Influenza vaccination and myo-pericarditis in patients receiving immune checkpoint inhibitors: investigating the likelihood of interaction through the Vaccine Adverse Event Reporting System and VigiBase

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SUPPLEMENTARY MATERIALS

Supplementary Table 1 – Case-by-case assessment of reports recorded in VAERS in which influenza vaccine and immune checkpoint inhibitors (ICIs) were concomitantly used.

Supplementary Table 2 – Application of the adapted version of Drug Interaction Probability Scale in cases of myocarditis/pericarditis in which immune checkpoint inhibitors (ICIs) and influenza vaccine were concomitantly administered.

Supplementary Table 1 – Case-by-case assessment of reports recorded in VAERS in which influenza vaccine and immune checkpoint inhibitors (ICIs) were concomitantly used.

Case ID	Drugs	Year	Age/Sex	Reporter country	Reporter qualification	Time to onset (days)	Reactions	Seriousness	Outcome	Concomitant medications	Comorbidities	Management
#1	Influenza vaccine Pembrolizumab	2018	NA/M	NA	Physician	NA	Allergy to vaccine	Not serious	NA	Oxycodone Ondansetron Prochlorperazine	Mesothelioma	NA
#2	Influenza vaccine Pembrolizumab	2018	63/F	US	Physician	1	Fall Head injury Loss of consciousness Lower limb fracture Nausea	Not serious	Recovered	Prednisone Bevacizumab Atorvastatin Losartan Pregabalin Bisacodyl Selenium Vitamin B2	NA	NA
#3	Influenza vaccine Nivolumab	2019	71/M	US	Physician	4 hours	Chills Pyrexia Vomiting	Not serious	Recovered	Gabapentin Triamterene Hydrochlorothiazide Levothyroxine Carbamazepine Phenytoin Budesonide/Formoterol	Seizure COPD Renal cell carcinoma metastazied to lung Previous reaction to influenza vaccine four years ago	Anti-emetics Fluids
#4	Influenza vaccine Nivolumab	2019	82/M	US	Physician	1	Feeling cold Muscular weakness Nausea Tremor Vomiting	Not serious	Recovered	Levothyroxine Prednisone Doxazosin Pneumococcal vaccine	Hypothyroidism Cancer not specified	NA
#5	Influenza vaccine Nivolumab	2018	67/M	NA	Physician	NA	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood bilirubin normal Blood calcium normal Blood chloride increased Blood creatinine normal	Not serious	Not recovered	Pazopanib	Hypertension Clear cell renal cell carcinoma Metastases to lung Alcohol use Metastases to bone Prostate cancer Malignant melanoma	NA

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							Blood potassium					
							normal					
							Blood sodium normal					
							Blood urea increased					
							Carbon dioxide					
							normal					
							Cough					
							Dyspnoea					
							Haematocrit					
							decreased					
							Haemoglobin					
							decreased					
							Mean cell volume					
							normal					
							Neurological					
							examination normal					
							Platelet count normal					
							Psychiatric evaluation					
							normal					
							Radiation					
							pneumonitis					
							Rales					
							Sleep disorder					
							Toxicity to various					
							agents					
							Weight decreased					
							White blood cell					
							count normal					_
#6	Influenza	2019	66/M	NA	Physician	21	Anti-neuronal	Serious	Not	-	Metastatic	Intravenous
	vaccine						antibody	(death)	recovered		melanoma	immunoglobulin
							Antibody test					Prednisone
	Nivolumab						negative					
							Areflexia					
							Asthenia					
							Autonomic nervous					
							system imbalance					
							Blood pressure					
							fluctuation					
							Bradycardia					
							Computerised					
							tomogram abdomen					
							abnormal					
							Computerised					
							tomogram pelvis					
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Withdrawal of life				1	Walking aid user			
support				1	Withdrawal of life			
support				1	support			

CSF: cerebrospinal fluid; COPD: chronic obstructive pulmonary disease; NA: not available

Supplementary Table 2 – Application of the adapted version of Drug Interaction Probability Scale in cases of myocarditis/pericarditis in which immune checkpoint inhibitors (ICIs) and influenza vaccine were concomitantly administered.

