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ORIGINAL RESEARCH

Immune checkpoint inhibitor rechallenge in patients who previously experienced immune-related inflammatory arthritis: a multicentre observational study

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ABSTRACT

Objective Another course of immune checkpoint inhibitors (ICIs) is often considered in patients with cancer progression and previous immune-related adverse events, including inflammatory arthritis (ICI-IA), but there are limited data regarding safety of ICI rechallenge in this setting. We aimed to assess the rate and clinical features associated with ICI-IA flare/recurrence on ICI rechallenge.

Methods We conducted a multicentre observational study including cancer patients with ICI-IA who started a second course of ICI more than 3 months after ICI discontinuation in four French university hospitals. Primary outcome was the frequency of ICI flare/recurrence after ICI rechallenge.

Results Twenty-three patients were included. At the time of ICI rechallenge, 18 patients reported no symptoms of ICI-IA (78%) and 5 had grade 1 (22%), 11 patients (48%) were not receiving any ICI-IA treatment, 11 (48%) were still on prednisone, 2 (9%) were on conventional synthetic disease-modifying antirheumatic drugs and 1 (4%) on anti-IL-6. ICI-IA flare/recurrence occurred in 12 patients (52%) with a median time of 1 month after ICI rechallenge. ICI-IA phenotype, disease activity and ICI-IA treatment at the time of ICI rechallenge did not differ according to ICI-IA flare/recurrence status.

Conclusion In this first observational study of ICI-IA patients rechallenged with ICI, about half of the patients experienced ICI-IA flare/recurrence with a similar phenotype but occurring earlier than the initial ICI-IA, warranting close monitoring during the first month of retreatment. Risk of flare did not differ according to baseline immunosuppressive treatment at the time of rechallenge.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Outcomes of immune checkpoint inhibitor (ICI)-inflammatory arthritis (IA) on ICI rechallenge remain largely unknown.

WHAT THIS STUDY ADDS

⇒ Half of ICI-IA patients will experience flare/recurrence on ICI rechallenge, earlier than the initial ICI-IA episode.
⇒ Severe ICI-IA during the first course of ICI is not associated with an increased risk of ICI-IA flare/recurrence on rechallenge.
⇒ ICI-IA flare had similar phenotype as initial presentation in all patients.
⇒ ICI continuation was possible in 75% of patients who flared.
⇒ ICI-IA phenotype, disease activity and immunosuppression at the time of rechallenge were not associated with an increased risk of ICI-IA flare/recurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that patients who have experienced ICI-IA can safely be rechallenged with an ICI if clinically indicated.
⇒ Future larger studies should clarify risk factors of ICI-IA flare/recurrence during ICI rechallenge.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) improve overall survival in many patients with cancer by activating their immune system. ICIs release the break on specific coinhibitory pathways including cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and/or programmed cell death-1 (PD-1), or its ligand PD-L1 and the resulting enhanced activation of the immune system leads to a potent antitumour response. However,

ICI can cause off-target immune-related adverse events (irAEs), including inflammatory arthritis (ICI-IA). ICI-IA affects about 5% of patients treated with ICI.[1 2] Several guidelines both from the oncology and rheumatology field have been published and are used to guide clinicians for the management of irAEs including ICI-IA.[3–7] ICI-IA differs from other irAEs in its capacity of becoming chronic and its frequency of persistence for months or even years after ICI discontinuation, thus often requiring long-term immunosuppressive treatment.[8] Severity of irAEs is rated according to the Common Terminology Criteria for Adverse Events (CTCAE)[9] and current oncological guidelines recommend holding ICI if the arthritis is grade 3–4 (severe) and to consider holding ICI if grade 2 (moderate) intensity. Rechallenging with an ICI is recommended in agreement with rheumatology opinion if ICI-IA resolves to grade≤1.[3]

Another course of ICI is now often considered in patients with cancer progression[10] and previous irAEs,[11] but there are limited data regarding the safety of ICI rechallenge in this context, including ICI-IA. One large study of irAEs rechallenged found that approximately 45% of patients with ICI-IA experience a flare/recurrence on ICI rechallenge.[12] However, this study did not include ICI-IA patients in whom ICI was discontinued for other reasons than ICI-IA. Another study reporting on the recurrence rate of grade ≥2 irAE after ICI rechallenge found a similar rate (56%) for arthralgia and arthritis pooled together, but data on ICI-IA itself were not specifically reported.[13] By their design, both these pharmacovigilance studies are at risk of reporting bias and have not used a standardised definition of ICI-IA.

