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Immune Checkpoint Inhibitor-induced Myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities

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ABSTRACT.

Background: In addition to restoring anti-tumor immune responses, immune checkpoint inhibitors (ICI) may also induce immune-related adverse events (irAE) that can affect any organ. We aim to determine the spectrum, timing, clinical features, and fatalities of rheumatic and musculoskeletal Immune-related adverse events (RMS-irAE) associated with ICI.

Patients Methods: We performed an observational, retrospective, pharmacovigilance study using the World Health Organization international pharmacovigilance database, VigiBase, from inception to January 2019. RMS-irAE reporting rate on ICI versus full database was performed using disproportionality analysis with computation of reporting-odds-ratios (ROR) and a Bayesian disproportional estimate (information component, IC). IC_{025} (lower end of the IC 95% credibility interval) >0 is deemed significant.

Results: We identified 1,288 RMS-irAE significantly associated with ICI : polymyalgia rheumatica (n=76, ROR=14.6 [11.6-18.4], IC_{025}=3.34), sarcoidosis (n=94; ROR=9.6 [7.9-11.9]; IC_{025}=2.85), Sjogren's syndrome (n=49; ROR=6.9 [5.2-9.2]; IC_{025}=2.24), myositis (n=465; ROR=4.9 [4.5-5.4]; IC_{025}=2.12), arthritis (n=606; ROR=1.4 [1.3-1.5]; IC_{025}=0.34) and scleroderma (n=17; ROR=2.0 [1.2-3.2]; IC_{025}=0.17). Arthritis, myositis, and Sjogren's syndrome were over-reported in patients treated with ICI combination versus those treated with ICI monotherapy (ROR=1.6-2.9, $p<0.05$) and more frequently reported on anti-PD1/PDL1 monotherapy vs. anti-CTLA4 monotherapy (2.1-4.4, $p<0.05$). Median time to onset occurred early for myositis (31 days [19.2-57.8]) and was the most delayed for scleroderma (395 days [323.8-457.2], $p<0.0001$). The fatality rate for RMS-irAE ranged from 24% for myositis (n=106/441) (up to 56.7% with concurrent myocarditis) to [0-6.7%] for other RMS-irAE ($p<0.0001$).

Conclusions: Clinicians should be aware of the spectrum of RMS-irAE. Myositis can be particularly life-threatening, particularly when associated with myocarditis.

Key words: immune checkpoint inhibitors, pharmacology, adverse drug reactions, myositis, rheumatology, myocarditis

Key messages

We identified over 1000 individual case safety reports related to rheumatic and muscular immune toxicities (RMS-irAE) induced by immune-checkpoint inhibitors (ICI). RMS-irAE encompassed arthritis, myositis, sarcoidosis, polymyalgia rheumatica, Sjogren's syndrome, and scleroderma. Myositis occurred early within weeks after initiation of ICI therapy and carried a high fatality rate, particularly when concurrent myocarditis was reported; whereas other RMS-irAE had a low mortality burden.

Introduction:

Immune checkpoint inhibitors (ICI) have shown unprecedented clinical activity in cancer treatment. Monoclonal antibodies blocking the CTLA4 (cytotoxic-T-lymphocyte-associated protein-4)[1] and PD1/PDL1 (programmed cell death-1 and its ligand) axis were first approved in melanoma. ICI are now recommended for the treatment of over 17 cancer types.[2] By restoring antitumor immune responses, ICI may also induce immune-related adverse events (irAE). irAE are common and their spectrum and frequency depend on the ICI regimen (ICI monotherapy vs. ICI combination), and may affect any organ.[3,4] Fatal toxic irAE may occur rarely in ~0.3-1.3% of treated patients.[5] We recently reported temporal arteritis as a vascular toxicity of ICI.[6] However, the association of ICI with other rheumatic and musculoskeletal irAE (RMS-irAE) remains unclear.[7]

Moreover, the characteristics, timing, and outcomes of these RMS-irAE are unknown. Defining these ICI-associated toxicities is a crucial issue for patient safety, especially given that ICI are combined with other drugs that have their own RMS toxicities. Here, we aimed to further characterize these RMS-irAE by using VigiBase, the international pharmacovigilance database of individual case safety reports (ICSR).

Methods:

Study design and data sources

The study is a disproportionality analysis based on adverse drug reactions (ADR) reported within VigiBase, the WHO global deduplicated database of ICSR, originating from >130 countries.[8] VigiBase contains over 19,000,000 ICSR of suspected ADR (as of 01/2019) submitted by national pharmacovigilance centres since 1967. These reports originate from different sources such as physicians or other healthcare professionals, pharmaceutical companies, and patients, and generally occur post-marketing. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. This study was approved by the Vanderbilt University Medical Center institutional review board (#181337).

Procedures

This observational retrospective study included all RMS-irAE classified by group queries according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) (Supplementary Table 1), between 2008 (date of first ICI ICSR) and 01/01/2019.

