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Chronic immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors: a systematic review

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ABSTRACT

Immune-related adverse events (irAEs) are toxicities resulting from use of immune checkpoint inhibitors (ICIs). These side effects persist in some patients despite withholding therapy and using immunosuppressive and immune-modulating agents. Little is known about chronic irAEs and they are felt to be rare. We performed a systematic review to characterize non-endocrine chronic irAEs reported in the literature and describe their management. Ovid MEDLINE and Embase databases were searched for reports of adult patients with solid cancers treated with ICIs who experienced chronic (>12 weeks) non-endocrine irAEs. Patient, treatment and toxicity data were collected. Of 6843 articles identified, 229 studies including 323 patients met our inclusion criteria. The median age was 65 (IQR 56–72) and 58% were male. Most patients (75%) had metastatic disease and the primary cancer site was melanoma in 43% and non-small cell lung cancer in 31% of patients. The most common ICIs delivered were pembrolizumab (24%) and nivolumab (37%). The chronic irAEs experienced were rheumatological in 20% of patients, followed by neurological in 19%, gastrointestinal in 16% and dermatological in 14%. The irAE persisted for a median (range) of 180 (84–2370) days and 30% of patients had ongoing symptoms or treatment. More than half (52%) of patients had chronic irAEs that persisted for >6 months. The ICI was permanently discontinued in 60% of patients and 76% required oral and/or intravenous steroids. This is the first systematic review to assess and report on moderate/severe chronic non-endocrine irAEs after treatment with ICI in the literature. These toxicities persisted for months-years and the majority required discontinuation of therapy and initiation of immunosuppression. Further research is needed to better understand chronic irAEs, which hold potential substantial clinical significance considering the expanded use of ICIs and their integration into the (neo)adjuvant settings.

BACKGROUND

The introduction of immune checkpoint inhibitors (ICIs) has changed the treatment landscape for many cancers. ICIs are monoclonal antibodies that target signaling through cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1) to inhibit tumor evasion and enhance the immune response.[1] Immune-related adverse events (irAE) are toxicities resulting from disruption of immune-checkpoint signaling with ICIs. irAEs may involve any organ system and can be variable in onset and severity.[2]

Most irAEs are acute and resolve with the use of glucocorticoids.[2] However, in some patients, they persist despite withholding therapy and initiating immunosuppressive and immune-modulating agents.[3] Few studies in the literature have described persistent irAEs and clinical trials do not routinely report on these events with updated safety data.[3] The best recognized chronic irAEs affect the endocrine organs such as the thyroid, pituitary and adrenal glands and are thought to represent permanent damage or dysfunction. Endocrine toxicities do not respond to high-dose steroids, and while they generally require lifelong hormone replacement, ICI treatment can usually be continued. Little is known about the incidence, clinical features and management of chronic non-endocrine irAEs.

While recent guidelines from American Society of Clinical Oncology (ASCO)[4] and European Society of Clinical Oncology (ESMO)[5] provide key recommendations for recognizing and managing acute irAE, there is no guidance for clinicians specific to managing chronic irAE. This can lead to long-term morbidity for patients and additional side effects from prolonged immunosuppression. With expanding indications for use of ICI, including in the neoadjuvant[6 7] and adjuvant[8] settings, clinicians need to better understand chronic irAEs to fully inform patients about the potential risks and benefits.

There are no previous studies that comprehensively summarize the features of chronic non-endocrine irAEs in patients treated with ICIs. For these toxicities, ICI treatment may be paused or discontinued, immunosuppression may be initiated, and the long-term implications are unknown. We performed a systematic review to characterize persistent non-endocrine irAEs reported in the literature and describe their management.

METHODS

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[9] The review was not registered and protocol is available on request.

