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BRIEF REPORT

Moderate-to-severe eosinophilia induced by treatment with immune checkpoint inhibitors: 37 cases from a national reference center for hypereosinophilic syndromes and the French pharmacovigilance database

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ABSTRACT

A better understanding of immune-related adverse events is essential for the early detection and appropriate management of these phenomena. We conducted an observational study of cases recorded at the French reference center for hypereosinophilic syndromes and in the French national pharmacovigilance database. Thirty-seven reports of eosinophilia induced by treatment with immune checkpoint inhibitors (ICIs) were included. The median [range] time to the absolute eosinophil count (AEC) peak was 15 [4–139] weeks. The median AEC was 2.7 [0.8–90.9] G/L. Eosinophil-related manifestations were reported in 21 of the 37 cases (57%). If administered, corticosteroids were always effective (n = 10 out of 10). Partial or complete remission of eosinophilia was obtained in some patients not treated with corticosteroids, after discontinuation (n = 12) or with continuation (n = 4) of the ICI. The AEC should be monitored in ICI-treated patients. If required by oncologic indications, continuation of ICI may be an option in asymptomatic hypereosinophilic patients, and in corticosteroid responders.

Introduction

Immunosuppressive molecules are markedly overexpressed in the microenvironment of both solid and hematologic tumors, which thereby promotes immune escape. However, these molecules can be specifically targeted by immune checkpoint inhibitors (ICIs), such as ipilimumab (a monoclonal antibody against the cytotoxic T-lymphocyte antigen 4 (CTLA4)), nivolumab, and pembrolizumab (both of which target programmed cell death protein 1 (PD-1) or its ligand (PD-L1)).[1] These drugs have been approved for the treatment of several cancers, including melanoma, non-small-cell lung cancer, urothelial carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and the neck, and/or Hodgkin's lymphoma.[2] However, ICIs are also associated with frequent and potentially organ- or life-threatening immune-related adverse events (irAEs), which generally mimic autoimmune or inflammatory conditions; indeed, up to 90% of patients treated with ipilimumab and up to 70% of those treated with PD-1/PD-L1 antibodies experience at least one irAE).[3,4] The early diagnosis and prompt management of irAEs are essential. Although an

effective ICI may not have to be discontinued after a mild irAE, specific treatments and/or discontinuation of the ICI must be considered in the most severe cases.[5]

In a recent retrospective single-center study, the prevalence of immune-related blood eosinophilia (an absolute eosinophil count (AEC) greater than 0.5 G/L) in patients treated with anti-PD1 or anti-PD-L1 drugs was 2.8%, and the median [range] peak AEC was 1.0 [0.6–5.6] G/L.[6] Although drug-induced eosinophilia (and thus, in theory, all other eosinophilic disorders) can be associated with eosinophil-induced organ damage, these cases of immune-related blood eosinophilia (Eo-ir) had a favorable outcome, and required neither specific treatment nor ICI discontinuation.[6]

At the French national reference center for hypereosinophilic syndromes (CEREO), we were solicited for several patients with severe, well-documented, eosinophil-induced adverse events (Eo-irAEs) and organ dysfunction. The objective of the present study was to describe the characteristics and outcomes of patients with moderate-to-severe eosinophilia (defined in this

study as an AEC >1G/L) and/or Eo-irAEs reported in CEREO's database and the French national pharmacovigilance database (FPVD).

Results

Thirty-seven patients were included in the study (Figure 1): 25 were treated with nivolumab, 6 with pembrolizumab, 4 with ipilimumab, and 2 with a combination of nivolumab and ipilimumab (1 case with the two drugs concomitantly, and 1 case with a switch from ipilimumab to nivolumab).

The indications were non-small-cell lung cancer (n = 18), melanoma (n = 18), and Hodgkin's lymphoma (n = 1), the median [range] age at Eo-ir or Eo-irAE onset was 68 [33–84] years, and the male:female ratio was 2.7:1.

Before ICI initiation, 7 patients (19%) already displayed eosinophilia (an AEC between 0.5 and 1.5 G/L), 28 patients did not display eosinophilia, and this information was missing for 2 patients.

Twenty-one patients (57%) had an Eo-irAE, 12 others (32%) had an Eo-ir, and data enabling the classification of an event as an Eo-irAE was missing for 4 patients (11%). The patients' individual data are given in Table 1 and the characteristics are summarized in Table 2.