Statistical analysis

VigiBase allows for case/non-case analysis (disproportionality analysis), which we utilized to study if suspected drug-induced RMS events were differentially reported with ICI compared with RMS events reported in the full database. Disproportionality can be either calculated by the information component (IC) or reporting odds-ratio (ROR) when using entire database as comparator. Details concerning Bayesian IC calculation are provided in Appendix-1 and have been recently used by our group, for

example to characterize cardiovascular and neurological irAE induced by ICI.[6,8,9] IC_{025} is the lower end of a 95% credibility interval for the IC. A positive IC_{025} (>0) is deemed significant.[6] As compared to Bayesian statistics, disproportionality in VigiBase can also be assessed using a frequentist approach by calculating the ROR-Chi^2.[10] The lower end of ROR 95% confidence interval (CI) ≥1 is the threshold deemed significant. ICI studied were anti-PD1 (nivolumab, pembrolizumab, cemiplimab), anti-PD-L1 (atezolizumab, avelumab, durvalumab), and anti-CTLA4 antibodies (ipilimumab, tremelimumab).

Characteristics of cases were described in terms of medians (with interquartile range) for quantitative variables, and in terms of effective and proportion for qualitative ones. Comparisons were performed by Chi^2 or Kruskal-Wallis with Dunn's post-tests, as appropriate. Time to onset was compared using Log-rank test. P-value<0.05 was deemed significant.

Ethical approval information: The use of confidential, electronically processed patient data was approved by the French National Commission for Data Protection and Liberties (Commission Nationale de l'Informatique et des Libertés; reference number, 1922081).

Results

Spectrum of RMS-irAE as a function of ICI regimen, sex and cancer type.

We found 54,416 ADR associated with ICI from a total of 14,988,450 ADR associated with any drug(s) in the full database since 2008 (date of first ICI-ADR report).

Six RMS-irAE representing a total of 1,288 ICSR were significantly over-reported with ICI versus the full database (Table 1, Table 2): polymyalgia rheumatica (PMR, n=76, ROR=14.6 [11.6-18.4], IC_{025}=3.34), sarcoidosis (n=94; ROR=9.6 [7.9-11.9]; IC_{025}=2.85), Sjogren's syndrome (n=49; ROR=6.9 [5.2-9.2]; IC_{025}=2.24), myositis (n=465; ROR=4.9 [4.5-5.4]; IC_{025}=2.12), arthritis (n=606; ROR=1.4 [1.3-1.5]; IC_{025}=0.34) and scleroderma (n=17; ROR=2.0 [1.2-3.2]; IC_{025}=0.17). IC values and their 95% credibility interval over time for these RMS-irAE are displayed in Figure 1. These RMS-irAE were rarely (19/1,288 (1.5%)) overlapping with each other's (Figure 2) but were more frequently overlapping with at least one irAE affecting other organs (11.8-54.6%). Most of these RMS-irAE were reported post-marketing (67.3-81.9%) by health professionals (82.3-93.8%). Fifty percent or more of the ICSR originated from either the Americas or Europe. Other RMS conditions (e.g. lupus) were not over-reported in ICI population (Table 1).

RMS-irAE over-reporting in relation to the ICI regimen is displayed in Table 2. Arthritis, myositis, and Sjogren's syndrome were over-reported in patients treated with ICI combination therapy versus those treated with ICI monotherapy (ROR=1.6-2.9, $p<0.05$) and more frequently reported on anti-PD1/PDL1 monotherapy vs. anti-CTLA4 monotherapy (ROR=2.1-4.4, $p<0.05$). Polymyalgia rheumatica irAE were more frequently reported on anti-PD1/PDL1 monotherapy vs. anti-CTLA4

monotherapy (ROR=5.6 [1.8-17.7]). ICI was reported as the only suspected drug in the vast majority of the ICSR. Sarcoidosis-irAE were more associated with melanoma (57 sarcoidosis-irAE occurred in patients treated for melanoma over a total of 82 sarcoidosis-irAE with an identifiable reported cancer, 69.5%) versus other RMS-irAE (34.1-46.7%, p<0.0001, Table 3). Myositis-irAE were more associated with renal carcinoma (11.8% vs 1.2-8.3%, p=0.02, Table 3). In addition, the proportion of male was higher in myositis-irAE (70.5%; p<0.0001, Table 3) whereas it ranged from 50% to 57.1% with other RMS-irAE.

Characteristics and outcomes of RMS-irAE

The main characteristics of the various RMS-irAE are shown in Table 4 and their times to onset are shown in Figure 2. Median time to onset occurred early for myositis (31 days [19.2-57.8]) and was the most delayed for scleroderma (395 days [323.8-457.2], p<0.0001). The fatality rate for RMS-irAE was 12.1% (n=132/1,087) ranging from 24% for myositis (n=106/441) to much lower rate for other RMS-irAE (0-6.7%, p<0.0001). Myositis-irAE fatality rate was unchanged over years of reporting (first case 2012, Figure 3, p=0.53). Myositis-irAE were particularly notable because of fatality rates, especially when concurrent with myocarditis (34/60, 56.7%) or with myasthenia gravis-like symptoms (17/61, 27.9%), compared to myositis without these latter irAE (55/344, 16%) (p<0.0001, Figure 3). ICI-induced myositis was the only RMS-irAE group with fatal cases due to the toxicity, when the cause of death was specified (n= 66/87, 75.9%).

