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Clinical spectrum and evolution of immune-checkpoint inhibitors toxicities over a decade—a worldwide perspective

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Summary

Background Immune-checkpoint inhibitors (ICI) have revolutionized cancer treatment by harnessing the immune system but ICI can induce life-threatening immune-related adverse events (irAE) affecting every organ.

Methods We extracted irAE from VigiBase, the international pharmacovigilance database, first reported in 2008 until 01/2023 to characterize irAE reporting trends, clinical features, risk factors and outcomes.

Findings We distinguished 25 types of irAE (n = 50,347cases, single irAE/case in 84.9%). Cases mainly involved anti-PD1 (programmed-death-1) monotherapy (62.4%) in male (61.7%) aged 64.3 ± 12.6 years. After 2020 vs. prior to 2016, proportion of anti-CTLA4 (Cytotoxic-T-Lymphocyte-Antigen-4) monotherapy prescription almost vanished (1.6% vs. 47%, respectively) contrasting with increased use of anti-PDL1 (PD1-ligand) monotherapy (18% vs. 0.9%) and anti-CTLA4+anti-PD(L)1 combination (20% vs. 8.9%). Anti-LAG3 (Lymphocyte-Activation-Gene-3) prescription was limited (<1%) in the studied timeframe. After 2020, over 14 different cancer types were treated vs. almost exclusively melanoma and lung cancers before 2016. Overall, the most reported irAE were skin reactions (22.9%), pneumonitis (18.5%), enterocolitis (14.4%) and thyroiditis (12.1%). ICI-myotoxicities (6.6%) included myositis, myocarditis and myasthenia-gravis like syndrome and were the most overlapping irAE (up to 30% overlap, vs. <3% in general for other inter-irAE overlap). The top factors associated with specific irAE (odds-ratio>5) were presence of thymic cancer for ICI-myotoxicities or hepatitis; presence of melanoma for vitiligo, uveitis or sarcoidosis; specific types of ICI regimen (anti-LAG3 for meningitis, anti-CTLA4 for hypophysitis); and specific reporting regions (eastern Asia for cholangitis). Median time-to-onset ranged from 31 to 273 days, being shortest for myotoxicities and most delayed for skin-bullous auto-immune reactions. Overall fatality was highest for myocarditis = 27.6%, myasthenia = 23.1%, severe cutaneous adverse reactions (SCAR) = 22.1%, myositis = 21.9%, pneumonitis = 21%, and encephalomyelitis = 18%; generally decreasing after 2020, except for myasthenia and SCAR. When reported, irAE recurrence rate after rechallenge was 28.9% (n = 275/951).

Interpretation This up-to-date comprehensive worldwide pharmacovigilance study defines the spectrum, characteristics, and evolution of irAE reporting summarizing over a decade of use. Multiple risk factors and clinical peculiarities for specific irAE have been identified as signals to guide clinical practice and future research.

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Keywords: Immune checkpoint inhibitors; Immune-related adverse events; Cancer; Pharmacology; Pharmacovigilance; Myotoxicity; Fatal

Research in context

Evidence before this study

Immune-checkpoint inhibitors (ICI) have revolutionized cancer therapy, providing unprecedented responses in a wide range of malignancies but they can lead to immune-related adverse events (irAE). While their efficacy is well-documented, the drawback associated with their potential toxicity has been a concern for clinicians. Prior to this study, a growing body of literature have detailed individual case reports, case series and institutional experiences with irAE, and eventually using the international pharmacovigilance database, VigiBase. We conducted a search on PubMed using "immune-checkpoint inhibitors", and "VigiBase" from inception to January 1st 2023. Dozens of studies had reported on specific adverse events, but a comprehensive global study of overall irAE reporting over the last decade was lacking. There was no large-scale analysis that offered a consolidated view of the full spectrum, severity, time to onset, risk factors, outcomes and clinical particularities of each irAE, particularly as compared to the others.

Added value of this study

Our research stands out as it incorporates a 2023 updated VigiBase query, providing a comprehensive view of fatal, severe and less severe cases of ICI-induced toxicity from around the globe since first ICI use in seminal clinical trials in 2008. We distinguished and analyzed 25 specific types of irAE from a dataset of 141,630 cases. Notably, we uncovered risk factors, clinical features, and the intricated relationship of these irAE with different ICI, demographics, cancer types, and geographical regions. This study offers a comprehensive picture of the overall irAE landscape with emphasis on life-threatening irAE which we have identified as myotoxicities, encephalomyelitis, pneumonitis, and severe cutaneous adverse reactions.

Implications of all the available evidence

The insights provided by this study on the regional variations, time-to-onset, fatality rate evolution, clinical features, discontinuation of therapy and rechallenge outcomes and risk factors of specific irAE will help guide monitoring strategies, diagnostic work-up and prognostication for the oncologists and multiple other specialists involved in the care of cancer patients.

Introduction

Immune-checkpoint inhibitors (ICI) have been pivotal in the treatment of multiple cancer types.[1] Immune-checkpoints are receptors on immune cells (usually T-lymphocytes) and by binding to their respective ligands on host cells provide a brake or "checkpoint" against autoimmunity. However, this system can be hijacked by various cancers to thrive rending immune cells inept to fight cancer cells.[1,2] Cytotoxic-T-lymphocyte–associated-antigen-4 (CTLA4), expressed on T-lymphocytes, is such immune checkpoint.[2] Ipilimumab, an antibody targeting CTLA4, was the first drug tested and approved in 2011 for the treatment of melanoma. Few years later, drugs blocking programmed-cell-death-protein-1 (PD1), and its ligand (PDL1) started to be developed as monotherapy or eventually combined with anti-CTLA4 in various cancer types, starting with lung cancers.[1] Lymphocyte-activation-gene-3 (LAG3) is the last immune-check point to have been shown (just approved in early 2022) as an effective targetable pathway, in combination with anti-PD1.[1,3] Conversely, ICI may harness auto-reactive T-cells, leading to the development of immune-related adverse events (irAE) potentially affecting any organs.[4,5] The severity of irAE can range from mild to life-threatening, and the onset of symptoms is scattered from a few weeks to months after ICI start.[1] Managing and treating irAE is challenging for healthcare providers due to their unpredictable nature and variety in terms of phenotypes and organs affected.[5] The continuous approval of new ICI combinations, eventually associated with other anticancer drug classes in multiple cancer settings, is adding further complexity.[3,6]

Pharmacovigilance is a critical tool to monitor the safety of drugs. VigiBase is managed by the WHO (World Health Organization) and represents a global pharmacovigilance database with over 30 million cases from over 130 countries. VigiBase analysis is particularly useful to study rare or emerging adverse drug reactions and is an ideal database to aggregate promptly reasonably sized cohorts of otherwise rare side effects,

generally overlooked in traditional clinical trial settings.[7,8] Its global reach allows the study of worldwide trends in reporting by regions and characteristics of specific toxicities. We and others have utilized VigiBase in 2017 for understanding irAE especially as ICI prescription was increasing dramatically, mainly in melanoma and lung cancers, their first approved indications. Initial VigiBase studies mostly focused on describing specific irAE types.[9–13] However, since 2017, ICI have dramatically increased, with introduction of new drugs, new targets, with a greater use for various stages of many cancer types. In addition, ICI are increasingly being used in combination (for example, anti-CTLA4+anti-PD1) as well as with existing chemotherapy or targeted therapy for specific cancer types. Similarly, cases of iAE reported in VigiBase for ICI have increased dramatically with about 5 times more irAE cases available now compared to our initial studies.[9] So far, no comprehensive integrative analysis of all irAE features of specific therapies or combinations of therapies through time and interconnections within the various irAE have been performed. The current study gathered nearly 150,000 adverse events on ICI extracted from VigiBase from 2008 to 2023, and included the entire spectrum of irAE, integrating tumor types, treatments, age, sex, reporting period and geographical regions. Multiple new risk factors for specific irAE reporting have been identified as signals and the clinical specifics of each irAE subtype including their time to onset, recurrence rate, and outcomes have been characterized to help guiding clinical practice and future researches.