In the cohort as a whole, the median times to new-onset eosinophilia and to the AEC peak were respectively 6 [1–52] and 15 [4–139] weeks after ICI initiation. The median AEC was 2.7 [0.8–90.9] G/L, although 2 patients had an AEC peak <1 G/L but proven tissue eosinophilia on biopsy.

The data on the AEC before ICI initiation are categorized in Table 2. The median peak AECs did not differ when comparing patients with Eo-ir and those with Eo-irAEs (3.3 [1.2–90.9] and 2.5[0.8–8.7] G/L, respectively, $p = .15$). The Eo-irAEs affected the skin (n = 10), lung (2 cases of eosinophilic pneumonia and 2 of eosinophilic bronchiolitis), kidneys (4 nephritis), liver (2 cholangitis), and heart (1 myocarditis). With regard to the severity of the Eo-irAEs, there were 1 grade IV case, 6 grade III cases, 8 grade II cases and 7 grade I cases. No deaths were attributable to Eo-irAEs (Table 1). The grade IV case was a maculopapular rash with laryngeal edema. The evolution was quickly favorable with corticosteroids. The other skin side effects were: maculopapular rashes (n = 3), eczematiform rashes (n = 2), lichenoid rashes (n = 2), bullous pemphigoid-like eruption and eosinophilic fasciitis (n = 1 each).

Overall, the ICI was discontinued in 26 of the 37 cases (70%); 13 of these (50%) were due to an Eo-ir or an Eo-irAE (Table 2).

The median length of follow-up after ICI initiation was 63 [7–300] weeks (n = 35). Nine deaths were reported during this period but none were attributable to Eo-irAEs.

Ten patients received corticosteroids for Eo-ir or Eo-irAEs; complete (n = 9) or partial (n = 1) disease remission was observed in all cases. Moreover, partial (n = 6) or complete (n = 10) remission of eosinophilia were reported in 16 other patients who did not receive corticosteroids, including 4 for whom ICI was continued. However, data on the time from corticosteroids onset to remission were not available for the great majority of cases. Lastly, 6 patients showed prolonged long-term eosinophilia (lasting for at least 6, 7, 59, 68 and 144 weeks after time of AEC peak) despite ICI discontinuation. Finally, 19 of 29 patients with Eo-ir or Eo-irAE were good responders to ICI (unknown outcome in n = 8), including 5 who kept stable (n = 4) or increased (n = 1) AEC (Table 3).

Discussion

Here, we report on the largest yet series of patients with moderate-to-severe Eo-ir and Eo-irAEs. Our results suggest that the AEC should be closely monitored during the course of ICI. We also reported on patients with a favorable outcome despite persistent blood eosinophilia, and we discuss below how to manage patients with Eo-ir or Eo-irAEs.

Considering the time to new-onset eosinophilia (median [range]: 6 weeks [1–52] or 1.4 months [0.2–12]), our results suggest that monthly monitoring of AEC is warranted during a course of treatment with an ICI. Moreover, this time to onset was shorter in our study than in Berrnard-Teissier et al.'s retrospective observational study of 26 cases with a normal AEC at baseline and an AEC >0.5G/L 3 [0.6–31.3] months after ICI initiation.[6] Although the time course of eosinophilia onset has yet to be characterized, one can reasonably hypothesize that moderate-to-severe eosinophilia may have an early onset. Similarly, the median time to the AEC peak observed in our study (3.4 months [1–32.4]), was shorter than that observed by Berrnard-Teissier et al. (6.4 months [1.4–32]). Fifty percent patients (13/26, see Table 1)
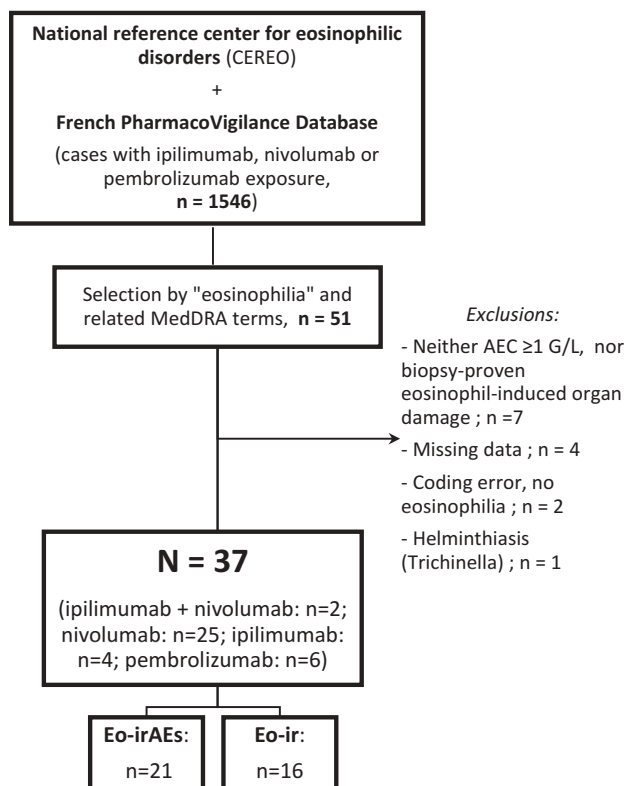

