ABSTRACT
Immune checkpoint inhibitors (ICIs) are newly approved treatments for advanced malignancies that are increasing survival. The mechanism of these drugs, non-specifically activating T cells, also leads to immune-mediated damage of tissue or immune-related adverse events (IRAE). IRAEs with rheumatic phenotypes are increasingly being recognised. Inflammatory arthritis, sicca syndrome, inflammatory myopathy, vasculitis and lupus nephritis have been described as a result of ICIs. Use of ICIs will be expanding in the coming years for several reasons. ICIs will be used in earlier stage cancer, for more indications, and additional drugs will be approved. The rheumatologist plays a critical role in evaluating and treating these patients. The expertise of rheumatologists in evaluating rheumatic signs and symptoms and treating patients with immunosuppression are critical in ensuring the optimal outcomes for patients with rheumatic IRAE. Collaboration between oncology and rheumatology for clinical care and research will enhance understanding of these new disease entities.

INTRODUCTION
Cancer therapy has evolved dramatically in recent years with the approval of immune checkpoint inhibitors (ICIs) as immunotherapies to treat advanced stage disease.1 These drugs work by inhibiting negative regulation of T cells, thus leading to heightened antitumour responses. Ipilimumab, targeting CTLA-4, nivolumab and pembrolizumab, targeting PD-1, and atezolizumab, targeting PD-L1, are FDA-approved, with the first three drugs also approved in the European Union. ICIs have improved survival for several cancers and, in a subset of patients, can lead to lasting tumour regression or complete remission. Currently approved indications include metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), Hodgkin’s lymphoma and urothelial carcinoma,2–7 with many other malignancies being studied and across all tumour stages.

Though these drugs have improved outcomes for some advanced malignancies, they are not without consequences. Owing to their non-specific mechanism of activating T cells, the main toxicities of ICIs are due to immunologically mediated and inflammatory damage of tissues, collectively referred to as immune-related adverse events (IRAEs). IRAEs have been described that affect nearly every organ system. Colitis, various rashes, pneumonitis, hepatitis, encephalopathy, neuropathy, thyroiditis and hypophysitis are some of the wide-ranging adverse effects attributed to ICIs. Biopsies from colitis have demonstrated diverse inflammatory cell infiltrates,9 and development of colitis has been shown to be associated with elevated levels of IL-17,10 highlighting the relationship between immune activation and tissue damage. In the 5 years since the first ICI was approved, reports have described a variety of IRAEs with clinical manifestations similar to rheumatic disease. Inflammatory arthritis has been described in case reports11–13 and a case series.14 In our own experience evaluating nine patients treated with ICIs who developed inflammatory arthritis, we observed three major types: polyarticular arthritis involving small and large joints similar to rheumatoid arthritis, a reactive arthritis-like
syndrome with urethritis, conjunctivitis and oligoarthri-
tis, and a large joint predominant seronegative spondy-
loarthritis. Many of these patients had severe, highly
inflammatory disease requiring higher doses of corticos-
teroids to control than traditional forms of inflammatory
arthritis. Several continued to have symptoms of inflam-
matory arthritis months to over a year after immunother-
apy was withdrawn. Sicca syndrome was also reported in
the same case series with patients experiencing severe
salivary hypofunction. Additional rheumatic manifesta-
tions of ICIs include vasculitis, inflammatory myopathy,
eosinophilic fasciitis and lupus nephritis. Within vasculitis,
giant cell arteritis and single organ vasculitis have been
reported. Cases of inflammatory myopathy similar to dermatomyositis and polymyositis
are both reported. There may be other rheumatic IRAEs resulting from treatment of ICIs that have not yet been
described in the published literature.

AN UNDER-REPORTED PROBLEM
All the aforementioned rheumatic IRAEs have only been
described in case reports or small series. Many clinical
trials that have published toxicity data either do not
report rheumatic IRAE, do not provide clinical descrip-
tions of rheumatic IRAE, or only report high-grade
adverse events, thus potentially excluding events such as
inflammatory arthritis. Additionally, no prospective
cohort study has evaluated a population of patients
referred to rheumatology, no evidence-based recommen-
dations for evaluation and treatment tailored to patients
who have active malignancy are available.

A RAPIDLY EXPANDING AREA
As we begin to understand the scope of rheumatic IRAE, it is important to note that ICIs are being used
with increasing frequency by oncologists. Excitement
surrounding this group of therapies will lead to expen-
tial growth in use for several reasons.

Expanding indications of existing drugs
In the past 2 years, ICIs went from having a single indi-
cation, metastatic melanoma, to having five approved
indications to date (melanoma, RCC, NSCLC, urothelial
carcinoma and Hodgkin’s lymphoma). There have been
positive results reported in other tumours such as colo-
rectal cancers with mismatch repair defects, Merkel
Cell carcinoma, and in relapse after haematopoietic
stem cell transplant for haematologic malignancies. The
non-specific mechanism of action of these drugs
along with these emerging data indicate that we should
expect to see approvals of ICIs for many new indications in
the upcoming years.

