Cutaneous Toxicities Associated with Immune Checkpoint Inhibitors: An Observational, Pharmacovigilance Study

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Cutaneous immune-related adverse events (cirAEs) are the most prevalent complication to arise from immunotherapy and cause significant morbidity. We aimed to determine the spectrum, timing, clinical features, and outcomes of cirAEs by conducting an observational pharmacovigilance study using VigiBase, the World Health Organization's global database of individual case safety reports from over 130 member countries (ClinicalTrials.gov, number NCT04898751). We compared adverse event reporting in patients who received immune checkpoint inhibitors (91,323 adverse events) with those of the full reporting database (18,919,358 adverse events). There were 10,933 cases of cirAEs within 51 distinct dermatologic types, with 27 specific eruptions with disproportionate signal represented (information component $[IC]_{025} > 0$). Of these 27 eruptions, there were eight cirAEs with $n > 100$ reports, including vitiligo ($IC_{025} = 4.87$), bullous pemphigoid ($IC_{025} = 4.08$), lichenoid dermatitis ($IC_{025} = 3.69$), erythema multiforme ($IC_{025} = 1.03$), toxic epidermal necrolysis ($IC_{025} = 0.95$), Stevens–Johnson syndrome ($IC_{025} = 0.41$), drug eruption ($IC_{025} = 0.11$), and eczematous dermatitis ($IC_{025} = 0.11$). There were differences in time to onset after immune checkpoint inhibitor initiation, with a median of approximately 1 month (erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis), 2 months (drug eruption and eczematous dermatitis), 4 months (lichenoid dermatitis), and 5–6 months (bullous pemphigoid and vitiligo). CirAEs are diverse, dependent on cancer type, and have distinct and different onset times that are linked to the cirAE subtype.

Journal of Investigative Dermatology (2022) **142,** 2896–2908; doi:10.1016/j.jid.2022.04.020

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Abbreviations: ADR, adverse drug reaction; CI, confidence interval; cirAE, cutaneous immune-related adverse event; EM, erythema multiforme; IC, information component; ICI, immune checkpoint inhibitor; ICSR, individual case safety report; IQR, interquartile range; irAE, immune-related adverse event; ROR, reporting OR; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

Received 7 October 2021; revised 20 March 2022; accepted 20 April 2022; accepted manuscript published online 20 May 2022; corrected proof published online 29 June 2022

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of multiple malignancies and are in widespread use (Kumar et al., 2017; Ribas and Wolchok, 2018). However, these new therapies also impair immunologic self-tolerance, leading to immune-related adverse events (irAEs) such as cutaneous irAEs (cirAEs). cirAEs are among the top three most commonly reported ICI-induced irAEs, often cited as the most frequent and earliest to occur (Ciccarese et al., 2016; Geisler et al., 2020). They arise in over one third of patients who are taking ICIs and can result in a significant decrease in QOL and treatment termination (Eigentler et al., 2016; Sibaud, 2018). Commonly reported cirAEs include maculopapular rash, pruritus, and psoriasiform/lichenoid eruptions (Geisler et al., 2020; Wongvibulsin et al., 2022). However, cirAEs can encompass a wide array of other cutaneous morphologies, including but not limited to acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, scleroderma, Grover's disease, generalized pruritus, dermatomyositis, and Sweet's syndrome (Coleman et al., 2019; Curry et al., 2017; Geisler et al., 2020; Le et al., 2021; Schneider et al., 2021; Sibaud, 2018; Terrier et al., 2020).

Pharmacovigilance databases have the ability to report on a large number of both common and rare cirAEs and are helpful in understanding the wide spectrum of cirAEs.

Whereas pharmacovigilance studies have been conducted already for other organ systems (Bai et al., 2020; Db et al. 2019; Salem et al., 2018), a study of this type characterizing the timing, characteristics, and outcomes of cirAEs is not yet available in the literature. Pharmacovigilance studies have been used to provide epidemiological evidence about the adverse events associated with ICIs, although this has been infrequently reported in the literature for cirAEs (Raschi et al., 2020). In this study, we employ surveillance data from VigiBase, the World Health Organization global database of individual case safety reports (ICSRs), to define and describe these cirAEs (Lindquist, 2008).

RESULTS

Initial characterization of cirAEs

From its inception, there were 18,919,358 ICSRs within VigiBase, of which 91,323 ICSRs were related to either pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab, avelumab, and ipilimumab. Of these 91,323 ICSRs, we identified 10,933 distinct cases of cutaneous ICSRs. These can be classified into 51 different dermatologic morphologies, of which 27 had a disproportionate signal indicated by a positive information component $(IC)_{025} > 0$ (Table 1). Of the cutaneous ICSRs with disproportionate signal, there were eight morphologies with n > 100 reports, which also had a significant reporting OR (ROR) >1 (Supplementary Table S1). We refer to these eight eruptions as cirAEs, and they include vitiligo ($IC_{025} = 4.87$, ROR = 40.98, 95% confidence interval [CI] = 37.19–45.16), bullous pemphigoid ($IC_{025} = 4.08$, ROR = 21.09, 95% CI = 18.96–23.47), lichenoid dermatitis ($IC_{025} = 3.69$, ROR = 16.37, 95% CI = 14.33–18.71), erythema multiforme (EM) ($IC_{025} = 1.03$, ROR = 2.72, 95% CI = 2.37–3.12), toxic epidermal necrolysis (TEN) ($IC_{025} = 0.95$, ROR = 2.60, 95% CI = 2.19–3.08), Stevens–Johnson syndrome (SJS) ($IC_{025} = 0.41$, ROR = 1.69, 95% CI = 1.49–1.92), drug eruption ($IC_{025} = 0.11$, ROR = 1.49, 95% CI = 1.27–1.73), and eczematous dermatitis ($IC_{025} = 0.11$, ROR = 1.42, 95% CI = 1.26–1.65). Notably, known cirAEs such as maculopapular eruption and psoriasiform dermatitis were not detected as significant signals in this analysis ($IC_{025} = -0.69$ and −0.04 repsectively), despite the large number of case reports within VigiBase (n = 400 and 437, respectively).

We also investigated whether these eight eruptions were more likely to be seen in PD-1/PD-L1 therapy versus in CTLA-4 monotherapy as well as in combination therapy versus in monotherapy. For monotherapy comparisons, aside from TEN and vitiligo, the remaining six eruptions were more frequently reported in patients treated with PD-1 or PD-L1 inhibitors in comparison with those treated with CTLA-4 inhibitors (Supplementary Table S1). Furthermore, aside from bullous pemphigoid and lichenoid dermatitis, patients receiving combination therapy were more likely to report the remaining six eruptions.

Characteristics of cirAEs

Each of our eight identified eruptions required multiple years of ICSR reporting before approaching a statistically detectable signal (Supplementary Figure S1). A majority of these were reported in males (59−74%), with a wide range of ages from 18 to 75+ years (Tables 2 and 3). The most common cancers treated with a cirAE-causing ICI were melanoma, lung cancers, and renal cancers. Using pair-wise chi-square tests, vitiligo was more commonly to be reported in patients with melanoma ($P < 0.001$), and SJS was more commonly reported in patients with urothelial carcinoma ($P < 0.007$). Occurrence of severe outcomes varied among the different cirAEs, with 46% of patients with vitiligo reporting a severe outcome compared with 100% of patients with TEN reporting a severe outcome. In particular, patients with bullous disorders were more likely to have a severe outcome, including bullous pemphigoid (96%) and severe cutaneous adverse reactions, which include EM (91%), SJS (97%), and TEN (94%). Death from irAEs ranged from uncommon (1.4% of patients with lichenoid dermatitis) to relatively frequent (15% of patients with SJS and 39% of patients with TEN). The suspected ICI was withdrawn in over 50% of cases for each of the eight cirAEs, and an ICI was rechallenged in at least 20−30% of cases reported.

Concurrent irAEs

cirAEs occurred relatively frequently with gastrointestinal irAEs (Tables 4 and 5). For example, 11% of patients with vitiligo also had colitis, and 9.2% of patients with drug eruption also had hepatitis. In addition, thyroid disorders seemed to occur in certain cirAEs, including in 11% of patients with vitiligo and 10% of patients with eczematous dermatitis. There was not an appreciable overlap between the different cirAEs, indicating that cirAEs in general did not often copresent with each other. However, 16 patients presented with both SJS and TEN, suggesting that their diseases progressed from SJS to TEN and that both events were documented. Although pruritus occurred to some extent in all cirAEs, it was more likely to be found in patients with eczematous dermatitis ($P < 0.001$). The full range of concurrent irAEs is reported in Tables 4 and 5.