Recent studies assessed the safety of ICI rechallenge in specific type of irAEs, such as ICI-related myositis,[11] but so far no study evaluated risk factors and outcomes of ICI rechallenge in patients who previously experienced ICI-IA. Therefore, we aimed to assess the frequency and clinical features associated with ICI-IA flare/recurrence on ICI rechallenge.

METHODS

Study design and population

We conducted a multicentre retrospective observational study in four French university hospitals (Bordeaux, Montpellier, Brest and Bicêtre). Charts of all patients with cancer referred to department of rheumatology for rheumatic irAEs were screened and patients were included if (1) they experienced ICI-IA (defined by either the presence of at least one joint with synovitis on physical examination and/or on imaging or polymyalgia rheumatica (PMR)-like symptoms) diagnosed by a rheumatologist and (2) they started a second course of ICI more than 3 months after ICI discontinuation regardless of the reason for discontinuation.[14] Patients with pre-existing rheumatic disease before the first course of ICI and those with a follow-up of less than 3 months after ICI rechallenge were excluded. For patients who have been rechallenged more than once, only the first rechallenge was included in the analyses. Charts were manually reviewed to extract data on baseline characteristics, investigations (laboratory and imaging), management and both ICI-IA and tumour outcomes.

Study outcomes

The primary outcome was the frequency of ICI-IA flare/recurrence after ICI rechallenge. ICI-IA flare/recurrence was defined as the reappearance of ICI-IA symptoms in patients who were asymptomatic at the time of ICI rechallenge or the worsening of ICI-IA symptoms using CTCAE grade in those who were still experiencing symptoms at the time of ICI rechallenge.

Secondary outcomes consisted in comparing patients who experienced a flare/recurrence of ICI-IA on rechallenge to those who did not. We also assessed ICI-IA flare severity as defined by the CTCAE grade and treatment, identification of risk factors of ICI-IA flare/recurrence and cancer response according to Response Evaluation Criteria in Solid Tumours.[15]

Data analysis

Descriptive analyses of baseline characteristics were performed using the number and associated percentages for categorical variables. Continuous variables were presented as median and IQR or mean and SD. Qualitative variables were compared using χ^2 test, or Fisher's exact test when needed. Quantitative variables were compared using non-parametric Mann-Whitney U test.

RESULTS

Patients characteristics and first episode of ICI-IA

Twenty-three patients have been identified, including 57% of men with a mean age of 69 years old (SD: 9.4) and a median follow-up duration of 26.5 months (IQR: 21.7–38) after ICI-IA onset. The most frequent malignancies were melanoma (n=9, 39%), lung (n=7, 30%) and genitourinary (n=4, 17%). Most patients were treated with PD1/PDL-1 in monotherapy (n=20, 87%), 2 (9%) patients received combination PD1/PDL-1 and CTLA-4 and 1 (4%) an anti-CLTA-4. Three (13%) patients had pre-existing non-rheumatic autoimmune diseases (hypothyroidism, n=2 and type I diabetes mellitus, n=1).

During the first course of ICI, ICI-IA occurred after a median exposure time of 4.1 months (IQR: 2.5–10.0). Most frequent presentations were symmetric polyarthritis (n=7, 30%), PMR-like (n=6, 26%) and PMR-like with peripheral synovitis (n=6, 26%) being of grade 1 severity (n=8, 35%), grade 2 (n=9, 39%) or grade 3 (n=6, 26%). Detailed ICI-IA characteristics are presented in table 1. Almost all patients were treated with prednisone (n=22, 96%), four with methotrexate (MTX) (17%) and one with anti-IL-6 (4%). The median maximum dose of prednisone was 20 mg (IQR: 15–60).

Reason for ICI discontinuation was ICI-IA (n=8; 35%), cancer progression (n=7, 30%), other irAE (n=4; 17%) and cancer stable or in remission (n=4; 17%).

