of follow-up after ICI-IA onset were not different between acute and chronic ICI-IA.

Median PFS and OS could not be measured because <50% of the cohort progressed or died during the follow-up period. The 25th percentile for PFS was 111.5 days for those with chronic ICI-IA and 67 days for those with acute ICI-IA (log-rank test $P = 0.013$, Figure 2). The 25th percentile for OS was 161 days for those with chronic ICI-IA and 130 days for those with acute ICI-IA (log-rank test $P = 0.348$; Figure 3). After adjusting for age, sex, tumor type, stage of cancer, ICI-IA treatment, and time from ICI initiation to ICI-IA onset, adjusted hazard ratio (aHR) for PFS was 0.27 in those with chronic ICI-IA (95% CI 0.08–0.98; $P = 0.046$), and the aHR for OS was 0.63 (95% CI 0.18–2.16; $P = 0.465$). Sensitivity analyses evaluating PFS 3 months after ICI discontinuation revealed that chronic ICI-IA had an aHR of 0.94 (95% CI 0.07–13.46; $P = 0.96$) for progression as compared to acute ICI-IA. There was no effect modification by sex using interaction terms of sex*chronicity in the fully adjusted models for both PFS and OS ($P = 0.826$ and $P = 0.584$, respectively).

DISCUSSION

In this multicenter retrospective cohort study, we found that the majority of ICI-IA become chronic, persisting even after ICI discontinuation. Those with chronic ICI-IA were more likely to be White and to have polyarthritis at presentation. Chronic ICI-IA was associated with longer PFS as compared to those with acute ICI-IA. Whether there are inherent differences in presentation and prognosis between acute and chronic ICI-IA that are present at disease onset (for example, inherent differences between rheumatoid arthritis and psoriatic arthritis at disease onset[23]) or if the evolution to chronic ICI-IA leads to differing outcomes and clinical

Table 1. Baseline and ICI-IA characteristics of patients with acute and chronic ICI-IA*

Characteristic	Acute (N = 15), n (%)	Chronic (N = 104), n (%)	*P* value
Sex			
Male	8 (53.3)	62 (59.6)	0.644
Female	7 (46.7)	42 (40.4)	0.644
Age, y	71.5 (13.3)	64.9 (13.3)	0.055
Ethnicity[a]			
White	5 (33.3)	54 (51.9)	0.014
Black	0 (0.0)	0 (0.0)	0.014
Asian	3 (20.0)	1 (1.0)	0.014
Other	0 (0.0)	3 (2.9)	0.014
Comorbidities			
None	6 (40.0)	39 (37.5)	0.963
Cardiovascular	0 (0.0)	3 (2.9)	0.963
Hypertension	6 (40.0)	39 (37.5)	0.963
COPD	1 (6.7)	3 (2.9)	0.963
Diabetes	1 (6.7)	7 (6.7)	0.963
Kidney failure	0 (0.0)	4 (3.8)	0.963
Medication at time of ICI-IA			
Antihypertensive	6 (40.0)	45 (43.3)	1.000
Insulin/oral hypoglycemic	3 (20.0)	16 (15.4)	1.000
PPI	3 (20.0)	30 (28.8)	1.000
Thyroid replacement therapy	2 (13.3)	22 (21.1)	1.000
Prednisone	0 (0.0)	9 (8.7)	1.000
Pre-existing autoimmune disease other than IA	1 (6.7)	9 (8.7)	0.615
Family history of rheumatic disease[b]	1 (6.7)	21 (20.2)	0.188
Tumor type			
Melanoma	4 (26.7)	53 (51.0)	0.154
Lung	7 (46.7)	24 (23.1)	0.154
GU	2 (13.3)	13 (12.5)	0.154
Other	2 (13.3)	14 (13.5)	0.154
Cancer treatment before ICI initiation			
Radiation	5 (33.3)	30 (28.8)	0.360
Surgical resection	8 (53.3)	63 (60.6)	0.360
Chemotherapy	9 (60)	31 (29.8)	0.360
Rituximab	0 (0)	0 (0)	0.360
Targeted therapy	1 (6.7)	15 (14.4)	0.360
Glucocorticoids	0 (0)	0 (0)	0.360
Stage of the cancer at ICI initiation[c]			
1–3	4 (26.7)	39 (37.5)	0.188
4	9 (60.0)	63 (60.6)	0.188
Type of ICI[d]			
Anti-PD-(L)1	10 (66.7)	65 (62.5)	0.614
Anti-CTLA-4	0 (0.0)	0 (0.0)	0.614
Combination	5 (33.3)	33 (31.7)	0.614
Other irAEs			
Colitis	0 (0)	10 (9.6)	0.527
Lung	0 (0)	5 (4.8)	0.527
Skin	0 (0)	5 (4.8)	0.527
Thyroid	1 (6.7)	4 (3.8)	0.527
Other	4 (26.7)	21 (20.2)	0.527
Pattern of joint involvement[e]			
Polyarthritis	7 (46.7)	85 (81.2)	0.011
Oligo-/monoarthritis	7 (46.7)	18 (17.3)	0.011
Affected joints			
Wrists	4 (26.7)	56 (53.9)	0.05
MCP	7 (46.7)	71 (68.3)	0.10
DIP	3 (20)	14 (13.5)	0.5
PIP	7 (46.7)	65 (62.5)	0.24
Shoulder	7 (46.7)	39 (37.5)	0.49
Hips	2 (13.3)	14 (13.5)	0.99
Knee	8 (53.3)	68 (65.4)	0.36
Ankle/feet	3 (20)	61 (58.7)	0.005