Methods

Data source

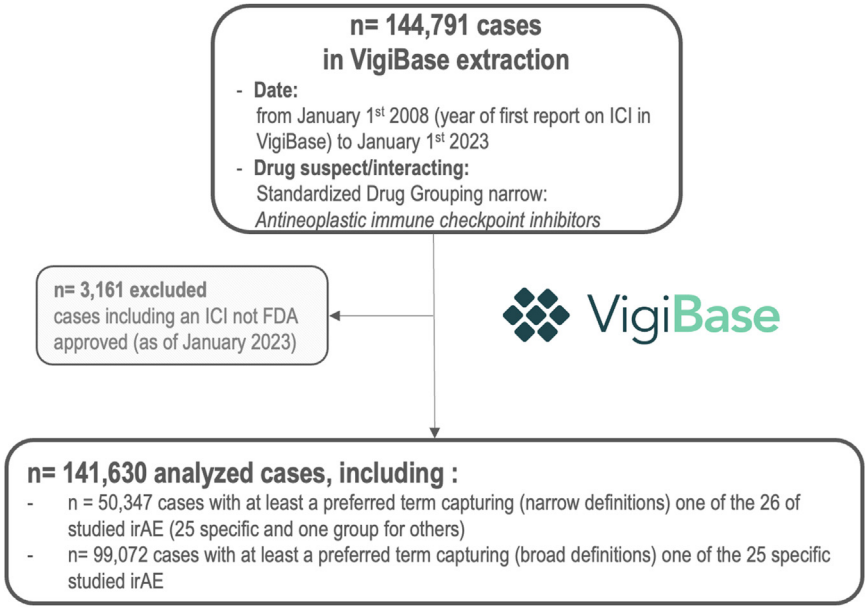
Data was extracted from VigiBase, the international pharmacovigilance database managed by the WHO. Since 1967, spontaneous reports from post-marketing use have been submitted to VigiBase, the WHO global database of individual case safety reports. Some countries also collect reports from pharmaceutical companies during trials and submit them to VigiBase. VigiBase, which is managed since 1978 by Uppsala Monitoring Center (UMC), contains over 30 million reports (as of January 2022) increasing exponentially over years and is currently aggregating reports from over 130 countries. It includes most of the data from other major databases such as those from the European Union, Japan, and the United States.[7] We extracted all adverse drug reaction cases associated with an ICI in which the ICI was suspect or interacting (not including cases in which the ICI was reported as concomitantly used, but not as a liable drug) starting in 2008 until January 1st, 2023. Cases mentioning an ICI not FDA (United States Food and Drug administration) approved as of January 2023 (see flow-chart, Fig. 1) were excluded. FDA-approved ICI included the following monoclonal antibodies: anti-PD1 (nivolumab, pembrolizumab, cemiplimab, dostarlimab), anti-PDL1 (atezolizumab, avelumab, durvalumab), anti-CTLA4 (ipilimumab, tremelimumab) and anti-LAG3 (relatlimab). Concomitant use of any other type of anticancer drug (e.g. antiangiogenics, cytotoxics) with ICI was not an exclusion criterion.

Definitions of immune-related adverse events

We used the preferred terms of the Medical Dictionary for Regulatory activities (MedDRA, version-25.1) to group the irAE into 25 distinct entities: anemia, arthritis, cholangitis, diabetes, encephalomyelitis, enterocolitis, esogastritis, hepatitis, hypophysitis, meningitis, myasthenia gravis-like syndrome (thereafter myasthenia-gravis), myocarditis, myositis, nephritis, pancreatitis, peripheral neuropathy, pneumonitis, sarcoidosis, severe cutaneous adverse reactions (SCAR), skin bullous autoimmune reactions, thrombopenia, thyroiditis, uveitis, vitiligo, various skin reactions (other than vitiligo, SCAR and skin bullous reaction). We generated a last miscellaneous entity merging all other rarer irAE into the "other irAE" (see Supplementary Table S1 for the list of preferred terms used to determine each narrow irAE, focusing more specifically an auto-immunity related terms). We also identified cases containing terms not included in the narrow definitions (e.g. symptoms and biomarkers abnormalities rather than diagnosis) potentially tagging less specifically one of these 25 irAE to establish the broad definitions of each irAE. The content of these broad definitions of irAE were generated by compiling the preferred terms significantly associated with cases previously identified as a narrow irAE. For example, the term *diarrhoea* was associated with the irAE enterocolitis (OR = 3.1 [2.9–3.4]), *respiratory failure* with pneumonitis (OR = 4.6 [3.9–5.3]) but also myocarditis (OR = 4.6 [3.3–6.3]), *hyperglycemia* with diabetes, (OR = 11 [8.0–14.0]) and *transaminases increased* with hepatitis, (OR = 4.9 [3.9–6.3]). The exhaustive list of terms used for defining these broad definitions of the 25 specific irAE are listed in Supplementary Table S2. Therefore, cases including a broad term for an irAE were excluded from the control group in our main analysis studying factors associated with specific narrow irAE as compared to controls without this irAE.

Patient demographics and covariates

Each case was analyzed for its administrative data (date, reporter's qualifications and region of reporting as defined in Supplementary Table S3), patient's demographics (sex attributed at birth, age, cancer type), treatment characteristics (ICI and other anticancer drugs, prescription indications, initiation and termination dates, administration route), and adverse reaction details (reported terms, onset and end date, severity, outcome including death and evolution after drug discontinuation, and rechallenge if any).



FDA: United States Food and Drug Administration; ICI: immune-checkpoint inhibitor; irAE: immune-related adverse events; VigiBase: the international pharmacovigilance database

Fig. 1: **Study flow-chart.**

Time to onset, overlap, fatality, drug discontinuation and rechallenge

Time to onset (TTO) was defined as the delay between ICI start and onset of the preferred term(s) associated with the studied irAE. The percentage of overlap was defined as $N_{overlap}/N_{irAE}$, where $N_{overlap}$ is the number of cases with both studied irAE are concurrently reported. A death was considered as "death from irAE" in a case if the preferred term(s) associated with this irAE in a case had an outcome labeled as "Died" or "Died–reaction may be contributory". All other fatal cases not specifically linking the irAE with death were qualified as "unspecified death". If reported, we analyzed (yes vs. no) ICI discontinuation status with irAE resolution and recurrence after rechallenge.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables as number (percentage); as appropriate. χ^2-trend test was used when comparing the evolution of qualitative variables over time. Univariate and multivariable logistic regressions with computation of an odds-ratio (OR) and its 95% confidence-interval ($^{95\%}$CI) were used to explain binomial variables (*i.e.,* fatality, presence of a specific irAE). Haldane-Anscombe correction was used for the calculation of OR's confidence intervals. Multivariate logistic analysis was done using stepwise minimization of the Bayesian Information Criterion for final selection of variables. Adjustment on multiple testing was performed using Bonferroni's correction, when indicated. Statistical analyses were performed using R-software version 4.1.3.

