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Association of good oncological response to therapy with the development of rheumatic immune-related adverse events following PD-1 inhibitor therapy

Running title:

Associations with anti-PD-1 rheumatic irAEs

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David Liew developed the initial manuscript and finalised for submission. All authors substantially contributed to the design of the work, revising the paper, critically regarding important intellectual content, approving the final version and agreeing to be accountable for the integrity of the work.

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Aim: To investigate whether any patient or treatment characteristics are associated with the development of rheumatic immune-related adverse events (irAEs) following PD-1 inhibitor therapy for cancer.

Method: This was a retrospective chart review of all patients who were dispensed nivolumab or pembrolizumab at a single centre before January 1, 2017, with follow-up until July 1, 2017.

Patients with any diagnosis of a non-cutaneous irAEs were identified, regardless of severity, and rheumatic irAEs were characterized.

Results: Of 244 episodes of therapy, a non-cutaneous irAE occurred in 72 (29.5%). Rheumatic irAEs were diagnosed in 19 episodes of therapy (7.8%), with 12 *de novo* diagnoses (5.1% of episodes without a pre-existing autoimmune rheumatic disease) and 7 exacerbations of existing disease. Review by a rheumatologist occurred in only 11 of these. A further 4 had possible rheumatic irAEs without diagnosis. Rheumatic irAEs were more common in patients with a good oncological response to therapy (RR 11.16), those being treated for melanoma (RR 2.94) and those who developed another non-cutaneous irAE (RR 2.64).

Conclusion: Rheumatic irAEs are relatively common with PD-1 inhibitor therapy, and appear to be associated with a good oncological response to therapy. Many rheumatic irAEs were not referred to rheumatological services. Prospective systematic investigation would be of benefit to explore these characteristics.

Keywords (MeSH):
Programmed Cell Death 1 Receptor; Antineoplastic Agents, Immunological; Drug-Related Side Effects and Adverse Reactions; Arthritis

Immunotherapy of cancer with checkpoint inhibitors has dramatically changed the field of oncology(1). Nivolumab and pembrolizumab, the programmed cell death protein 1 (PD-1) inhibitors, were initially shown to be effective in metastatic melanoma and non-small cell lung cancer (NSCLC) but are now being used in the treatment of a wide range of other cancers.

By inhibiting specific suppressor and regulatory T cell pathways, checkpoint inhibitors may lead to a distinctive spectrum of immune-related adverse events (irAEs) including some potentially resembling known classical autoimmune diseases(2). Data from registration trials have given some indication about the frequency of irAEs, but reporting is suboptimal(3). While other irAEs have been more extensively discussed, rheumatic irAEs in particular have previously not been well described(4). Registration trials have used standard oncological adverse event reporting, which poorly serves rheumatic adverse events(5) as it characterizes the nature of these events in limited detail. Of ten trials involving PD-1 inhibitors captured in a systematic review, only nine reported arthralgias as an adverse event and none reported arthritis as an adverse event(4). Additionally, patients with existing autoimmune disease were largely excluded so relatively few data exist on exacerbations of existing disease(6, 7). Given that the clinical use of PD-1 inhibitors is likely to continue to increase, the associated development of irAEs is likely to also grow.

To date most of the established reports of rheumatic irAEs remain descriptions of case series(8-10), with the inherent difficulty in determining frequency or disease associations. Additionally, in clinical practice milder manifestations are not universally acknowledged, and may not be referred by oncologists to rheumatology clinics and thus not captured in case series reliant on such referrals(11). The true frequency of rheumatic irAEs has therefore been difficult to determine, as has their relationship to drug dose, duration or type of therapy(1). Oncological response(12) and combination therapy with ipilimumab(13) have been shown to be associated to other irAEs, and also hypothesized to be associated to rheumatic irAEs, but few supportive data exist in this important area(14). This study set out to identify the frequency of rheumatic irAEs in a comprehensively inclusive cohort of patients receiving PD-1 inhibitors as well as any associations with patient or treatment characteristics.

In this article, we report our retrospective analysis of all rheumatic irAEs in all patients within our institution's cohort receiving a PD-1 inhibitor, and the characteristics associated with their development.

Methods

All patients treated with nivolumab or pembrolizumab at the Olivia Newton-John Cancer Wellness & Research Centre (Melbourne, Australia) prior to January 1, 2017 were identified by pharmacy dispensing records from its parent health service, Austin Health. This facilitated a retrospective chart review which included all eligible episodes of therapy in the whole cancer cohort, and were followed until July 1, 2017. The retrospective study was approved by the Austin Health Human Research Ethics Committee (LNR/17/Austin/192). Both patients enrolled in trials and treated as part of standard practice were captured by this method. All analyses were performed per episode of therapy, considered to be the initiation of a drug for a patient until permanent cessation of that drug with no plans for recommencement. Four patients who received both pembrolizumab and nivolumab sequentially in the specified time period were assessed as having two separate episodes of therapy, with features classified by those corresponding to the relevant exposure. Episodes of therapy from blinded placebo-controlled trials were excluded if blinding was still in place at the end of follow-up. Information sought included demographic details, as well as details regarding malignancy and its therapy. Oncological response to therapy was determined by the relevant trial criteria or treating clinician, but were generally based on the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1(15). A good oncological response to therapy was defined as either a complete response or partial response, as opposed to stable disease or progression of disease.