(Continued)

Table 1. (*Cont'd*)

Characteristic	Acute (N = 15), n (%)	Chronic (N = 104), n (%)	*P* value
Symmetry of joint involvement			
Symmetric	10 (66.7)	79 (77.5)	0.36
Palindromic	1 (6.7)	8 (7.7)	0.88
Additional features			
PMR symptoms	0 (0)	6 (5.8)	0.34
Inflammatory back pain	0 (0)	0 (0)	NA
Tenosynovitis	4 (26.7)	16 (15.4)	0.28
Enthesitis	2 (13.3)	10 (9.6)	0.66
Bursitis	1 (6.7)	11 (10.6)	0.64
CDAI	21 (11.1)	27.3 (11.8)	0.109
Time from ICI initiation to ICI-IA onset, mean ± SD, wk	18.7 ± 19.4	32.7 ± 33.7	0.142
ICI-IA duration at the time of ICI discontinuation, mean ± SD, wk	37 ± 44.0	12.7± 37.6	0.03
Time from ICI-IA onset to ICI-IA treatment, mean ± SD, wk	6.9 ± 5.6	11.9 ± 19.4	0.994
ICI-IA treatment			
NSAIDs	9 (60.0)	53 (51.0)	0.512
Intra-articular GCs	4 (26.7)	30 (28.8)	0.512
GCs	6 (40.0)	73 (70.2)	0.512
DMARDs	4 (26.7)	88 (77.9)	0.512
Maximal dose of prednisone, mg/d	32.5 ± 17.8	35.9 ± 24.4	0.930
Duration of prednisone use, mean ± SD, wk	18.1 ± 22.7	56.2 ± 57.5	0.04
Timing of initiation of prednisone after ICI-IA, mean ± SD, wk	3.5 ± 3.8	11.3 ± 17	0.26
Duration of DMARD use, mean ± SD, wk	46.4 ± 75.5	70.7 ± 55.1	0.03
Timing of initiation of DMARDs after ICI-IA, mean ± SD, wk	35.9 ± 87.8	72.2 ± 57.8	0.99
ICI management in response to ICI-IA, n (%)			
Continued	9 (60)	53 (51)	0.002
Temporarily held	6 (40)	12 (11.5)	0.002
Discontinued	0 (0)	39 (37.5)	0.002

*All values are expressed as frequency, n, and percentage (%) or mean ± SD. CDAI, Clinical Disease Activity Index; COPD, chronic obstructive pulmonary disease; CTLA, cytotoxic T lymphocyte–associated protein; DIP, distal interphalangeal; DMARD, disease-modifying antirheumatic drug; GC, glucocorticosteroid; GU, genitourinary; ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis; irAE, immune-related adverse event; MCP, metacarpophalangeal; NSAID, nonsteroidal anti-inflammatory drug; PD-(L), programmed cell death (ligand); PIP, proximal interphalangeal; PMR, polymyalgia rheumatica; PPI, proton pump inhibitor.
[a]Missing data for ICI-IA are as follows: acute n = 7, and chronic n = 46.
[b]Missing data for ICI-IA are as follows: acute n = 1, and chronic n = 6.
[c]Missing data for ICI-IA are as follows: acute n = 2, and chronic n = 2.
[d]Missing data for chronic ICI-IA are n = 6.
[e]Missing data for ICI-IA are as follows: acute n = 1, and chronic n = 1.

features is unknown. Our primary evaluation examining the difference in PFS and OS included all progression events after ICI-IA onset and evaluated differences at ICI-IA onset between those who develop chronic ICI-IA and those who do not. Thus, we included sensitivity analysis, in which we only examine progression events that occur after ICI-IA chronicity is established (three months after ICI discontinuation).

