

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 metastasized 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

							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 vaccine Nivolumab	2019	66/M	NA	Physician	21	Anti-neuronal antibody Antibody test negative Areflexia Asthenia Autonomic nervous system imbalance Blood pressure fluctuation Bradycardia Computerised tomogram abdomen abnormal Computerised tomogram pelvis abnormal CSF lymphocyte count normal CSF monocyte count increased CSF protein increased CSF red blood cell count positive	Serious (death)	Not recovered	-	Metastatic melanoma	Intravenous immunoglobulin Prednisone

							CSF white blood cell count increased Cytology normal Death Decreased vibratory sense Demyelinating polyneuropathy Electromyogram abnormal Endotracheal intubation Gait inability Guillain-barre syndrome Heart rate abnormal Hepatic mass Hypotension Immunoglobulin therapy Mechanical ventilation Metastases to central nervous system Muscular weakness Nerve conduction studies abnormal Nuclear magnetic resonance imaging brain abnormal Paraesthesia Plasmapheresis Respiratory distress Sensory loss Tachycardia Walking aid user Withdrawal of life support					
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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 (Influenza vaccine-Nivolumab)	Case #2 (Influenza vaccine-Pembrolizumab)	Case#3 (Influenza vaccine-Nivolumab/Ipilimumab)
#1	NA (0 pts) A retrospective case-control study [15] reported cases of myocarditis in patients treated with ICIs exposed to influenza vaccine, although less severe compared to cases of myocarditis in non-vaccinate patients	NA (0 pts) A retrospective case-control study [15] reported cases of myocarditis in patients treated with ICIs exposed to influenza vaccine, although less severe compared to cases of myocarditis in non-vaccinate patients	NA (0 pts) A retrospective case-control study [15] reported cases of myocarditis in patients treated with ICIs exposed to influenza vaccine, although less severe compared to cases of myocarditis in non-vaccinate patients
#2	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking
#3	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking	NA (0 pts) A possible PD mechanism of the interaction could be theoretically hypothesized although literature data are lacking
#4	NA (0 pts) Onset time was not available for this report	NA (0 pts) Onset time was not available for this report	NA (0 pts) Onset time was not available for this report
#5	NA (0 pts) Dechallenge is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Dechallenge is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Dechallenge is unfeasible for vaccines considering the peculiarities of their administration
#6	NA (0 pts) Rechallenge is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Rechallenge is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Rechallenge is unfeasible for vaccines considering the peculiarities of their administration
#7	No (+1 pts) No underlying diseases or concomitant drugs known to cause or precipitate myocarditis were reported	No (+1 pts) No underlying diseases or concomitant drugs known to cause or precipitate myocarditis were reported	No (+1 pts) No underlying diseases or concomitant drugs known to cause or precipitate myocarditis were reported
#8	NA (0 pts) PD interactions usually do not entail changes in the concentrations of the object drug, and nivolumab concentrations were not monitored	NA (0 pts) PD interactions usually do not entail changes in the concentrations of the object drug, and pembrolizumab concentrations were not monitored	NA (0 pts) PD interactions usually do not entail changes in the concentrations of the object drug, and ipilimumab/nivolumab concentrations were not monitored
#9	NA (0 pts) No other evidence of the interaction was reported	NA (0 pts) No other evidence of the interaction was reported	Yes (+1 pts) Increase in troponin concentration was reported
#10	NA (0 pts) Dose adjustments is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Dose adjustments is unfeasible for vaccines considering the peculiarities of their administration	NA (0 pts) Dose adjustments is unfeasible for vaccines considering the peculiarities of their administration
Total score	1 (Doubtful)	1 (Doubtful)	2 (Possible)

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.