Figure 1. Flow chart showing the case selection process. AEC: absolute eosinophil count; Eo-irAEs: eosinophil-induced adverse events; Eo-ir: immune-related blood eosinophilia.

Table 1. Case-series with patients'individual data.

Cases	Age (y)	Gender	Neoplastic disease	Stage	Previous ICI	Eosinophilia > 0.5 G/L before ICI initiation	ICI	Time between ICI and AEC >0.5 G/L (w)	Peak of AEC (G/L)	Time of peak (w)	Eo-irAE	Grade	Tissue eosinophilia
1	72	M	NSCLC	–	–	no	nivolumab	6	2.500	6	–	na	–
2	75	M	NSCLC	4	–	yes (1.0)	nivolumab	2	90.920	21	no	na	no (normal echocardiography)
3	82	M	Melanoma	4 M1c	ipilimumab	no	nivolumab	20	5.370	38	eosinophilic pneumonia	3	yes (bronchoalveolar lavage with eosinophils)
4	53	F	NSCLC	4	–	no	nivolumab	4	1.960	11	no	na	not applicable
5	64	M	NSCLC	4	–	no	nivolumab	15	2.130	17	no	na	not applicable
6	49	M	Melanoma	4 M1c	–	no	ipilimumab + nivolumab	4	1.200	4	maculopapular rash and laryngeal edema	4	no cutaneous biopsy
7	68	M	Melanoma	4	–	yes (0.600)	nivolumab	not applicable	1.200	4	no	na	not applicable
8	76	M	NSCLC	4	–	yes (1.500)	nivolumab	not applicable	8.000	6	no	na	not applicable
9	59	F	Melanoma	4 M1c	–	no	ipilimumab nivolumab	17 / 4	0.900 / 0.900	17 / 4	cholangitis	3	yes (liver biopsy: inflammatory infiltrate with eosinophils, consistent with drug-induced liver injury)
10	59	F	NSCLC	3A	–	no	nivolumab	20	1.300	21	cholangitis	2	no liver biopsy
11	70	M	NSCLC	4 M1b	–	no	nivolumab	8	2.970	139	asymptomatic abnormalities on cardiac MRI	2	no
12	52	F	Melanoma	4 M1c (CNS+)	–	yes (1.172)	nivolumab	not applicable	6.000	9	no	na	not applicable
13	70	M	NSCLC	4 M1c (CNS+)	–	no	nivolumab	39	2.030	40	no	na	not applicable
14	76	F	NSCLC	4	–	no	nivolumab	1	3.660	27	no	na	not applicable
15	65	M	NSCLC	4 M3	–	no	nivolumab	6	3.600	6	extensive maculopapular rash	2	no cutaneous biopsy
16	62	M	Melanoma	4 M1a	–	no	nivolumab	28	3.700	35	nephritis	1	no renal biopsy (no eosinophiluria)
17	74	M	NSCLC	–	–	no	nivolumab	–	0.800	–	psoriasiform rash and eczematiform dermatitis	3	yes (cutaneous biopsy: aspect of psoriasiform dermatosis and lichenoid with eosinophils and keratinocytic necrosis, compatible with a drug eruption)
18	61	M	NSCLC	4	–	no	nivolumab	4	1.200	26	lichenoid rash	2	yes (cutaneous biopsy: drug lichenoid rash, with infiltrate of rare eosinophils)
19	49	M	Melanoma	4	ipilimumab	yes (0.960 under ipilimumab)	nivolumab	not applicable	1.170	4	no	na	not applicable
20	59	F	NSCLC	3B	–	no	nivolumab	18	1.090	18	nephritis	3	yes (renal biopsy: acute tubulointerstitial nephropathy, presence of eosinophils, and moderate chronic tubulointerstitial nephropathy.)
21	53	M	NSCLC	4 M1c (CNS+)	–	–	nivolumab	2	3.070	6	eosinophilic pneumonia	2	Details of the bronchoalveolar lavage not communicated
22	84	M	NSCLC	–	–	no	nivolumab	18	6.900	35	–	na	–