Eligibility criteria

We included case reports, case series, retrospective and prospective cohorts and clinical trials in which at least one adult patient (>18 years) with a solid cancer received an ICI and developed a chronic irAE. Studies in which ICIs were delivered as single or dual-agent immunotherapy, or with chemotherapy or targeted therapy were included. A chronic irAE was defined as persisting for greater than 12 weeks since onset with ongoing symptoms and/or need for immunosuppression. Our study was developed prior to publication of the Society for Immunotherapy of Cancer (SITC) consensus definition terminology.[10] We excluded patients that developed chronic endocrine irAEs (pituitary dysfunction, thyroid dysfunction, type 1 diabetes mellitus, hypoparathyroidism, hypoadrenalism) as these are common, occurring in 15%–40% of patients and are already well described in the literature.[3] These are thought to be irreversible, are treated with long-term hormone replacement, do not require high-dose steroids and generally do not require disruption of ICI therapy.[11] For this reason, we also excluded irAE that did not produce symptoms or require treatment and were diagnosed solely on imaging or blood work, as these are unlikely to affect patients' quality of life or lead to interruption of cancer treatment. We excluded studies in which patients were treated with an ICI plus another immunogenic agent capable of causing autoimmune side effects such as vaccines, oncolytic viruses, interleukins or chimeric antigen receptor T cells.

Information sources

We searched Ovid MEDLINE and Embase databases from inception to March 19 2021 with no language restrictions. Our search strategy was developed in collaboration with an information specialist using controlled vocabulary (eg, programmed cell death-Ligand) and keywords (eg, anti-PD-L1). Prior to final implementation, the search strategy was peer reviewed by an independent senior information specialist. The full search strategy can be found in online supplemental file 1.

Selection process

Studies were screened independently by two reviewers using dedicated cloud-based software (DistillerSR, Evidence Partners, Ottawa, Canada). An accelerated screening method was used for the titles and abstracts in which both reviewers were needed to exclude an article, one reviewer was needed to include, and the second reviewer reviewed records excluded by the first reviewer.[12] Second-level screening (full study) was performed independently in duplicate. Disagreements were resolved by consensus or by consultation with a senior team member when necessary.

Data collection process

Electronic data extraction forms were prepared a priori, and information inputted by one reviewer. This was verified by a second reviewer, with disagreements resolved by consultation with a third team member.

Data items

Extracted data included study characteristics, patient characteristics (age, sex, history of autoimmune condition, cancer type and stage and response to ICI), ICI characteristics (class, delivery and number of cycles), irAE characteristics (number, certainty of diagnosis, type, duration, grade) and management (discontinuation of ICI, hospital admission, use of steroid and additional immunosuppressive agents). We developed criteria to assess the certainty of diagnosing an irAE. Diagnosis was evaluated as 'certain' if a biopsy, pathognomonic imaging or laboratory feature, consistent with an autoimmune cause was reported; 'probable' if clinical findings were reported, and 'possible' if expected clinical features or investigations were missing or yielded negative results, or if alternative causes (such as infection) could not be definitively ruled out. In cases where the study did not provide details about the workup of the patient (eg, cohort and phase I/II studies), the certainty of diagnosis of the irAE was evaluated as 'unclear'. Study authors were contacted to provide additional details when the above information was incomplete.

Ratings of the quality of the evidence

The rating of each of the included studies was based on a scheme modified from Oxford Centre for Evidence-based Medicine. A rating of 1 was given to properly powered and conducted randomized clinical trials or systematic reviews with meta-analysis, 2 for well-designed controlled trials without randomization or prospective comparative cohort trials, 3 for case–control studies or retrospective cohort studies, 4 for case series with or without intervention or cross-sectional studies, and 5 for case reports.

Statistical analysis

Descriptive statistics (means, medians, SD, IQRs) are presented for continuous variables. Frequency tables are presented for categorical variables. Pearson correlation co-efficient and Fisher's exact test were used to look for an association between year of publication and duration of chronic irAE and use of additional immunosuppressants.

Table 1 Patient characteristics

Characteristic	Value
Median age (IQR)	65 (56–72)
Male/female n (%)	188 (58)/107 (33)
History of autoimmune condition n (%)	27 (8)
Metastatic disease n (%)	242 (75)
Cancer type: n (%)	
Melanoma	140 (43)
Non-small cell lung cancer	98 (30)
Other thoracic	17 (5)
Renal cell carcinoma	28 (9)
Bladder cancer	7 (2)
Gynecological	6 (2)
Head and neck	5 (2)
Gastrointestinal	10 (3)
Other	10 (3)
Unknown	2 (0.6)
Best response to ICI: n (%)	
Complete	42 (13)
Partial	74 (23)
Stable disease	53 (16)
Progression	39 (12)
Not reported/adjuvant setting	115 (35)

ICI, immune checkpoint inhibitor.