Time to onset

Survival curves showing the time to onset for the different cirAE presentations are shown in Figure 1. Time to onset ranged greatly, from 1−2 days to several years (Tables 2 and 3). Using a posthoc Dunn's test after a Kruskal–Wallis test, we discovered that the eight cirAEs of interest in this study tended to aggregate in four different groups (Supplementary Figure S2 and Supplementary Table S2). The group with the shortest time to onset had a median onset of approximately 1 month (median = 27 days, interquartile range [IQR] = 13−79 days) and included severe cutaneous adverse reactions (SJS, EM, and TEN). The second group had a median onset of approximately 2 months (median = 53 days, IQR = 22−168 days) and included eczematous dermatitis and drug eruption. The third group had a median onset of 4 months (median = 119 days, IQR = 60−240 days) and included lichenoid dermatitis. Finally, the fourth group had a median onset of 5−6 months (median = 168 days, IQR = 88−336 days) and included vitiligo and bullous pemphigoid.

DISCUSSION

This pharmacovigilance study represents the largest global characterization of ICI-associated cirAEs in the literature. We report 10,933 distinct cases of cirAEs and identified eight

Table 1. Dermatologic Reactions Identified in VigiBase with Associated IC_{025} and IC Values for Significant Signal Detection

Adverse Reaction	n (%) N = 91323[1]	IC_{025}[2]/IC
Vitiligo	**508 (0.56%)**	**4.87/5.00**
Bullous pemphigoid	**372 (0.41%)**	**4.08/4.23**
Lichenoid dermatitis	**234 (0.26%)**	**3.69/3.88**
Cutaneous sarcoidosis	**25 (0.03%)**	**3.43/4.05**
Dermatomyositis	**48 (0.05%)**	**2.79/3.23**
Oral lichen planus	**20 (0.02%)**	**2.52/3.22**
Granulomatous dermatitis	**9 (0.01%)**	**2.31/3.41**
Transient acantholytic dermatosis	**9 (0.01%)**	**1.93/3.02**
Lichen sclerosus	**14 (0.02%)**	**1.85/2.70**
Prurigo/lichen simplex chronicus	**22 (.02%)**	**1.79/2.45**
Scleroderma	**41 (0.04%)**	**1.22/1.70**
Panniculitis	**20 (0.02%)**	**1.22/1.92**
Subacute cutaneous lupus erythematosus	**13 (0.01%)**	**1.07/1.96**
Perivascular dermatitis	**7 (0.01%)**	**1.03/2.29**
Erythema multiforme	**205 (0.22%)**	**1.03/1.24**
Myxedema	**6 (0.01%)**	**0.97/2.35**
Toxic epidermal necrolysis	**136 (0.15%)**	**0.95/1.21**
Pityriasis rubra pilaris	**5 (0.01%)**	**0.85/2.38**
Eosinophilic cellulitis	**5 (0.01%)**	**0.78/2.30**
Seborrheic dermatitis	**17 (0.02%)**	**0.54/1.31**
Stevens–Johnson syndrome	**245 (0.27%)**	**0.41/0.61**
Pemphigus vulgaris	**12 (0.01%)**	**0.29/1.22**
Parapsoriasis	**5 (0.01%)**	**0.21/1.73**
Drug eruption	**163 (0.18%)**	**0.11/0.36**
Eczematous dermatitis	**164 (0.18%)**	**0.11/0.35**
Skin depigmentation	**13 (0.01%)**	**0.02/0.91**
Acute febrile neutrophilic dermatosis	**11 (0.01%)**	**0.02/0.99**
Psoriasiform dermatitis	437 (0.48%)	−0.04/0.1
Palmar-plantar erythrodysaesthesia syndrome	85 (0.09%)	−0.5/−0.17
Xeroderma	298 (0.33%)	−0.56/−0.4
Anhidrosis/hyperhidrosis	6 (0.01%)	−0.61/0.77
Rash NOS	3977 (4.35%)	−0.61/−0.56
Rash maculopapular	400 (0.44%)	−0.69/−0.54
Nail disorders	98 (0.11%)	−0.71/−0.41
Pruritus	2168 (2.37%)	−0.95/−0.88
Exfoliative rash	192 (0.21%)	−1.02/−0.81
Hair color/texture change	77 (0.08%)	−1.31/−0.97
Rosacea	13 (0.01%)	−1.35/−0.46
Cutaneous lupus erythematosus[3]	16 (0.02%)	−1.39/−0.6
Hyperpigmentation	28 (0.03%)	−1.45/−0.87
Systemic lupus erythematosus	27 (0.03%)	−1.51/−0.92
DRESS syndrome	38 (0.04%)	−1.56/−1.06
Alopecia	242 (0.26%)	−1.97/−1.78
Hidradenitis	6 (0.01%)	−2.17/−0.79
Erythema annulare	2 (0.002%)	−2.18/0.41
Dermatitis acneiform	91 (0.1%)	−2.2/−1.88
Angioedema	241 (0.26%)	−2.96/−2.77
Dysaesthesia	54 (0.06%)	−3.23/−2.82
Pityriasis	1 (0.001%)	−3.32/0.48
Urticaria	222 (0.24%)	−3.52/−3.33
Fixed eruption	1 (0.001%)	−9.13/−5.33

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; IC, information component; ICSR, individual case safety report; NOS, not otherwise specified.

[1]Total number of ICSRs reported within VigiBase

[2]Positive IC_{025} value indicates a significant signal within VigiBase detected within the bottom end of the 95% confidence interval.

[3]Excluding subacute cutaneous lupus erythematosus.

Bolded reactions indicate those with significant signals ($IC_{025} > 0$).

Table 2. Summary Characteristics of Selected Inflammatory Cutaneous irAEs in VigiBase

Characteristic	Vitiligo, n (%) (N = 508)	Bullous Pemphigoid, n (%) (N = 372)	Lichenoid Dermatitis, n (%) (N = 234)	Drug Eruption, n (%) (N = 163)	Eczematous Dermatitis, n (%) (N = 164)
Year reported					
2009	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)
2011	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2012	1 (0.2)	0 (0)	1 (0.4)	1 (0.6)	0 (0)
2013	8 (1.6)	0 (0)	0 (0)	2 (1.2)	1 (0.6)
2014	9 (1.8)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
2015	13 (2.6)	5 (1.3)	4 (1.7)	2 (1.2)	4 (2.4)
2016	62 (12)	9 (2.4)	12 (5.1)	6 (3.7)	5 (3.0)
2017	62 (12)	53 (14)	35 (15)	48 (29)	34 (21)
2018	130 (26)	95 (26)	61 (26)	38 (23)	35 (21)
2019	150 (30)	153 (41)	100 (43)	49 (30)	51 (31)
2020	73 (14)	57 (15)	20 (8.5)	17 (10)	32 (20)
Sex					
Data available	473 (93)	349 (94)	213 (91)	159 (98)	158 (96)
Female	187 (40)	90 (26)	94 (44)	61 (38)	44 (28)
Male	286 (60)	259 (74)	119 (56)	98 (62)	114 (72)
Age					
Data available	311 (61)	251 (67)	145 (62)	115 (71)	103 (63)
18–44 y	48 (15)	11 (4.4)	10 (6.9)	11 (9.6)	9 (8.7)
45–64 y	123 (40)	59 (24)	47 (32)	44 (38)	35 (34)
65–74 y	85 (27)	93 (37)	51 (35)	38 (33)	31 (30)
≥75 y	39 (13)	88 (35)	37 (26)	22 (19)	28 (27)
Notifier					
Physician	207 (41)	227 (61)	128 (55)	109 (67)	77 (47)
Pharmacist	91 (18)	24 (6)	7 (3)	8 (5)	28 (17)
Other health professional	139 (27)	79 (21)	83 (35)	32 (20)	36 (22)
Patient	57 (11)	34 (9)	15 (6)	11 (7)	20 (12)
Unknown	14 (3)	8 (2)	1 (0.4)	3 (2)	3 (2)
Treatment indication					
Melanoma	385 (76)	122 (33)	74 (32)	55 (34)	63 (38)
Lung	28 (5.5)	110 (30)	82 (35)	58 (36)	54 (33)
Renal	6 (1.2)	39 (10)	17 (7.3)	16 (9.8)	6 (3.7)
H&N	1 (0.2)	10 (2.7)	7 (3.0)	2 (1.2)	7 (4.3)
GI	0 (0)	7 (1.9)	4 (1.7)	2 (1.2)	1 (0.6)
CNS	0 (0)	2 (0.5)	2 (0.9)	0 (0)	0 (0)
Liver	1 (0.2)	2 (0.5)	4 (1.7)	2 (1.2)	0 (0)
Lymphoma	2 (0.4)	1 (0.3)	4 (1.7)	0 (0)	3 (1.8)
Gynecologic	2 (0.4)	1 (0.3)	4 (1.7)	1 (0.6)	1 (0.6)
Metastases	5 (1.0)	7 (1.9)	3 (1.3)	1 (0.6)	1 (0.6)
Urothelial	3 (0.6)	13 (3.5)	1 (0.4)	3 (1.8)	3 (1.8)
Unknown indication	54 (11)	18 (4.8)	3 (1.3)	3 (1.8)	5 (3.0)
Other/missing	21 (4.1)	40 (11)	29 (12)	20 (12)	20 (12)
Time to onset (d)					
Data available	244 (48)	141 (38)	85 (36)	65 (40)	100 (61)
Median (IQR)	160 (92–283)	204 (77–414)	119 (60–240)	48 (19–173)	63 (26–164)
(max–min)	(14–1,159)	(3–1,211)	(9–1,557)	(1–676)	(1–906)
Serious					
Data available	494 (97)	366 (98)	233 (100)	161 (99)	161 (98)
	227 (46)	352 (96)	144 (62)	122 (76)	86 (53)
Death					
Data available	221 (44)	352 (95)	144 (62)	122 (75)	86 (52)
	7 (3.2)	10 (2.8)	2 (1.4)	10 (8.2)	7 (8.1)
Initial ICI management					
Data available	294 (58)	265 (71)	154 (66)	105 (64)	110 (67)
Dose Increased	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Dose not changed	132 (45)	56 (21)	51 (33)	33 (31)	46 (42)
Drug withdrawn	160 (54)	209 (79)	103 (67)	72 (69)	64 (58)