(Continued)

Table 1. (Continued).

Eo-ir and Eo-irAEs

Cases	Age (y)	Gender	Neoplastic disease	Stage	Previous ICI	Eosinophilia > 0.5 G/L before ICI initiation	ICI	Time between ICI and AEC >0.5 G/L (w)	Peak of AEC (G/L)	Time of peak (w)	Eo-irAE	Grade	Tissue eosinophilia
23	33	M	Hodgkin's lymphoma	4	–	yes (0.300–1.400)	nivolumab	not applicable	5.500	7	no	na	not applicable
24	78	M	NSCLC	4	–	yes (0.700)	nivolumab	not applicable	3.027	36	bullous pemphigoid-like eruption	1	yes (cutaneous biopsy: pemphigoid bullous dermatosis)
25	78	M	NSCLC	4 M1c (CNS+)	–	no	nivolumab	8	1.000	8	lichenoid rash	1	yes (cutaneous biopsy: lichenoid dermatitis)
26	78	M	NSCLC	4	–	no	nivolumab	2	3.089	4	–	na	–
27	72	M	Melanoma	4	–	no	nivolumab	8	6.700	16	myocarditis	3	no endomyocardial biopsy, diagnosis on cardiac MRI
28	65	F	Melanoma	4 M1b	–	no	pembrolizumab	2	2.520	13	maculopapular rash	2	no cutaneous biopsy
29	48	F	Melanoma	4 M1b	–	no	pembrolizumab	4	1.670	16	eosinophilic bronchiolitis	2	yes (bronchoalveolar lavage with eosinophils and bronchial biopsy with chronic inflammatory changes rich in eosinophils of the bronchial mucosa)
30	76	M	Melanoma	4	–	no	pembrolizumab	2	7.900	15	eosinophilic bronchiolitis, asymptomatic abnormalities on cardiac MRI	1	no bronchial biopsy
31	81	M	Melanoma	4	–	no	pembrolizumab	11	1.048	32	eczematiform dermatitis	1	no cutaneous biopsy
32	66	F	Melanoma	4	ipilimumab nivolumab	no	pembrolizumab	52	8.700	75	nephritis	1	no renal biopsy (no eosinophiluria)
33	45	F	Melanoma	4	–	no	pembrolizumab	31	3.100	40	eosinophilic fasciitis	3	yes (cutaneous biopsy: eosinophilic fasciitis)
34	78	M	Melanoma	4 M1c	–	no	ipilimumab	1	4.040	6	maculopapular rash	2	no cutaneous biopsy
35	84	M	Melanoma	4 M1c	–	no	ipilimumab	8	1.466	8	nephritis	1	no renal biopsy (no eosinophiluria)
36	58	M	Melanoma	4	–	no	ipilimumab	2	86.000	6	no	na	not applicable
37	79	M	Melanoma	4	–	–	ipilimumab	2	1.575	5	–	na	–

Outcome

Cases	Other irAEs	ICI withdrawal	Reason of the withdrawal	Follow up of the AEC	Follow up	Overall follow up (w)	Best clinical response with ICI
1	no	no	–	PHR	dead	56	progressive disease
2	thyroiditis, colitis	yes	irAEs	increased eosinophilia	dead	22	progressive disease
3	–	yes	Eo-irAEs	PHR (with CS)	lost to follow-up	63	partial improvement
4	no	yes	progressive disease	CHR	lost to follow-up	14	progressive disease
5	colitis (grade II)	yes	irAEs	CHR	lost to follow-up	34	partial improvement
6	no	yes	Eo-irAEs	PHR	lost to follow-up	14	progressive disease
7	granulomatosis, thyroiditis, vitiligo	no	–	CHR	alive	300	complete improvement
8	colitis	no	–	PHR	lost to follow-up	36	–
9	–	yes	progressive disease	CHR (with CS)	dead	84	progressive disease
		yes	Eo-irAEs	CHR (with CS)	dead	71	stable disease

(Continued)

Table 1. (Continued).

