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As shown by Kostine et al.[1], and recently underlined by Ceccarelli et al.[2], rheumatic inflammatory disorders induced by anti-cancer therapy are becoming a major concern for rheumatologists at the era of immune checkpoint inhibitors (ICIs). Beyond inflammatory arthritis, which may concern 10-20% of patients, myositis represents a rare (<1%) but potentially life-threatening event. We thus aimed at investigating the risk of ICI-related myositis in real-life setting using VigiBase, the World Health Organization's pharmacovigilance database.

First, we analyzed the myositis case associated with ICIs (anti-PD-1/PD-L1 and anti-CTLA-4 agents) reported to VigiBase. From 14,786,263 adverse drug reactions (ADRs) recorded between January 1st, 2008 to February 12th, 2019, we identified 54,085 ICI-related-ADRs including 345 myositis (0,6%) (Table 1). Among myositis cases, 85,2% occurred with anti-PD-1 or anti-CTLA-4 monotherapies, while 14,8% with combination therapy. Lung (34.8%) and skin cancers (34.2%) were the most frequent indications for ICI therapy. ICI-related-myositis was more frequent in male patients, and over 65 years. The median time to onset was 4 to 5 weeks ranging from 1 day to 20 months, consistently with other reports[3,4]. Almost all ICI-related-myositis (95,3%) were considered serious (*i.e.* requiring at least a hospitalization), with a fatality rate of 22.3%. Myocarditis and myasthenia were associated with ICI-related-myositis in 11.3% and 11.9% of cases and resulted in death in 51.3% and 26.8%, respectively.

Second, using case/non-case analyses[5], we found that myositis was more than seventeen times more reported with ICI agents than with any other drugs (Reporting Odds Ratio (ROR) 17.3; 95% CI: 15.5–19.2). Moreover, myositis was more reported in the group of anti-PD-1/PD-L1 monotherapy compared to anti-CTLA-4 monotherapy (OR=2.4, 95% CI 1.6–3.5). Myositis was also more frequently reported in patients using ICI combination therapy versus those using ICI monotherapy (OR=1.8, 95% CI 1.3–2.4). Similar results were obtained after adjusting for potential confounders such as sex, age and reporter type.

Herein, we report a considerable outbreak of ICI-related myositis in the past years. Vigibase represents the largest medical post-marketing surveillance database allowing the study of ADRs in real conditions of use and facilitates the study of rare ADRs such as myositis, which is hardly observed in clinical trials or observational studies with limited sample size. A previous work by Anquetil *et al.* identified 180 ICI-related-myositis reported through March 2018 [6]. With 165 additional cases, we report the largest series of ICI-related-myositis and further characterize this unique ICI-related-ADR using disproportionality (case/non-case) analyses, a method designed for early detection of pharmacovigilance signals[41]. Although disproportionality estimates cannot be interpreted as risk estimates, they have been shown to be significantly correlated to risk estimates[7].

Interestingly, ICI-related-myositis seems to differ greatly in comparison to primitive inflammatory muscle disorders (IMD), suggesting a novel and unique emerging autoimmune entity with specific concerns. Indeed, clinical manifestations in ICI-related-myositis include frequent bulbar symptoms, ptosis and oculomotor impairment, whereas those are rare in primitive myositis, but may occur in myasthenia gravis, a disorder affecting neuromuscular junction. Hence, the association between immune-related myositis and myasthenia gravis may not be fortuitous as shown here and by others even if specific antibodies against acetylcholine receptor may be lacking[8–10,]. Interestingly, the great majority of myasthenia gravis cases was not observed with anti-CTLA-4 agents, but rather with anti-PD-1/PD-L1 agents, suggesting an increased risk with the latter, in line with our proper observations[15].