(*continued*)

Table 2. Continued

Characteristic	Vitiligo, n (%) (N = 508)	Bullous Pemphigoid, n (%) (N = 372)	Lichenoid Dermatitis, n (%) (N = 234)	Drug Eruption, n (%) (N = 163)	Eczematous Dermatitis, n (%) (N = 164)
Rechallenge outcome					
Data available (rechallenge conducted and documented)	110 (22)	108 (29)	51 (22)	35 (21)	46 (28)
Reaction recurred	0 (0)	5 (4.6)	1 (2.0)	1 (2.9)	1 (2.2)
No recurrence	6 (5.5)	5 (4.6)	2 (3.9)	3 (8.6)	0 (0)
Unknown	104 (95)	98 (91)	48 (94)	31 (89)	45 (98)
Monotherapy PD-1/PD-L1					
Pembrolizumab	220 (43)	126 (34)	70 (30)	45 (28)	46 (28)
Nivolumab	111 (22)	155 (42)	119 (51)	63 (39)	63 (38)
Atezolizumab	7 (1.4)	8 (2.2)	6 (2.6)	5 (3.1)	9 (5.5)
Cemiplimab	0 (0)	6 (1.6)	0 (0)	1 (0.6)	3 (1.8)
Avelumab	0 (0)	1 (0.3)	1 (0.4)	0 (0)	1 (0.6)
Durvalumab	1 (0.2)	7 (1.9)	2 (0.9)	1 (0.6)	3 (1.8)
Monotherapy CTLA-4					
Ipilimumab	41 (8.1)	5 (1.3)	6 (2.6)	6 (3.7)	7 (4.3)
Combination therapy					
Ipilimumab + nivolumab	102 (20)	34 (9.1)	20 (8.5)	32 (20)	32 (20)
Nivolumab + pembrolizumab	0 (0)	14 (3.8)	0 (0)	0 (0)	0 (0)
Avelumab + pembrolizumab	0 (0)	2 (0.5)	0 (0)	0 (0)	0 (0)
Ipilimumab + pembrolizumab	14 (2.8)	8 (2.2)	4 (1.7)	4 (2.5)	0 (0)
Ipilimumab + nivolumab + pembrolizumab	12 (2.4)	6 (1.6)	6 (2.6)	6 (3.7)	0 (0)
Ipilimumab dosage					
Data available	48 (28)	19 (36)	6 (17)	15 (31)	16 (41)
1–3 mg/kg	29 (60)	14 (74)	3 (4.3)	9 (60)	8 (50)
5–10 mg/kg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10 mg/kg	2 (4.2)	2 (11)	0 (0)	0 (0)	0 (0)
<500 mg	17 (35)	3 (16)	3 (50)	6 (40)	8 (50)
≥500 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nivolumab dosage					
Data available	101 (45)	114 (55)	69 (48)	39 (39)	62 (65)
1–2 mg/kg	11 (11)	2 (1.8)	3 (50)	5 (13)	3 (4.8)
>2 mg/kg	20 (20)	52 (46)	29 (42)	24 (62)	18 (29)
<240 mg	38 (38)	43 (38)	26 (38)	8 (21)	31 (50)
≥240 mg	32 (32)	17 (15)	11 (16)	2 (5.1)	10 (16)
Pembrolizumab dosage					
Data available	147 (60)	72 (46)	34 (43)	35 (64)	26 (57)
2 mg/kg	34 (23)	16 (22)	11 (32)	5 (14)	4 (15)
>2 mg/kg	2 (1.4)	2 (2.8)	1 (2.9)	0 (0)	0 (0)
<200 mg	107 (73)	50 (69)	22 (65)	30 (86)	22 (85)
≥200 mg	4 (2.7)	4 (5.6)	0 (0)	0 (0)	0 (0)
Suspected drug(s)					
ICIs only	484 (95)	331 (89)	214 (92)	92 (56)	149 (91)
ICI + one other drug	17 (3.3)	17 (4.6)	10 (4.3)	25 (15)	7 (4.3)
ICI + >1 drug	7 (1.4)	24 (6.5)	10 (4.3)	46 (28)	8 (4.9)

Abbreviations: GI, gastrointestinal; H&N, head and neck; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; max, maximum; min, minimum.
The denominator is with all available data unless otherwise noted.

specific morphologies with a disproportionate signal and n > 100 ISCRs: vitiligo, drug eruption, lichenoid dermatitis, eczematous dermatitis, bullous pemphigoid, EM, SJS, and TEN. This study highlights the diversity and wide variety of different dermatologic adverse events (Eggermont et al., 2018; Hellmann et al., 2018; Robert et al., 2015).

Our study shows the importance of considering cirAEs in the context of multiple organ system toxicities. There was a co-occurrence between cirAEs, gastrointestinal irAEs, and thyroid irAEs, such as vitiligo with colitis and thyroid disorders and eczematous dermatitis with thyroid disorders. This is not a phenomenon limited to just cirAEs—pneumonitis,

Table 3. Summary Characteristics of the Selected Severe cirAEs in VigiBase

Characteristic	Erythema Multiforme, n (%) (N = 205)	Stevens–Johnson Syndrome, n (%) (N = 245)	Toxic Epidermal Necrolysis, n (%) (N = 136)
Year reported			
2009	1 (0.5)	0 (0)	1 (0.7)
2011	0 (0)	0 (0)	0 (0)
2012	0 (0)	0 (0)	1 (0.7)
2013	0 (0)	0 (0)	0 (0)
2014	1 (0.5)	1 (0.4)	2 (1.5)
2015	2 (1.0)	2 (0.8)	4 (2.9)
2016	18 (8.8)	15 (6.1)	9 (6.6)
2017	37 (18)	49 (20)	25 (18)
2018	56 (27)	61 (25)	31 (23)
2019	85 (41)	98 (40)	36 (26)
2020	5 (2.4)	19 (7.8)	27 (20)
Sex			
Data available	198 (97)	222 (91)	119 (88)
Female	80 (40)	77 (35)	53 (45)
Male	118 (60)	145 (65)	66 (55)
Age			
Data available	171 (83)	164 (67)	98 (72)
18–44 y	10 (5.8)	10 (6.1)	3 (3.1)
45–64 y	49 (29)	69 (42)	44 (45)
65–74 y	71 (42)	58 (35)	36 (37)
≥75 y	41 (24)	27 (16)	15 (15)
Notifier			
Physician	148 (72)	139 (57)	77 (57)
Pharmacist	17 (8)	25 (10)	13 (10)
Other health professional	22 (11)	40 (16)	20 (15)
Patient	7 (3)	24 (10)	21 (15)
Unknown	11 (5)	17 (7)	5 (4)
Treatment indication			
Melanoma	63 (31)	46 (19)	40 (29)
Lung	76 (37)	89 (36)	44 (32)
Renal	20 (9.8)	16 (6.5)	7 (5.1)
H&N	10 (4.9)	18 (7.3)	5 (3.7)
GI	4 (2.0)	7 (2.9)	4 (2.9)
CNS	0 (0)	0 (0)	0 (0)
Liver	1 (0.5)	2 (0.8)	0 (0)
Lymphoma	2 (1.0)	4 (1.6)	3 (2.2)
Gynecologic	0 (0)	1 (0.4)	1 (0.7)
Metastases	0 (0)	1 (0.4)	0 (0)
Urothelial	2 (1.0)	21 (8.6)	8 (5.9)
Unknown indication	19 (9.3)	38 (16)	19 (14)
Other/missing	8 (3.9)	2 (0.8)	5 (3.7)
Time to onset (d)			
Data available	106 (52)	105 (43)	58 (43)
Median (IQR)	30 (12–82)	29 (15–92)	24 (11–49)
(min–max)	(1–492)	(1–644)	(2–223)
Serious			
Data available	205 (100)	237 (97)	128 (94)
	187 (91)	235 (99)	128 (100)
Death			
Data available	187 (91)	234 (96)	128 (94)
	8 (4.3)	34 (15)	50 (39)
Initial ICI management			
Data available	132 (64)	125 (51)	48 (35)
Dose Increased	0 (0)	0 (0)	0 (0)
Dose not changed	26 (20)	4 (3.2)	2 (4.2)
Drug withdrawn	106 (80)	121 (97)	46 (96)
Rechallenge outcome			
Data available (rechallenge conducted and documented)	69 (34)	75 (31)	23 (17)
Reaction recurred	0 (0)	1 (1.3)	0 (0)
No recurrence	3 (4.3)	3 (4.0)	0 (0)
Unknown	66 (96)	71 (95)	23 (100)
Monotherapy PD-1/PD-L1			
Pembrolizumab	53 (26)	87 (36)	54 (40)
Nivolumab	79 (39)	90 (37)	38 (28)
Atezolizumab	14 (6.8)	5 (2.0)	3 (2.2)
Cemiplimab	0 (0)	1 (0.4)	1 (0.7)
Avelumab	0 (0)	0 (0)	0 (0)
Durvalumab	3 (1.5)	6 (2.4)	1 (0.7)
Monotherapy CTLA-4			
Ipilimumab	8 (3.9)	11 (4.5)	9 (6.6)
Combination therapy			
Ipilimumab + nivolumab	46 (22)	42 (17)	30 (22)
Nivolumab + pembrolizumab	2 (1.0)	0 (0)	0 (0)
Avelumab + pembrolizumab	0 (0)	0 (0)	0 (0)
Ipilimumab + pembrolizumab	0 (0)	0 (0)	0 (0)
Ipilimumab + nivolumab + pembrolizumab	0 (0)	3 (1.2)	0 (0)
Ipilimumab dosage			
Data available	26 (48)	17 (30)	8 (21)
1–3 mg/kg	20 (77)	10 (59)	6 (75)
5–10 mg/kg	0 (0)	0 (0)	0 (0)
10 mg/kg	0 (0)	0 (0)	0 (0)
<500 mg	5 (19)	7 (41)	1 (12)
≥500 mg	1 (3.8)	0 (0)	1 (12)
Nivolumab dosage			
Data available	72 (57)	65 (48)	28 (41)
1–2 mg/kg	11 (15)	6 (9.2)	6 (21)
>2 mg/kg	24 (33)	19 (29)	16 (57)
<240 mg	33 (46)	33 (51)	4 (14)
≥240 mg	4 (5.6)	7 (11)	2 (7.1)
Pembrolizumab dosage			
Data available	41 (75)	56 (62)	31 (57)

