Correspondence on 'Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation' by Braaten *et al*

We read with interest the study published by Braaten and colleagues, analysing the long-term outcomes of 60 patients developing persistent inflammatory arthritis (IA) after immune checkpoint inhibitors (ICIs) cessation. The most relevant result of the study was the presence of active arthritis in more than half of the patients at the last follow-up visit.[1]

We report here our experience in the context of a joint oncology/rheumatology outpatient clinic, in order to evaluate the risk of developing IA in patients treated by anti-PD1 drugs. During 1-year period, we consecutively assessed all the adult patients candidate to anti-PD1 treatment, referring to the Oncology Unit at the Sapienza University of Rome. After treatment starts, in the case of musculoskeletal manifestations, patients were referred to the Sapienza Arthritis Center, Rheumatology Unit, Sapienza University of Rome. Arthritis was defined as the occurrence of at least one episode of clinical synovitis, with morning stiffness lasting at least 30 min. IA activity was assessed by disease activity score on 28 joints by ESR (DAS28-ESR).[2] We investigated the presence of rheumatoid factor (RF), anticitrullinated protein (ACPA) and antinuclear antibodies. In the clinically involved joints, ultrasonographic assessment was performed according to EULAR guidelines.[3]

We evaluated 72 patients (M/F 48/24, median age 66 years, IQR 13.0) affected by lung cancer (75.1%), renal cancer (15.3%), melanoma skin cancer (6.9%), or other neoplastic diseases (2.7%). Sixty-seven patients were treated with nivolumab and the remaining with pembrolizumab (median treatment duration 7 months, IQR 13.0). After 3 months of follow-up, the malignant disease had not progressed in 48 patients (66.7%), whereas an *exitus* was registered in 21 patients (29.2%). During the follow-up period, seven Caucasian patients (9.7%) developed clinically evident synovitis (absolute risk for IA 0.1, incidence rate 0.01). Table 1 reports the main demographic, oncologic and rheumatological features of these patients. Two patients could be classified as affected by rheumatoid arthritis (RA) according to ACR/EULAR 2010 criteria,[4] seropositive in one case (RF and ACPA). Autoantibodies assessment was negative in the remaining patients. Five patients (71.4%) were treated with prednisone (starting dosage 10–12.5 mg/daily, with 2.5 mg reduction every 2 weeks until drug stopping) and the remaining two with non-steroidal anti-inflammatory drugs (NSAIDs) (diclofenac 150 mg/daily for 15 consecutive days). The above-mentioned treatments induced a quick, complete and persistent response in all the patients, except for the seropositive RA subject, in which subcutaneous methotrexate (10 mg/weekly) was added after 4 weeks, achieving a remission status in 3 months. All the patients continued ICIs treatment.

Several differences could be identified by comparing our cohort with the one described by Braaten and colleagues. The previous study included patients developing IA after ICIs cessation, whereas in our cohort, IA appeared during treatment. Nonetheless, in the majority of our patients with IA, treatment with glucocorticoids or NSAIDs was able to induce a prompt and persistent remission. The only patient requiring a disease-modifying anti-rheumatic drug (DMARD) was affected by seropositive RA. Conversely, more than half of the patients evaluated in the Braaten's study showed an active disease at the last visit, as confirmed by the need to introduce synthetic and/or biological DMARDs. In our opinion, this is the most relevant difference between the two cohorts, and this could be explained by the different ICIs treatment. We selected patients treated by anti-PD1, in order to make the cohort homogeneous, whereas the other study included different ICIs. In conclusion, the high risk to develop IA in ICs inhibitors-treated patients confirms the need to include the rheumatologist in the management of these subjects, as recently underlined in the literature review conducted by Jamal and colleagues.[5] The longitudinal assessment of these patients could allow the identification of subjects at risk to develop this specific adverse event.

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Table 1 Demographic features, malignancy history, rheumatological, clinical and ultrasonographic manifestations, time to onset, autoantibody profile and treatment of the seven patients developing synovitis. Active synovitis was defined by the presence of power Doppler signal.

Pt	Sex	Age (years)	Malignancy (treatment)	Clinical manifestations	Interval (weeks)	Autoantibody assessment	US	Diagnosis	Treatment
1	F	55	RCC (nivolumab)	Simmetric polyarthritis	3	RF, ACPA, ANA neg	Active synovitis	RA	PDN 12.5 mg/daily
2	F	61	Melanoma (nivolumab)	Simmetric polyarthritis	3	RF 22 UI/mL, ACPA >300 UI/mL, ANA+ (sp), a-SSA+	Active synovitis	RA	PDN 10 mg/daily MTX 10 mg/weekly
3	M	68	NSCLC (nivolumab)	Monoartrhritis	8	RF, ACPA, ANA neg	Synovitis	UA	NSAIDs
4	F	72	NSCLC (nivolumab)	Polyarthritis	18	RF, ACPA, ANA neg	Synovitis	UA	PDN 12.5 mg/daily
5	M	77	NSCLC (nivolumab)	Oligoarthritis	4	RF, ACPA, ANA neg	Synovitis	UA	NSAIDs
6	M	70	NSCLC (nivolumab)	Simmetric polyarthritis	2	RF, ACPA, ANA neg	Active synovitis	UA	PDN 10 mg/daily
7	M	61	NSCLC (nivolumab)	Simmetric polyarthritis	36	RF, ACPA, ANA neg	Synovitis	UA	PDN 10 mg/daily

ACPA, anti-citrullinated protein antibodies; ANA, anti-nuclear antibodies; a-SSA, anti-SSA; MTX, Methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; PDN, prednisone; RA, rheumatoid arthritis; RCC, renal cell carcinoma; RF, rheumatoid factor; sp, Speckled; UA, undifferentiated arthritis; US, ultrasonographic.

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Contributors FCe, AB, PM and FC make substantial contributions to the conception or design of the work, the acquisition, analysis and interpretation of data, to draft the work and revising it critically for important intellectual content. AG, IL, RL contributed to data acquisition and interpretation and to draft paper. GV make substantial contributions to the conception or design of the work and revising it critically for important intellectual content. All the authors provided a final approval of the version published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Ceccarelli F, Botticelli A, Gelibter AJ, *et al*. *Ann Rheum Dis* 2022;**81**:e13.

Received 19 December 2019
Accepted 21 December 2019
Published Online First 6 January 2020

► http://dx.doi.org/10.1136/annrheumdis-2019-216892

Ann Rheum Dis 2022;**81**:e13. doi:10.1136/annrheumdis-2019-216867

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