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Challenge of immune-mediated adverse reactions in the emergency department

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Received 19 October 2018
Revised 1 March 2019
Accepted 6 April 2019
Published Online First 21 May 2019

To cite: Daniels GA, Guerrera AD, Katz D, *et al*. *Emerg Med J* 2019;**36**:369–377.

ABSTRACT

Multiple drugs of a new class of cancer treatments called immune checkpoint inhibitors, which work by enabling the immune system to attack tumour cells, have been approved for a variety of indications in recent years. Immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 and programmed death-1, are part of the normal immune system and regulate immune activation. Treatment with inhibitors of these checkpoints can significantly improve response rates, progression-free survival and overall survival of patients with cancer; it can also result in adverse reactions that present similarly to other conditions. These immune-mediated adverse reactions (IMARs) are most commonly gastrointestinal, respiratory, endocrine or dermatologic. Although patients' presentations may appear similar to other types of cancer therapy, the underlying causes, and consequently their management, may differ. Prompt recognition is critical because, with appropriate management, most IMARs resolve and patients can continue receiving immune checkpoint inhibitor treatment. Rarely, these IMARs may be life-threatening and escape detection from the usual evaluations in the emergency environment. Given the unusual spectrum and mechanism of IMARs arising from immune checkpoint inhibitors, emergency departmentED staff require a clear understanding of the evaluation of IMARs to enable them to appropriately assess and treat these patients. Treatment of IMARs, most often with high-dose steroids, differs from chemotherapy-related adverse events and when possible should be coordinated with the treating oncologist. This review summarises the ED presentation and management of IMARs arising from immune checkpoint inhibitors and includes recommendations for tools and resources for ED healthcare professionals.

INTRODUCTION

The immune system balances complex interactions of danger-recognising defences against external threats, which include both infections and cancer, with tight regulation preventing immune-driven toxicity. This is achieved by distinguishing 'self' from 'non-self' and mounting an attack on invasive, infected or mutated cells, including tumour cells expressing 'non-self' antigens.[1] Some tumours escape elimination by deploying natural immune regulatory molecules which, when released by non-cancerous cells, have a role in suppressing immune recognition and thereby protecting against autoimmunity. These molecules include immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin-containing and mucin domain-containing molecule-3 (TIM-3).[1–5]

Drugs that inhibit immune checkpoints allow the immune system to detect and mount a defence against some cancers (table 1). Since the US Food and Drug Administration approval of ipilimumab to treat metastatic melanoma (in 2011), several intravenous immune checkpoint inhibitors (ICIs) have been approved to treat a range of cancers, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) colorectal cancer (CRC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), cervical cancer, Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma (table 1).[6–11] Members of the ICI class can also be combined, including coadministration of nivolumab with ipilimumab for: (1) unresectable or metastatic melanoma; (2) intermediate- or poor-risk, previously untreated advanced RCC or (3) MSI-H/dMMR metastatic CRC that has progressed after chemotherapy (ie, fluoropyrimidine, oxaliplatin, irinotecan).

ICIs can be administered for first-line therapy of unresectable or metastatic melanoma, NSCLC, and Merkel cell carcinoma, either as monotherapy or in combination with chemotherapy. Candidates for second-line ICI treatment include patients with metastatic, recurrent or locally advanced NSCLC, SCLC, SCCHN or UC who experience disease progression on or after platinum-based chemotherapy; RCC after antiangiogenic therapy; or progressive HCC after sorafenib. Patients with metastatic NSCLC and *EGFR* or *ALK* gene aberrations are eligible to receive medications targeting the PD-1/PD-1 ligand (PD-L1) axis after disease progression with a US-approved tyrosine kinase inhibitor for these abnormalities.

The ICIs are administered as intravenous infusions over 30–90 min, and dosages vary across tumour types. The infusion rate can be decreased (or the infusion interrupted) in the event of mild or moderate infusion reactions (or treatment discontinued in the event of severe or life-threatening reactions). When nivolumab and ipilimumab are combined, nivolumab is administered first (at a dose of 1 mg/kg for unresectable or metastatic melanoma or 3 mg/kg for advanced RCC), followed by ipilimumab (at a dose of 3 mg/kg for unresectable or metastatic melanoma or 1 mg/kg for RCC), for four doses (one every 3 weeks). After this weight-adjusted induction period, nivolumab is

Table 1 Target molecules/mechanism of action and current indications for ICIs[6–11]