Table 1 Baseline characteristics of ICI-IA patients

Gender, N (%)	Male	13 (56.5)
	Female	10 (43.5)
Age, mean (SD)		69.0 (9.4)
Tumour type, N (%)	Melanoma	9 (39.1)
	Lung	7 (30.4)
	Genitourinary	4 (17.4)
	Other	3 (13.0)
ICI type, N (%)	CTLA-4	1 (4.3)
	PD1/PDL-1	20 (87.0)
	Combination	2 (8.7)
Other combined oncological treatment, N (%)	Chemotherapy	4 (17.4)
	BRAF/MEK inhibitors	0 (0.0)
	Tyrosine kinase inhibitors	1 (4.3)
	Other	4 (17.4)
	None	14 (60.1)
ICI-IA type, N (%)	PMR-like	6 (26.1)
	PMR-like with peripheral synovitis	6 (26.1)
	Symmetrical polyarthritis	7 (30.4)
	Psoriatic arthritis	2 (8.7)
	Oligoarthritis	2 (8.7)
CTCAE grade, N (%)	Grade 1	8 (34.7)
	Grade 2	9 (39.1)
	Grade 3	6 (26.1)
Time to ICI-IA onset in months, median (IQR)		4.1 (2.5–10.0)
Laboratory	CRP (mg/L), median (IQR)	37.5 (13.8–73.5)
	Positive RF, N (%)	3 (13.0)
	Positive anti-CCP, N (%)	2 (8.7)
Imaging		
X-ray	OA, N (%)	9 (39.1)
Ultrasound*	Synovitis, N (%)	8 (34.8)
	Tenosynovitis, N (%)	7 (30.4)
	Bursitis, N (%)	9 (39.1)
ICI-IA treatment	Prednisone, N (%)	22 (95.6)
	Maximal daily dose in mg of prednisone equivalent, median (IQR)	20 (15–60)
	csDMARDs, N (%)	4 (17.4)
	Methotrexate, N (%)	4 (100)
	bDMARDs, N (%)	1 (4.3)
	Anti-IL-6†, N (%)	1 (100)
Total duration of ICI in months, median (IQR)		12.0 (5.1–19.5)
Best cancer response	Progression, N (%)	3 (13.0)
	Stability, N (%)	3 (13.0)
	Partial response, N (%)	11 (47.8)
	Complete response, N (%)	6 (26.1)
Reason for ICI discontinuation	Cancer progression, N (%)	7 (30.4)
	Cancer stable/ remission, N (%)	4 (17.4)
	ICI-IA, N (%)	8 (34.8)
	Other irAE, N (%)	4 (17.4)
No of other irAE during the first course of ICI	0, N (%)	12 (52.2)
	1, N (%)	7 (30.4)
	≥2, N (%)	4 (17.4)

*Data available for 16 participants.
†Anti-IL-6 started concomitantly to rechallenge given MTX inefficacy.
anti-CCP, anti-cyclic citrullinated peptide; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic DMRADs; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors; ICI-IA, ICI-induced inflammatory arthritis; irAE, immune-related adverse events; MTX, methotrexate; OA, osteoarthritis; PMR, polymyalgia rheumatica; RF, rheumatoid factor.

ICI rechallenge and ICI-IA flare/recurrence

Reason for ICI rechallenge was cancer progression in all but one patient (n=22, 96%) (table 2). Most patients were rechallenged with the same ICI as in the first ICI course (n=18, 78%) and none received ICI combination as rechallenge strategy. Median follow-up after ICI rechallenge was 8 months (IQR: 4.5–19.5). At the time of ICI rechallenge, 18 patients (78%) reported no symptoms of ICI-IA, 5 patients (22%) had grade 1 ICI-IA and none had grade 2 or grade 3 ICI-IA. Regarding baseline ICI-IA treatment, 11 patients (48%) were not receiving any ICI-IA treatment at the time of ICI rechallenge, 11 (48%) were still on prednisone with a median dose of 5 mg/day (IQR: 5–6.25), 2 (9%) were on MTX and 1 (4%) had just been switched from MTX to an anti-IL6 due to MTX inefficacy. All ongoing disease-modifying antirheumatic drug (DMARDs) were continued in combination with the second course of ICI.