An irAE was defined as an adverse event with a potential immunologic basis which was considered to be treatment-related, and its presence was defined by a documented definitive diagnosis by the treating clinician. Clinical documentation was used to identify non-cutaneous irAEs to PD-1 inhibitor therapy, whether they were *de novo* diagnoses or exacerbations of existing autoimmune disease, as well as any assessment and treatment. Cutaneous irAEs were excluded as documentation of these was considered insufficiently detailed. Rheumatic irAEs were specifically assessed for details of management, and time to first onset of symptoms was

recorded in whole weeks. Rheumatic irAEs were also retrospectively assessed for likelihood of diagnosis, character and severity by consensus of an assessment panel of three rheumatological investigators (DL, JL and RB), with severity defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the criteria routinely used in oncological therapeutic trials. Symptoms which resembled a rheumatic irAE without a definitive diagnosis made by the treating clinician were considered possible rheumatic irAEs, and assessed separately. Where available, both diagnosed and possible rheumatic irAEs were correlated with findings from imaging studies. The relative risk for individual characteristics associated with rheumatic irAEs was calculated, including for age, sex, cancer stage, cancer type, the use of combination therapy with ipilimumab, oncological response to therapy, and the development of another non-cutaneous irAE. In determining an association with oncological response to therapy, episodes of therapy where patients died or were palliated prior to an assessment of response being made were excluded from the main analysis.

Results

Demographics and oncological history

Either pembrolizumab or nivolumab was administered in 244 episodes at our center; 141 episodes involved nivolumab and 103 episodes involved pembrolizumab (Table 1). Eighteen episodes also included ipilimumab in combination. The patients were male in 152 episodes (62.3%). While fourteen different cancer types were represented, 101 episodes were for the treatment of melanoma and 95 non-small cell lung cancer. The majority of episodes (218, 89.3% of total) were in stage 4 disease.

Characteristics of irAEs

A non-cutaneous irAE occurred in 72 episodes (29.5% of total). Rheumatic irAEs occurred in 19 episodes (7.8% of total), of which 12 involved *de novo* disease (5.1% of episodes without a pre-existing autoimmune rheumatic disease), and seven involved exacerbations of pre-existing autoimmune disease (Table 2). None of the definitive diagnoses made by the treating clinician

were overturned by the assessment panel. Inflammatory arthritis made up the majority of rheumatic irAEs, although polymyalgia rheumatica-like disease was also identified. The single episode of *de novo* polymyalgia rheumatica-like disease met the EULAR/ACR 2012 provisional classification criteria for polymyalgia rheumatica, and there were supportive findings on ultrasound. No *de novo* disease was associated with positive rheumatoid factor or anti-CCP serology. The median time to onset was 24 weeks for *de novo* rheumatic irAEs and six weeks for exacerbations of pre-existing autoimmune disease. With respect to the severity of the rheumatic irAEs, seven were CTCAE grade 1 (mild pain), eleven were grade 2 (moderate pain limiting instrumental activities of daily living) and one was grade 3 (severe pain limiting self care activities of daily living).

In three episodes the development of a rheumatic irAE led to permanent cessation of PD-1 inhibitor therapy. Glucocorticoids were not universally utilized, primarily due to concerns regarding attenuation of the anti-tumour effect of immunotherapy, but were still used in the majority of patients. In the twelve episodes of treatment where glucocorticoids were used and PD-1 inhibitor therapy was not permanently ceased because of an irAE, nine sustained a good oncological response, of which two were also initiated on conventional synthetic DMARDs without an impaired oncological response. In the remaining three of twelve episodes, two had had an initial good response prior to commencement of glucocorticoids. Of the other non-cutaneous irAEs, the most common was thyroiditis, occurring in 26 episodes (10.7 of total). Pneumonitis occurred in 13 episodes (5.3%), hepatitis in nine (3.7%) and colitis in nine (3.7%).