Table 2. Percentage of ongoing ICI-IA according to timepoint after ICI discontinuation*

Timepoint after ICI discontinuation, mon	Patients with active ICI-IA/patients still at risk, n/n (%)
3	106/119 (89)
6	90/106 (84.9)
9	83/90 (92.2)
12	73/83 (88)
24	35/73 (47.9)

*ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis.

In our study, polyarthritis at ICI-IA presentation was associated with the development of chronic ICI-IA as compared to oligo- or monoarthritis. Braaten et al[13] found that higher tender joint count, but not swollen joint count or CDAI, after ICI cessation was associated with longer ICI-IA duration. They also found that exposure to combination ICI, longer duration of total ICI treatment, and the presence of more than two irAEs were associated with longer duration of ICI-IA. Although their study did not examine baseline characteristics of ICI-IA in relation to the recently proposed definition of chronic ICI-IA, our results align to suggest that higher number of involved joints is associated with longer ICI-IA duration. Consistent with results from Braaten et al,[13] in our study, class of monotherapy ICI and tumor type were not associated with ICI-IA chronicity. Importantly, fewer patients with acute ICI-IA were treated with DMARDs. Although the reason for this was not ascertained, we hypothesize that perhaps the higher incidence of polyarthritis in the group with chronic ICI-IA prompted rheumatologists to start DMARDs given the similar presentation to classic rheumatoid arthritis.

Table 3. Tumor outcomes of patients with acute and chronic ICI-IA*

Characteristic	Acute	Chronic	*P* value
Best cancer response, n (%)			
Complete response	5 (33.3)	35 (33.7)	0.889
Partial response	5 (33.3)	37 (35.6)	0.889
Stable	3 (20.0)	20 (19.2)	0.889
Progressive disease	2 (13.3)	7 (6.7)	0.889
Not restaged	0 (0.0)	3 (2.9)	0.889
Total duration of ICI treatment, median (IQR), wk	39 (26.2–95.2)	34 (14.8–68.3)	0.21
Duration of follow-up after ICI-IA onset, mean (±SD), wk	27 (±19.5)	34.5 (±17.2)	0.072
25th percentile progression-free survival (25%) from ICI initiation, log-rank test, wk	67.1	111.5	0.013
Death	5 (33.3)	30 (28.8)	0.466
25th percentile overall survival from ICI initiation, log-rank test, wk	129.8	161.2	0.348

*ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis; IQR, interquartile range.

More recently, a study by Cappelli et al[24] found that combination ICI treatment and use of glucocorticoids were associated with persistent ICI-IA at six months after ICI discontinuation. In our study, taking glucocorticoids was not associated with chronic ICI-IA. Interestingly, pre-existing nonrheumatic autoimmune disease has been found to be associated with de novo ICI-IA but was not associated with chronicity in our study,[25] and patients with pre-existing nonrheumatic autoimmune disease were excluded from the only other study on duration of ICI-IA.[13] It appears that factors associated with the development of de novo ICI-IA are not necessarily associated with ICI-IA chronicity.

Our finding of similar percentages of prednisone users in both the groups with acute and chronic ICI-IA are consistent with the results of the multicenter retrospective cohort study by Patrinely et al,[9] which also found that treating acute irAEs with glucocorticoids was not associated with the development of chronic irAEs. The reason why certain irAEs such as ICI-IA and neurologic and ocular toxicities tend to become chronic when compared to colitis or hepatitis, for example, which rarely become chronic, remains unknown.[9] One hypothesis is that ICI-IA is underreported in clinical trials and underrecognized, resulting in treatment delay, which could lead to establishment of chronic ICI-IA.[26–28] In one study, the mean duration between diagnosis of ICI-IA and initial symptom onset was five months.[12] However, in our study, although there was a significant lag between ICI-IA symptoms onset and ICI-IA treatment, this time between ICI-IA symptoms