Table 3. Continued

Characteristic	Erythema Multiforme, n (%) (N = 205)	Stevens–Johnson Syndrome, n (%) (N = 245)	Toxic Epidermal Necrolysis, n (%) (N = 136)
2 mg/kg	1 (2.4)	1 (1.8)	2 (6.5)
>2 mg/kg	0 (0)	1 (1.8)	0 (0)
<200 mg	40 (98)	54 (96)	27 (87)
≥200 mg	0 (0)	0 (0)	2 (6.5)
Suspected drug(s)			
ICIs only	136 (66)	189 (77)	99 (73)
ICI + one other drug	35 (17)	23 (9.4)	17 (13)
ICI + >1 drug	34 (17)	33 (13.5)	34 (17)

Abbreviations: cirAE, cutaneous immune-related adverse event; GI, gastrointestinal; H&N, head and neck; ICI, immune checkpoint inhibitor; IQR, interquartile range; max, maximum; min, minimum.
The denominator is with all available data unless otherwise noted.

myocarditis, and ICI-related neuropathy have also been associated with irAEs in multiple organ systems (Dubey et al., 2019; Mahmood et al., 2018; Naidoo et al., 2017). Future analyses could focus on clarifying further the patterns of potential multisystem irAEs that are discernible through analyzing large databases such as VigiBase and whether this implies a need for specialized screening tests for potentially co-occurring irAEs in patients with cirAEs such as vitiligo, drug eruption, or eczematous dermatitis (Shankar et al., 2020).

In general, the suspected ICI was withdrawn in over 50% of cases for each of the eight cirAEs. However, multiple factors may cause treatment discontinuation. For example, in the context of multisystem irAEs, co-occurring noncutaneous toxicities could have contributed to the over 50% ICI discontinuation rate among patients experiencing cirAEs. Furthermore, only a subset of patients responds to ICI therapy (Haslam and Prasad, 2019), and the decision to discontinue treatment could have been due to a combination of cirAE morbidity and disease progression. VigiBase is not able to discern these nuanced reasons for treatment discontinuation. However, the high ICI discontinuation rate in the setting of cirAEs still suggests that the appearance of cirAEs warrants monitoring by oncologists, with early referral to dermatology to prevent significant morbidity and potential treatment cessation due to these events. Future studies should aim to elucidate the optimal management strategies to avoid treatment cessation if possible and to maximize the QOL of patients with these cirAEs in a multidisciplinary context.

In addition to cirAE morbidity, mortality from cirAEs such as SJS and TEN are also of particular concern. Mortality due to SJS, SJS/TEN, and TEN have been reported to be 4.8, 19.4, and 14.8%, respectively (Hsu et al., 2016). However, in this study, the mortality of ICI-related SJS and TEN was notably higher at 15 and 39%, respectively. This finding justifies a lower threshold for dermatology referral among ICI patients to prevent significant mortality as well as future investigation into the cause of this increased mortality associated with ICIs.

Vitiligo was reported more commonly among those with melanoma (76% of vitiligo cases) than among those with other cancers. Reports of vitiligo among patients with melanoma have been cited in the literature (Balabanov et al., 1969) and are due to the activity of cytotoxic T cells to recognize antigens on both melanoma cells and normal melanocytes (Failla et al., 2019). Of interest, although vitiligo is one of the first irAEs to show a correlation with antitumor response in ICI therapy (Hua et al., 2016; Teulings et al., 2015), multiple varied cirAEs have been associated with increased survival in anti–PD-1 and anti–PD-L1 therapy (Tang et al., 2022). Future studies could focus on investigating the prognostic information for cirAEs arising from immunotherapy and their use in clinical decision making.

Our analysis revealed that cirAEs are more commonly reported among patients receiving PD-1 and PD-L1 inhibitors than among those receiving anti–CTLA-4 monotherapy, which corroborates previous studies (Wongvibulsin et al., 2022). The exact mechanism for cirAE appearance is still not clearly understood, especially among different organ systems and cutaneous morphologies. However, it has been hypothesized that adverse event incident differences between the two classes of drugs could be due to differences in T-cell proliferation, regulatory T-cell immunosuppression, or activation of T-cell clones (Buchbinder and Desai, 2016).

cirAEs were reported more commonly among patients receiving combination therapy than among those receiving monotherapy, which is concordant with other reports in the literature (Geisler et al., 2020). Combination therapy, in theory, produces a greater immune response than either anti–PD-1/PD-L1 or anti–CTLA-4 monotherapy alone through a stronger T-cell immune response and downplayed regulatory T-cell immunosuppression, but this mechanism has the potential to induce greater immune toxicity as well (Buchbinder and Desai, 2016).

Although cirAEs are the first types of irAEs to occur (Haanen et al., 2017), our findings show that morphology can dictate the time to onset, ranging from days to years as seen in Tables 2 and 3 and Figure 1. Presumably, these differences in onset times are due to differing underlying mechanisms, which still require further investigation. Our findings reinforce those of other studies showing that severe cutaneous adverse reactions (EM, SJS, and TEN) appear within 1 month (Maloney et al., 2020; Zhao et al., 2018), lichenoid dermatitis appears within 6–12 weeks (Geisler et al., 2020), and vitiligo and bullous pemphigoid appear 5–6 months (Babai et al., 2020; Siegel et al., 2018; Tsiogka et al., 2021) after ICI initiation. It is important to note that although we report the differences in time to onset of cirAEs, the distribution of these times can still vary greatly even within a given cirAE.

Although there are reports of maculopapular rash and psoriasiform dermatitis as prevalent cirAEs (Geisler et al., 2020), our study did not detect a significant signal of any of these reactions as unique to ICI therapy. Maculopapular rashes are common drug reactions that have a high likelihood of a false negative signal because the IC calculation compares the ICI–cirAE signal with those of all other drugs within VigiBase. Psoriasiform dermatitis had a borderline IC (−0.04) and may convert to a significant signal in the future, as seen with other cirAEs within this study in Supplementary Figure S1.