Discussion

This study is the largest and most comprehensive clinical characterisation of RMS-irAE associated with ICI utilizing an analysis of ICSR from the WHO's pharmacovigilance database. We identify 6 groups of RMS-irAE: arthritis, myositis, sarcoidosis, Sjogren's syndrome, scleroderma, and polymyalgia rheumatica. No other systemic condition, like systemic lupus erythematosus or mixed connective tissue disorder, had a significant over-reporting signal (Table 1). Among these RMS-irAE, myositis-irAE is the toxicity of most concern. It occurred earliest after initiation of ICI therapy (almost all within 3 months, median 31 days after first ICI exposure) and carried the highest fatality rate, particularly when concurrent myocarditis was reported (56.7%). Clinicians should be vigilant and assess for myocardial pathology in case of myositis presentation.[11] Another important cause of death in ICI-myositis patients was respiratory failure, presumably due to diaphragmatic involvement, which can present as a myasthenia gravis-like syndrome.[12] High fatality rates in myositis patients contrast with the low (<5%) fatality rate with other RMS-irAE. These disparities in terms of outcome may have an impact for the treatment of RMS-irAE. Due to its severity, myositis, especially with concomitant myocarditis or myasthenia gravis like symptoms, requires immunosuppressive treatments. Yet, the therapeutic strategy needs to be improved with currently no decrease of the mortality rate over time. New targeted treatment, such as CTLA-4 agonist (e.g., abatacept) has shown preliminary signs of efficacy. [13] As for the other RMS-irAE, the best treatment management is still debated in the literature. [14]

We found that ICI-arthritis (Supplemental Table 2) were numerically the most frequent irAE within RMS-irAE. ICI combination therapy was a risk factor for ICI-arthritis stressing the synergistic roles of PD1 and CTLA4 pathways in inflammatory

arthritis. Consistently, mice genetically deficient in PD-1 develop severe collagen-induced arthritis[15]; moreover, rheumatoid arthritis is associated with PD1 gene polymorphisms.[16]. Abatacept, a CTLA-4 agonist, showed efficacy in RA and juvenile idiopathic arthritis and has been approved for these indications.[17] Use of CTLA-4 agonists in other RMS diseases (herein, associated with ICI) might deserve further exploration. Conversely, ICI were not associated with over-reporting of lupus in this study; consistently abatacept failed to demonstrate therapeutic effects in lupus setting.[18]

Although the incidence of these RMS-irAEs cannot be determined from VigiBase, some data from clinical trials and single center prospective studies are available.[19,20] According to FDA labels, incidence of arthritis, myositis, PMR and sarcoidosis reported during trials were low (<1%). Interestingly, scleroderma and Sjogren's syndrome have been rarely reported and are two irAE identified in this work and not referenced by ICI FDA's labels. Real-life data from a cohort including 504 patients on ICI have estimated that rheumatic manifestations (including rheumatoid arthritis (RA) (n=7), PMR (n=11), psoriatic arthritis (n=2) and non-inflammatory conditions (n=15)) were retrieved in 6.6% (n=35/504).[19] Another study of 908 patients treated by ICI found that systemic immune irAE (including polyarthritis (n=12), Sjogren's syndrome (n=3), sarcoidosis (n=2) and autoimmune cytopenia (n=2)) were observed in 2.3% of patients (n=21/908).[20]

The limitations of this study include the method of data collection and the presence of missing data. Indeed, we used a declarative pharmacovigilance database with a limited access to precise data including biological tests and imaging results. The RMS-irAE were defined as reported terms in the database and we could not review the cases to confirm the diagnosis or reassess the liability of the drug in the

occurrence of the toxicities. Despite these limitations, we were able to characterise large series of RMS-irAE. In many cases, the phenotypes of these RMS-irAE are different from spontaneous autoimmune diseases. The myositis-irAE is a specific clinical entity with frequent oculomotor disorders and cardiac involvement, characteristics that are not associated with idiopathic inflammatory myopathies.[21] Compared to spontaneous autoimmune diseases, RMS-irAE occurred more frequently in men with a higher median age, an observation that was confirmed by other studies. In a series of 26 patients with Sjogren's syndrome, 58% were men with a mean age at diagnosis of 63.6 years and a seronegative profile (only 20% with anti-SSA antibodies). [22] In a series of 49 patients with PMR-like irAE, 75% of the patients met the ACR/EULAR (American College of Rheumatology / European League Against Rheumatism) criteria of PMR but frequently with atypical features.[23] Altogether, these data suggest that RMS-irAE may have different pathophysiological mechanisms as compared to the primitive RMS conditions.

To conclude, using a large pharmacovigilance database we were identified the spectrum and fatalities of RMS-irAE. We showed that myositis is the most severe RMS-irAE, and arthritis is the most frequent RMS whereas sarcoidosis, Sjogren's syndrome, scleroderma, and polymyalgia rheumatica occur less frequently. Additionally, RMS-irAE have different time to onset and the type RMS-irAE may depend on the type of ICI regimen (PD1/PDL1 versus CTLA4, monotherapy versus combination therapy). This observation highlights the possible relevance of immune checkpoint pathways as therapeutic options in some spontaneous autoimmune rheumatic and musculoskeletal diseases.