Cases	Other irAEs	ICI withdrawal	Reason of the withdrawal	Outcome			
				Follow up of the AEC	Follow up	Overall follow up (w)	Best clinical response with ICI
10	thyroiditis, auto-immune hypophysitis	yes	Eo-irAEs	CHR (with CS)	alive	93	stable disease
11	no	no	–	stable AEC	alive	155	partial improvement
12	thyroiditis	no	–	CHR (with CS)	alive	13	progressive disease
13	–	no	–	CHR	alive	68	partial improvement
14	thyroiditis	yes	progressive disease	CHR	dead	76	stable disease
15	no	yes	Eo-ir	CHR	lost to follow-up	7	–
16	–	yes	Eo-irAEs	PHR	alive	104	–
17	no	yes	Eo-irAEs	–	–	–	–
18	no	yes	Eo-irAEs	PHR	lost to follow-up	34	stable disease
19	no	yes	AEs	stable AEC	alive	148	complete improvement
20	no	yes	Eo-irAEs	CHR (with CS)	dead	70	progressive disease
21	–	no	–	CHR (with CS)	dead	20	progressive disease
22	–	yes	–	increased eosinophilia	lost to follow-up	36	–
23	thyroiditis	yes	progressive disease	CHR	lost to follow-up	67	stable disease
24	–	yes	–	stable AEC	dead	104	–
25	–	no	–	stable AEC	alive	113	complete improvement
26	–	no	–	–	–	–	–
27	no	yes	progressive disease	CHR (with CS)	alive	22	progressive disease
28	pulmonary granulomatosis	no	–	stable AEC	alive	116	partial improvement
29	thyroiditis	yes	progressive disease	CHR	dead	44	stable disease
30	no	yes	Eo-irAEs	CHR	alive	102	complete improvement
31	–	yes	progressive disease	PHR	lost to follow-up	57	stable disease
32	auto-immune hypophysitis	yes	Eo-ir	increased eosinophilia	lost to follow-up	134	stable disease
33	auto-immune hypophysitis	yes	Eo-irAEs	CHR (with CS)	alive	44	stable disease
34	no	yes	progressive disease	CHR	dead	13	progressive disease
35	thyroiditis	no	–	CHR (with CS)	alive	192	partial improvement
36	no	yes	Eo-ir	increased eosinophilia	lost to follow-up	12	–
37	–	–	–	–	–	–	–

y: years; w: weeks; ICIs: immune checkpoints inhibitors; AEC: absolute eosinophil count; irAEs: immune related advert events; Eo-irAE: eosinophil-induced organ dysfunction; Eo-ir: immune related eosinophilia; AEs: advert events; M: male; F: female; NSCLC: non-small cell lung cancer; CHR: complete hematologic remission with AEC < 0.5 G/L; PHR: partial hematologic remission, with AEC > 0.5 G/L and a decrease in the AEC of >50%; stable eosinophilia: AEC between 50% and 150% of baseline AEC; increased eosinophilia: AEC > 150% of baseline AEC, or unstable; CS: corticosteroid.

Table 2. Characteristics of the eosinophil-induced immune-related adverse events.