Role of funding

Paul Gougis was supported by the academic program: "Contrats ED: Programme blanc Institut Curie PSL" for the conduct of his PhD. The RT2L research group (Institut Curie) was supported by the academic program "SHS INCa", Sanofi iTech award, and by Monoprix*.

Results

Population

A total of 144,791 adverse drug reaction cases were extracted from VigiBase, of which 3161 included an ICI that was not FDA approved (exclusion criteria). Among the remainder 141,630 cases, 50,347 reported at least one clearly identified irAE (narrow definition) and 99,072 reported at least one possible irAE (broad definition) among the 25-specific studied irAE (Fig. 1). The main characteristics of the 50,347 cases (narrow definition) are detailed in Table 1 with 61.7% male (28,717/46,527) and a median age of 64.3 ± 12.6 years. Cases were mostly from Europe (23,350/50,347; 46.4%), north America (15,743/50,347; 31.3%) and East Asia (7758/50,347; 15.4%) and were mostly reported by physicians or pharmacists (32,178/49,372; 65.2%) following routine care. The most common cancer types associated with irAE were non-small cell lung cancer (15,397/44,589,

34.5%), followed by melanoma (14,630/44,589, 32.8%) and renal cancer (4265/44,589, 9.6%) (Supplementary Fig. S1 for the detailed list of cancers involved). Patients received anti-PD1 or anti-PDL1 monotherapies in 62.4% (31,409/50,347) and 12.8% (6422/50,347), respectively; a combination of anti-CTLA4+antiPD(L)1 involved 16.3% (8215/50,347). Patients taking anti-LAG3-based combinations were rare (73/50,347, 0.1%, Supplementary Fig. S2). Evolution of ICI regimen and cancer types associated with irAE varied significantly over the 4 studied time periods of reporting in VigiBase (≤2016, 2017–2018, 2019–2020, 2021–2022). These trends are shown in Fig. 2A and B. The proportion of anti-CTLA4 monotherapy-associated irAE almost vanished representing 47% of prescriptions of ICI before 2017 vs. 1.6% in 2021–2022 ($p < 1 \times 10^{-160}$), in contrast to combination of anti-CTLA4+anti-PD(L)1 in the same time periods (8.9% vs. 20%, $p = 2 \times 10^{-90}$). Concomitant cytotoxic drugs used with ICI concerned 8.5% (4,304, mostly in lung cancer), and molecular targeted therapies 7.7% (3,882, mostly in renal cancer) of these 50,347 cases (Supplementary Fig. S1).

Prevalence of irAE and their co-reporting

In total, there were 60,323 different irAE (narrow definition) identified among 50,347 cases. The most reported irAE were skin reactions (22.9%, 11,537/50,347), pneumonitis (18.5%, 9317/50,347), enterocolitis, (14.4%, 7246/50,347) and thyroiditis (12.1%, 6070/50,347) (Fig. 3A, Supplementary Fig. S3 for the absolute counts of the 25 studied irAE). Most cases (84.9%, 42,741/50,347) described a single irAE, and, in the rest, two or more irAE were co-reported (Supplementary Fig. S3). The most significantly overlapping irAE included myositis, myocarditis and myasthenia-gravis (overlapping proportion between 12 and 30%), with OR = 13 ($^{95\%}$CI = 9.7–16) for myositis-myocarditis, OR = 16 ($^{95\%}$CI = 12–21) for myositis-myasthenia and OR = 8.2 ($^{95\%}$CI = 5.9–12) for myocarditis-myasthenia (Supplementary Fig. S4 and Table S4 for the details of all significantly overlapping irAE). Other significantly overlapping irAE included thrombopenia with anemia (OR = 10 ($^{95\%}$CI = 4–26)), meningitis with encephalomyelitis (OR = 5.4 ($^{95\%}$CI = 2.5–12)), and esogastritis with enterocolitis (OR = 2.6 ($^{95\%}$CI = 1.9–3.6)). In the rest of non-significantly overlapping irAE, median inter-irAE overlap was of 0.7% IQR [0.2–2.2] within the 25 studied irAE. Evolution of reporting of the different types of irAE through time is shown in Fig. 2D. Proportion of gastro-intestinal irAE (*i.e.,* esogastro-enterocolitis) decreased importantly representing 23% of total irAE before 2017 vs. 12% in 2021–2022 ($p = 7 \times 10^{-53}$), in contrast to a steep increase in myotoxicities (i.e. myocarditis or myositis or myasthenia-gravis, 3.7% vs. 8.3%, $p = 6 \times 10^{-43}$) and pancreatico-hepatic irAE in the same time-periods (8.2% vs. 11%, $p = 6 \times 10^{-15}$).

Time to onset

Median TTO of irAE from initiation of ICI therapy ranged from 1 to 9 months (Fig. 3B). Myotoxicities had the shortest median TTO and were consistent between myasthenia-gravis (31 days, IQR = 22–60), myositis (31days, IQR = 21–67), and myocarditis (33 days, IQR = 21–91). SCAR had also among the shortest TTO (40 days, IQR = 14–119). Most other irAE had a median TTO within 1 and 3 months, except for more delayed TTO in arthritis (104 days, IQR = 31–224), diabetes (114 days, IQR = 45–243), pancreatitis (121 days, IQR = 41–261), esogastritis (126 days, IQR = 45–295), sarcoidosis (141 days, IQR = 75–274), vitiligo (170 days, IQR = 89–326) and extremely delayed in skin bullous auto-immune reactions (273 days, IQR = 93–487).

Factors associated with irAE reporting

To better understand the evolution of irAE reporting, we studied which contributing demographical (e.g cancer, ICI type, age, sex), time-period and regional factors were the most influential. The summary results of the multivariate analyses are shown in Fig. 4 and each detailed univariate and multivariate analysis for the 25 specific irAE (narrow defintions used for the main analysis) are displayed in Supplementary Fig. S5. The top ten factors associated with increased reporting of a specific irAE (multivariate analysis) revealed presence of thymic cancer vs. none for ICI-myotoxicities (OR = 51, $^{95\%}$CI = 31–81 for myasthenia-gravis; OR = 32, $^{95\%}$CI = 19–51 for myocarditis; and OR = 28, $^{95\%}$CI = 16–45 for myositis) and hepatitis (OR = 6.7, $^{95\%}$CI = 3.5–12); presence of melanoma vs. none for vitiligo (OR = 13, $^{95\%}$CI = 11–16), uveitis (OR = 6.2, $^{95\%}$CI = 5.2–7.5) and sarcoidosis (OR = 5.6, $^{95\%}$CI = 4.4–7.2); and specific type of ICI regimen vs. anti-PD1 monotherapy including anti-LAG3 based therapies with meningitis (OR = 15, $^{95\%}$CI = 5.4–35), and anti-CTLA4 monotherapy with hypophysitis (OR = 7.0, $^{95\%}$CI = 6.0–8.1); lastly specific reporting regions with the highest association being eastern Asia with cholangitis (5.2, $^{95\%}$CI = 3.9–6.8) vs. the other regions in the world.