ICI-IA flare/recurrence occurred in 12 patients (52%) after a median time of 1 month (IQR: 0.0–2.5) after ICI rechallenge. ICI-IA flare had similar phenotype as initial presentation in all patients. Only three flares (25%) were grade 3, four flares (33%) were grade 2 and five flares (42%) were grade 1. All ICI-IA flares were treated with prednisone with a median maximum dose of 15 mg/day (IQR: 5–60). Four (33%) were treated with conventional

Table 2 Characteristics of ICI-IA patients at the time of rechallenge

Reason for rechallenge	Cancer progression, N (%)	22 (95.7)
	Intolerance to actual treatment, N (%)	1 (4.3)
Time between cessation of the first course of ICI and rechallenge in months, median (IQR)		9.0 (6.5–19.5)
ICI-IA treatment at the moment of rechallenge	No treatment, N (%)	11 (47.8)
	Prednisone, N (%)	11 (47.8)
	Maximal daily dose in mg of prednisone equivalent, median (IQR)	5.0 (5.0–6.3)
	csDMARDs, N (%)	2 (8.7)
	MTX, N (%)	2 (100)
	bDMARDs, N (%)	1 (4.3)
	Anti-IL-6†, N (%)	1 (100)
ICI-IA disease activity at the moment of rechallenge	Remission, N (%)	18 (78.3)
	Grade 1, N (%)	5 (21.7)
Duration of ICI rechallenge in months, median (IQR)		5.0 (2.5–7.0)
Reason for ICI rechallenge discontinuation	Cancer progression, N (%)	12 (52.2)
	Cancer stable/ remission, N (%)	1 (4.3)
	ICI-IA, N (%)	3 (13.0)
	Other irAE, N (%)	0 (0.0)
	Patient still on ICI at last follow-up, N (%)	7 (30.4)
ICI (second course)	CTLA-4, N (%)	0 (0.0)
	PD1/PDL-1, N (%)	23 (100.0)
	Combination, N (%)	0 (0.0)
Other treatment concomitant to ICI	Chemotherapy, N (%)	1 (4.3)
	BRAF/MEK inhibitors, N (%)	0 (0.0)
	Tyrosine kinase inhibitors, N (%)	2 (8.7)
	Other, N (%)	1 (4.3)
	None, N (%)	19 (82.6)
No of other irAE during the second course of ICI	0, N (%)	18 (78.3)
	1, N (%)	3 (13.0)
	≥2, N (%)	2 (8.7)
Duration of ICI before ICI-IA flare in months, median (IQR)		1.0 (0.0–2.5)
CTCAE grade of the flare	Grade 1, N (%)	5 (41.7)
	Grade 2, N (%)	4 (33.3)
	Grade 3, N (%)	3 (25.0)
ICI-IA flare treatment	Prednisone, N (%)	12 (100.0)
	Median maximal daily dose, median (IQR)	15 (5–60)
	csDMARDs, N (%)	4 (33.3)
	MTX, N (%)	3 (75.0)
	MTX+HCQ, N (%)	1 (25.0)
	bDMARDs, N (%)	2 (16.7)
	Anti-IL-6*, N (%)	2 (100)
Progression after ICI rechallenge, N (%)		16 (69.6)
Death, N (%)		4 (17.4)
Follow-up time after second course of ICI in months, median (IQR)		8.0 (4.5–19.5)

*Those two patients were concomitantly treated with MTX.
†Anti-IL-6 started concomitantly to rechallenge given MTX inefficacy
bDMARDs, biological disease-modifying antirheumatic drugs; csDMARD, conventional synthetic DMARD; CTCAE, Common Terminology Criteria for Adverse Events; HCQ, hydroxychloroquine; ICI, immune checkpoint inhibitors; ICI-IA, ICI-induced inflammatory arthritis; irAE, immune-related adverse events; MTX, methotrexate.

synthetic (cs)DMARDs, one (8%) with MTX, one (8%) with combination MTX and HCQ and two (17%) patients with combination MTX and anti-IL-6.

Three patients experienced grade 3 ICI-IA flare during ICI rechallenge, among which, only one patient had initial grade 3 ICI-IA (online supplemental table 1). In this patient, initial ICI-IA occurred immediately after the first course of durvalumab which has thereafter been discontinued. ICI-IA was well controlled with prednisone and MTX which has successfully been stopped. The patient experienced a flare immediately after the ICI rechallenge, 17 months after the first ICI course. The workup revealed that the patient was high-titre seropositive for rheumatoid factor (RF) and anticyclic citrullinated peptide (CCP) antibodies. Pembrolizumab was discontinued due to grade 3 ICI-IA after two doses and arthritis was again well controlled with MTX. Another patient developed grade 3 ICI-IA 4 months after starting pembrolizumab, well-controlled with prednisone and MTX. Alongside with other simultaneous toxicities, ICI was discontinued after 10 months. Later, the patient experienced a flare after 2 months of pembrolizumab rechallenge that was resistant to prednisone 20 mg/day, MTX 20 mg/week subcutaneous and tocilizumab leading to pembrolizumab discontinuation and then ICI-IA remission. The third patient with grade 3 ICI-IA had grade 1 ICI-IA during his first course of pembrolizumab which was successfully treated with a short course of glucocorticoids 60 mg/day allowing him to continue ICI for 6 months with no ICI-IA symptoms until ICI was discontinued for cancer progression. Rechallenge with