RESULTS

Study selection

Our electronic database search identified 6843 records (online supplemental figure 2). After deduplication, 4872 studies were screened by title and abstract of which 2434 were reviewed by full text. Of these studies, 2206 were excluded because they did not report a chronic non-endocrine irAE (n=1951), fit our study population (n=167), delivered ICIs with another immune activating agent (n=72) or did not deliver an ICI (n=25). This resulted in 219 studies that met our criteria and was supplemented by hand searching of references in published articles where 9 additional studies met our criteria, for a total of 228 studies including 323 individual patients (online supplemental file 5).

Study characteristics

The included studies were published over a 13-year period (2008–2021). The study types were predominately case reports/series (n=184), as well as retrospective cohorts (n=35), prospective cohorts (n=5) and phase I/II studies (n=4).

Patient characteristics

In patients with reported age and gender, the median age was 65 (IQR 56–72) and 58% were male (table 1). Eight per cent of patients had a pre-existing autoimmune condition, with 16 of out of these 27 patients experiencing a chronic irAE affecting the same system. Most patients (75%) had metastatic disease. The primary cancer of the included patients was melanoma (43%), non-small cell lung cancer (NSCLC) (30%), renal cell carcinoma (9%), bladder cancer (2%), gynecological cancer (2%), head and neck cancer (2%) and other thoracic (5%) (table 1, online supplemental table 1). The best response to treatment with ICI was complete in 13%, partial in 23%, stable disease in 16% and progression in 12% of patients.

Chronic irAE characteristics

The median number of cycles of ICI before development of the chronic irAE was 3 with a range of 1–42 (table 2). The median number of irAE experienced by each patient was 1 with a range of 1–4, meaning some patients developed other irAE in addition to the chronic irAE of interest. The treatment leading to a chronic irAE was a rechallenge after previous immune-related toxicity in 9% of patients. We evaluated the certainty of irAE diagnosis as 'certain' in 31% of patients, probable in 41% and possible in 9%. For 19% of patients, there was not enough information to assess for certainty based on reporting within the study.

The ICI leading to irAE was pembrolizumab (24%), nivolumab (38%), durvalumab (2%), atezolizumab (3%), avelumab (0.8%), ipilimumab (21%), tremelimumab (0.5%), or other anti-PD-1 (8%) or anti-CTLA-4 antibodies (3%). ICIs were delivered as single agents in the majority (76%) of patients, and as dual agent in 16%, or with chemotherapy (4%) or targeted therapy (2%).

The type of chronic irAE can be seen in figure 1. The most common chronic irAE was rheumatological in 20% of patients, followed by neurological in 19%, gastrointestinal in 16% and dermatological in 14%. Arthritis was the most common rheumatological chronic irAE seen in 55% of patients followed by myositis in 9% of patients. There was a broad spectrum of neurological chronic irAEs. These included potentially fatal toxicities such as myasthenia gravis (25%) and encephalitis (13%), as well as several peripheral nervous system toxicities including peripheral neuropathy (12%), polyradiculoneuropathy (5%) and polyneuropathy (3%). Hepatitis (53%) and colitis (37%) were the predominant gastrointestinal chronic irAEs. Dermatological chronic irAEs were also varied ranging from dermatitis (11%) and vitiligo (11%) to more severe cutaneous toxicities such as bullous pemphigoid (20%). Description of individual chronic irAEs can be found in online supplemental tables 1 and 2.