Other relevant factors (OR between 2 and 5 for positive, and between 0.1 and 0.9 for negative associations, Supplementary Fig. S5) included elder age positive association with ICI-myotoxicities, and auto-immune skin bullous reactions, while age was negatively associated with sarcoidosis and pancreatitis. Female were less associated with skin bullous reactions. As compared to the rest of the world (overwhelmingly north American and European countries), east Asian reported notably less arthritis, myocarditis, nephritis, and vitiligo but more meningitis and pneumonitis. As compared to anti-PD1 monotherapies; anti-PDL1 monotherapies were generally associated with less irAE, particularly for skin bullous auto-immune reaction (OR = 0.27 $^{95\%}$CI = 0.18–0.39), SCAR (OR = 0.39, $^{95\%}$CI

	Overall	Narrow irAE
	n = 141,630	n = 50,347
Sex		
Female	49,169 (38.5)	17,810 (38.3)
Male	78,677 (61.5)	28,717 (61.7)
Data available, n (%)	127,846 (90.2)	46,527 (92.4)
Age (years)		
Mean (SD)	64 (12.8)	64.3 (12.6)
Age class (years)		
<50	13,100 (14.1)	4798 (13.4)
50–59	18,609 (20.0)	6998 (19.5)
60–69	30,803 (33.2)	11,983 (33.4)
70–79	24,022 (25.9)	9617 (26.8)
≥80	6326 (6.8)	2447 (6.8)
Data available, n (%)	92,860 (65.6)	35,843 (71.2)
Year of first report class		
2016 or before	15,569 (11.0)	4919 (9.8)
2017–2018	37,856 (26.7)	13,889 (27.6)
2018–2019	44,661 (31.5)	17,149 (34.1)
2020–2022	43,544 (30.7)	14,390 (28.6)
Clinical trial[a]		
No	56,671 (64.6)	25,263 (71.7)
Yes	31,098 (35.4)	9972 (28.3)
Data available, n (%)	87,769 (62.0)	35,235 (70.0)
Country group		
Eastern Asia	20,254 (14.3)	7758 (15.4)
Europe	51,513 (36.4)	23,350 (46.4)
North America	55,741 (39.4)	15,743 (31.3)
Other country	14,122 (10.0)	3496 (6.9)
Notifier type		
Physician or pharmacist	77,978 (56.3)	32,178 (65.2)
Other health professional	33,046 (23.8)	11,907 (24.1)
Consumer or non-health professional	27,538 (19.9)	5287 (10.7)
Data available n (%)	138,562 (97.8)	49,372 (98.1)
Cancer type[b]		
Breast	2521 (2.1)	758 (1.7)
Endometrium	2308 (1.9)	591 (1.3)
Gastroesophageal	2662 (2.2)	671 (1.5)
Head & neck	3962 (3.3)	1100 (2.5)
Liver	2473 (2.1)	459 (1.0)
Lymphoma	2075 (1.7)	685 (1.5)
Melanoma	31,074 (26)	14,630 (32.8)
Non-small cell lung cancer + cytotoxic	5735 (4.8)	2117 (4.7)
Non-small cell lung cancer w/o cytotoxic	33,072 (27.7)	13,280 (29.8)
Renal + antiangiogenic	3411 (2.9)	1013 (2.3)
Renal w/o antiangiogenic	8532 (7.1)	3252 (7.3)
Small cell lung cancer	2311 (1.9)	677 (1.5)
Thymus	139 (0.1)	71 (0.2)
Urothelial & bladder	5757 (4.8)	1766 (4.0)
Other cancer	13,981 (11.7)	3707 (8.3)
Data available n (%)	119,520 (84.4)	44,589 (88.6)
	(Table 1 continues on next column)	

	Overall	Narrow irAE
	n = 141,630	n = 50,347
(Continued from previous column)		
ICI regimen		
Anti-PD1 monotherapy	91,888 (64.9)	31,409 (62.4)
Anti-CTLA4 monotherapy	11,176 (7.9)	4169 (8.3)
Anti-PD(L)1+anti-CTLA4	17,195 (12.1)	8215 (16.3)
Anti-PDL1 monotherapy	21,007 (14.8)	6422 (12.8)
Anti-LAG3 combinations	221 (0.2)	73 (0.1)
Anti-PD1+anti-PDL1	143 (0.1)	59 (0.1)
Fatal outcome	27,786 (19.6)	5709 (11.3)

CTLA4: cytotoxic T-lymphocyte-associated antigen 4; ICI: immune checkpoint inhibitors; irAE: immune-related adverse event; LAG3: Lymphocyte-activation gene 3; PD(L)1: programmed death 1 (ligand); SD: standard deviation; w/o: without. [a]Study status was considered as unknown when "unknown" was informed in the study name section of the case report, or when the type of study was doubtful with available information. Of note, all cases from the USA were considered as unknown as USA cases does not report this information to VigiBase. [b]Several cancer types could be reported within the same report, with a total of 142,634 and 50,688 cancer types in the overall and narrow irAE cases, respectively.

Table 1: **Cases characteristics.**

= 0.29–0.52), vitiligo (OR = 0.45, $^{95\%}$CI = 0.3–0.65), hypophysitis (OR = 0.47, $^{95\%}$CI = 0.34–0.62), arthritis (OR = 0.51, $^{95\%}$CI = 0.42–0.60), myasthenia-gravis (OR = 0.52 $^{95\%}$CI = 0.40–0.65), and except for pneumonitis (OR = 1.71 $^{95\%}$CI = 1.6–1.8) and meningitis (OR = 1.79, $^{95\%}$CI = 1.2–2.6); contrasting with anti-PD(L)1+anti-CTLA4 generally associated with higher rates of irAE than anti-PD1, particularly for hypophysitis (OR = 3.91, $^{95\%}$CI = 3.4–4.4), enterocolitis (OR = 3.53, $^{95\%}$CI = 3.3–3.8) and hepatitis (OR = 3.23, $^{95\%}$CI = 3.0–3.5). As compared to anti-PD1 alone, an increased reporting rate was also observed for enterocolitis on anti-CTLA4 monotherapy; myocarditis on anti-LAG3-based regimen. In general, irAE reporting rates were higher with melanoma compared to other cancer types, contrasting with liver and head and neck cancer patients associated with lower rates. In renal cancer on ICI, concomitant use of antiangiogenics was associated with less diabetes, hypophysitis, myasthenia-gravis, pneumonitis, uveitis and more hepatitis as compared to absence of antiangiogenics. In a post-hoc sensitivity analysis integrating broad irAE definitions as cases instead of only narrow definitions, results of factors associated with each specific irAE reporting were globally confirming those of the main analysis using narrow definitions (Supplementary Fig. S5 for detailed results of the main and sensitivity analyses).