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Table 1. Rheumatic and musculo-skeletical immune-related adverse events reported with ICI versus those reported in the full database from VigiBase, from Jan 01, 2008, to Jan 01, 2019.

	Overall ICI	Full database (starting 2008)	IC / IC_{025}
Total number of ICSR available	54,416	14,988,450	
Number of ICSR by irAE subgroups			
Acute and chronic sarcoidosis	**94 (0.17%)**	**2,772 (0.02%)**	**3.16/2.85**
Myositis	**465 (0.86%)**	**26,722 (0.18%)**	**2.26/2.12**
Connective tissue disorders	**196 (0.36%)**	**27,115 (0.18%)**	**0.99/0.78**
- Polymyalgia rheumatica	**76 (0.14%)**	**1,504 (0.01%)**	**3.68/3.34**
- Sjogren's syndrome	**49 (0.09%)**	**2,000 (0.01%)**	**2.67/2.24**
- Scleroderma	**17 (0.03%)**	**2,385 (0.02%)**	**0.93/0.17**
- Mixed connective tissue disease	3 (0.006%)	189 (0.001%)	1.56/-0.49
- Lupus erythematosus	34 (0.06%)	15,774 (0.11%)	-0.74/-1.27
Arthritis	**606 (1.11%)**	**121,811 (0.81%)**	**0.45/0.34**
Synovial and bursal disorders	39 (0.07%)	10,689 (0.07%)	0.01/-0.48
Musculoskeletal and connective tissue neoplasms (excl. metastases)	28 (0.05%)	7,381 (0.05%)	0.06/-0.52
Fractures	220 (0.40%)	111,133 (0.74%)	-0.87/-1.07
Bone disorders (excl. congenital and fractures)	256 (0.47%)	134,807 (0.90%)	-0.93/-1.12
Amyloidosis	5 (0.009%)	1,065 (0.007%)	0.33/-1.19
Musculoskeletal and connective tissue deformities (including intervertebral disc disorders)	55 (0.10%)	41,111 (0.27%)	-1.43/-1.84
Tendon, ligament and cartilage disorders	38 (0.07%)	46,315 (0.31%)	-2.13/-2.63
Osteonecrosis	27 (0.05%)	31,974 (0.21%)	-2.08/-2.68
Immunodeficiency syndrome (not HIV or not Primary)	7 (0.01%)	5,606 (0.04%)	-1.48/-2.74
Osteoporosis	17 (0.03%)	26,445 (0.18%)	-2.46/-3.23
Musculoskeletal and connective tissue disorders congenital	2 (0.004%)	10,006 (0.07%)	-3.88/-6.47

Data are n (%) unless otherwise stated. ICI refers to any ICSR reported for treatment with nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. A positive IC025 value (>0) is the traditional threshold used in statistical signal detection with VigiBase.

Abbreviations: Excl: excluding; ICSR: individual case safety reports; ICI: immune checkpoint inhibitors; IC: information component; IC_{025}: lower end of a 95% credibility interval for the IC.

Table 2. Selected rheumatic and musculoskeletal immune-related adverse events (detected as signals) reported for ICI versus the full database from VigiBase, from Jan 01, 2008, to January 01, 2019.

Total number of ICSR	Overall ICI (n:54,416)			Full database (full; starting 2008*; n:14,988,450)	ROR and 95% CI [,] anti-PD-1 or anti-PD-L1 vs anti-CTLA-4 monotherapy	ROR and 95% CI [,] combination ICI vs monotherapy	ROR and 95% CI [,] ICI vs full database	IC/IC_{025} ICI vs full database
	MONO (n:49,393)		COMBO (n:5,023)					
	MONO-PD1 (n:39,768)	MONO-CTLA4 (n:9,625)						
Number of ICSR by RMS-irAE subgroups								
Polymyalgia rheumatica	69 (0.17%)	3 (0.03%)	4 (0.08%)	1,504 (0.01%)	**5.6 [1.8-17.7]**	0.55 [0.20-1.50]	**14.6 [11.6-18.4]**	**3.68/3.34**
Acute and chronic sarcoidosis	63 (0.16%)	17 (0.18%)	14 (0.28%)	2,772 (0.02%)	0.9 [0.5-1.5]	1.72 [0.98-3.04]	**9.6 [7.9-11.9]**	**3.16/2.85**
Sjogren's syndrome	36 (0.09%)	2 (0.02%)	11 (0.22%)	2,000 (0.01%)	**4.4 [1.0-18.1]**	**2.85 [1.46-5.58]**	**6.9 [5.2-9.2]**	**2.67/2.24**
Myositis	355 (0.89%)	31 (0.32%)	79 (1.57%)	26,722 (0.18%)	**2.8 [1.9-4.0]**	**2.03 [1.59-2.59]**	**4.9 [4.5-5.4]**	**2.26/2.12**
Arthritis	467 (1.17%)	54 (0.56%)	85 (1.69%)	121,811 (0.81%)	**2.1 [1.6-2.8]**	**1.61 [1.28-2.03]**	**1.4 [1.3-1.5]**	**0.45/0.34**
Scleroderma and associated disorders	15 (0.04%)	2 (0.02%)	0 (0%)	2,385 (0.02%)	1.8 [0.4-7.9]	NA	**2.0 [1.2-3.2]**	**0.93/0.17**

Data are n (%) unless otherwise stated. ICI refers to nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, ipilimumab, and tremelimumab. Anti-PD1 or anti-PDL1 monotherapy refers to any ICSR associated with any of the following six drugs when used without other ICI: nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, or durvalumab. Anti-CTLA4 monotherapy refers to any ICSR associated with ipilimumab or tremelimumab used without other ICI. Combination ICI refers to any ICSR reported with at least one anti-PD1 or anti-PDL1 combined with an anti-CTLA4.