The irAE persisted for a median of 180 days with a range of 84–2370 days and 30% of patients had ongoing symptoms or treatment for the chronic irAE at the time of publication. Among the patients with reported resolution of their chronic irAEs, the determination was made based on symptom resolution in 45% of patients and the date of discontinuation of immunosuppression without recurrent symptoms in 26% of patients. A breakdown of the duration in months can be seen in figure 2. Approximately one-quarter of patients had chronic irAEs that

Table 2 Characteristics of chronic irAE

Characteristic	Value
Median prior cycles of ICI (range)	3 (1–42)
Median no of irAE per patient (range)	1 (1–4)
Rechallenge after previous toxicity n (%)	29 (9)
Certainty of irAE diagnosis: n (%)	
Certain	101 (31)
Probable	131 (41)
Possible	29 (9)
Unclear	62 (19)
ICI: n (%)	
Pembrolizumab	91 (24)
Nivolumab	141 (38)
Other anti-PD-1	29 (8)
Durvalumab	7 (2)
Atezolizumab	10 (3)
Avelumab	3 (0.8)
Ipilimumab	80 (21)
Tremelimumab	2 (0.5)
Other anti-CTLA-4	11 (3)
Unknown—blinded study	2 (0.5)
ICI delivered as: n (%)	
Single agent	246 (76)
Dual agent	53 (16)
With chemotherapy	14 (4)
With targeted therapy	8 (2)
Not reported	2 (1)
Median days duration (range)	180 (84–2370)
irAE ongoing at time of publication	98 (30)
irAE resolution based on: n (%)	
Symptoms resolved	146 (45)
Immunosuppression discontinued	82 (26)
Grade: n (%)	
1–2	97 (30)
3–4	122 (38)
Not reported	104 (32)

anti-CTLA-4, anti- cytotoxic T lymphocyte antigen-4; anti-PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events.

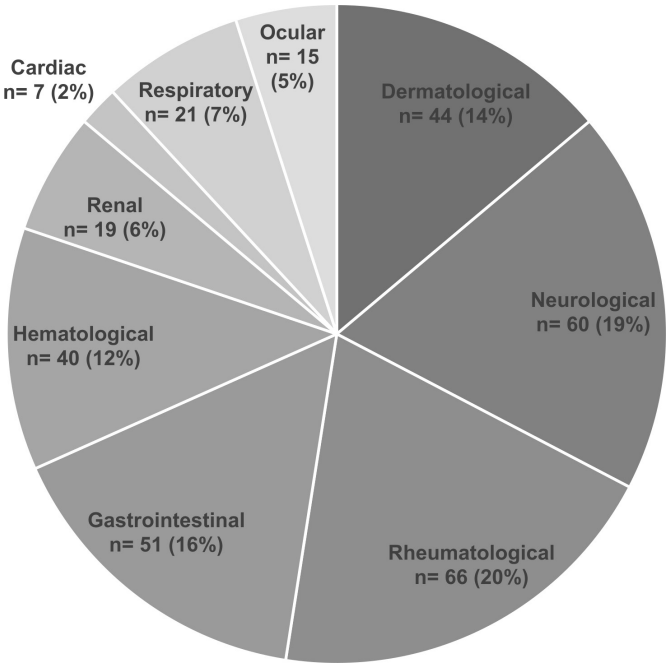

Figure 1 Categories of chronic immune-related adverse events. Pie-chart showing the percentage of included chronic immune-related adverse events affecting each organ system.

persisted for more than 6–9 months. The chronic irAE persisted for over 6 months in more than half of patients (52%) and over a year in 13% of patients. There was no association between the year article was published and duration of the patients chronic irAE (r=0.012, p=0.84). The severity of the chronic irAE was grades 1–2 in 30% of patients and grades 3–4 in 38% of patients.

Chronic irAE treatment

The ICI was permanently discontinued in 60% of patients (table 3). Twenty-four per cent of patients were admitted to hospital for management of their irAE. Treatment of the chronic irAEs included oral (67%), intravenous (31%) and topical (7%) steroids. Seventy-six per cent of all patients, and 91% of those with grades 3–4 toxicities, received oral and/or intravenous steroids. The median duration of steroid treatment was 120 days (range 1–1443 days) and 16% of patients were reported to have remained on steroids at last follow-up.