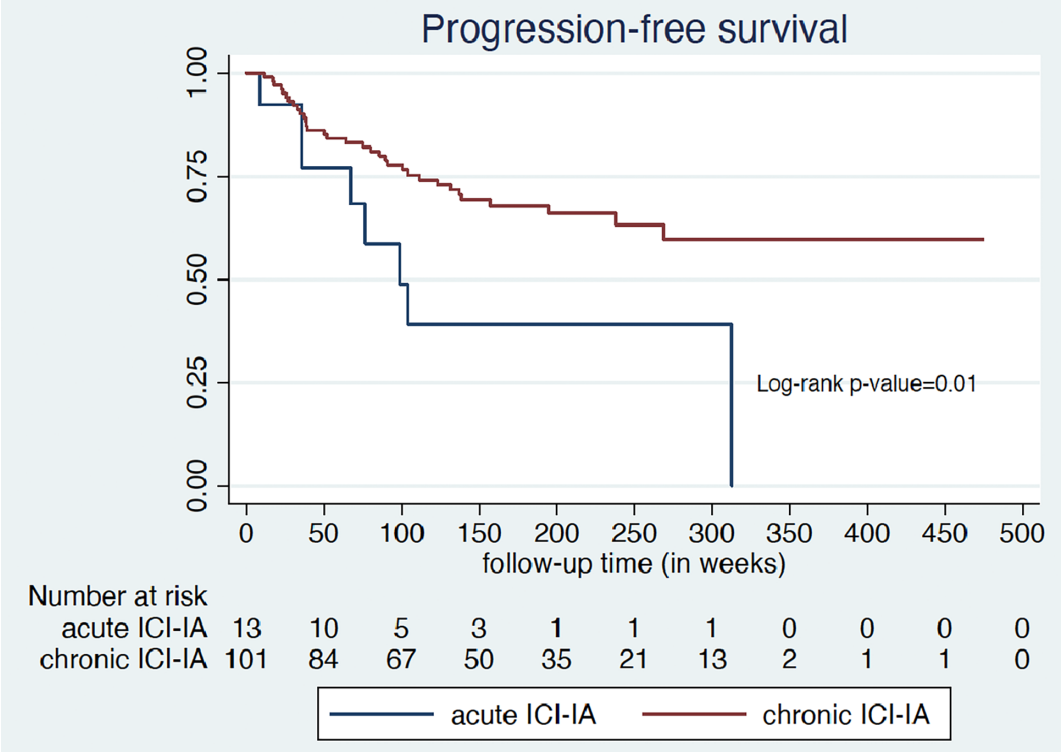

Figure 2. Kaplan–Meier curves for progression-free survival by ICI-IA chronicity. Time 0 is ICI initiation and excludes all patients who progressed before ICI-IA onset. ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis.