Fatality

Death was reported in 5709/50,347 (11.3%) within the narrow irAE population. Highest overall and irAE-related fatality rate was reported for myocarditis (27.6% and 19.2%, respectively), myasthenia-gravis

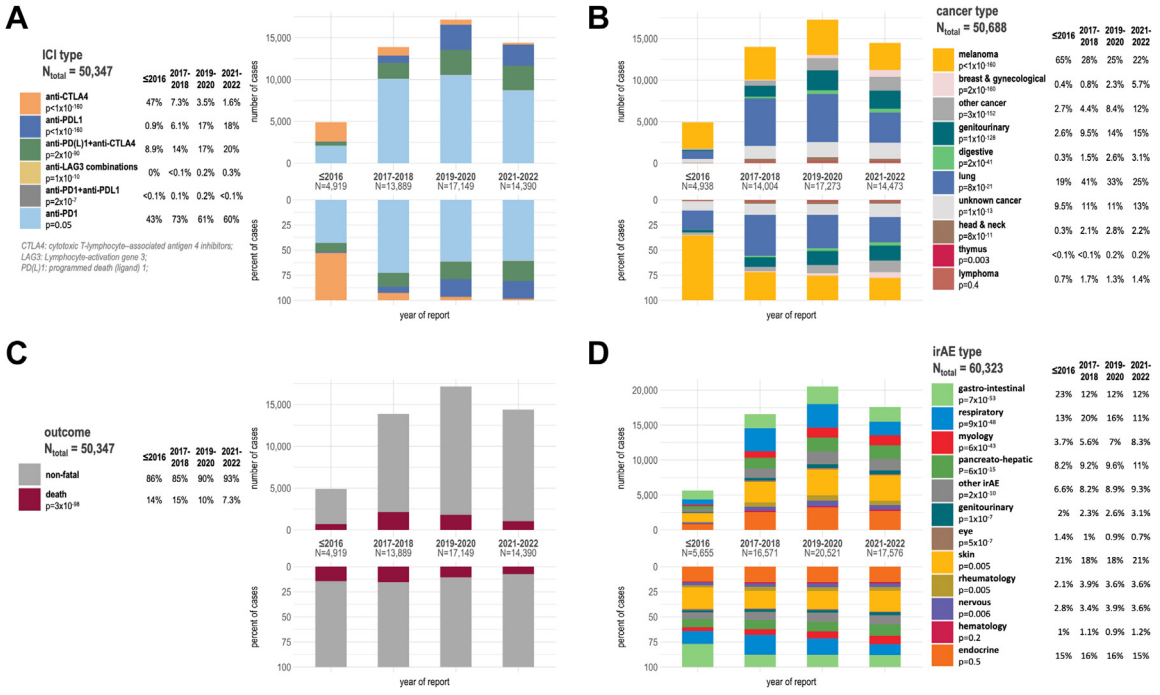


***Fig. 2:* Evolution of the reporting.** Evolution of the reporting of ICI (immune checkpoint inhibitor) and their combinations (A), of cancer indications (B), and fatality rate (C) in the 50,347 cases associated with an immune related adverse event (irAE, narrow definition) in VigiBase since 2008 until 2023, by period of time. In D is shown the evolution of the different types of reported irAE (n = 60,323 narrow irAE) within 50,347 cases. p-values were computed by χ^2-trend. Anti-PD1+anti-PDL1 represented 0.1% of ICI types and is not shown.

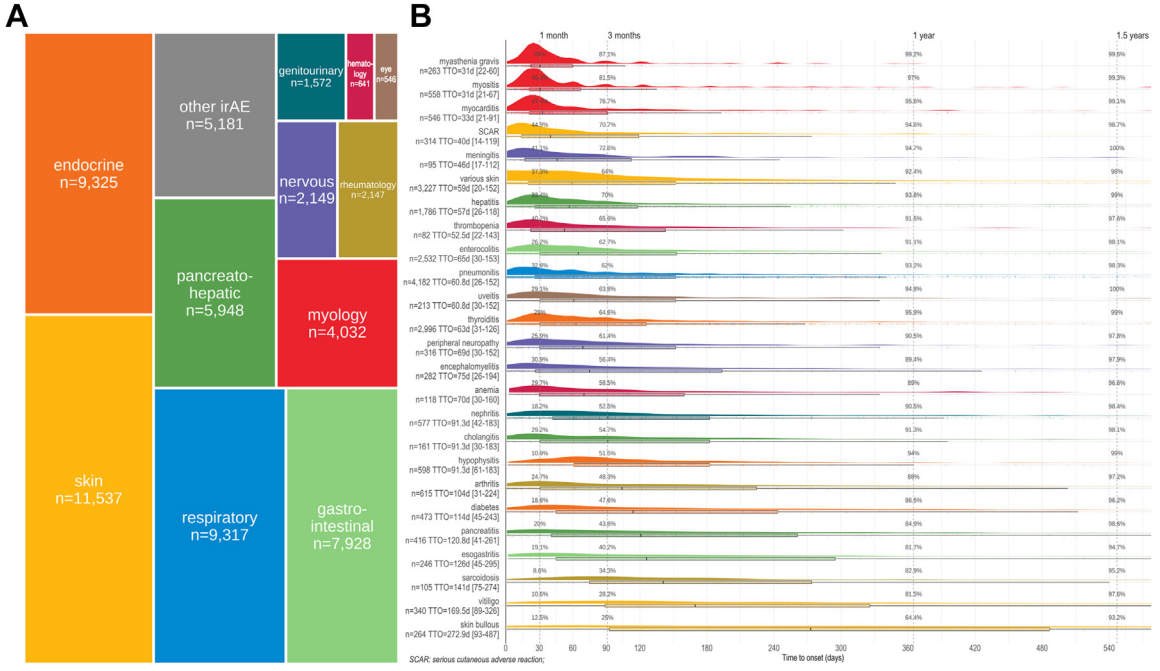


***Fig. 3:* Counts of immune-related adverse events (irAE) reported in VigiBase by organ system (A) and time to onset (TTO) per specific irAE (B).** Overall number of irAE per organ system (narrow definitions, n = 50,347 cases and n = 60,323 distinct irAE). Details of the different specific irAE within each organ system is available in Supplementary Fig. S4. TTO were calculated using the delay between ICI start and irAE onset. "n" is the number of irAE with TTO available (N_{total} = 21,305). Boxplots represents the median, [interquartile, IQR, edge of the box] and 1.5 x IQR (moustache) for the TTO of each irAE. The percentage of patients having developed the specific irAE is indicated at the level of the dotted line at 1 month, 3 months, 1 year, and 1.5 years for each irAE.