Characteristics associated with irAEs

A number of possible characteristics were associated with irAEs (Table 3). A good oncological response to PD-1 inhibitor therapy was associated with the development of a non-cutaneous irAE (relative risk (RR) 2.23, 1.45 – 3.42), and was even more strongly associated with rheumatic irAEs (RR 11.16, 2.65 – 46.98). Combination therapy where ipilimumab was added to a PD-1 inhibitor, was also associated with the development of any non-cutaneous irAE (RR 2.03, 1.27 – 3.22) but for rheumatic irAEs the trend was not statistically significant in our cohort (RR 2.51,

0.81 – 7.82). Melanoma was associated with the development of rheumatic irAEs (RR 2.94, 1.11 – 7.80) but there was no significant association with age nor sex. The presence of a non-cutaneous, non-rheumatic irAE was also associated with the development of a rheumatic irAE (RR 2.64, 1.13 – 6.20).

Exacerbations of existing autoimmune disease

Eight episodes involved documented pre-existing autoimmune rheumatic diseases under the care of a rheumatologist. In seven episodes an exacerbation of disease occurred despite well-controlled rheumatic disease prior to PD-1 inhibitor therapy and no reduction of existing rheumatic disease therapy, although one patient with Sjogren's syndrome did not have an exacerbation of disease noted. One patient had an inflammatory arthritis as an irAE to pembrolizumab which resolved on its permanent cessation only to redevelop when she was exposed to the combination of nivolumab and ipilimumab. Another patient had an inflammatory arthritis as an irAE to ipilimumab, a different class of immunotherapy agent, which was controlled with methotrexate, prednisolone and cessation of ipilimumab. With the introduction of nivolumab, the arthritis substantially worsened despite continuation of methotrexate and prednisolone. Of note, six of these seven episodes of exacerbations of disease were associated with a good oncological response to therapy. An additional patient with familial Mediterranean fever also had no change in disease activity when treated with nivolumab.

Patients not reviewed by a rheumatologist

A number of patients with *de novo* definite diagnoses of rheumatic irAEs were not reviewed by a rheumatologist (8/12). Of these, five had findings on an imaging study to support the diagnosis. In four episodes this consisted of scintigraphic confirmation of inflammatory arthritis on PET/CT scans performed for oncological staging purposes.

Discussion

In our study, we examined all patients within an entire cancer cohort where each individual episode of PD-1 inhibitor therapy was assessed with detailed regard to rheumatic irAEs as well as other irAEs. This has allowed us to determine characteristics associated with the development of both rheumatic and non-rheumatic irAEs as well as detect the frequency of rheumatic irAEs of all severities.

This approach has allowed us to gain insights not previously reported. Registration trials have detected the frequency of rheumatic irAEs but do so without sufficient frequency or detail to understand their characteristics. Case series have described the nature of rheumatic irAEs in far greater detail(16) but have relied on referrals to rheumatology clinics(8-10, 14) or pharmacovigilance registries(11, 17). This may exclude irAEs which are milder but are still useful in developing pathophysiological insights. These series also have not compared all patients receiving a PD-1 inhibitor with respect to rheumatic irAEs, and without a denominator cannot accurately determine characteristics associated with the development of irAEs. Our approach of reviewing each individual episode of PD-1 inhibitor therapy enables a description sufficiently detailed to be useful for rheumatological insights. It also allows for determination of the frequency of rheumatic irAEs, associated characteristics and the detection of milder rheumatic irAEs.

In our cohort, the development of a rheumatic irAE was strongly associated with a good oncological response to PD-1 inhibitor therapy. While this has also been recently observed elsewhere(18), we additionally found that the association with a good oncological response to therapy was stronger for rheumatic irAEs than for non-cutaneous irAEs overall. Rheumatic irAEs may therefore be of specific further interest to oncologists.

Associations do not necessarily imply causation and one potential confounder may be that the duration of PD-1 inhibitor therapy in non-responders is insufficient to allow development of a rheumatic irAE. This effect, however, is not diluted in the subgroup of patients with therapy for greater than twelve weeks. Melanoma was also associated with rheumatic irAEs, although this

may relate to its increased use with combination therapy. It is notable that rheumatic irAEs were associated with the development of another non-cutaneous, non-rheumatic irAE, and this might suggest that some individuals have an overall increased propensity to autoimmunity. These associations nevertheless warrant more detailed study in larger cohorts to determine potential pathophysiological mechanisms.

We included all patients likely to have developed a rheumatic irAE, whereas most other reports have only included those assessed by a rheumatologist. The inclusion of all irAE reports is useful in capturing milder irAEs, which are still likely to provide insights into disease development despite being less problematic for oncological therapy. The frequency of *de novo* rheumatic irAEs we report for patients without pre-existing autoimmune rheumatic diseases is similar to that in a cohort of melanoma patients treated with PD-1 inhibitors, who were all without pre-existing autoimmune rheumatic disease, for *de novo* arthritis irAEs of all severities(18). Many other reports, which have only captured more severe rheumatic irAEs, have however reported lower frequencies and our approach needs to be repeated more broadly.