pembrolizumab 5 months later led to grade 3 ICI-IA after two ICI administration, requiring pulses of glucocorticoids, MTX and anti-IL-6 combination. The patient still had active ICI-IA at last follow-up. Those 3 cases were the only ones who discontinued ICI due to ICI-IA recurrence thus, rechallenge ICI was continued in 9/12 (75%) of those who flared.

Five (21.7%) patients experienced at least one other irAE during ICI rechallenge including cutaneous (n=5), colitis (n=3), thyroid disorder (n=1), hepatitis (n=1) and chronic inflammatory demyelinating polyneuropathy (n=1).

Patient characteristics according to ICI-IA flare/recurrence status

We aimed to compare patients who experienced ICI-IA flare/recurrence and those who did not (table 3). There was no difference in gender, age, first ICI treatment and type of cancer between those who flared and those who did not. The ICI duration and the median follow-up time post-ICI rechallenge were comparable in those who flared compared with those who did not flare (p=0.5 and 0.4, respectively).

Regarding autoantibodies status, two of three RF positive patients (67%) and the two patients who were anti-CCP positive flared. The presence of ultrasound-synovitis, tenosynovitis and bursitis at baseline was comparable in both groups. The proportion of grade ≥2 ICI-IA occurring during the first course of ICI was similar in those who flared versus those who did not (58% vs 73%; p=0.87).

ICI-IA phenotype, disease activity and ICI-IA treatment at the time of ICI rechallenge did not differ according to ICI-IA flare/recurrence status. Notably, the proportion of patients on immunosuppressive treatment with either glucocorticoids, csDMARDs or biologics at the time of rechallenge was similar in those who experienced a flare/recurrence and those who did not and median daily dose of prednisone was 5 mg/day in both groups.

Over two-thirds of patients progressed after rechallenge (n=16, 70%) and 4 (17%) died. Cancer progression occurred in 7/12 patients (58%) who flared and in 9/11 who did not flare (82%). Median total duration of second course of ICI was 4.5 months (IQR: 1.8–7.0) in those who flared and 6 months (IQR: 3.0–7.5) in those who did not flare. Three patients who flared (25%) and 1 (9%) of those who did not flare died.

DISCUSSION

In this first observational study assessing safety and outcomes of ICI-IA rechallenge, we found that about half of the patients experienced ICI-IA flare/recurrence, similar to the initial ICI-IA clinical presentation but occurring earlier than during the first course of ICI. ICI continuation was possible in 75% of those who flared.

The rate of ICI-flare was comparable to what has been found in the pharmacovigilance study of Dolladille *et al*.[12] In their study, ICI had been discontinued because of the first episode of ICI-IA in all participants whereas this reason accounted for only 35% of the patients included in our cohort. In another pharmacovigilance study, Allouchery *et al* also reported a comparable frequency of flare in 14 patients with grade ≥2 ICI-IA and arthralgias.[13] In their study, serious initial irAE (all category confounded) was not associated with an increased risk of recurrence.[12] Conversely, one retrospective cohort study found trend towards more frequent recurrence in patients with more severe initial irAE.[16] In our cohort, six patients had initial ICI-IA grade 3 with three experiencing a flare on ICI rechallenge, however, only one of those patients experienced a grade 3 flare leading to ICI discontinuation on rechallenge. Altogether our results align with what has been reported and suggest that about 50% of patients experiencing ICI-IA during a first course of ICI will flare on rechallenge and that severity of the initial episode of ICI-IA is not associated with an increased risk.

Although the largest pharmacovigilance study on rechallenge could not assess severity of irAE flare,[12] some studies have suggested that ICI rechallenge is not associated with more severe irAEs.[13 16] Such as the retrospective study of Simonaggio *et al* reporting that flares of ICI-induced arthralgia were not more severe than initial event,[16] the proportion of grade≥2 ICI-IA was similar between the first course of ICI and during rechallenge in our study. Furthermore, ICI-IA led to ICI discontinuation more frequently during the first course of ICI than during rechallenge, suggesting that ICI-IA flares on rechallenge are not more severe.