Abbreviations: MONO: monotherapy; COMB: combination therapy; PD1/PDL1: Programmed death-1/ligand-1; CTLA4: cytotoxic T lymphocyte antigen-4, CI=confidence interval, ICSR=individual case safety reports, IC=information component. IC_{025}=lower end of the 95% credibility interval for the IC; ICI=immune checkpoint inhibitors, NA= not applicable, ROR=reporting odds ratio, irAE: immune-related adverse event.

*First reports of ICSR associated with ICI started in 2008.

Table 3. Demographics of reported individual case safety reports (ICSR) with rheumatic and musculoskeletal immune-related adverse events (detected as signals) reported for ICI in VigiBase.

	Arthritis		**Myositis**		**Polymyalgia rheumatica**		**Sarcoidosis**		**Scleroderma**		**Sjogren's syndrome**	
Total ICSR number (N)	606		465		76		94		17		49	
Age: years, median [IQR], (n available)	66	[57-72] (n=377)	70	[63-76] (n=357)	74	[65.3-78] (n=46)	57	[48-65.3] (n=64)	65	[61-70] (n=13)	68	[60.5-70.3] (n=40)
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Male sex	301/534	56.4%	310/440	70.5%	32/56	57.1%	47/87	54.0%	7/14	50.0%	27/48	56.3%
Indications												
Melanoma	194/503	38.6%	139/408	34.0%	25/56	44.6%	57/82	69.5%	7/15	46.6%	22/48	45.8%
Pulmonary cancer	209/503	41.6%	151/408	37.0%	23/56	41.1%	17/82	20.7%	2/15	13.3%	12/48	25.0%
Renal cancer	34/503	6.7%	48/408	11.8%	4/56	7.1%	1/82	1.2%	1/15	6.7%	4/48	8.3%
Urothelial and bladder cancer	12/503	2.4%	17/408	4.2%	2/56	3.6%	2/82	2.4%	1/15	6.7%	2/48	4.2%
Hematology	13/503	2.6%	2/408	0.5%	0/56	0%	3/82	3.6%	3/15	20.0%	4/48	8.3%
Other cancers	41/503	8.1%	51/408	12.5%	2/56	3.6%	2/82	2.4%	1/15	6.7%	5/48	10.4%
ICI regimen												

Monotherapy	521/606	86.0%	386/465	83.0%	72/76	94.7%	80/94	85.1%	17/17	100.0%	38/49	77.6%
Nivolumab	264/521	50.7%	203/386	52.6%	27/72	37.5%	18/80	22.5%	7/17	41.2%	16/38	42.1%
Pembrolizumab	178/521	34.2%	129/386	33.4%	39/72	54.2%	41/80	51.3%	7/17	41.2%	18/38	47.4%
Avelumab	1/521	0.2%	3/386	0.8%	0/72	0%	1/80	1.2%	0/17	0%	0/38	0%
Durvalumab	10/521	1.9%	6/386	1.5%	1/72	1.3%	1/80	1.2%	1/17	5.8%	0/38	0%
Atezolizumab	12/521	2.3%	13/386	3.4%	2/72	2.8%	2/80	2.5%	0/17	0%	1/38	2.6%
Sequential anti PD1/PDL1 monotherapy	2/521	0.4%	1/386	0.3%	0/72	0%	0/80	0%	0/17	0%	1/38	2.6%
Ipilimumab	54/521	10.3%	31/386	8.0%	3/72	4.2%	17/80	21.3%	2/17	11.8%	2/38	5.3%
Combination therapy	85/606	14.0%	79/465	17.0%	4/76	5.3%	14/94	14.9%	0/0	0%	11/49	22.4%
Nivolumab and ipilimumab	71/85	83.5%	76/79	96.2%	4/4	100.0%	11/14	78.6%	0/0	0%	9/11	81.8%
Other combinations	14/85	16.5%	3/79	3.8%	0/4	0%	3/14	21.4%	0/0	0%	2/11	18.2%

Abbreviations: ICI: immune checkpoint inhibitors; ICSR: individual case safety reports; IQR: inter-quartile range; PD1/PDL1: Programmed death-1/ligand-1

Table 4. Spectrum and outcomes of rheumatic and musculoskeletal immune-related adverse events