Characteristics	n = 37 cases
Age (years)	68 [33–84]
Gender *M:F*	27:10
Neoplastic disease	
NSCLC (stages III & IV)	18/37 (49%)
nivolumab	18
Melanoma (stage IV)	18/37 (49%)
ipilimumab/nivolumab/pembrolizumab/ipilimumab +nivolumab	4/6/6/2
Hodgkin's lymphoma (stage IV)	1/37 (2%)
nivolumab	1
Eosinophil-related data	
Eosinophilia >0.5 G/L at baseline and >1 G/L thereafter	
Number of patients	7/37 (19%)
Range of AECs at diagnosis (G/L)	[0.6–1.5]
Peak AEC (G/L)	5.5 [1.2–90.9]
Time to peak (weeks)	7 [4–36]
Eo-irAEs	1/7 (14%)
Eosinophilia <0.5 G/L at baseline and >1 G/L thereafter	
Number of patients	28/37 (76%)
Time to onset of AEC >0.5 G/L (weeks)	8 [1–52]
Peak AEC (G/L)	2.5 [0.8–86]
Time to peak (weeks)	17 [4–139]
Eo-irAEs	20/28 (71%)
Eosinophil-induced organ damage	
Skin manifestations	10
Eosinophilic pneumonia or bronchiolitis	4
Nephritis	4
Cholangitis	2
Myocarditis	1
Asymptomatic abnormalities on cardiac MRI	2
Cases with at least one other irAE (unrelated to eosinophil toxicity)	13/26 (50%)
Thyroiditis	8
Colitis	3
Auto-immune hypophysitis	3
Granulomatosis	2
Vitiligo	1
ICI discontinuation	26/37 (70%)
Reasons:	
Eo-irAE	10
Eo-ir	3
Disease progression	8
Other AEs	3
Total duration of follow-up (weeks)	63 [7–300]
Best clinical response on ICIs	
Complete improvement	4/29 (14%)
Partial improvement	6/29 (21%)
Stable disease	9/29 (31%)
Progressive disease	10/29 (34%)

M: male; F: female; NSCLC: non-small-cell lung cancer; ICI: immune checkpoints inhibitor; AEC: absolute eosinophil count; irAE: immune-related advert event; Eo-irAE: eosinophil-induced organ dysfunction; Eo-ir: immune-related eosinophilia; AE: adverse event.

Table 3. The AEC outcome, depending on the clinical response to ICI.

AEC follow-up		Clinical responders	Non-responders
		n = 19[#]	n = 10[#]
CHR	n (%)	11 (58%)	7 (70%)
	Treated with CSs	4	5
PHR	n (%)	3 (16%)	2 (20%)
	Treated with CSs	1	0
Stable AEC[1]	n	4 (21%)	0
Increased AEC[2]	n	1 (5%)	1 (10%)

ICI: immune checkpoint inhibitor; AEC: absolute eosinophil count; CHR: complete hematologic remission with AEC < 0.5 G/L; PHR: partial hematologic remission, with AEC > 0.5 G/L and a decrease in the AEC of >50%;:[1] AEC between 50% and 150% of baseline AEC;:[2] AEC > 150% of baseline AEC or unstable; CS: corticosteroid; #: nine patients with missing data.

developed another irAE before or at the same time of Eo-irAE. The time to onset of moderate-to-severe eosinophilia reported in our study is in line with that described for other irAEs that typically arise within a few weeks or months of ICIinitiation.[7]

Given our stringent inclusion criteria, our objective here was to describe the patients with the most severe ICI-induced AEs; according to Bernard-Teissier *et al.* these patients may account for up to 1–2% of people treated with ICIs.[6] We found that a high proportion of these patients developed Eo-irAEs (57%) – suggesting that although blood eosinophilia is highly unusual,[6] it should not be neglected by attending physicians because severe eosinophil-related organ dysfunction is likely to occur. In the present study, we chose to include patients (n = 7) with an AEC >0.5 G/L at baseline (i.e. before ICI initiation), only one developed an Eo-irAE. This suggests that an elevated AEC at baseline is not associated with more severe eosinophilia during treatment with ICIs. Furthermore, an elevated eosinophil count prior to treatment was associated with longer overall survival in several studies.[8–12] Since there was a trend toward a higher median AEC in asymptomatic patients than in patients with Eo-irAEs (3.3[1.2–90.9] and 2.5[0.8–8.7] G/L, respectively), our case-series suggests that AECs and new-onset Eo-irAEs are not correlated. Hence, a high AEC alone is not an index of severity. Moreover, this observation is also supported by reports of an association between elevated eosinophil counts, better clinical responses and longer overall survival in several types of advanced cancer; this association might be stronger and more clinically relevant for patients treated with ICIs than with conventional chemotherapy.[8–11,13-17] Considering that eosinophils can have a role in the response against cancer,[17–20] an elevated AEC might be a marker of effectiveness in some patients. Further research is needed to determine the mechanisms involved in Eo-ir, the clinical significance of high blood eosinophilia on cancer outcome, and whether eosinophils are involved in ICIT effectiveness or just a reactive "biological" phenomenon.[17,21]

Given its retrospective design, our study had several inherent limitations: misclassification, missing data, and the risk of selection bias due to the FPVD's self-reporting procedure (emphasizing the most symptomatic cases). However, this case series enabled to consider differential diagnoses and the management of Eo-irAEs.