There were 27% of patients who required additional immunosuppressive agents beyond steroids, which varied by the organ system affected by the chronic irAE. Mycophenolate was administered to 29% of patients who experienced gastrointestinal or cardiac toxicities, as well as to 13% of all patients with ocular toxicities, 10% with respiratory toxicities, 5% with renal toxicities, and 3% of patients with hematological, neurological, or rheumatological toxicities. Infliximab was administered to 13% of patients who experienced ocular toxicities, 10% with respiratory toxicities, 8% with gastrointestinal toxicities, 7% with neurological toxicities, 6% with rheumatological toxicities and 2% of dermatological toxicities. IVIG was administered to three patients with thymic cancer (accounting for 43% of all cardiac toxicities) within the same study who developed myocarditis.[13] IVIG was also administered to 32% of all patients with neurological toxicities, 25% with hematological toxicities, 8% with rheumatological toxicities, 7% with ocular toxicities and 2% with dermatological or gastrointestinal toxicities. Plasma exchange was used in 17% of all patients with neurological toxicities.

There were no differences in the proportion of patients who received an additional immunosuppressive agent according to the year of publication (p=0.50). Only 2% of patients received a non-steroid immunosuppressive agent alone. Six per cent of patients experienced toxicities

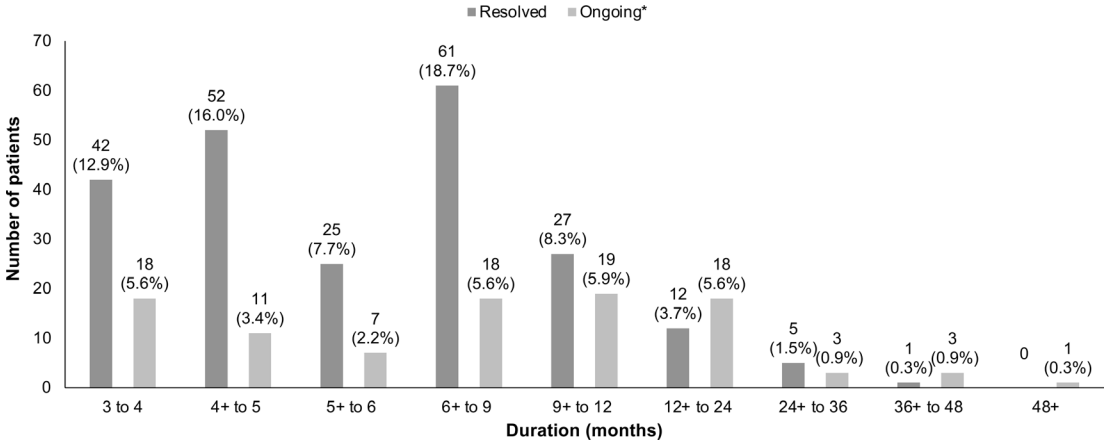

Figure 2 Duration of chronic immune related adverse events The reported duration in months of each chronic immune related adverse event included in our review. *ongoing at last follow-up or time of publication.

related to the treatment of their chronic irAE including infections (urinary tract infection, pneumonia, abscess), steroid-induced diabetes and compression fractures (online supplemental table 2).

Ratings of the quality of the evidence

The rating of each of the included studies based on a scheme modified from Oxford Centre for Evidence-based Medicine can be seen in online supplemental table 1. The majority of studies received a low-quality rating of 4 or 5 as they were case series or case reports.

DISCUSSION

To our knowledge, this is the first systematic review in the literature to summarize chronic non-endocrine irAEs after treatment with ICI. Our study demonstrated several important features of chronic non-endocrine irAE including the severity, most frequently affected systems, and variable duration, with over half of cases persisting for greater than 6 months. With expanding indications for ICI in the neoadjuvant setting,[6 7] and recent evidence that chronic irAEs occurred in >40% of patients in the adjuvant setting,[14] it is crucial for these toxicities to be recognized and managed.