	Arthritis		**Myositis**		**Polymyalgia rheumatica**		**Sarcoidosis**		**Scleroderma**		**Sjogren's syndrome**	
Total ICSR number (N)	606		465		76		94		17		49	
***De novo* irAE**	561/606	92.6%	463/465	99.6%	66/76	86.8 %	94/94	100%	17/17	100%	49/49	100%
Overlap of RMS-irAE												
Arthritis	NA	NA	4/465	0.9%	6/76	7.9%	0/94	0%	2/17	11.8%	3/49	6.1%
Myositis	4/606	0.7%	NA	NA	1/76	1.3%	0/94	0%	0/17	0%	1/49	2.0%
Polymyalgia rheumatica	6/606	1%	1/465	0.2%	NA	NA	0/94	0%	0/17	0%	2/49	4.1%
Sarcoidosis	0/606	0%	0/465	0%	0/76	0%	NA	NA	0/17	0%	0/49	0%
Scleroderma	2/606	0.3%	0/465	0%	0/76	0%	0/94	0%	NA	NA	0/49	0%
Sjogren's syndrome	3/606	0.5%	1/465	0.2%	2/76	2.6%	0/94	0%	0/17	0%	NA	NA
Associated non-RMS concurrent irAE*												
Endocrine	67/606	11.1%	37/465	8.0%	6/76	7.9%	9/94	9.6%	1/17	5.9%	12/49	24.5%
Hepatic	22/606	3.6%	80/465	17.2%	1/76	1.3%	5/94	5.3%	0/17	0%	1/49	2.0%
Gastrointestinal	52/606	8.6%	9/465	1.9%	4/76	5.3%	2/94	2.1%	0/17	0%	8/49	16.3%
Cutaneous	77/606	12.7%	19/465	4.1%	5/76	6.6%	10/94	10.6%	1/17	5.9%	4/49	8.2%
Nephrological	6/606	1%	21/465	4.5%	4/76	5.3%	1/94	1.1%	1/17	5.9%	3/49	6.1%
Neuro-ophthalmologic - Myasthenia gravis-like	14/606 0/606	2.3% 0%	87/465 71/465	18.7% 15.3%	3/76 0/76	3.9% 0%	5/94 0/94	5.3% 0%	0/17 0/17	0% 0%	3/49 0/49	6.1% 0%
Pulmonary	27/606	4.5%	34/465	7.3%	2/76	2.6%	3/94	3.2%	1/17	5.9%	5/49	10.2%
Cardiotoxicity - Myocarditis	9/606 3/606	1.5% 0.05%	104/465 60/465	22.4% 12.9%	1/76 0/76	1.3% 0%	1/94 0/94	1.1% 0%	0/17 0/17	0% 0%	0/49 0/49	0% 0%

Time to onset												
Median, days [IQR], n available	81	[25-166.5], n=173	31	[19.3-57.8], n=174	110	[63-140], n=25	174	[71.5-275.8], n=10	395.5	[323.8-457.2], n=4	88	[47.8-145.8], n=16
Outcome of irAE												
Death	22/458	4.8%	106/441	24.0%	1/60	1.7%	2/86	2.3%	1/15	6.7%	0/46	0%
Severe outcome**	158/458	34.5%	340/441	77.1%	21/60	35.0 %	23/86	26.7%	3/15	20.0%	9/46	19.6%

Abbreviations: RMS: rheumatic and musculoskeletal; ICSR: individual case safety reports; IQR: inter-quartile range; irAE: immune-related adverse events; NA: Not applicable; PD1/PDL1: Programmed death-1/ligand-1

* Associated non-RMS concurrent irAE classified by group queries were performed according to the Medical Dictionary for Drug Regulatory Activities (MedDRA), detailed in supplementary table 3.

** Severe outcome was defined by at least one of the following terms: death, life threatening, disabling/incapacitating, caused/prolonged hospitalization.

Figure legends.

Figure 1. Information component (IC) and its 95% credibility interval over time for arthritis (A), myositis (B), sarcoidosis (C), polymyalgia rheumatica (D), Sjogren's syndrome (Sd, E) and scleroderma (F). The error bars show the 95% credibility interval of the information component (IC_{025}–IC_{975}). An IC_{025} value>0 is deemed significant.

Figure 2. Time to onset for the rheumatic and musculoskeletal immune-related adverse events (RMS-irAE); comparison between curves was performed using log rank test (A). Overlap between RMS-irAE identified as signals (B). Due to diagram limitation, overlap between myositis and Sjogren's syndrome (n=1) was not displayed.

Figure 3. Mortality rate of reported immune checkpoint inhibitors-associated myositis depending on the concurrent clinical presentation (association or not with myocarditis or myasthenia gravis like syndrome) (A); and their evolution over years of reporting (B).

Figure 1.