Rechallenge after irAE development is associated with lower safety but with efficacy similar to that of initial ICI

Table 4. Concurrent irAEs among Selected Cutaneous irAEs in VigiBase

Concurrent irAEs	Vitiligo, n (%) (N = 508)	Bullous Pemphigoid, n (%) (N = 372)	Lichenoid Dermatitis, n (%) (N = 234)	Drug Eruption, n (%) (N = 163)	Eczematous Dermatitis, n (%) (N = 164)
Only adverse event reported	168 (34)	180 (48%)	80 (34)	28 (17)	20 (12%)
GI					
GI hemorrhage	3 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.6)
Pancreatitis	12 (2.4)[1]	0 (0)	1 (0.4)	0 (0)	0 (0)
Hepatitis	37 (7.3)[2]	3 (0.8)	10 (4.3)[1]	15 (9.2)[2]	8 (4.9)[1]
Colitis	56 (11)[2]	8 (2.2)[1]	4 (1.7)	6 (3.7)[1]	13 (7.9)[2]
Endocrine/metabolic					
Hypophysitis	26 (5.1)[2]	1 (0.3)	1 (0.4)	1 (0.6)	11 (6.7)
Electrolyte disorders	5 (1.0)	2 (0.5)	5 (2.1)[1]	5 (3.1)	7 (4.3)[1]
Thyroid disorders	57 (11)[2]	9 (2.4)[1]	13 (5.6)[2]	5 (3.1)[1]	17 (10)[2]
Adrenal insufficiency	6 (1.2)	2 (0.5)	1 (0.4)	5 (3.1)[1]	6 (3.7)[1]
Type 1 diabetes mellitus	15 (3.0)[1]	4 (1.1)	0 (0)	1 (0.6)	2 (1.2)
Pulmonary					
Pneumonitis	13 (2.6)[1]	1 (0.3)	7 (3.0)[1]	5 (3.1)[1]	5 (3.0)[1]
Pleural effusion	0 (0)	0 (0)	1 (0.4)	2 (1.2)	1 (0.6)
Airway disease	4 (0.8)	1 (0.3)	2 (0.9)	1 (0.6)	2 (1.2)
Pulmonary embolism	2 (0.4)	1 (0.3)	1 (0.4)	3 (1.8)	1 (0.6)
Parenchymal disease	5 (1.0)	0 (0)	1 (0.4)	6 (3.7)[2]	3 (1.8)
Circulatory					
Arrhythmia	4 (0.8)	1 (0.3)	0 (0)	1 (0.6)	1 (0.6)
Myocardial infarction	2 (0.4)	0 (0)	2 (0.9)	0 (0)	1 (0.6)
Heart failure	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Myocarditis	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
Vasculitis	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.6)
Renal					
Nephropathy	2 (0.4)	0 (0)	0 (0)	2 (1.2)	4 (2.4)[1]
AKI	2 (0.4)	3 (0.8)	5 (2.1)[1]	6 (3.7)[1]	0 (0)
Hematology					
Leukopenia	2 (0.4)	0 (0)	0 (0)	2 (1.2)	2 (1.2)
Thrombocytopenia	3 (0.6)	1 (0.3)	0 (0)	0 (0)	3 (1.8)
Eosinophilia	1 (0.2)	5 (1.3)	3 (1.3)	3 (1.8)	2 (1.2)
DIC	2 (0.4)	0 (0)	0 (0)	1 (0.6)	0 (0)
Neurologic					
Myasthenia gravis and myasthenic syndromes	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)
Guillain–Barre syndrome	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.2)
Encephalitis/meningitis	1 (0.2)	0 (0)	0 (0)	1 (0.6)	0 (0)
Stroke	1 (0.2)	0 (0)	1 (0.4)	0 (0)	0 (0)
Peripheral neuropathy	7 (1.4)	1 (0.3)	0 (0)	0 (0)	3 (1.8)
Rheumatologic					
Myositis/dermatomyositis	4 (0.8)	0 (0)	1 (0.4)	1 (0.6)	2 (1.2)
Joint inflammation	13 (2.6)[2]	0 (0)	1 (0.4)	4 (2.5)[1]	0 (0)
Ophthalmologic					
Uveitis	7 (1.4)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Vision disorders	7 (1.4)	0 (0)	1 (0.4)	2 (1.2)	4 (2.4)[1]
Dermatologic					
Vitiligo	—	6 (1.6)	7 (3.0)[1]	2 (1.2)	2 (1.2)
Bullous pemphigoid	6 (1.2)	—	3 (1.3)	2 (1.2)	1 (0.6)
Lichenoid dermatitis	7 (1.4)	3 (0.8)	—	4 (2.5)[2]	2 (1.2)
Drug eruption	2 (0.4)	2 (0.5)	4 (1.7)	—	2 (1.2)
Eczematous dermatitis	4 (0.8)	1 (0.3)	2 (0.9)	2 (1.2)	—
Erythema multiforme	0 (0)	2 (0.5)	0 (0)	0 (0)	0 (0)

(*continued*)

Table 4. Continued

Concurrent irAEs	Vitiligo, n (%) (N = 508)	Bullous Pemphigoid, n (%) (N = 372)	Lichenoid Dermatitis, n (%) (N = 234)	Drug Eruption, n (%) (N = 163)	Eczematous Dermatitis, n (%) (N = 164)
Stevens–Johnson Syndrome	3 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.6)
Toxic epidermal necrolysis	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
Pruritus	42 (8.3)[2]	11 (3.0)[1]	9 (3.8)[1]	3 (1.8)	41 (25)[2]

Abbreviations: AKI, acute kidney infection; DIC, disseminated intravascular coagulation; GI, gastrointestinal; irAE, immune-related adverse event.
The denominator is with all available data.
[1]Prevalence of irAE >2%
[2]Prevalence of irAE >5%

treatment (Allouchery et al., 2020; Zhao et al., 2021). Rechallenge of ICIs after a cirAE is of clinical interest; however, there is a lack of current literature regarding outcomes and safety of rechallenge after the development of cirAEs. A previous VigiBase study found that colitis, hepatitis, and pneumonitis were associated with a higher recurrence rate after rechallenge than other irAEs (Dolladille et al., 2020). The lack of association for cirAEs in that study was most likely due to the relatively limited number of outcomes documented for rechallenges associated with cutaneous cirAEs, which we also noted in our analysis (~90% of rechallenges had no outcome documented). In the future, this rechallenge data may be more available within VigiBase as more cutaneous toxicities related to ICIs are documented. Future studies may seek to understand the best practices for rechallenging ICIs after cirAE development, which may include prophylaxing against cirAEs and adjusting ICI regimens owing to concurrent immunosuppressive treatment (Haanen et al., 2020).

Limitations

Our study did have several limitations. Clinical information such as physical examination, laboratory values, and imaging and healthcare outcomes such as progression-free survival and mortality are not available. Pharmacovigilance databases are subject to over- and under-reporting, competition bias, incomplete reporting, heterogeneous data, misleading disproportionality comparisons, quality management, and erroneous data (Lindquist, 2004; Salem et al., 2018). This may explain the discrepancies between our studies and others in the literature. For example, one United States–based controlled study found no increased incidence rate between ICI and non-ICI patients for the cirAEs identified in this study, such as EM, SJS, TEN, and eczematous dermatitis (Wongvibulsin et al., 2022). Despite these limitations, the Bayesian confidence propagation neural network model behind the IC was designed to handle these various sources of noise to identify positive signals for further investigation.

Furthermore, IC values cannot determine the causation of cirAE by drug(s), only the quantitative dependency. Because of this, one cannot deduce incidence rates from pharmacovigilance studies directly. Current data reports incidence rates for the following conditions: maculopapular rash (49–68% for anti–CTLA-4, 20% for anti–PD-1/anti–PD-L1), pruritus (≤21% for anti–PD-1/anti–PD-L1), vitiligo (11% for anti–CTL-4, 25% for anti–PD-1), and alopecia (1–2%) (Geisler et al., 2020). Data have also been presented in patients with advanced melanoma with the following conditions: rash (14.5–26% for anti–CTL-4, 13–21.5% for anti–PD-1, 58.5–71.5% for combination), pruritus (24.5–35.5% for anti–CTL-4, 14–21% for anti–PD-1, 33–47% for the combination), and vitiligo (1.5–8.5% for anti–CTL-4, 7.5–11% for anti–PD-1, 6.5–11% for the combination) (Sibaud, 2018).

Although drug eruption was defined at the preferred term level, it is a relatively ambiguous description. Further evaluation of the lowest-level terms below this preferred term description shows multiple descriptors such as drug rash, drug eruption, exanthematic drug eruption, papuloerythematous drug eruption, and dermatitis medicamentosa—making it unclear whether these lowest level terms represent a morphology such as morbilliform eruption or other drug eruption that did not have a clear clinical morphology and was documented more generally. Diagnostic uncertainty also exists for dermatologic morphologies such as SJS, TEN, EM, and bullous pemphigoid, morphologies difficult to distinguish clinically. For SJS (affecting <10% body surface area) and TEN (affecting >30% body surface area), there is no overlap syndrome for body surface area affecting 10–30% body surface area. There also has been a unique bullous eruptive cirAE mimicking SJS and TEN, however with rapid response to immunosuppression and lower mortality (Molina et al., 2020). Because VigiBase does not have the clinical nuance to identify this morphology, this was unable to be studied. The diagnostic uncertainty surrounding these morphologies is not unique to our study—in pharmacologic and clinical trial adverse event reporting, these morphologies are typically grouped together as a high-grade rash (Cohen et al., 2019; Larkin et al., 2018). In light of these challenges, we urge ICI and oncologic stakeholders to commit to routinely reporting toxicities in a standardized fashion and accurately documenting dermatologic morphologies to improve the quality and accuracy of pharmacovigilance studies in the future.