Our approach has a number of limitations. As it is a retrospective review, irAEs may only be detected through existing documentation rather than from direct validation by rheumatologists. This means that the nature of the often complex manifestations and attribution of their causality cannot be confirmed. This was partially mitigated by the frequent presence of incidental imaging which assisted in validating manifestations, but this was not available for all patients. Existing autoimmune inflammatory disease may not have been recorded as it may not have been the focus of oncological treating teams, especially if patients did not develop an irAE. In addition, prospective testing of autoantibodies and other diagnostic tests was not possible.

Future prospective study will therefore be useful, not only to determine the nature of rheumatic irAEs and their best management, but also to understand more about the classical autoimmune rheumatic diseases which they resemble. Low PD-L1 expression has already been

identified in GCA-affected temporal arteries(19), and further insights are likely to be possible in the future. Polymyalgia rheumatica-like disease in particular has been widely identified as a common rheumatic irAE, both in our cohort and others, but the pathophysiology of classical disease is poorly understood and it would benefit from 'bedside-to-bench' observations made from patients with rheumatic irAEs that resemble it. For this to occur, prospective study would ideally include assessment of all patients within a whole cancer cohort, although to conventionally assess this might be resource intensive. Real-time biosurveillance of clinical data may enable this type of study to proceed in the future.

In conclusion, rheumatic irAEs are common, although they vary in severity. There are a number of associated characteristics including a good oncological response to therapy. Improved collaboration between rheumatologists, oncologists, pharmacologists and other relevant specialties would not only improve the care of patients receiving checkpoint inhibitor therapy but may also provide a basis for better understanding of classical autoimmune rheumatic diseases.

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Tables

Table 1. Demographic features and cancer characteristics[a]

Category	Overall	Patients experiencing rheumatic irAEs	Patients experiencing any non-cutaneous irAE
Total	244	19 (7.8%)	72 (29.5%)
Malignancy type			
Melanoma	101	13 (12.9%)	32 (31.7%)
Non-small cell lung cancer	95	4 (4.2%)	31 (32.6%)
Lymphoma	19	1 (5.3%)	3 (15.8%)
Renal cell carcinoma	8	0 (0.0%)	0 (0.0%)
Urothelial	5	1 (20.0%)	3 (60.0%)
Stage			
Stage 4	218	17 (7.8%)	66 (30.3%)
PD-1 inhibitor			
nivolumab	141	7 (5.0%)	41 (29.1%)

pembrolizumab	103	12 (11.7%)	31 (30.1%)
Combination therapy with ipilimumab	18	3 (16.7%)	10 (55.6%)
Median age, years (range)	66 (18-88)	71 (53-85)	69 (18-88)
Median duration of therapy, weeks	19	55	21

[a]Values are the number of episodes of therapy (percentage of overall category experiencing non-cutaneous/rheumatic irAEs) unless otherwise indicated.

Table 2. Characteristics of rheumatic irAEs[b]

		irAEs: *de novo*	irAEs: exacerbations of pre-existing autoimmune disease
Median time to first onset of symptoms, weeks (range)		24 (8-123)	6 (1-57)
Median doses to first onset of symptoms (range)		8 (1-46)	2 (1-19)
Total		12	7
Manifestation	Inflammatory arthritis	11	5
	Polymyalgia rheumatica or polymyalgia rheumatica-like disease	1	2
Treatment	Prednisolone use	8	7
	DMARD use	3	1

PD-1 inhibitor permanently discontinued for an irAE	2	1
Reviewed by a rheumatologist	4	6
Objective finding on imaging study to support diagnosis	8	3
PET helpful	7	2
RF positive/tested	0/7	1/6
anti-CCP positive/tested	0/6	1/4
CTCAE graded severity:		
grade 1	4	3
grade 2	8	3
grade 3	0	1

[b]Values are the number of episodes of therapy unless otherwise indicated.

Table 3. Associations with irAEs

	Unadjusted relative risk of rheumatic irAE	Unadjusted relative risk of any non-cutaneous irAE
Age: >70y	1.97 (0.83 – 4.66)	1.27 (0.86 – 1.87)
Sex: female	2.27 (0.95 – 5.44)	1.11 (0.75 – 1.65)
Stage 4	0.94 (0.23 – 3.81)	1.21 (0.59 – 2.49)
Malignancy: melanoma	2.94 (1.11 – 7.80)	1.13 (0.77 – 1.67)
Combination therapy with ipilimumab	2.51 (0.81 – 7.82)	2.03 (1.27 – 3.22)
Good oncological response to therapy, at best response[c]	11.16 (2.65 – 46.98)	2.23 (1.45 – 3.42)
Development of a non-rheumatic, non-cutaneous irAE	2.64 (1.13 – 6.20)	-

[c]excludes patients ceasing PD-1 inhibitor therapy before being due to be assessed for oncological response