Of note, the majority of the reports were merely qualified as “myositis”, even if some also referred to specific entities. This may originate from reporting difficulties but questions the complex nosology in IMD. Actually, the classification of IMD improved considerably in the last years and now distinguishes definite entities according to clinical presentation, specific auto-antibody profiles, histological patterns, associated with distinct prognoses. If these data may be lacking in Vigibase, case reports have characterized ICI-myositis as driven by T-CD8-lymphocyte and macrophages infiltrates together with fiber necrosis, a description close to necrotizing myositis[16]. Reports have described circulating antibodies against anti-synthetase, PM-SCL, SRP and TIF-1-gamma[12,14]. Noteworthily, the latter is strongly associated with cancer and considered as a paraneoplastic syndrome (PNS) in this context. By analogy with other preexisting autoimmune conditions, the use of ICIs in the context of PNS may be associated with an increased risk for immune toxicity, including PNS flare[14]. Beyond these considerations, the association with other autoimmune entities may also be of interest, since myositis can also stand as a manifestation of other connective tissue disorders, such as lupus, scleroderma or Sjögren syndrome[15].

Importantly, another major concern with ICI-related-myositis is the strong association with myocarditis. In accordance with our results, other series [6 12] revealed high prevalence of myocarditis (ranging from 15 to 32%) in patients with ICI-related-myositis, together with high lethality (up to 50%). In another study on VigiBase, which focused on ICI-related myocarditis, musculoskeletal disorders were the most frequent concurrent complications occurring along with myocarditis[16]. Thus, the increased prevalence of myocarditis may explain the higher mortality rate in ICI-related-myositis compared with primitive IMD, and prompts for a systematic cardiac screening in these patients.

In conclusion, despite the limitations inherent to pharmacovigilance studies which are concerned with under-reporting, we confirm a strong signal suggesting an increasing risk of myositis associated with ICIs, especially anti-PD-1/PD-L1 agents or when these drugs were used in combination with anti-CTLA-4 agents. Prospective studies will be necessary to better investigate this risk, and better define the place of ICI-related-myositis within the spectrum of IMD. In the meantime, clinicians' awareness and vigilance are needed to improve early detection and management of this unique and severe complication. In this context, the specific risk of myocarditis, a life-threatening complication, prompts to a systematic screening.

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Table. Characteristics of ICI-exposed myositis cases

Characteristics	ICI-exposed myositis cases (n= 345)
Age (years), median (P25-P75) (n=265)	71 (63-76)
Sex, n (%)	
Male	228 (69.7)
Female	99 (30.3)
Unknown	18
Reporter type, n (%)	
Health professional	293 (86.2)
Other	47 (13.8)
Unknown	5
Reporting year, n (%)	
2019	4 (1.2)
2018	184 (53.3)
2017	90 (26.1)
2016	47 (13.6)
2008-2015	20 (5.8)
Cancer type, n (%)	
Lung cancer	111 (34.8)
Skin cancer	109 (34.2)
Melanoma	102 (32.0)
Other cancers	32 (31%)
Exposure to ICIs	
Monotherapy, n (%)	294 (85.2)
Anti-PD-1	252 (73.0)
Nivolumab	154 (44.6)
Pembrolizumab	97 (28.1)
Nivolumab or pembrolizumab	1 (0.3)
Anti-PD-L1	15 (4.3)
Atezolizumab	7 (2.0)
Avelumab	3 (0.9)
Durvalumab	5 (1.4)
Anti-CTLA-4	27 (7.8)
Ipilimumab	27 (7.8)
Tremelimumab	0 (0.0)
Combination therapy	51 (14.8)
Nivolumab/ipilimumab	49 (14.2)
Pembrolizumab/ipilimumab	1 (0.3)
Durvalumab/tremelimumab	1 (0.3)
Time to onset (days) (n=97)	
Median (P25-P75)	33 (19 -57)
Min–Max	1–606
Reported myositis term	
Myositis	276 (80.0)
Dermatomyositis	25 (7.2)
Polymyositis	20 (5.8)
Immune-mediated necrotizing myopathy	13 (3.8)
Orbital myositis	8 (2.3)
Inclusion body myositis	2 (0.6)
Anti-synthetase syndrome	1 (0.3)
Specific co-reported irAEs	
Myocarditis	39 (11.3%)
Myasthenia	41 (11.9%)
Death, n (%)	77 (22.3)