Target	Function of targeted checkpoint	Immune checkpoint inhibitor	FDA-approved tumour type*
CTLA-4	► Expressed on: T-cells ► Mechanism: inhibits T-cells after initial activation ► Active in: lymph nodes	Ipilimumab (Yervoy)	► Melanoma ► RCC ► MSI-H/dMMR colorectal cancer
PD-1	► Expressed on: various immune cells ► Mechanism: binds to PD-L1 and PD-L2 on tumour or immune cells to inhibit T-cell activity ► Active in: peripheral tissues with pre-existing inflammation	Nivolumab (Opdivo) Pembrolizumab (Keytruda)	► Melanoma ► SCCHN ► UC ► NSCLC ► SCLC ► MSI-H/dMMR cancers, including colorectal cancer ► Hodgkin's lymphoma ► RCC ► HCC ► Cervical cancer ► Primary mediastinal large B-cell lymphoma ► Merkel cell carcinoma
PD-L1	► Expressed on: various immune cells and tumour cells ► Mechanism: binds to PD-1 and CD80 on T-cells and inhibits T-cell proliferation ► Active in: peripheral tissues	Atezolizumab (Tecentriq) Durvalumab (Imfinzi) Avelumab (Bavencio)	 ► NSCLC ► UC ► Merkel cell carcinoma ► UC

*ICIs are FDA-approved for certain subtypes of patients with these tumour types.
CTLA-4, cytotoxic T-lymphocyte antigen-4; dMMR, mismatch repair deficient; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small cell lung cancer; UC, urothelial carcinoma.

administered at 240 mg every 2 weeks (Q2W) or 480 mg Q4W until disease progression or unacceptable toxicity.[6 7] Patients should be provided information on possible adverse events, including IMARs, with triggers for contacting the treating team and seeking emergency care. This would include symptoms of colitis (>3 stools per day), pneumonitis (worsening cough or shortness of breath) and other moderated changes in symptoms.

The efficacy and safety/tolerability of ICIs have been established in numerous pivotal clinical trials, where these agents have significantly improved various efficacy outcomes across multiple tumour types.[6–11] However, the antitumour effects of ICIs may be accompanied by immune-mediated adverse reactions (IMARs) that resemble autoimmune diseases and can lead to organ dysfunction.[2] These autoimmune conditions may not routinely present to the emergency physician under other circumstances. Early recognition with appropriate evaluation, therapy and triage for further inpatient versus outpatient management is vital to decreasing morbidity for this patient population.[12] IMARs of ICIs may present similarly to adverse events associated with chemotherapy or targeted therapies, but they require different management.[12] Although the oncology team is the first point of contact for patients experiencing IMAR symptoms, these may occur outside hours for the oncology team and many patients will seek help at their local emergency department ED.

Overview of presentation and management principles via case vignettes

Following are examples of cases that may be encountered in the ED, with consideration of consensus clinical practice guidelines to manage them.[12–14]

Vignette 1: ICI-associated colitis

A woman aged 48 years with metastatic melanoma who had been receiving an ICI (CTLA-4 inhibitor) for 4 months presented to the ED with worsening diarrhoea (four to six stools per day more than baseline), abdominal pain and blood in stool. She informed the ED that she was 'on chemo'.

A complete blood count with differential and comprehensive metabolic panel were conducted, with testing for thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate and C reactive protein. To rule out infectious causes, a stool culture was performed and assessed for the presence of *Clostridium difficile*; viruses, including cytomegalovirus; and ova and parasites, which were all negative. She received hydration and was discharged (with email communication to her oncologist) and referred for a gastroenterology consultation. The patient was subsequently prescribed antidiarrhoeal medications after the consult because of continued severity. When the diarrhoea did not abate, the patient underwent colonoscopy, which supported a diagnosis of immune-mediated colitis. Immunotherapy was immediately discontinued, and the patient treated with corticosteroids (prednisone at an initial daily dose of 1 mg/kg). She suffered from immune-mediated colitis for 8 months. Once symptoms returned to grade 1, corticosteroids were tapered over 4–6 weeks.

As illustrated in this vignette (consistent with grade 3 gastrointestinal [GI] toxicity), early recognition and prompt treatment of IMARs are essential to improve patient outcomes (table 2).[15 16] Prompt administration of steroids to balance immune overactivation is also crucial and may prevent multiorgan failure or permanent treatment discontinuation.[15] Systemic immune suppression should have been initiated sooner after ruling out infectious aetiologies. Intravenous steroids were indicated with the first ED evaluation and discharge on oral steroids with follow-up arranged within 1–2 days. Colonoscopy is considered but not always required unless needed for additional diagnostic information. CT of the abdomen and pelvis during workup (or after discharge or hospitalisation) may also be performed to identify immune-mediated colitis early.[13] It is also important in this case to be mindful that GI metastases, which can develop secondary

Table 2 Critical IMARs requiring intervention and management[12–14 18]