There are several results of our analysis that corroborate other smaller, detailed datasets. These features include the top cancers being melanoma, lung carcinoma, and renal cell carcinoma, the three most common diseases for which ICIs are approved; consistent timing with other studies; and cirAEs identified that are consistent with other studies. Yet, this study moves understanding beyond previous research by examining cirAEs in a multisystem context and by examining cirAEs on a global scale through VigiBase's over 130 reporting

Table 5. Concurrent irAEs among Severe Cutaneous irAEs in VigiBase

Concurrent irAEs	Erythema Multiforme, n (%) (N = 205)	Stevens–Johnson Syndrome, n (%) (N = 245)	Toxic Epidermal Necrolysis, n (%) (N = 136)
Only adverse event reported	56 (27)	81 (33)	32 (24)
GI			
GI hemorrhage	1 (0.5)	1 (0.4)	0 (0)
Pancreatitis	0 (0)	6 (2.4)[1]	0 (0)
Hepatitis	8 (3.9)[1]	18 (7.3)[2]	12 (8.8)[2]
Colitis	8 (3.9)[1]	5 (2.0)[1]	5 (3.7)[1]
Endocrine/metabolic			
Hypophysitis	6 (2.9)[1]	1 (0.4)	4 (2.9)[1]
Electrolyte disorders	2 (1.0)	3 (1.2)	3 (2.2)[1]
Thyroid disorders	5 (2.4)[1]	11 (4.5)[1]	1 (0.7)
Adrenal insufficiency	5 (2.4)[1]	1 (0.4)	2 (1.5)
Type 1 diabetes mellitus	2 (1.0)	1 (0.4)	1 (0.7)
Pulmonary			
Pneumonitis	0 (0)	9 (3.7)	5 (3.7)
Pleural effusion	0 (0)	1 (0.4)	0 (0)
Airway disease	3 (1.5)	5 (2.0)	3 (2.2)[1]
Pulmonary embolism	0 (0)	1 (0.4)	5 (3.7)[1]
Parenchymal disease	13 (6.3)[2]	5 (2.0)[1]	2 (1.5)
Circulatory			
Arrhythmia	1 (0.5)	5 (2.0)	0 (0)
Myocardial infarction	1 (0.5)	0 (0)	1 (0.7)
Heart failure	0 (0)	1 (0.4)	0 (0)
Myocarditis	1 (0.5)	2 (0.8)	0 (0)
Vasculitis	0 (0)	2 (0.8)	0 (0)
Renal			
Nephropathy	0 (0)	0 (0)	2 (1.5)
AKI	3 (1.5)	11 (4.5)	2 (1.5)
Hematology			
leukopenia	0 (0)	0 (0)	0 (0)
thrombocytopenia	0 (0)	2 (0.8)	1 (0.7)
eosinophilia	0 (0)	0 (0)	0 (0)
DIC	2 (1.0)	4 (1.6)	2 (1.5)
Neurologic			
Myasthenia gravis and myasthenic syndromes	1 (0.5)	0 (0)	0 (0)
Guillain-Barre syndrome	2 (1.0)	0 (0)	0 (0)
Encephalitis/ meningitis	0 (0)	0 (0)	0 (0)
Stroke	0 (0)	2 (0.8)	2 (1.5)
Peripheral neuropathy	0 (0)	0 (0)	2 (1.5)
Rheumatologic			
Myositis/ dermatomyositis	0 (0)	2 (0.8)	0 (0)
Joint inflammation	0 (0)	3 (1.2)	0 (0)
Ophthalmologic			
Uveitis	1 (0.5)	0 (0)	0 (0)
Vision disorders	0 (0)	3 (1.2)	1 (0.7)
Dermatologic			
Vitiligo	0 (0)	3 (1.2)	0 (0)
Bullous pemphigoid	2 (1.0)	0 (0)	0 (0)
Lichenoid dermatitis	0 (0)	0 (0)	0 (0)
Drug eruption	0 (0)	0 (0)	1 (0.7)
Eczematous dermatitis	0 (0)	1 (0.4)	0 (0)
Erythema multiforme	—	3 (1.2)	2 (1.5)
Stevens-Johnson Syndrome	3 (1.5)	—	16 (12)
Toxic epidermal necrolysis	2 (1.0)	16 (6.5)[2]	—
Pruritus	1 (0.5)	4 (1.6)	1 (0.7)

Abbreviations: AKI, acute kidney infection; DIC, disseminated intravascular coagulation; GI, gastrointestinal; irAE, immune-related adverse event.

The denominator is with all available data.

[1]Prevalence of irAE >2%

[2]Prevalence of irAE >5%

countries (Uppsala Monitoring Centre). Furthermore, by including the largest collection of cirAEs to date, this study allows for signal detection and comparison of rarer cirAEs that may have only been detected through case reports or case series. A detailed look at different cirAE types is necessary owing to the wide diversity of cirAEs, as shown in this study. Studies such as this observational pharmacovigilance study represent a model to detect the global trends that can be delineated further through prospective analyses, especially as it applies to cirAEs.

METHODS AND MATERIALS

Data sources and classification

This is an observational, cross-sectional study using data from VigiBase, the World Health Organization database of global, deidentified ICSRs depicting adverse drug reactions (ADRs) due to pharmaceutical causes (VigiBase). VigiBase receives reports from a variety of sources from its monitoring centers in >130 countries. The largest database of its kind in the world, VigiBase is managed by the Uppsala Monitoring Center in Sweden, and since its inception in 1967, it has received approximately 19 million ICSRs. These ICSRs are generated from a variety of sources, including healthcare professionals, patients, pharmaceutical companies, and clinical trials. One ICSR represents one patient who has developed one or more irAEs after ICI administration.

The classifications used within VigiBase are derived from MedDRA (Medical Dictionary for Regulatory Activities, version 23.0), which organizes terms into a five-level hierarchy: system organ class, high-level group term, high-level term, preferred term, and the most granular lowest level terms. In general, we focused on cirAE classifications at the preferred term level (Supplementary Table S3) and focused on the appearance of these reported cirAEs suspected to be associated with the seven current United States Food and Drug Administration–approved ICIs. These include the ICIs that block CTLA-4 (anti–CTLA-4; ipilimumab), PD-1 (anti–PD-1; nivolumab, pembrolizumab, cemiplimab), and PD-L1 (anti–PD-L1; atezolizumab, avelumab, durvalumab) pathways. Because the first reports from ICIs only appeared in VigiBase after 2008, we focused our

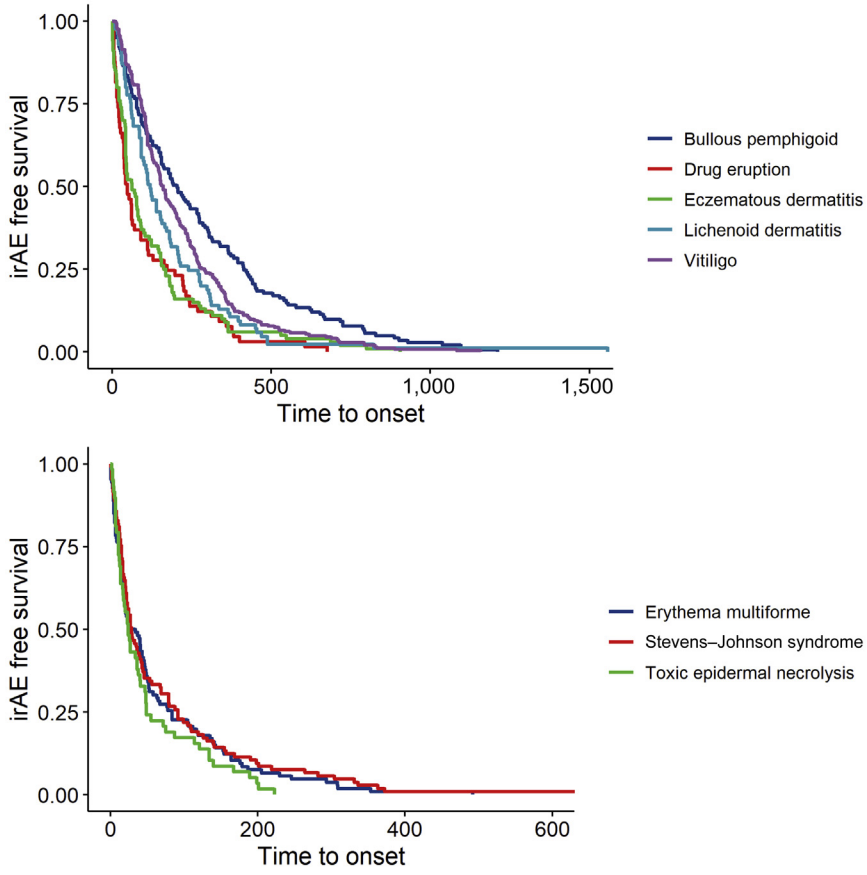

Figure 1. Time to onset versus irAE-free survival in percentage for cirAEs bullous pemphigoid, drug eruption, eczematous dermatitis, lichenoid dermatitis, and vitiligo as well as for severe cutaneous adverse reactions erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. cirAE, cutaneous immune-related adverse event; irAE, immune-related adverse event.

analysis of ICSRs from January 1, 2008 to August 30, 2020. This study is registered with ClinicalTrials.gov, number NCT04898751.