In our cohort, ICI-IA flare tended to occur earlier than the initial ICI-IA episode. One hypothesis might be an already primed immune system as some patients still had active disease or needed immunosuppression at the time of ICI rechallenge. It is noteworthy that ICI-IA persists at least 6 months after ICI discontinuation in 50% of patients[8] and that the median time between the two ICI courses did not allow total clearance of ICI antibodies.[17] The timing of the initial irAEs might also impact the risk of new or recurrent irAEs after ICI rechallenge.[16]

Our data suggested that patients on prednisone or biologic/csDMARDs to control their ICI-IA at the time of rechallenge seemed to have a similar risk of flaring as those who discontinued specific rheumatic treatment before ICI rechallenge. Similar data were reported on immune-related myositis rechallenge with no impact of glucocorticoid coverage on relapse/recurrence of myositis.[11] However, another study reported that the proportion of ICI-induced arthralgia patients treated with systemic glucocorticoids was higher in the group with recurrence compared with the group with no recurrence, although the difference was not statistically significant.[16] PD-1 rechallenge after a severe irAE under combination ICI was associated with an increased risk of irAE flare in patients still receiving glucocorticoids at the time of ICI rechallenge.[18] Of note, immunosuppressants

Table 3 Clinical characteristics and outcomes of patients who flared ICI-IA on rechallenge and those who did not flare

		ICI-IA flare after rechallenge (N=12)	No ICI-IA flare after rechallenge (N=11)
Gender, N (%)	Male	7 (58.3)	6 (54.5)
	Female	5 (41.7)	5 (45.5)
Age, median (IQR)		68.5 (61.4–74.1)	69.0 (65.3–74.1)
Tumour type, N (%)	Melanoma	3 (25.0)	6 (54.5)
	Lung	5 (41.7)	2 (18.2)
	Genitourinary	3 (25)	1 (9.1)
	Other	1 (8.3)	2 (18.2)
ICI type (first course), N (%)	CTLA-4	0 (0.0)	1 (9.1)
	PD1/PDL-1	11 (91.7)	9 (81.8)
	Combination	1 (8.3)	1 (9.1)
Type of ICI-IA, N (%)	PMR-like	7 (58.3)	5 (45.5)
	Symmetrical polyarthritis	3 (25.0)	4 (36.4)
	Psoriatic arthritis	1 (8.3)	1 (9.1)
	Oligoarthritis	1 (8.3)	1 (9.1)
CTCAE grade, N (%)	Grade 1	5 (41.7)	3 (27.3)
	Grade 2	4 (33.3)	5 (45.5)
	Grade 3	3 (25.0)	3 (27.3)
Laboratory	CRP (mg/L), median (IQR)	27.0 (15.5–57.0)	51.0 (14.3–80.5)
	Positive RF, n (%)	2 (16.7)	1 (9.1)
	Positive anti-CCP, n (%)	2 (16.7)	0 (0.0)
Imaging			
X-ray, N (%)	OA	5 (41.7)	4 (36.4)
US, N (%)	Synovitis	4 (33.3)	4 (36.4)
	Tenosynovitis	4 (33.3)	3 (27.3)
	Bursitis	6 (50.0)	3 (27.3)
Time from ICI start to ICI-IA symptoms (first course), median (IQR)		3.5 (1.0–8.8)	7.0 (3.5–12.0)
Total duration of the first course of ICI, median (IQR)		8.5 (5.3–20.5)	13.0 (8.0–17.0)
Time between cessation of the first course of ICI and rechallenge, median (IQR)		12.0 (8.7–19.1)	7.0 (6.0–16.5)
ICI-IA treatment at the moment of rechallenge, N (%)	No treatment	5 (41.7)	6 (54.5)
	Prednisone	6 (50.0)	5 (45.5)
	Maximal dose, median (IQR)	5.0 (4.0–7.5)	5.0 (5.0–5.0)
	MTX	2 (16.7)	0 (0.0)
	Anti-IL6*	0 (0.0)	1 (9.1)
ICI-IA disease activity at the time of rechallenge, N (%)	Remission	10 (83.3)	8 (72.7)
	Grade 1	2 (16.7)	3 (27.3)
ICI type (second course), N (%)	CTLA-4	0 (0.0)	0 (0.0)
	PD1/PDL-1	12 (100.0)	11 (100.0)
	Combination	0 (0.0)	0 (0.0)
Same ICI as first ICI course, N (%)		11 (91.7)	7 (63.6)
Total duration of the second course of ICI, median (IQR)		4.5 (1.8–7.0)	6.0 (3.0–7.5)
Progression after ICI rechallenge, N (%)		7 (58.3)	9 (81.8)
Progression-free survival after rechallenge, days (IQR)		152 (75–273)	91 (61–214)
Death, N (%)		3 (25.0)	1 (9.1)
Follow-up after the second course of ICI, median (IQR)		6.7 (4.5–12.8)	11.0 (5.5–23.5)