Items	Case #1	Case #2	Case#3
	(Influenza vaccine-Nivolumab)	(Influenza vaccine-Pembrolizumab)	(Influenza vaccine-Nivolumab/Ipilimumab)
#1	NA (0 pts)	NA (0 pts)	NA (0 pts)
	A retrospective case-control study [15]	A retrospective case-control study	A retrospective case-control study [15]
	reported cases of myocarditis in patients	[15] reported cases of myocarditis in	reported cases of myocarditis in patients
	treated with ICIs exposed to influenza	patients treated with ICIs exposed to	treated with ICIs exposed to influenza
	vaccine, although less severe compared to	influenza vaccine, although less	vaccine, although less severe compared to
	cases of myocarditis in non-vaccinate	severe compared to cases of	cases of myocarditis in non-vaccinate
	patients	myocarditis in non-vaccinate patients	patients
#2	NA (0 pts)	NA (0 pts)	NA (0 pts)
	A possible PD mechanism of the	A possible PD mechanism of the	A possible PD mechanism of the interaction
	interaction could be theoretically	interaction could be theoretically	could be theoretically hypothesized although
	hypothesized although literature data are	hypothesized although literature data	literature data are lacking
	lacking	are lacking	
#3	NA (0 pts)	NA (0 pts)	NA (0 pts)
	A possible PD mechanism of the	A possible PD mechanism of the	A possible PD mechanism of the interaction
	interaction could be theoretically hypothesized although literature data are	interaction could be theoretically hypothesized although literature data	could be theoretically hypothesized although
	**	are lacking	literature data are lacking
#4	lacking NA (0 pts)	NA (0 pts)	NA (0 pts)
# -	Onset time was not available for this	Onset time was not available for this	Onset time was not available for this report
	report	report	Onset time was not available for this report
#5	NA (0 pts)	NA (0 pts)	NA (0 pts)
""	Dechallenge is unfeasible for vaccines	Dechallenge is unfeasible for vaccines	Dechallenge is unfeasible for vaccines
	considering the peculiarities	considering the peculiarities	considering the peculiarities
	of their administration	of their administration	of their administration
#6	NA (0 pts)	NA (0 pts)	NA (0 pts)
	Rechallenge is unfeasible for vaccines	Rechallenge is unfeasible for vaccines	Rechallenge is unfeasible for vaccines
	considering the peculiarities	considering the peculiarities	considering the peculiarities
	of their administration	of their administration	of their administration
#7	No (+1 pts)	No (+1 pts)	No (+1 pts)
	No underlying diseases or concomitant	No underlying diseases or	No underlying diseases or concomitant drugs
	drugs known to cause or precipitate	concomitant drugs known to cause or	known to cause or precipitate myocarditis
	myocarditis were reported	precipitate myocarditis were reported	were reported
#8	NA (0 pts)	NA (0 pts)	NA (0 pts)
	PD interactions usually do not entail	PD interactions usually do not entail	PD interactions usually do not entail changes
	changes in the concentrations of the object	changes in the concentrations of the	in the concentrations of the object drug, and
	drug, and nivolumab concentrations were	object drug, and pembrolizumab concentrations were not monitored	ipilimumab/nivolumab concentrations were
#9	not monitored		not monitored Yes (+1 pts)
#9	NA (0 pts)	NA (0 pts)	
	No other evidence of the interaction was reported	No other evidence of the interaction was reported	Increase in troponin concentration was reported
#10	NA (0 pts)	NA (0 pts)	NA (0 pts)
"10	Dose adjustments is unfeasible for	Dose adjustments is unfeasible for	Dose adjustments is unfeasible for vaccines
	vaccines considering the peculiarities	vaccines considering the peculiarities	considering the peculiarities
	of their administration	of their administration	of their administration
Total score	1 (Doubtful)	1 (Doubtful)	2 (Possible)
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ICIs were considered as the objective drugs (i.e., the one affected by the presence of another drug), while influenza vaccine was considered as the precipitant drug (i.e., the one causing a change on the object drug).

PD: pharmacodynamic; NA: unknown or non-applicable.