When eosinophilia occurs during treatment with an ICI, differential diagnoses must be considered: another medication, helminthiasis (mainly toxocara) and atopic disease, for example. Furthermore, the AEC, clinical symptoms, electrocardiogram, and laboratory markers of heart/kidney/liver status must be closely monitored. In previous reports, eosinophilia sometimes resolved spontaneously.[6] Hence, in patients with Eo-ir but no evidence of eosinophil-related organ dysfunction, we suggest that ICIs can be continued with caution as long as the patients are closely monitored for at least 6 months. In contrast, we observed 7 cases of severe (grades 3 and 4) organ damage (myocarditis, eosinophilic pneumonia, cholangitis, skin rash, eosinophilic fasciitis, and nephritis) and 15 cases of mild-to-moderate (grades 1 and 2) organ damage[22] (Table 1). Interestingly, high remission rates were obtained when corticosteroids were given – even when the ICI was not discontinued (n = 3). Corticosteroids are the usual first-line treatment for both

reactive eosinophilic disorders and irAEs.[2,7,23] Our results suggest that corticosteroids constitute an effective treatment for moderate-to-severe eosinophilia, even though the dosage was not specified in the pharmacovigilance reports. Phillips et al. recently reported a large cohort of 285 patients with immune-related cutaneous AEs, including 7 (2.4%) who were refractory to corticosteroids. Increased AEC, serum IL-6, Il-10 and IgE levels were associated with corticosteroid-refractory adverse events and with grade 3 or greater cutaneous AEs, but the direct accountability of eosinophils was not assessed in these exceptional cases.[24] Even if some severe cutaneous AEs like drug reaction with eosinophilia and systemic symptoms (DRESS) require high-dose corticosteroids,[25,26] multiple recent reports of Eo-irAEs like eosinophilic fasciitis[27-30] or eosinophilic granulomatosis with polyangiitis[31] suggest that topical or low-dose oral corticosteroids, with or without CS-sparing treatments, can give excellent results. Taking account these data, and given that in our work (i) Eo-ir and Eo-irAEs accounted for half of all ICI discontinuations and (ii) no deaths were directly attributable to eosinophil-organ damage, we suggest that the initiation of corticosteroids and the maintenance of the ICI might be an effective therapeutic strategy in patients with moderate-to-severe eosinophilia and whose cancer is under control. Although most international guidelines recommend higher doses of corticosteroids (from 0.5 to 2 mg/kg/day) for other irAEs,[5,32,33] eosinophilia and eosinophil-induced organ dysfunction typically respond quickly to corticosteroids, and some non-severe cases respond to low doses. Progressive corticosteroid tapering may be warranted after 1 or 3 weeks, depending on the severity and the initial clinical response. Hence, considering that high-dose corticosteroids could reduce the ICI's effectiveness, it would be possible to reach a dose of 10 mg/d.[34] In the other hand, early use of steroids was associated with worse clinical outcomes and remarkable modulation of peripheral blood immune cells (including the decrease of the AEC), which could contribute to restraining the activation of antitumour immunity.[35] Eosinophilic heart involvement can be asymptomatic, whereas myocarditis is a life-threatening complication. The electrocardiogram and serum levels of troponin and brain-natriuretic peptide should be monitored every 2 or 4 weeks, and echochardiography should be performed at least at when hypereosinophilia is diagnosed. Cardiac MRI should be considered in the event of doubt or if myocarditis is suspected.