Continued

Table 3 Continued

	ICI-IA flare after rechallenge (N=12)	No ICI-IA flare after rechallenge (N=11)

None of the differences are statistically significant (all p>0.05).
*Anti-IL-6 started concomitantly to rechallenge given MTX inefficacy.
anti-CCP, anti-cyclic citrullinated peptide; CRP, C reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors; ICI-IA, ICI-induced inflammatory arthritis; MTX, methotrexate; OA, osteoarthritis; PMR, polymyalgia rheumatica; RF, rheumatoid factor.

for autoimmune disease at ICI initiation were found to be associated with worse tumour outcomes,[19] but their effect at the time of ICI rechallenge has never been studied. Future studies should assess the effect of immunosuppressive treatments at the time of rechallenge on tumour outcomes.

In a recent systematic review and meta-analysis, PD1/PDL-1 rechallenge was associated with a lower exacerbation rate of all-grade irAE compared with rechallenge with anti-CTLA-4 or combination ICI.[20] Notably, this has been shown in ICI-colitis patients where recurrence of colitis was less frequent after resumption of an anti-PD-1 than with an anti-CTLA4.[21] Furthermore, irAE recurrence on rechallenge seems to depend on the type of irAE occuring during the first course of ICI with two studies reporting a higher rate of gastrointestinal irAE recurrence while endocrine irAE were less likely to recur on rechallenge.[12 16] In a case series of three metastatic melanoma patients who developed severe irAE on combination ICI and rechallenged with the same ICI combination regimen, recurrent irAE occurred in two patients, both requiring high-dose steroids and second-line immunosuppressive drugs.[22] In our study, all patients were rechallenged with PD1/PDL-1 in monotherapy, making our results not generalisable to those rechallenged with combination ICI or non PD1/PDL-1 ICI since the safety profile seems to be different. Of note, two patients from our study that have been rechallenged with combination ICI after two courses of ICI did not flare, providing some reassurance although the risks and benefits must be weighted on a case-by-case basis.

The strenghts of this multicentre study are that (1) all patients were diagnosed and treated by a rheumatologist, allowing exclusion of arthralgias and selection of a homogeneous population, (2) a clear definition of ICI-IA was provided, (3) various grades of severity were included and (4) the follow-up was adequate to capture ICI-IA flare with a median time after ICI rechallenge of 8 months. The first course of ICI was discontinued for diverse reasons and reinitiated at different time interval, patients having different ICI-IA activity and baseline medication at the time of ICI rechallenge, reflecting real-life practice. Our study also ackowledges some limitations beyond its retrospective design with potential reporting bias. Since all patients discontinued ICI for at least 3 months in this study, our results might not be applicable to patients who only hold one or two doses of ICI. Furthermore, all but one patient was rechallenged owing to cancer progression. The risk/benefit balance is always considered for ICI rechallenge leading to potential selection bias in our study with patients having favourable factors. Finally, as a pilot study, our small sample size allowed more descriptive data rather than robust statistical analyses and we could have possibly missed some associations due to a lack of power for group comparison. Future larger studies will likely help to better identify specific factors associated with ICI-IA flare/recurrence.

In this first observational study on ICI-IA rechallenge, about half of the patients experienced ICI-IA flare/recurrence with a similar phenotype than the initial ICI-IA. Flare/recurrence occurred earlier than the initial ICI-IA, highlighting the need for a close monitoring, but ICI continuation was generally allowed except for grade 3 ICI-IA flares. Patients still on prednisone or biologic/csDMARDs to control ICI-IA at the time of rechallenge did not seem at increased risk of flaring and baseline immunosuppresive treatment did not seem to prevent flare occurence, as reported in studies assessing rechallenge of other type of irAEs.

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