New targets
Presently, hundreds of trials are ongoing internationally
using ICIs. Other immune checkpoint targets with drugs
in clinical trials include B7, CD137, T-cell immunoglobu-
lin and mucin domain-3 (TIM-3) and lymphocyte activa-
tion gene-3 (LAG-3). It remains to be seen how the
risk of IRAE may differ by which immune checkpoint is
targeted, but at minimum, approvals of drugs targeting
these related pathways will increase the use of ICIs.

Combination therapy
There is currently one FDA-approved combination ICI
regimen, ipilimumab and nivolumab for metastatic mel-
anoma. The combination group in the phase III trial for
that regimen had higher rates of IRAEs than both mono-
otherapy groups. In our series of 13 patients, 8 were
on combination therapy, while 5 were on mono-
otherapy. Many of the ongoing trials use ICIs in combi-
nation. Thus, the rate of IRAE is likely to increase as
more regimens are studied and indications approved.

Earlier use of ICIs
Among the many trials of immunotherapy are those
focusing on ICIs as neo-adjuvant therapy and in earlier
stage disease. This is important for two reasons. First,
perhaps more importantly, earlier use of ICIs means a
higher likelihood of inducing a lasting remission and
thus a longer lifespan in which ongoing management of
rheumatic IRAEs may be required. Second, earlier use
of the drugs and approval of ICIs as first-line therapy
will expand the total number of patients exposed.

Use of ICIs in those with pre-existing autoimmunity
In clinical trials of immunotherapy, known autoimmune
disease has been an exclusion criterion. Now that several
ICIs are approved and can be used as standard of care
therapy, they can potentially be given to patients with
pre-existing autoimmune disease. In one study evaluat-
ing 30 patients with known autoimmune disease treated
with ipilimumab, 8 experienced flares of their under-
lying autoimmune disease, and 10 developed a new
RAE. These data suggest that as ICIs are given to
patients with known autoimmunity, the rates of IRAEs,
including rheumatic IRAEs, will be greater.

WHY THE RHEUMATOLOGIST MATTERS
Rheumatologists have a unique role to play in managing
IRAE. Patients with rheumatic IRAE differ from patients
with traditional rheumatic disease in several important
ways. First, it appears that their IRAEs do not behave
like traditional rheumatic disease in several important
ways. Observations to date show a lack of the trad-
itional autoantibodies associated with RA and Sjogren’s
syndrome in most patients with ICI-induced inflammatory arthritis and sicca syndrome, respectively.\textsuperscript{13} Also, the steroid requirements of therapy for control may be much higher than typically required to manage ‘classic’ inflammatory arthritis.\textsuperscript{13} Importantly, all patients with rheumatic IRAE have or recently had advanced stage cancer, so there would be concerns about using immunosuppression in them. These concerns are compounded in patients whose cancer has responded to immunotherapy with further concerns about impairing a salutary response to the malignancy with concomitant or subsequent immunosuppression.

**Diagnosis and evaluation**

Rheumatologists can help in determining whether the symptoms experienced by patients on ICIs and those more commonly recognised by oncologists (eg, arthralgias, myalgias) represent a true inflammatory arthritis or other rheumatic IRAEs. Another area of importance will be determining whether patients presenting with symptoms may be manifesting exacerbation of a pre-existing autoimmune disease or really have a new ICI-emergent IRAE. Further, assessment by rheumatologists will be very important in recognising and describing the differences between ICI-induced rheumatic IRAEs and traditional rheumatic diseases to inform how evaluation and management should differ.

**Management of immunosuppression**

As rheumatologists, we are comfortable with adjusting biologics and conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) to achieve optimal outcomes. Our familiarity with TNF inhibitors and other medications that may be needed to treat IRAEs put us in a position to monitor for toxicities and to consider combinatorial induction and/or tapering strategies using immunomodulators. The logistics of obtaining approval for biological medications in patients who may not meet classification criteria for traditional rheumatic diseases can also benefit from the rheumatologist’s experience.

**CONCLUSIONS**

Rheumatic IRAEs are likely under-reported to date, and the trend towards vast expansion in use of ICI drugs suggests that ICI-induced rheumatic disease will be an increasing problem encountered by oncologists and rheumatologists in the near future and over time. Increased awareness of the potential for an array of rheumatic IRAEs is critical to early recognition, evaluation and therapy, which will hopefully foster better long-term outcomes. Careful tracking of patients treated with ICIs with a registry would provide more comprehensive epidemiologic data for rheumatic and other IRAEs. The expertise of rheumatologists will be critical to successful management of patients with ICI-induced rheumatic disease, particularly in the use of biologics and immunosuppressant/immunomodulatory medications in general. Collaboration with oncology to research the pathogenesis of rheumatic IRAE and to define appropriate treatment algorithms will lead to better understanding of this growing phenomenon and identify potential targets for treatment.

**Contributors**

LCC and COB planned the manuscript. All authors composed and edited the manuscript.

**Funding**

This study was supported by Jerome L. Greene Foundation Scholar Award and National Institute of Arthritis and Musculoskeletal and Skin Diseases (P01-AR053503; K23-AR061439).

**Competing interests**

COB has served as a consultant for Bristol-Myers Squibb.

**Provenance and peer review**

Commissioned; externally peer reviewed.

**Data sharing statement**

No additional data are available.

**Open Access**

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/