Analytic procedure

Assessment of drug safety using pharmacovigilance databases requires specialized techniques to detect significant drug–ADR signals among baseline noise. The IC is a measure of the strength of the quantitative dependency using a Bayesian confidence propagation neural network model to find drug–ADR combinations that have been disproportionately reported by relating the likelihood of a drug–ADR signal against all the ICSRs of the ADR and the drug in question (Bate et al., 1998; Bihan et al., 2020). The IC utilizes information theory to handle various problems in large datasets such as incomplete data and complex variables and has been used to identify early drug adverse event signals, such as between captopril and cough. We used the IC to identify the cirAEs with a significant signal within VigiBase by identifying cirAEs with a positive (>0) value of IC_{025}, the lower end of the 95% credibility interval of the IC.

This study focused on terms within the system organ class skin and subcutaneous disorders, which were then further analyzed as disaggregated cirAEs. ICSRs were chosen if one of the seven ICIs was suspected of having caused an ADR. ADRs were excluded if they were not an immune-related phenomenon, for example, if they had a neoplastic or infectious etiology. We then chose to focus our analysis on cirAEs with at least n = 100 ICSRs associated with one of our seven ICIs of interest to further examine their characteristics. This resulted in eight remaining cirAEs—vitiligo, drug eruption, lichenoid dermatitis, eczematous dermatitis, bullous pemphigoid, EM, SJS, and TEN.

Disproportionality for these eight remaining cirAEs was further assessed through RORs, which have been previously described and validated for VigiBase (Bihan et al., 2020; Vogel et al., 2020). The threshold for significant signal detection was a ROR >1 at the lower end of the 95% CI. We assessed for the disproportionality of drug–ADR signal compared with that of the ADR in question within the full database. We also assessed for disproportionality as a variable of ICI regimen, that is, monotherapy with PD-1 or PD-L1 inhibitors versus monotherapy with CTLA-4 inhibitors and combination therapy (PD-1 or PD-L1 therapy with CTLA-4 inhibitor) versus monotherapy.

These eight cirAEs were analyzed using descriptive statistics, reporting variables such as demographic factors, the ICI drugs suspected, dosing, time to onset, outcome, indication, and concurrent irAEs within one ICSR. The outcomes of interest were whether the collection of irAEs associated with an ICI resulted in death or a severe outcome, defined as causing death, being life threatening, requiring hospitalization (initial or prolonged), leading to persistent or significant disability, or any other medically important chronic conditions.

Categorical variables were reported with frequency and percentage, with continuous variables reported with median, IQR, and range. Time to onset distributions was compared with a Kruskal–Wallis test with posthoc pairwise comparisons using Dunn's test. Disproportionality was assessed using chi-square tests, pairwise as appropriate. *P*-values were adjusted for multiple comparisons using the Benjamini–Hochberg procedure. Alpha level was set at $P = 0.05$.

All analysis was conducted using R, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Data availability statement

Requests for access to the VigiBase dataset can be made directly to the Uppsala Monitoring Center (Uppsala, Sweden).

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CONFLICT OF INTEREST

JN declares research funding from Merck, AstraZeneca, and Bristol Myers Squibb and is an advisory board member/consultant for Merck, AstraZeneca, Bristol Myers Squibb, Takeda, Pfizer, Kaleido Biosciences, and Daiichi Sankyo. SGK is an advisory board member/consultant for Abbvie, Celldex Therapeutics, Galderma, Incyte Corporation, Johnson & Johnson, Novartis Pharmaceuticals, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Kiniksa Pharmaceuticals and has served as an investigator for Galderma, Kiniksa Pharmaceuticals, Pfizer, and Sanofi. The remaining authors state no conflict of interest.

ACKNOWLEDGMENTS

The information within VigiBase, the World Health Organization's global database of individual case safety reports, comes from a variety of sources, and the probability that the suspected adverse effect is drug related is not the same in all cases. The authors would like to thank Uppsala Monitoring Center Custom Searches for their help in conducting this study. SGK is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award number K23AR077073-01A1. LCC received support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award number K23AR075872. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. TKL, SGK, and YRS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This study was conducted in Baltimore, MD.

AUTHOR CONTRIBUTIONS

Conceptualization: TKL, JN, YRS, SGK; Data Curation: TKL, YRS, SGK; Formal Analysis: TKL, YRS, SGK; Funding Acquisition: SGK; Investigation: TKL, YRS, SGK; Methodology: TKL, JN, YRS, SGK; Project Administration: YRS, SGK; Resources: TKL, YRS, SGK; Software: TKL, YRS, SGK; Supervision: YRS, SGK; Visualization: TKL, KLR, SGK; Writing — Original Draft Preparation: TKL, RG, MTT, YRS, SGK; Writing — Review and Editing: TKL, IB, RG, MTT, JD, VP, ZAB, MPA, MMK, VN, AG, JA, NL, KR, LCC, JN, JB, SK, YRS, SGK

Disclaimer

The findings of this article do not represent the opinion of the Uppsala Monitoring Center or the World Health Organization. The funding to LCC had no involvement in the design or interpretation of this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.04.020

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Supplementary Table S1. Reported ORs Comparing PD-1/PD-L1 Monotherapy with CTLA-4 Monotherapy, Combination Therapy with Monotherapy, and ICI Treatment with Full Database (Since 2008)

	ICI Total (N = 91,322)									
	Mono (N = 81,571)[1]									
	Mono PD1/PDL1 (N = 71,057)	Mono CTLA-4 (N = 10,514)	Combo[2] (N = 9,751)	Total AE in Database Since 2008 (N = 18,919,358)	Mono PD-1 Versus Mono CTLA-4	95% CI[3]	Combo Versus Mono	95% CI[3]	Any ICI Versus Full Database	95% CI[3]
Erythema multiforme, n (%)	151 (0.21)	8 (0.08)	46 (0.47)	15,761 (0.08)	2.80	(1.37–5.70)	2.43	(1.75–3.37)	2.72	(2.37–3.12)
Stevens–Johnson syndrome, n (%)	189 (0.27)	11 (0.10)	45 (0.46)	30,125 (0.16)	2.55	(1.39–4.68)	1.89	(1.36–2.61)	1.69	(1.49–1.92)
Drug eruption, n (%)	115 (0.16)	6 (0.06)	42 (0.43%)	22,778 (0.12)	2.84	(1.25–6.45)	2.91	(2.05–4.15)	1.49	(1.27–1.73)
Toxic epidermal necrolysis, n (%)	97 (0.14)	9 (0.09)	30 (0.31)	10,939 (0.06)	1.60	(0.81–3.16)	2.37	(1.58–3.56)	2.60	(2.19–3.08)
Bullous pemphigoid, n (%)	319 (0.45)	5 (0.05)	48 (0.49)	4,022 (0.02)	9.48	(3.92–22.93)	1.24	(0.92–1.68)	21.09	(18.96–23.47)
Vitiligo, n (%)	339 (0.46)	41 (0.39)	128 (1.3)	2,974 (0.02)	1.22	(0.89–1.69)	2.84	(2.32–3.48)	42.70	(38.80–46.99)
Lichenoid dermatitis, n (%)	198 (0.28)	6 (0.06)	30 (0.31)	3,188 (0.02)	4.89	(2.17–11.03)	1.23	(0.84–1.81)	16.37	(14.33–18.70)
Eczematous dermatitis, n (%)	125 (0.18)	7 (0.07)	32 (0.33)	24,037 (0.13)	2.65	(1.24–5.66)	2.03	(1.38–2.99)	1.42	(1.26–1.65)

Abbreviations: AE, adverse event; CI, confidence interval; Combo, combotherapy; ICI, immune checkpoint inhibitor; mono, monotherapy;

[1]Mono was defined as an individual case safety report being associated with only one class of treatment, either PD-1 (pembrolizumab, nivolumab, cemiplimab) and PD-L1 (atezolizumab, avelumab, durvalumab) or CTLA-4 (ipilimumab).