Conclusion

Taken as a whole, our results suggest that moderate-to-severe eosinophilia can occur soon after ICI initiation and can lead to severe eosinophilic-related organ damage. Further prospective studies are warranted, in order to assess, the risk factors to develop Eo-ir or Eo-irAE, the long-term outcomes of Eo-irAEs and to better define the optimal management of these complications. Lastly, given the ICIs' potency against cancer, our observations suggest that asymptomatic blood eosinophilia and Eo-irAEs (grade ≤3) do not necessarily constitute sufficient grounds for treatment discontinuation.

Methods

Data source

The CEREO and FPVD databases were searched for cases of moderate-to-severe eosinophilia or Eo-irAEs. Briefly, the FPVD has recorded all adverse drug reactions spontaneously notified to France's 31 regional pharmacovigilance centers since 1985.[36] Indeed, French legislation requires healthcare professionals to report all adverse drug reactions to their regional pharmacovigilance center. Although patient consent is not required, the records remain fully anonymous. Next, each adverse drug reaction report is analyzed by pharmacologists with expertise in the field. Causality is assessed according to the French method[37] which is based on both intrinsic imputability (i.e. cross-checking against chronologic and semiologic criteria) and extrinsic imputability (i.e. based on literature data). Lastly, the case is recorded in the database after being coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

Case selection

The FPVD was searched up until November 1st, 2017, whereas the CEREO's records were searched up until January 15th, 2019.

In the FPVD, cases were selected using logical combinations of the MedDRA preferred terms "eosinophilia", "eosinophil count abnormal", "eosinophil count increased", "eosinophil percentage abnormal", "eosinophil percentage increased", "eosinophilic cellulitis", "eosinophilic fasciitis", "eosinophilic pustular folliculitis", "eosinophilic pustulosis", "drug reaction with eosinophilia and systemic symptoms", "eosinophilia myalgia syndrome", "allergic eosinophilia", "pulmonary eosinophilia", "eosinophilic pleural effusion", "eosinophilic bronchitis", "eosinophilic pneumonitis", "eosinophilic pneumonitis acute", "eosinophilic pneumonitis chronic", "gastroenteritis eosinophilic", "eosinophilic colitis", "eosinophilic oesophagus", "hepatic infiltration eosinophilic", "eosinophilic myocarditis", "eosinophilic cystitis", "eosinophilic granulomatosis with polyangiitis", "meningitis eosinophilic", "panniculitis eosinophilic", "hypereosinophilic syndrome" AND "ipilimumab", "nivolumab" or "pembrolizumab" exposure; only cases where an adverse reaction to the drugs were "suspected" were selected.[38]

Patients were included if at least one AEC after initiation of ICI therapy (nivolumab, pembrolizumab or ipilimumab) was >1 G/L and/or eosinophil-induced organ damage was confirmed on biopsy.[39] We excluded patients with other likely etiologies for eosinophilia (e.g. helminthiasis) and/or missing data.

Data collection

For each case, we noted the patient's demographic and clinical characteristics (age, gender, neoplastic disease, and length of follow-up), data regarding the ICI (dose, duration of treatment, the best anti-tumor response during treatment (according to the oncologist), potential discontinuation and other irAEs,) and history of eosinophilia (time to onset and to peak, confirmed or suspected Eo-irAEs and their outcomes) were recorded. Data were collected from FPVD reports, and

missing data were extracted from corresponding medical charts by each regional pharmacovigilance coordinator. After careful analysis of both the patient's medical charts and the chronologic relationship between blood eosinophilia and onset of organ dysfunction, the adverse drug reaction were classified either as Eo-ir (i.e. no organ dysfunction was attributed to eosinophilia) or Eo-irAEs (i.e. organ dysfunction was considered to have been induced by proven tissue eosinophilia and/or potentially induced by eosinophils after a chart review of the organ dysfunction and the presence of a consistent chronologic relationship between blood eosinophilia and the onset of organ dysfunction).

Ethics

According to French legislation, formal approval by an investigational review board is not required for this type of study (performed here by the French Pharmacovigilance Network).

Statistics

Quantitative variables were quoted as the median [range], and qualitative variables were quoted as the number (percentage). Median values were compared using a Wilcoxon rank sum test with continuity correction. All tests were two-tailed, and the threshold for statistical significance was set to $p < .05$. All statistical analysis were performed using R software via R studio (R version 3.4.0., The R Foundation for Statistical Computing, Vienna, Austria).

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Conflicts of interest

Disclosure of Potential Conflicts of Interest

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