(23.1% and 13.6%), SCAR (22.1% and 12.3%), myositis (21.9% and 11.3%), pneumonitis (21.0% and 10.4%) and encephalomyelitis (18% and 10.9%) (Fig. 5 for overall fatality rates and Supplementary Fig. S6A for irAE-related fatality rates and absolute counts). Overall reported fatality generally decreased throughout time for most life-threatening irAE types except for SCAR and myasthenia-gravis (Supplementary Fig. S6B for the evolution comparing rates between ≤2016, 2017–2018, 2019–2020, and 2021–2022). Most other irAE had overall and irAE-related fatality rates ranging between 5 and 15%, and between 2 and 5%, respectively. Arthritis, hypophysitis, diabetes, vitiligo, skin bullous reactions, uveitis, and sarcoidosis had the lowest overall (<5%), and very low irAE-related (<2%) fatality. Proportion of severe vs. non-severe irAE by subtype are reported in Supplementary Fig. S7. Within the narrow irAE population (n = 50,347), factors associated with overall fatality using univariate and multivariable analysis adjusted on age, sex, ICI, cancer, reporting region, and time period are presented in Fig. 6. In the multivariate analysis, myotoxicities, pneumonitis, SCAR and encephalomyelitis confirmed their higher association with overall death (OR = 1.7–3.3) as compared to the other irAE types (Fig. 6). Beyond irAE types, other factors associated with increased fatality included age (OR = 1.16, $^{95\%}$CI = 1.1–1.2 for ≥65 years vs. <65years), eastern Asia as compared to the rest of the world (OR = 1.9, $^{95\%}$CI = 1.7–2.0), and some cancer types as compared to all the others with OR ranging from 1.5 to 2.7 (urothelial, gastro-oesophageal, head and neck, lung and liver cancers, ordered by increasing OR). Factors associated with decreased fatality included female (OR = 0.85, $^{95\%}$CI = 0.8–0.9 vs. male), and most recent reporting period (OR = 0.53, $^{95\%}$CI = 0.5–0.6 for 2017–2022 vs. ≤2016). Since myotoxicities (myocarditis and/or myositis and/or myasthenia-gravis) often overlapped and carried the highest fatality burden, we performed a subgroup analysis in the patients with a myotoxicity in VigiBase (n = 3,311, narrow definitions). Results of univariate and multivariate analysis are shown in Supplementary Fig. S8. In multivariate analysis, female sex was protective (OR = 0.8, $^{95\%}$CI = 0.6–0.9 vs. male) contrasting with multiple concomitant myotoxicities, associated with higher fatality (OR = 1.6, $^{95\%}$CI = 1.3–1.9 for 2 vs. 1 myotoxicity, and OR = 2.7, $^{95\%}$CI = 1.8–4.0 for 3 vs. 1 myotoxicity).

Drug discontinuation and rechallenge

Of the 60,323 identified specific irAE within the 50,347 narrow cases, 27,471 irAE within 23,942 cases had documented outcomes (Yes vs. No) for both ICI discontinuation and irAE resolution. In these fully informative cases, a total of 88.1% irAE were managed by an ICI discontinuation, and a total of 73.9% had an irAE considered as resolved. The difference in the resolution rates between those flagged as ICI withhold (74.6%) or pursued (68.9%) was low. Supplementary Fig. S9 show the Sankey diagram of the flux of overall irAE evolution as a function of ICI discontinuation, resolution status and fatality. Fig. 5 displays these data per specific irAE. The resolution rate per irAE (in non-fatal cases subset) ranged from 32.5% to 88.5%. Most irAE had a resolution rate ≥70%, except for peripheral neuropathy (65%), and vitiligo (32.5%), with the lower resolution rates. Few cases identified as resolved after ICI withdrawal were flagged as being restarted (rechallenged) on ICI (N = 951 within the 25 specific irAE). Among them, a total of 28.9% (275/951) reported an irAE recurrence. The recurrence rate per specific irAE (with ≥10 cases available) is shown in Fig. 5 and ranged from 9.5% to 62.5%. Highest recurrence rates were observed for skin bullous reactions (62.5%), nephritis (36.8%), myocarditis (37.5%), enterocolitis (35.6%) and pneumonitis (32.2%).

Discussion

This VigiBase study used the largest cohort of irAE on ICI ever studied by several folds. Over 60,000 irAE were collected worldwide between 2008 and January 2023. We determined and compared the reporting rates, main clinical features including TTO, outcomes and risk factors associated with the main irAE divided into 25 entities. Overall, the relative prevalence of these different irAE in VigiBase was concordant with that expected from prospective trials, with skin, gastro-intestinal, endocrine, lung and hepatic irAE being 5 to 10 times more frequent as compared to uncommon neurological, cardio-muscular, ocular, renal and rheumatological irAE.[14,15]

A major novelty of this work was the evolution of irAE reporting with ICI prescription in the last decade with the multiplication of cancer settings and potential drug combinations. The evolution of the types of cancers and ICI suspected of inducing irAE observed in VigiBase within the studied timeline tracked with ICI approved indications worldwide. Ipilimumab was the first ICI approved in 2011 for melanoma, followed by anti-PD1 monotherapies for melanoma and lung cancers starting in 2014.[1] Subsequent approvals followed quickly including anti-PD(L)1 monotherapies and combinations of anti-PD1+anti-CTLA4 in a large variety of other cancer types, corresponding to decreased use of anti-CTLA4 monotherapies.[1] Interestingly, the latest development with the approval of anti-LAG3 (relatlimab) plus nivolumab (anti-PD1) in 2022 was also marginally captured in this work.[6] Accordingly, the types of irAE reported throughout time evolved with an observed proportional reduction in enterocolitis cases (mostly associated with anti-CTLA4), and an upsurge in myotoxicity reports, likely favored by increased use of ICI combinations.[9,16,17] Indeed, we observed a ~2-fold increased reporting rate of ICI-myocarditis on anti-

