Checkpoint inhibitor-associated immune arthritis

We read with interest the paper by Kostine *et al.*¹ Immune checkpoint inhibitors (ICIs) have dramatically improved clinical outcomes in various cancer types and are increasingly being used in earlier disease settings and in combination.² The main targets of ICIs, programmed cell death 1 (PD-1) and its ligand PD-L1 as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are involved in downregulating autoimmunity, with PD-1-deficient C57BL/6 mice exhibiting lupus-like features and CTLA-4 enabling Treg suppression of autoreactive T cell activation.³ It was therefore no surprise that immune-related adverse events (irAEs) such as immune arthritis, rheumatoid arthritis or systemic lupus erythematosus have occurred from ICIs use. However, the characteristics, timing and outcomes of those irAEs in the setting of ICIs remain poorly known.⁴

Here, we used VigiBase (<http://www.vigiaccess.org/>), the WHO database of individual safety case reports, to identify 86 cases of immune arthritis (searching the preferred terms among the 36 973 adverse events reported following treatment with ICIs.⁵

Patients had a wide spectrum of age (median: 63 years (range: 40–90)), cancer types (mostly lung cancer (39.7%) and melanoma (36.8%)) and geographic locations (table 1). Most patients (82.6%) received anti-PD-1 monotherapy, whereas 10.5% received a combination of anti-PD-1/PD-L1 and anti-CTLA-4.

Reported irAEs (table 1) included rheumatoid arthritis (68%), autoimmune arthritis (16%) or lupus (15%).

The median timing of irAEs onset in relation to ICI initiation was 2.7 (IQR: 0.5–7.3) months (available in 18 patients), with 50% occurring in the first 8 weeks of treatment. Further, several other irAEs occurred in 22 cases (25.6%), most commonly muscle disorder and colitis.

In general, grade 3 toxicities generally warrant⁶ suspension of ICIs and initiation of high-dose corticosteroids, while discontinuation of ICIs is recommended with grade 4 toxicities (with the exception of endocrinopathies). The detailed management of individual cases was not available in VigiBase. However, the main outcome of irAEs was available in 36 (41.9%) patients, with 26 (72.2%) patients recovering or having recovered at the time of the last evaluation. Among all cases, death occurred in 3 (4.1%).

Notably, we observed a dramatic increase in reporting incidence over time (n=45 (52.3%) in 2017 and 14 additional cases until 16 February 2018). We speculate that this is due to an increased usage of ICIs as well as a better recognition of these new associations with ICIs.

While irAEs have been reported as individual cases or short series, this analysis is the first comprehensive series to report its detailed clinical features on a larger scale, including the median delay between ICI treatment and irAEs.

The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the WHO.

Laurent Arnaud,¹ Bénédicte Lebrun-Vignes,² Joe-Elie Salem²

¹Department of Rheumatology, Hôpitaux Universitaires de Strasbourg & INSERM UMRS-1109, Strasbourg, France

²AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology, CIC-1421, Pharmacovigilance Unit; INSERM, UMR ICAN 1166; Sorbonne Universités, UPMC Univ Paris 06, Faculty of Medicine; Institute of Cardiometabolism and Nutrition (ICAN), F-75013, Paris, France

Table 1 Detailed characteristics of the 86 cases

Characteristics	N (%)	Data availability, n (%)
Reporting year		86 (100%)
2018 (through 16 February 2018)	14 (16.3)	
2017	45 (52.3)	
2016	18 (20.9)	
2015	6 (7.0)	
2012–2014	3 (3.6)	
Region reporting, n (%)		86 (100)
Americas	50 (58.1)	
Europe	27 (31.4)	
Australia	5 (5.8)	
Asia	4 (4.6)	
Africa	0 (0)	
Reporters		81 (94.2)
Health professional	63 (77.7)	
Non-health professional	18 (22.3)	
Gender		77 (89.5)
Male	41 (53.2)	
Female	36 (46.8)	
Age at onset, median (IQR)	63.5 (55–76)	52 (60.4)
Drugs		86 (100)
Monotherapy with anti-PD1/PD-L1	71 (82.6)	
Nivolumab	46 (53.5)	
Pembrolizumab	20 (23.3)	
Durvalumab	3 (3.5)	
Atezolizumab	2 (2.3)	
Monotherapy with anti-CTLA4	6 (7.0)	
Ipilimumab	6 (7.0)	
Combination therapy	9 (10.5)	
Nivolumab+Ipilimumab	6 (7.0)	
Pembrolizumab+Ipilimumab	3 (3.5)	
Indications		68 (79.1)
Lung cancer	27 (39.7)	
Malignant melanoma	25 (36.8)	
Urothelial carcinoma	5 (7.4)	
Renal carcinoma	4 (5.9)	
Neoplasm malignant (tissue not specified)	3 (4.4)	
Ductal adenocarcinoma of pancreas	1 (1.5)	
Melanoma+Renal cell carcinoma	1 (1.5)	
Oesophageal carcinoma	1 (1.5)	
Squamous cell carcinoma of head and neck	1 (1.5)	
Reported autoimmune diseases		86 (100)
Rheumatoid arthritis	59 (68.6)*	
Autoimmune arthritis	14 (16.3)	
Cutaneous lupus erythematosus	7 (8.1)	
Systemic lupus erythematosus	5 (5.8)	
Lupus erythematosus (unspecified type)	1 (1.2)	
Median delay between treatment and autoimmune AE, median (IQR)	2.7 (0.5–7.3) months	18 (22.1)
Severity of AEs (severe)	73 (84.9)	86 (100)
Death	3 (4.1)	73 (84.9)
Concurrent immune-related adverse events		86 (100)
Muscle weakness/disorder	6 (7.0)	
Colitis	5 (5.8)	
Thyroid disease	4 (4.6)	
Sjögren's syndrome	1 (1.2)	
Mixed connective tissue disease	1 (1.2)	
Duodenitis	1 (1.2)	
Oesophagitis	1 (1.2)	
Enteritis	1 (1.2)	
Hepatitis	1 (1.2)	
Cold agglutinin disease	1 (1.2)	
Autoimmune haemolytic anaemia	1 (1.2)	
Myocarditis	1 (1.2)	
Interstitial lung disease	1 (1.2)	
Raynaud's phenomenon	1 (1.2)	
Uveitis	1 (1.2)	
Pleural effusion	1 (1.2)	
Vitiligo	1 (1.2)	

*Including 13 cases with aggravated rheumatoid arthritis.

Correspondence to Professor Laurent Arnaud, Department of Rheumatology Hôpitaux Universitaires de Strasbourg & INSERM UMRS-1109 Strasbourg France; laurent.arnaud@chru-strasbourg.fr

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REFERENCES

- 1 Kostine M, Rouxel L, Barnette 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**:393–8.
- 2 Weber J, Mandala M, Del Vecchio M, *et al*. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med* 2017; **377**:1824–35.
- 3 Kong YC, Flynn JC. Opportunistic Autoimmune Disorders Potentiated by Immune-Checkpoint Inhibitors Anti-CTLA-4 and Anti-PD-1. *Front Immunol* 2014;**5**:206.
- 4 Moslehi JJ, Salem JE, Sosman JA, *et al*. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet* 2018;**391**:933.
- 5 Lindquist M. VigiBase, the WHO Global ICSR Database system: basic facts. *Drug Inf J* 2008;**42**:409–19.
- 6 Brahmer JR, Lacchetti C, Schneider BJ, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018;**JCO.2017.77.638**.