The median duration of chronic irAEs in our review was 180 days with the longest persisting for 2370 days. In 30% of patients the irAE was not resolved at the time of publication, meaning our study likely underestimates the duration of chronic non-endocrine irAEs. At the time of our analysis, approximately 13% of patients who developed a chronic irAE had this persist for greater than 1 year. While an irAE persisting for years may bode well from a prognostic standpoint,[15] it is important to recognize the potential effects on a patients' function and quality of life. Data from a small series of patients with persistent ICI-induced inflammatory arthritis suggested a major emotional and functional impact of this irAE, even in the context of advanced cancer.[16] This highlights the importance of better understanding chronic irAEs as patients can experience significant morbidity for many months. Whether some of these toxicities represent irreversible damage versus ongoing inflammation with waxing and waning symptoms remains to be determined.

Our results differ from a retrospective study by Patrinely *et al* which is likely a reflection of several key differences between our study population and their cohort. Their study was a multicenter retrospective cohort study that reviewed patient records from eight participating institutions to identify chronic irAE. Our study was a systematic review from which the incidence and prevalence of chronic toxicities cannot be calculated. In their study, all patients received ICI as adjuvant therapy. However, in our review 75% of patients were treated in the metastatic setting which may impact the reporting of late-occurring low-grade events. Most of the chronic irAE in their study were endocrinopathies and we had specified a priori in our inclusion criteria to exclude patients with endocrine toxicities. Our rationale was that endocrine irAE seldom recover and, rather than being treated with immunosuppression, are treated with generally well-tolerated hormone replacement. Only 49% of patients in their study were symptomatic, whereas all patients in our study were symptomatic or required treatment due to the severity of the chronic irae, such as elevated liver tests with hepatitis.

Given the differences in study design and inclusion criteria, it is not surprizing that most (96.4%) chronic irAE from anti-PD-1 therapy in their patients with resected melanoma were mild at grades 1–2[14], in contrast to the substantial proportion of patients with severe (grade≥3) toxicities in our study. We applied these inclusion criteria to reflect a clinically complex population where initiating immunosuppression would be considered, and the treating oncologist would have to weigh the risks and benefits of continuing ICI therapy or rechallenging in the future. We acknowledge that the estimate of high-grade toxicities in our review is likely driven by publication bias, with reports of patients with more severe toxicities being more likely to be submitted and published. Even taking this into account, some patients may opt to decline ICI

Table 3 Treatment of chronic irAE

Characteristic	N (%)
ICI permanently discontinued	194 (60)
Hospital admission	79 (24)
Steroids:	
Any	270 (84)
Oral	217 (67)
IV	99 (31)
Topical	22 (7)
Other	11 (3)
Ongoing steroid use at last follow-up:	
Yes	52 (16)
No	200 (62)
Unclear	71 (22)
Steroid+additional immunosuppressive agent	87 (27)
Additional immunosuppressive agent:	
Mycophenolate	27 (8)
Infliximab	17 (5)
Cyclosporine	6 (2)
Methotrexate	15 (5)
Tacrolimus	4 (1)
Adalimumab	3 (1)
Vedolizumab	6 (2)
Rituximab	11 (3)
Cyclophosphamide	4 (1)
Hydroxychloroquine	6 (2)
Azathioprine	6 (2)
IVIG	40 (12)
Plasma exchange	10 (3)
Non-steroid immunosuppressive agent alone	5 (2)
Toxicity from treatment of irAE	19 (6)

ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; IV, intravenous.

therapy if the potential of morbid and prolonged irAEs like those captured in our review were presented to them upfront. Therefore, our study reflects an important population of patients where chronic toxicities from ICI caused some degree of harm, often severe, and persisted for many months-years. Oncologists must be aware of this possibility when counseling patients.

The most frequent categories of chronic irAEs in our review were rheumatological, neurological, gastrointestinal and dermatological. While gastrointestinal and dermatological irAEs are commonly observed and typically readily identified, rheumatological and neurological toxicities are rarer in the acute setting. Moreover, these irAEs can present with non-specific symptoms that make them challenging to recognize and diagnose. In the study by Patrinely *et al* most chronic irAEs occurred in nonvisceral systems such as the joints, eyes, salivary glands and nervous system.[14] Whether this reflects differences in the populations being studied, publication bias in toxicities reported, or underlying immunological differences in the response and tolerance to ICI in different tissues of origin remains to be determined.