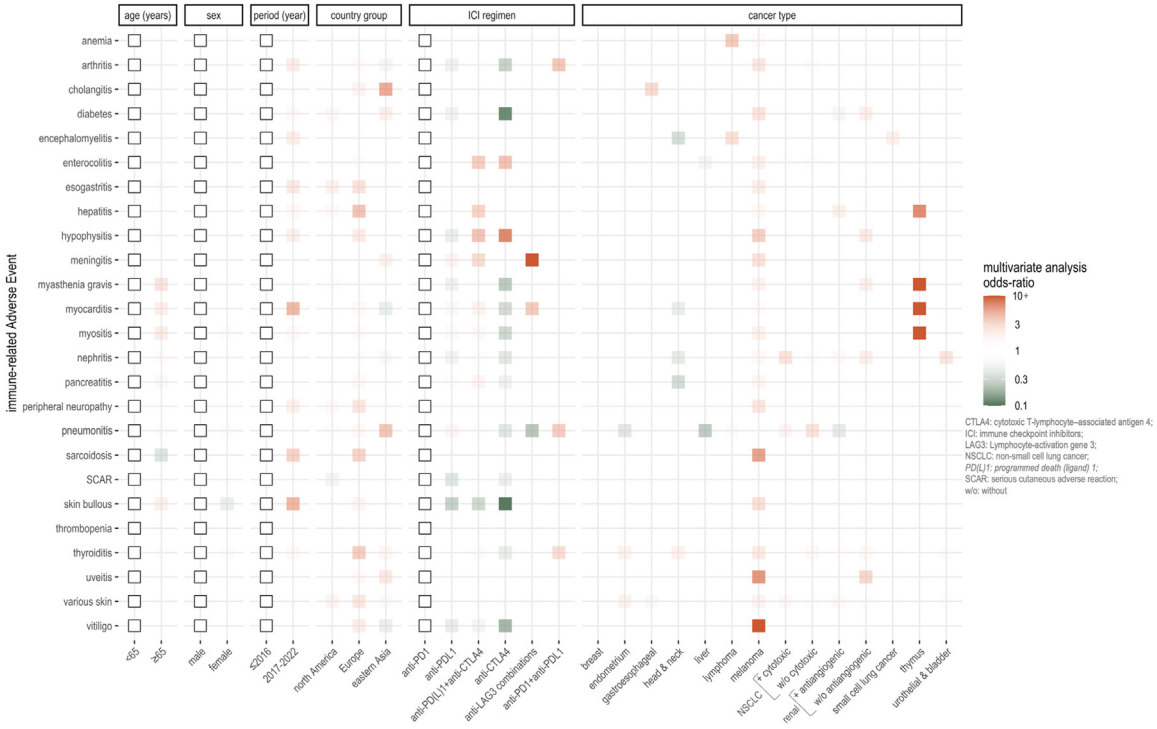


Fig. 4: **Heatmap of risk factors associated with the reporting of the 25 specific irAE (immune-related adverse events).** Each irAE (narrow definitions) was compared with the control population including overall cases without those carrying a term associated with a broad or narrow definition of the studied irAE. The OR (odds-ratio, only shown if significant; empty squares for reference) were computed by multivariate logistic regression. For cancer and country types, the reference group was cases without the studied cancer or country type. Detailed analysis per irAE is available in Supplementary Fig. S6.

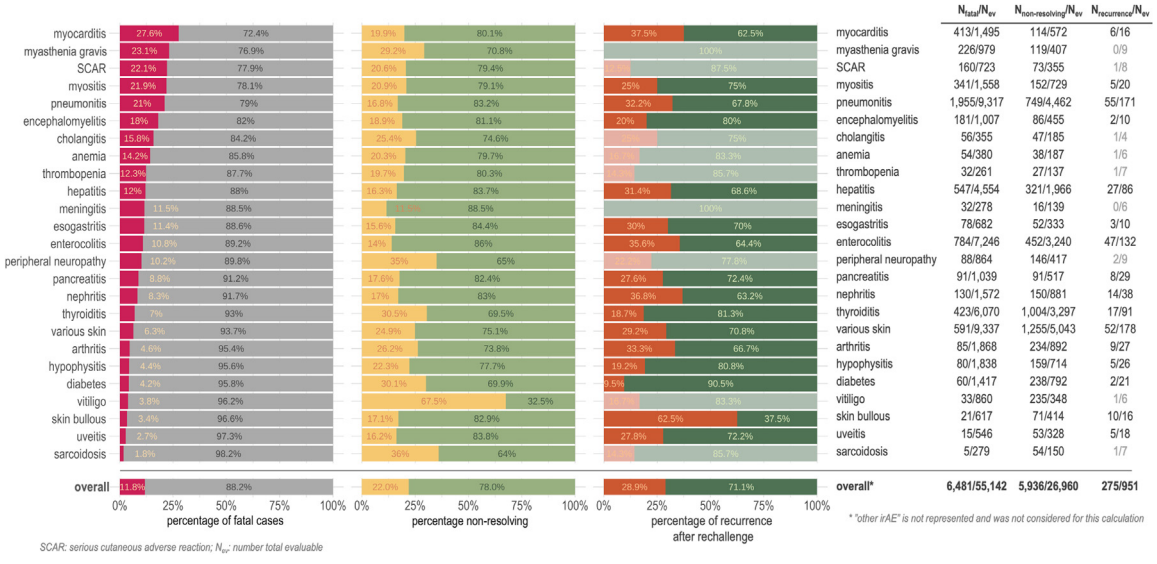


Fig. 5: **Overall fatality, resolution and recurrence rates after rechallenge per specific immune-related adverse event (irAE).** Overall fatality (red), resolution rate (non-resolved in yellow, ICI being withdrawn or pursued in the subset of non-fatal cases), and recurrence rate (orange) after ICI rechallenge (in cases with a first irAE previously resolved after ICI withdrawal) for the 25 specific irAE. Resolution of an irAE can also correspond to adequate medical intervention resolving the condition (such as substitution of an endocrine defect), and not necessarily reversion ad-integrum to the physiological status prior to ICI start. N_{ev} is the total number of cases in which the data was evaluable. Data with less than 10 cases as N_{ev} are grayed out.

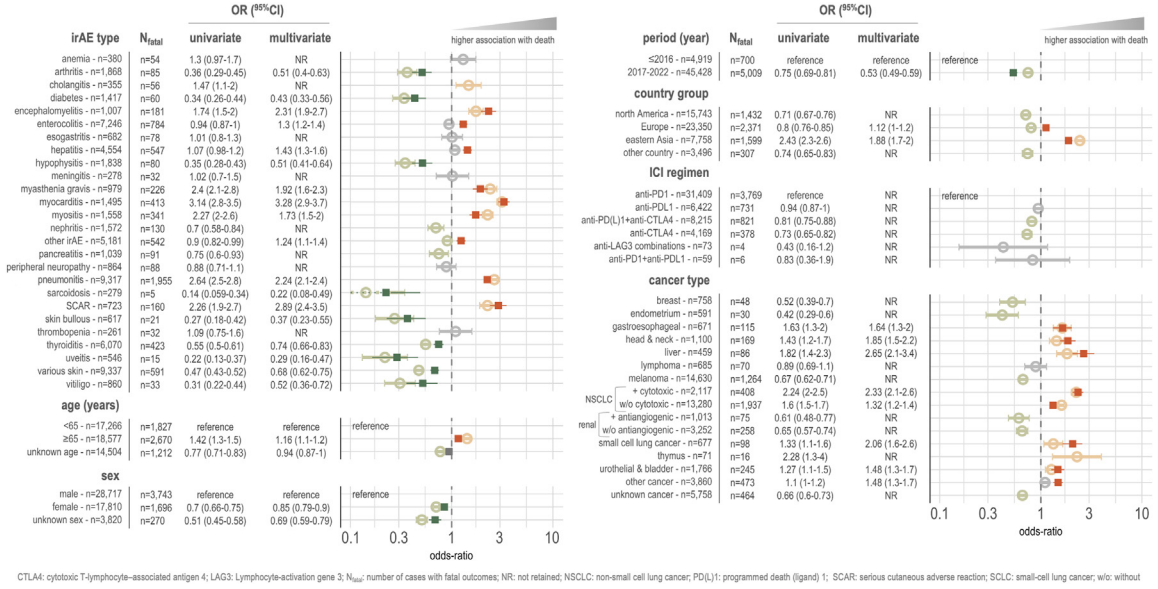


***Fig. 6:* Factors associated with overall fatality.** Univariate (circles) and multivariate (squares) analysis (OR ($^{95\%}$CI), odds-ratio and its 95% confidence interval) of factors associated with overall fatality (n = 5709) in cases with immune-related adverse events (irAE, n = 50,347 narrow).