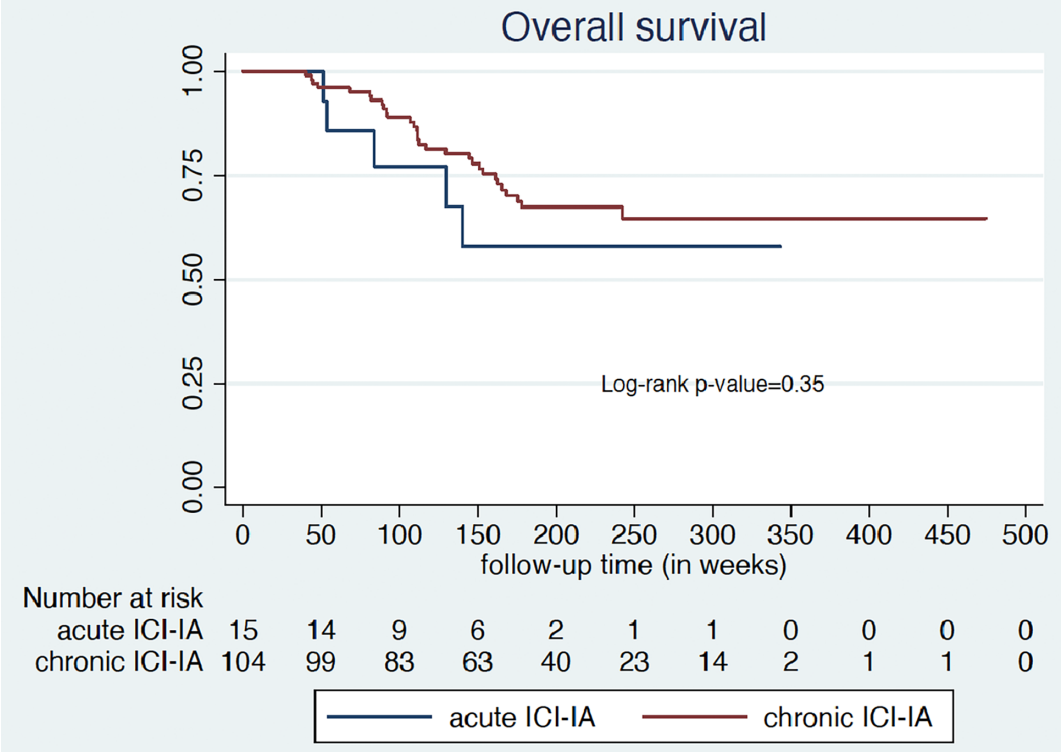

Figure 3. Kaplan–Meier curves for overall survival by ICI-IA chronicity. Time 0 is ICI initiation. ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis.

and ICI-IA treatment initiation was not associated with the development of chronic ICI-IA.

In a single-center prospective study of 42 patients with ICI-IA, CDAI was found to be associated with earlier cancer progression after controlling for time from ICI initiation to arthritis onset and DMARD use.[15] Several papers have reported that Rh-irAEs were associated with good tumor outcomes determined by best cancer response (complete or partial response).[4,14,29,30] Braaten et al[13] found that ICI-IA chronicity was possibly associated with better cancer response (complete or partial response) but did not evaluate PFS and OS, which are standardized outcome measures in cancer studies. Our study is the first to show that chronic ICI-IA is associated with improved PFS.

This is the first study to examine the proportion of ICI-IA that becomes chronic using a recently published definition.[11] This study includes the largest cohort of patients with cancer with rheumatologist-confirmed de novo ICI-IA using a consistent definition of ICI-IA across sites. Despite the retrospective nature of this cohort, the CanRIO sites systematically capture clinical data, and thus, the CanRIO database has captured the most important covariates well, allowing adjustment for important potential confounders. Further, this multicenter study reflects the treatment patterns of many rheumatologists and sites from across Canada, increasing the generalizability of the findings we present.

One limitation of this study is there may be selection bias in the CanRIO database because these patients likely reflect those with more severe or chronic ICI-IA because those with milder or quickly resolving ICI-IA may not have been referred to rheumatologists. Thus, the estimated proportion of chronic ICI-IA reflects the population of patients with ICI-IA referred to rheumatology. Moreover, because the cohort selected for this study only included patients with ICI-IA who had discontinued ICIs, our results might not be generalizable to patients with ICI-IA who are actively treated with ICIs. Although we were able to evaluate a large number of baseline characteristics, there are other potentially important covariates, such as socioeconomic factors that were not recorded in the CanRIO retrospective database. Tumor type may be an effect modifier in the association between outcomes and ICI-IA chronicity. Although we controlled for type of cancer in our multivariable survival analyses, our sample size was inadequate to perform subgroup analyses by tumor type. Further, there may be heterogeneity of outcomes by specific types of tumors within these broad categories of cancer type. As a result of its retrospective design, there were variables with missing values, such as race, which reduced our ability to examine race or ethnicity differences. Although this is the largest cohort of ICI-IA published to date, our sample size still limited the number of variables we could include in our models. The three-month definition for chronicity, although aligning with the Society for Immunotherapy of Cancer consensus definition of irAE chronicity, may not be the most clinically relevant time point to consider for ICI-IA. Larger studies with longer follow-up data will allow sufficient

power to perform sensitivity analysis with various time frames such as 6 or 12 months. Last, sensitivity analysis examining cancer progression that occurred at least three months after ICI discontinuation (after establishment of chronic ICI-IA) showed that the association between chronic ICI-IA and better PFS was no longer statistically significant, although there was a trend toward better PFS. It is unclear whether there is truly no difference in progression events three months after ICI discontinuation or if these results are due to insufficient sample size. Larger studies are needed to confirm our findings.