Previous studies have shown that the frequency of acute adverse events is higher with combination (ie, PD-1 plus CTLA-4 inhibitors) therapy than monotherapy.[17] In our review, 76% of the patients with chronic irAEs received single agent ICI therapy which were most commonly PD-L1 inhibitors. This reflects the historical patterns of clinical use of these agents with PD-L1 inhibitors used more frequently and limited indications for combination therapy. In the acute setting, irAEs were reported more often in responding patients than those who do not respond to ICI.[18] The proportion of patients with a complete or partial response to treatment in our review was 36%. The relationship between chronic irAEs and response to ICI remains to be determined. These patterns should be explored in within the context of clinical trials.

There is no consensus to guide the management of chronic non-endocrine irAEs and our review is the only comprehensive summary of what has been used in the literature. We observed varying practices for the patients in our study, with the ICI being permanently discontinued in 60% of patients. Most patients received oral or intravenous steroids, consistent with the recommendations for managing acute irAE. In comparison to the study by Patrinely *et al*, in which only 33% of patients received steroids (likely reflecting the high proportion of endocrine irAEs), 76% of patients received oral and/or intravenous steroids in our population, and this was as high as 91% in those with severe chronic irAEs. Additional immunosuppressive agents, or therapies such as IVIG or plasma exchange, were required in several patients. It is worth noting that the proportion of patients receiving additional immunosuppressive agents was not increased in recent years, suggesting that despite changes in management of acute irAEs with clinical practice guidelines, practice patterns for chronic irAEs may not have evolved similarly. It is clinically important that almost one-quarter of patients required admission to hospital and 6% of patients developed a side effect related to their immunosuppression. The therapeutic algorithms for management of irAEs should be updated to incorporate chronic toxicities as our understanding of the mechanisms and most effective therapies improves.

Our review has several limitations and is biased by its retrospective nature. Chronic irAEs were reported most commonly in disease sites that had early adoption of ICI therapy such as metastatic melanoma and NSCLC. Similarly, most patients in our study were treated with pembrolizumab and nivolumab which reflects the historical studies and approval of these agents. As previously mentioned, our review is affected by publication bias with

reports of severe and persistent irAE more likely to be published. The workup of these toxicities in the included studies may not reflect real-world practices as there were high rates of biopsies performed with increased certainty of diagnosis. Although we contacted study authors to provide additional details when needed, we were limited in our summary by the reporting in the original articles. We are unable to make statistical comparisons based on a lack of control group. The majority of included articles were case reports/series with no reports coming from phase III trials. Detailed follow-up data from randomized trials would be the ideal source to understand the true incidence of chronic irAEs, yet in our review of hundreds of phase II and III trials there was a lack of updated safety data describing prolonged toxicities. This is a crucial gap in the literature for which previously collected data could be disseminated, and standardized reporting of chronic irAEs as part of clinical trial safety and quality of life outcomes can be considered.

Our systematic review was designed and conducted prior to the publication of the (SITC) consensus definition for chronic irAEs.[10] Their definition specifies that for an irAE to be considered chronic the ICI must be discontinued with an adverse event persisting beyond 3 months. While our definition also used a duration of 12 weeks or beyond, we included patients in which the ICI had not been stopped. We recognize the importance of adopting a standardized vocabulary to describe irAE going forwards.

In summary, we described a population of patients in the literature that developed chronic moderate/severe non-endocrine irAEs after treatment with ICI. These toxicities are unique in that they can have long-term implications and affect systems that may be under-recognized by clinicians. This is the first study to detail the management of a wide variety of chronic non-endocrine irAEs which often included long-term steroid use. Discussing the potential for other chronic irAEs, in addition to routine counseling about permanent endocrine irAEs, is critical for counseling patients about the risks and benefits of ICIs. This becomes relevant for a greater number of patients with the increasing use of ICI in the neoadjuvant and adjuvant settings. Further data from randomized trials, and updated safety and adverse event data from previous studies, are needed to better understand and manage chronic irAEs.

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