PD(L)1+anti-CTLA4 vs. anti-PD1 and ~4-fold increased risk of enterocolitis on anti-CTLA4 vs. anti-PD1, in line with multiple previous clinical and translational studies supporting the causality of these latter associations.[16–18] This work also confirmed a higher reporting of hypophysitis on anti-CTLA4 based regimen vs. anti-PD1 alone, and a lower reporting of thyroiditis on anti-CTLA4 monotherapy vs. anti-PD1 based therapies.[19] Novel signals included anti-LAG3 based regimens surfacing as a potential risk factor for both meningitis and myocarditis vs. anti-PD1 (~4-fold and ~15-fold reporting increase, respectively). Among tumor-specific risks identified in this analysis, the overall increased reporting of irAE in melanoma contrasted with lower rates observed in the head & neck or liver cancers population, potentially explained by higher ipilimumab dose used in melanoma vs. other cancer types[1] and the differences in the immunosuppression states or immunogenicity associated with the different cancer types.[20,21] Otherwise, melanoma cases confirmed a previously known association with vitiligo[22] and this study further identified an increased reporting for uveitis and sarcoidosis in melanoma. The top association retrieved between a specific cancer type and a specific irAE in this analysis was between thymic tumor and ICI-myotoxicity, in line with our recent work explaining this association mechanistically.[23,24] Indeed, myotoxicities (e.g. myocarditis, myositis, and myasthenia-gravis) had this unique peculiarity in this VigiBase analysis of being the most co-reported/overlapping irAE, sharing most of their reporting risk factors (including thymic cancer, elder age, and ICI combination) and clinical peculiarities with similar TTO and highest fatality rates (~20–25%). These findings are concordant with recent reports showing that myositis potentially mimicking myasthenia-gravis was almost universally found on muscular biopsies of patients with ICI-myocarditis.[23] This VigiBase analysis further highlighted that ICI-myotoxicities are likely clinical polymorphic entities of a same ICI-induced condition, likely secondary to ICI harnessing resident auto-reactive T-cells against muscle antigens.[23,25,26] Other significantly co-reported irAE in VigiBase were rare and respected the same principle of likely shared auto-antigens triggering the observed association, including esogastritis with enterocolitis, and meningitis with encephalomyelitis.[27] Intriguingly, eastern Asian countries had among highest reporting rates for cholangitis. Some explanatory hypothesis to further explore may include differences in genetic ancestry backgrounds or regional exposure to specific triggering agents (e.g. infectious, dietary). Overall, this analysis showed more males than females with an irAE contrasting with more global post-marketing surveillance data from VigiBase indicating that females are generally more associated with adverse drug reaction reports than males.[28] However, the higher prevalence of males in our analysis is actually in line with the expected increased incidence in the cancers eligible to ICI in males as compared to females during the studied period.[29]

Overall, life-threatening irAE, even after adjustment for cancer types and general demographics showed top-values for ICI-myotoxicities, SCAR, encephalitis and pneumonitis. Though, we generally observed a significant drop in mortality rates through the last decade, particularly for ICI-myocarditis, likely reflecting a better recognition of this latter disease including smoldering,

non-fulminant cases and advances in appropriate therapeutic management.[25] Contrasting with this general observation, SCAR and myasthenia-gravis maintained unchanged fatality rates around 20% and still represent clearly unmet medical needs. This observation for ICI-induced myasthenia-gravis may be explained by the potential confusion in the discrimination between idiopathic myasthenia-gravis (an humoral mediated disease) and ICI-mediated "myasthenia gravis-like syndrome," which mimics clinically idiopathic myasthenia but is a T-cell and macrophages mediated diseases, requiring similar treatment to the other ICI-myotoxicities, rather than the therapeutics generally used and recommended for idiopathic myasthenia (and ineffective to treat cellular mediated autoimmune diseases).[23,25,30]

Several limitations need to be recognized for VigiBase analysis.[7] Pharmacovigilance analysis allow for signal detection and generate hypothesis which need to be replicated ideally by prospective or translational mechanistic studies.[23,31,32] An unclear number of irAE are not reported to the national drug authorities, and therefore not submitted to VigiBase (under-reporting known to increase over time after drug approval, and particularly affecting non-severe cases).[7,33] This may potentially skew observed fatality rates in pharmacovigilance studies toward higher-ends. The exact denominator of patients exposed to the different ICI regimen cannot be evaluated. Instead, total number of irAE cases is used as denominator for the disproportionality analysis for signal detection. Our data concerning the influence of geographical regions in irAE reporting should be cautiously interpreted, because drug approvals and prescription habits and pharmacovigilance systems are different worldwide. Outcomes after ICI discontinuation and rechallenge (if any) provided by this study may be biased by the intrinsic characteristics of complete vs. incomplete cases; potentially impacting the global generalization of the findings drawn from complete cases. However, a major strength is that VigiBase aggregates cases collected worldwide, which enables accumulation of the biggest cohorts available, and broader generalization of the findings. Though, sources of reports are nonhomogeneous, and there is limited possibility of verification of the findings justifying the reported diagnosis. Clinical trials are mandatory to establish efficacy but may not allow definitive conclusions on drug safety in part due to selected populations and limited power to detect balances in rare adverse events. Spontaneous notifications remain the cornerstone for adverse drug reactions evaluation despite their limitations.[7]

In conclusion, this study offers the most comprehensive analysis of the full spectrum, clinical features, and evolution since their introduction in care up to date of irAE associated with ICI. The knowledge gained from this large-scale analysis will aid in designing future strategies in terms of patient monitoring, risk prediction, translational explanatory studies, and definitions of persistently unmet medical needs in irAE management strategies.

Contributors

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Guarantors: PG accepts full responsibility for data analysis and data integrity. JES accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Data sharing statement

VigiBase, the WHO international pharmacovigilance database was used in this study. The database can be obtained from: www.vigiaccess.org.

Declaration of interests

Dr Gougis declares participation to advisory board from BMS, travel support from Eisai, and an academic grant from Sanofi. Dr Abbar reports consulting fees or honoraria from Novartis, AstraZeneca, BMS, MSD, Astellas, and Sanofi. Dr Salem have participated to advisory boards, consultancy or received grants from BMS, Novartis, AstraZeneca, CRC-Oncology, EISAI, IPSEN, Bayer, Banook Group, and BeiGene. Dr Spano have participated to advisory boards, consultancy from Roche, MSD, BMS, Lilly, AstraZeneca, Daiichi-Sankyo, Mylan, Novartis, Pfizer, PFO, LeoPharma and Gilead, and Grant for MSDAvenir. Dr Moslehi served on advisory boards for Bristol-Myers Squibb, Takeda, AstraZeneca, Myovant, Kurome Therapeutics, Kiniksa Pharmaceuticals, Daiichi Sankyo, CRC Oncology, BeiGene, Prelude Therapeutics, TransThera Sciences, BitterRoot Bio, Deciphera, Regeneron, Teva and Cytokinetics and is supported by the NIH (R01HL141466, R01HL155990, R01HL156021, R01 HL160688, R01 HL170038). All other authors report no COI.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102536.

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