[2]Comb was defined as an individual case safety report being associated with the combination of PD-1 or PD-L1 treatment and CTLA-4 treatment

[3]Significance assessed at alpha = 0.05 after adjustment for 24 comparisons using the Benjamini–Hochberg procedure

Supplementary Table S2. Posthoc Dunn's Test Comparing Time to Onset between Drug Eruption, Eczematous Dermatitis, Erythema Multiforme, Lichenoid Dermatitis, Bullous Pemphigoid, Stevens–Johnson Syndrome, and Toxic Epidermal Necrolysis

	Drug Eruption	Eczematous Dermatitis	Erythema Multiforme	Lichenoid Dermatitis	Bullous Pemphigoid	Stevens–Johnson syndrome	Toxic Epidermal Necrolysis
Eczematous dermatitis	0.3153						
Erythema multiforme	0.0146	0.0012					
Lichenoid dermatitis	<0.001	0.0013	<0.001				
Bullous pemphigoid	<0.001	<0.001	<0.001	0.0206			
Stevens–Johnson syndrome	0.0286	0.0034	0.3648	<0.001	<0.001		
Toxic epidermal necrolysis	0.005	<0.001	0.248	<0.001	<0.001	0.1695	
Vitiligo	<0.001	<0.001	<0.001	0.0455	0.2677	<0.001	<0.001

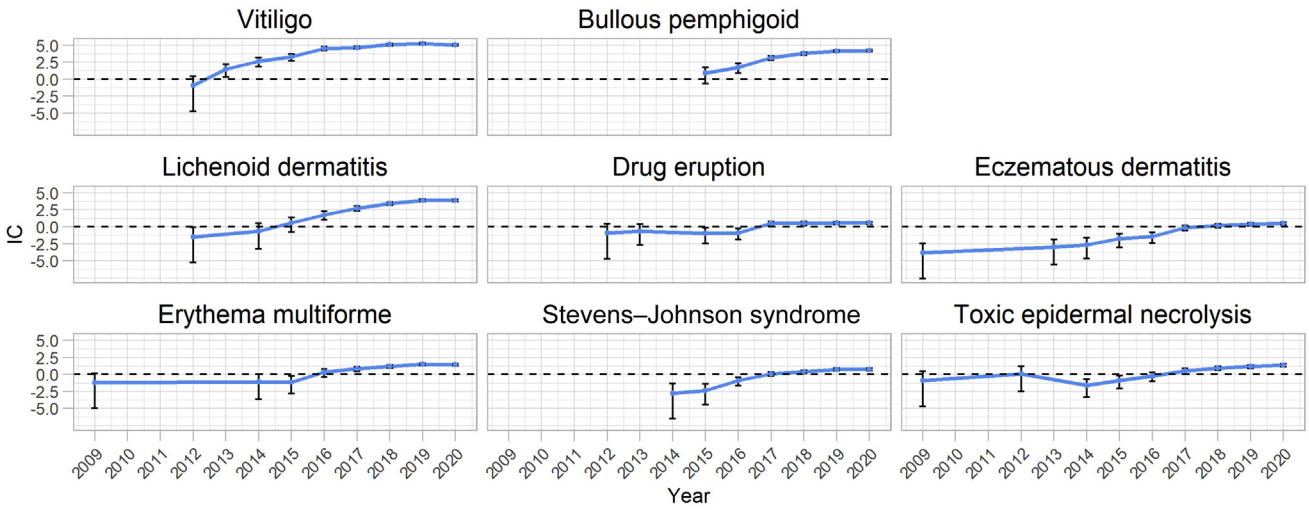
P-values were adjusted using the Benjamini–Hochberg procedure; alpha = 0.05.
Kruskal–Wallis $P < 0.001$.

Supplementary Table S3. Classifications Used for Cutaneous Immune-Related Adverse Events within the MedDRA

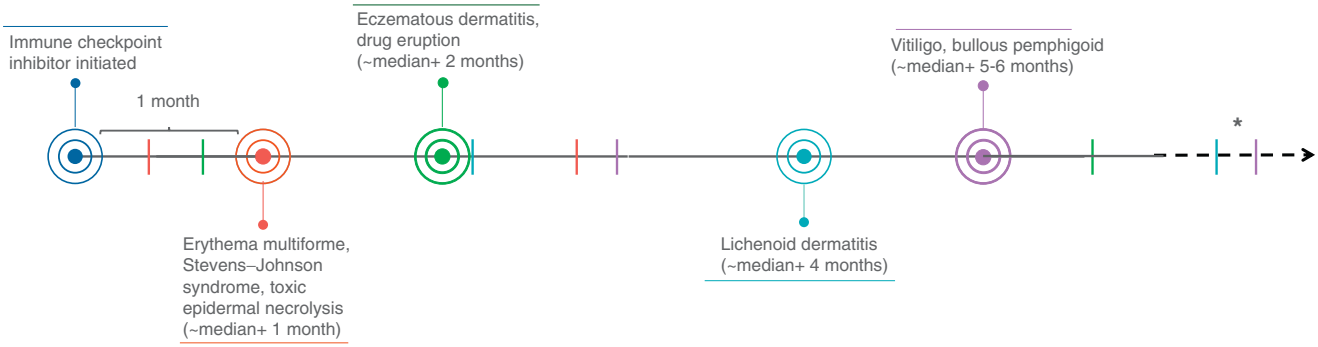
Cutaneous Immune-Related Adverse Event[1]	Term(s) Queried in VigiBase Using MedDRA Classifications
Vitiligo	Vitiligo (PT), skin depigmentation (PT)
Bullous pemphigoid	Pemphigoid (PT)
Lichenoid dermatitis	Lichenoid keratosis (PT), lichen planus (PT)
Cutaneous sarcoidosis	
Dermatomyositis	
Oral lichen planus	Oral lichenoid reaction (PT), oral lichen planus (PT)
Granulomatous dermatitis	
Transient acantholytic dermatosis	
Lichen sclerosus	
Prurigo/lichen simplex chronicus	Neurodermatitis (PT), lichen simplex chronicus (PT), prurigo (PT)
Scleroderma	Scleroderma (PT), morphea (PT), systemic scleroderma (PT), scleroderma-like reaction (PT)
Panniculitis	Panniculitides (HLT)
Subacute cutaneous lupus erythematosus	
Perivascular dermatitis	
Erythema multiforme	
Myxedema	Myxoedema (PT)
Toxic epidermal necrolysis	
Pityriasis rubra pilaris	
Prurigo/lichen simplex chronicus	
Eosinophilic cellulitis	
Skin hypopigmentation	
Seborrheic dermatitis	Seborrhoeic dermatosis (PT)
Stevens–Johnson syndrome	
Pemphigus vulgaris	Pemphigus (PT)
Parapsoriasis	
Drug eruption	
Eczematous dermatitis	Eczema (PT)
Skin depigmentation	
Acute febrile neutrophilic dermatosis	
Psoriasiform dermatitis	Dermatitis psoriasiform (PT), guttate psoriasis (PT), psoriasis (PT), erythrodermic psoriasis (PT), pustular psoriasis (PT)
Palmar–plantar erythrodysesthesia syndrome	
Xeroderma	Xeroderma (PT), dry skin (PT)
Anhidrosis/hyperhidrosis	
Rash NOS	Rash macular (PT), rash pruritic (PT), rash pustular (PT), rash follicular (PT), rash (PT), dermatitis (PT), rash morbilliform (PT), rash vesicular (PT), rash papular (PT), perineal rash (PT), vasculitic rash (PT), eyelid rash (PT), rash papulosquamous (PT), nodular rash (PT), rash scarlatiniform (PT), genital rash (PT), butterfly rash (PT), rash erythematous (PT), mucocutaneous rash (PT), infusion site rash (PT), catheter site rash (PT)
Rash maculopapular	
Nail disorders	Nail and nailbed conditions (excluding infections and infestations) (HLT)
Pruritus	Pruritus (PT), pruritus allergic (PT), eyelids pruritus (PT), pruritus genital (PT)
Exfoliative rash	Dermatitis exfoliative (PT), skin exfoliation (PT), exfoliative rash (PT), dermatitis exfoliative generalized (PT)
Hair color/texture change	Hair texture abnormal (PT), trichorrhexis (PT), hypertrichosis (PT), hirsutism (PT), hair color changes (PT), achromotrichia acquired (PT), hair growth abnormal (PT)
Rosacea	Rosacea (HLT)
Cutaneous lupus erythematosus (excluding subacute cutaneous lupus erythematosus)	Lupus-like syndrome (PT), cutaneous lupus erythematosus (PT)
Hyperpigmentation	Hyperpigmentation disorders (HLT)
Systemic lupus erythematosus	
DRESS syndrome	
Alopecia	Alopecias (HLT)
Dermatitis acneiform	Dermatitis acneiform (PT), acne (PT), acne pustular (PT)
Angioedema	Angioedemas (HLT)
Dysaesthesia	Dysaesthesia (PT), skin burning sensation (PT), the pain of skin (PT)
Urticaria	Urticaria (PT), urticarial vasculitis (PT), urticaria papular (PT)
Fixed eruption	

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

[1]No terms listed indicate that the exact classification was used as a PT term.



Supplementary Figure S1. IC values and IC_{025} and IC_{095} credibility intervals (error bar) from 2008 to 2020 for vitiligo, bullous pemphigoid, lichenoid dermatitis, drug eruption, eczematous dermatitis, erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. The lower end of the credibility interval >0 ($IC_{025} > 0$) is considered significant. IC, information component.



Supplementary Figure S2. Timeline showing four distinct groups of time to onset, dependent on dermatologic type. The bars show the lower and upper quartiles for the four groups. Asterisk (*) indicates quartile ranges at approximately 8 months for lichenoid dermatitis and 11 months for vitiligo and bullous pemphigoid.