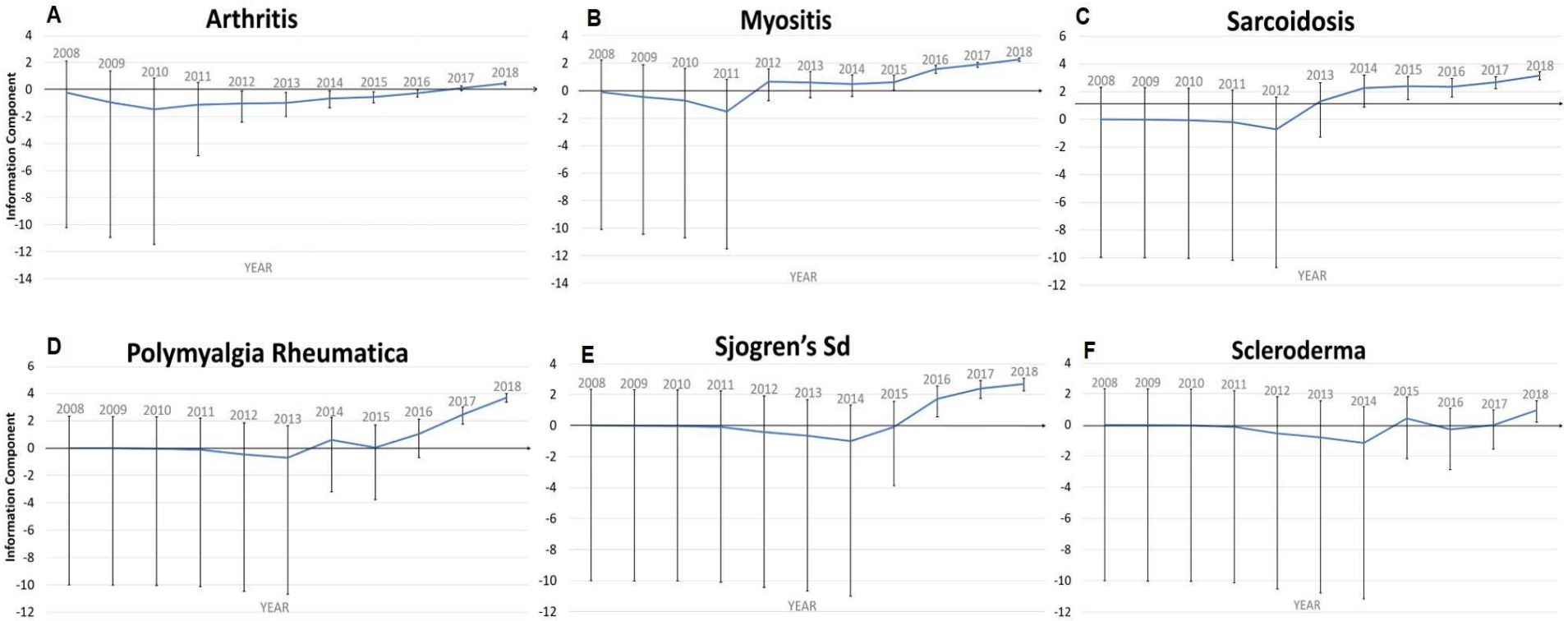

A
Arthritis
B
Myositis
C
Sarcoidosis
D
Polymyalgia Rheumatica
E
Sjogren's Sd
F
Scleroderma
Information Component
YEAR

Figure 2.