In conclusion, this study shows that the vast majority of ICI-IA is chronic, using the recent definition of chronic irAEs,[11] and patients with chronic ICI-IA had better PFS but not OS, as compared with acute ICI-IA. This new knowledge will be important when clinicians are trying to make the best treatment decisions for their patients with ICI-IA and consider the best balance of risks and benefits of potentially long-term ICI-IA treatment. Studies are needed to investigate if early initiation of steroid-sparing drugs to limit glucocorticoid exposure and toxicity such as recommended in primary rheumatic diseases is associated with less toxicity and better outcomes in those with ICI-IA. More research is required to better understand the predictors of ICI-IA chronicity and its implications on tumor outcomes, with the ultimate goal of optimizing management of ICI-IA and the underlying malignancy.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ladouceur confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Sharma P, Siddiqui BA, Anandhan S, et al. The next decade of immune checkpoint therapy. Cancer Discov 2021;11(4):838–857.
2. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Netw Open 2019;2(5):e192535.
3. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. Annu Rev Pathol 2021;16:223–249.
4. Roberts J, Ennis D, Hudson M, et al. Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. Autoimmun Rev 2020;19(8):102595.
5. Suarez-Almazor ME, Pundole X, Abdel-Wahab N, et al. Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of immune-mediated cardiovascular, rheumatic, and renal toxicities from checkpoint inhibitors. Support Care Cancer 2020;28(12):6159–6173.
6. Calabrese C, Kirchner E, Kontzias A, et al. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open 2017;3(1):e000412.
7. Richter MD, Crowson C, Kottschade LA, et al. Rheumatic syndromes associated with immune checkpoint inhibitors: a single-center cohort of sixty-one patients. Arthritis Rheumatol 2019;71(3):468–475.
8. Ksienski D, Wai ES, Croteau N, et al. Efficacy of nivolumab and pembrolizumab in patients with advanced non-small-cell lung cancer needing treatment interruption because of adverse events: a retrospective multicenter analysis. Clin Lung Cancer 2019;20(1):e97–e106.
9. Patrinely JR Jr, Johnson R, Lawless AR, et al. Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma. JAMA Oncol 2021;7(5):744–748.
10. Weber JS, Dummer R, de Pril V, et al; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119(9):1675–1682.
11. Naidoo J, Murphy C, Atkins MB, et al. Society for Immunotherapy of Cancer (SITC) consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events (irAEs) terminology. J Immunother Cancer 2023;11(3):e006398.
12. Cappelli LC, Brahmer JR, Forde PM, et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. Semin Arthritis Rheum 2018;48(3):553–557.
13. Braaten TJ, Brahmer JR, Forde PM, et al. Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. Ann Rheum Dis 2020;79(3):332–338.
14. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis 2018;77(3):393–398.
15. Chan KK, Tirpack A, Vitone G, et al. Higher checkpoint inhibitor arthritis disease activity may be associated with cancer progression: results from an observational registry. ACR Open Rheumatol 2020;2(10):595–604.
16. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer 2018;124(18):3706–3714.
17. Tison A, Quere G, Misery L, et al. Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: a nationwide, multicenter cohort study. Arthritis Rheumatol 2019;71(12):2100–2111.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
19. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67(2):93–99.
20. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012;64(5):640–647.
21. Bass AR, Abdel-Wahab N, Reid PD, et al. Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis. Ann Rheum Dis 2023;82(7):920–926.
22. McCarter KR, Wolfgang T, Arabelovic S, et al. Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: a

retrospective, comparative, cohort study. Lancet Rheumatol 2023; 5(5):e274–e283.

23. Yoshii I, Sawada N, Chijiwa T. Clinical characteristics and variants that predict prognosis of difficult-to-treat rheumatoid arthritis. Rheumatol Int 2022;42(11):1947–1954.
24. Cappelli LC, Kamal O, Jones M, et al. Baseline predictors of disease severity in immune checkpoint inhibitor-induced inflammatory arthritis. Rheumatology (Oxford) 2024;63(6):1518–1522.
25. Cunningham-Bussel A, Wang J, Prisco LC, et al. Predictors of rheumatic immune-related adverse events and de novo inflammatory arthritis after immune checkpoint inhibitor treatment for cancer. Arthritis Rheumatol 2022;74(3):527–540.
26. Calabrese L, Mariette X. Chronic inflammatory arthritis following checkpoint inhibitor therapy for cancer: game changing implications. Ann Rheum Dis 2020;79(3):309–311.
27. Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. Nat Rev Rheumatol 2018;14(10):569–579.
28. Cappelli LC, Gutierrez AK, Bingham CO III, et al. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res (Hoboken) 2017;69(11):1751–1763.
29. Liew DFL, Leung JLY, Liu B, et al. Association of good oncological response to therapy with the development of rheumatic immune-related adverse events following PD-1 inhibitor therapy. Int J Rheum Dis 2019;22(2):297–302.
30. Mathias K, Rouhani S, Olson D, et al. Association between rheumatic autoantibodies and immune-related adverse events. Oncologist 2023;28(5):440–448.