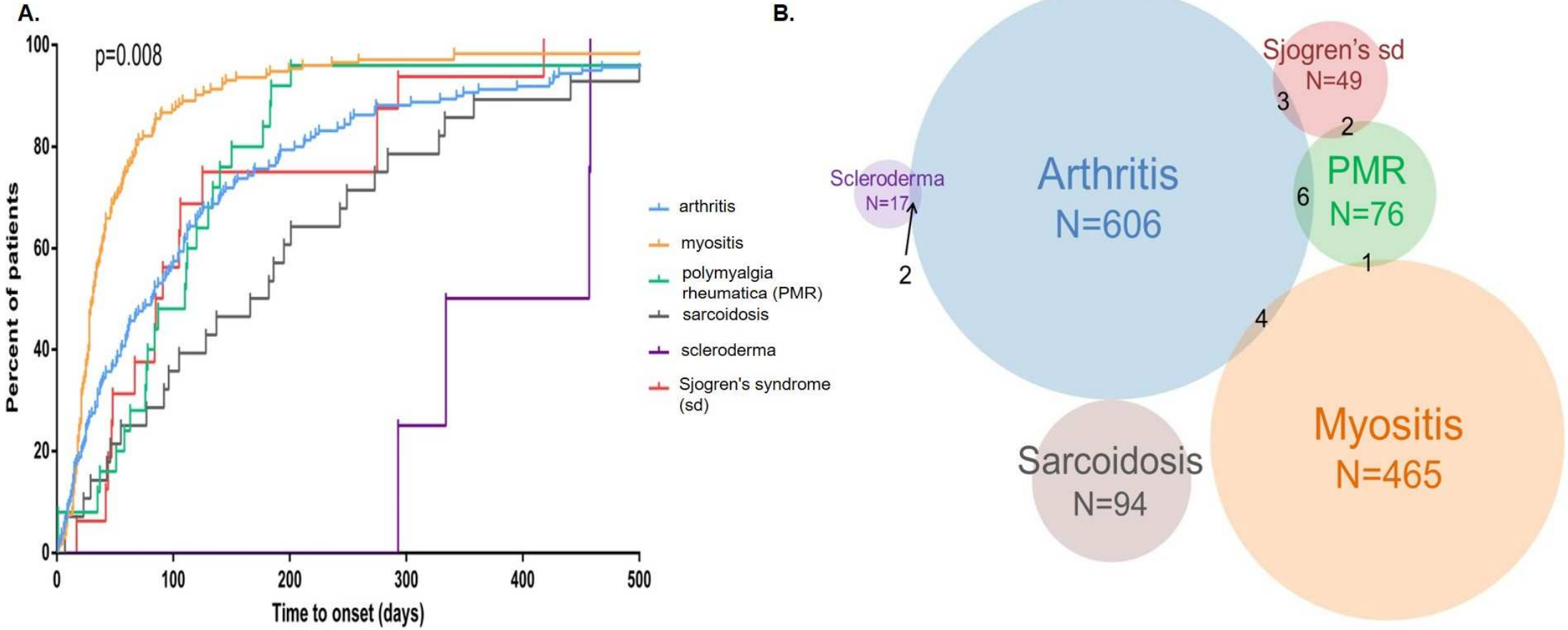
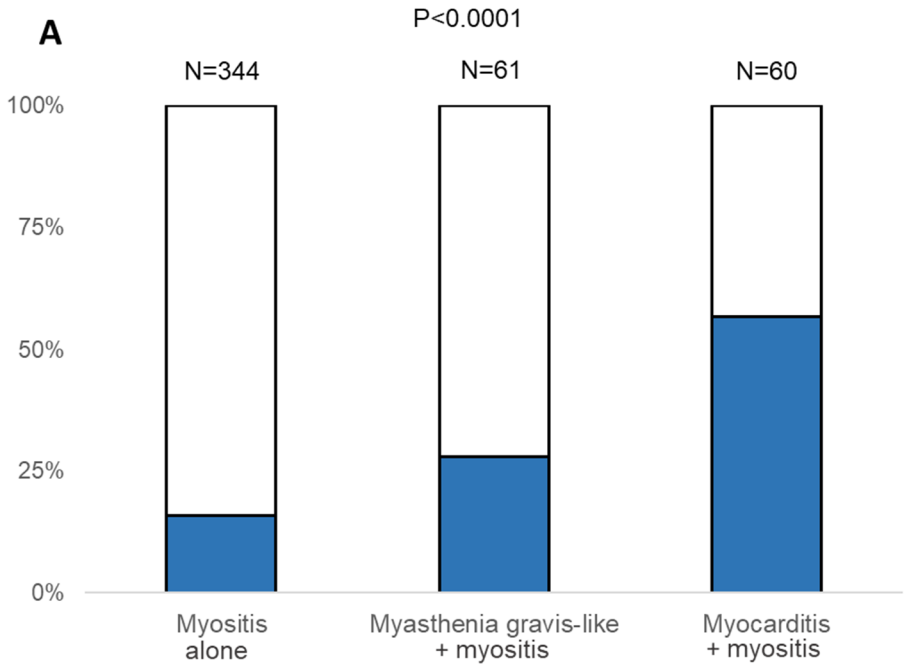
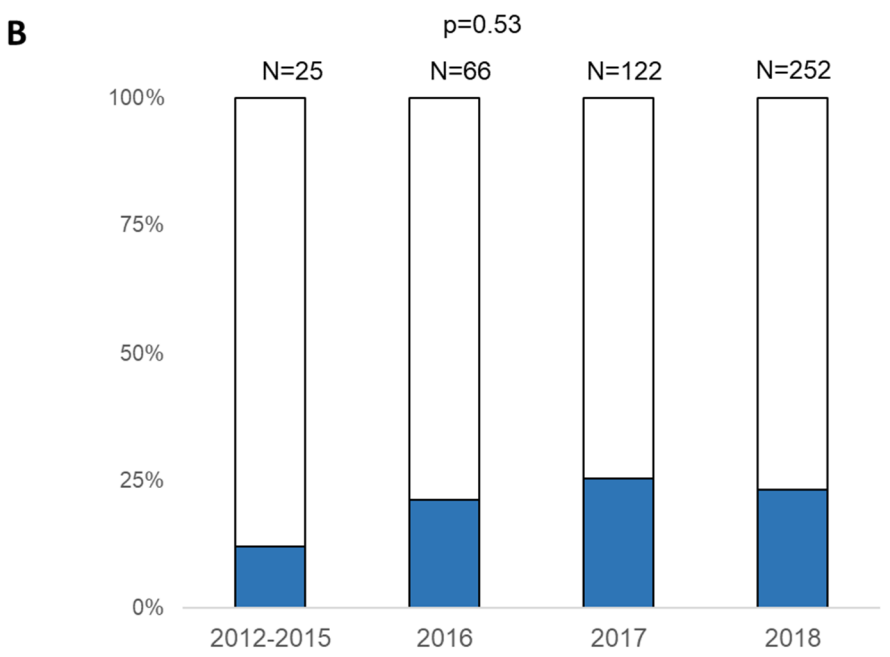

A.
p=0.008
Percent of patients
Time to onset (days)
arthritis
myositis
polymyalgia rheumatica (PMR)
sarcoidosis
scleroderma
Sjogren's syndrome (sd)
B.
Scleroderma N=17
2
Arthritis N=606
Sjogren's sd N=49
3
2
PMR N=76
6
1
4
Sarcoidosis N=94
Myositis N=465

Figure 3.



Mortality rate of myositis patients depending on the concurrent clinical presentation



Evolution of mortality rate over time for myositis patients