IMAR*	Possible presenting signs/ symptoms	Recommended workup	Grade†	Management
Always inform the patient's oncology team so that the ICI can be withheld or discontinued. Inform the on-call oncology coverage for the patient if a decision is made to initiate systemic immunosuppression				
Colitis **prevalence**[6–9]: Anti-PD-(L)1: 1.5% Anti-CTLA-4: 8% Anti-PD-1+anti-CTLA-4: 7%–10% **Rare but serious IMAR to consider: enterocolitis**	▶ Diarrhoea ▶ Abdominal pain ▶ Nausea ▶ Cramping ▶ Blood or mucus in stool ▶ Changes in bowel habits ▶ Fever ▶ Abdominal distension ▶ Obstipation ▶ Constipation	▶ CBC, UEC, LFTs, CRP, TFTs ▶ *Clostridium difficile/cryptosporidium* screening ▶ Consider: – Stool microscopy for leucocytes/parasites – Culture including drug-resistant organisms – Viral PCR – X-ray or CT abdomen/pelvis for colitis, particularly if abdominal pain – TB screen – CT abdomen/pelvis if moderate-to-severe abdominal pain and/or fever and/or vomiting are present – Gastroenterology input – Surgical review for bleeding, pain, distension	Grade 4: life-threatening consequences; urgent intervention indicated	▶ Admission/isolation until infection ruled out ▶ 1–2 mg/kg/day methylprednisolone or equivalent ▶ Consider infliximab if already on steroids for >4 days
			Grade 3: >6 liquid stools per day OR within 1 hour of eating; limiting self-care ADL	▶ Admission if dehydration or electrolyte imbalance ▶ 1–2 mg/kg/day methylprednisolone
			Grade 2: 4–6 liquid stools per day over baseline, or ≥1 of: ▶ Abdominal pain ▶ Mucus or blood in stool ▶ Nausea ▶ Nocturnal episodes	▶ Symptomatic management including fluids ▶ Outpatient management possible with next-day follow-up ▶ Consider 1 mg/kg/day methylprednisolone and/or prednisone at 1/mg/kg/day
Dermatologic (rash, Stevens-Johnson syndrome or toxic epidermal necrolysis) **prevalence (all dermatologic toxicities)**[6 7 10 12 28 29]: Anti-PD-(L)1: 9%–11% Anti-CTLA-4: 29%–50% Anti-PD-1+anti-CTLA-4: 23% **Rare but serious IMAR to consider: Stevens-Johnson syndrome**	▶ Rash ▶ Blistering ▶ Erythema ▶ Skin sloughing ▶ Purpura ▶ Epidermal detachment ▶ Mucous membrane detachment	▶ Physical examination ▶ Exclude other causes	Grade 4: skin sloughing >30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	▶ Intravenous (methyl)prednisolone 1–2 mg/kg ▶ Urgent dermatology review ▶ Inpatient admission; ICU may be required
			Grade 3: rash >30% BSA with moderate or severe symptoms	▶ Topical treatment (potent) ▶ Initiate steroids – If mild to moderate, 0.5–1 mg/kg prednisolone once daily for 3 days – If severe, intravenous (methyl)prednisolone 0.5–1 mg/kg and convert to oral steroids ▶ Consider inpatient admission
			Grade 2: rash covering 10%–30% BSA, potentially symptoms of pruritus or tenderness	▶ Topical emollients ▶ Topical steroids (moderate to potent) once or twice daily±oral/topical antihistamines for itch
Adrenal insufficiency **prevalence: see hypophysitis, which causes central/secondary adrenal insufficiency and other endocrinopathies** Primary adrenal insufficiency is rare but can be serious	▶ Headache ▶ Vision changes ▶ Fatigue ▶ Weakness ▶ Dizziness ▶ Nausea ▶ Vomiting ▶ Diarrhoea	▶ Pituitary axis labs: 09:00 hour cortisol (or random if unwell and treatment cannot be delayed), ACTH, ACTH stimulation test for indeterminate results, metabolic panel (Na, K, CO_2, glucose) ▶ If primary adrenal insufficiency found: – Assess for cause (eg, infection) – Perform adrenal CT for metastasis/haemorrhage ▶ Endocrinology referral	Grade 3/4: severe symptoms: ▶ Severe hypoadrenalism, adrenal crisis (ie, hypotension, severe electrolyte disturbance)	▶ Normal saline 2 L ▶ Intravenous stress-dose corticosteroids – Hydrocortisone 100 mg OR – Dexamethasone 4 mg if stimulation test needed to confirm diagnosis ▶ Consider admission
			Grade 2: moderate symptoms: ▶ Headache but no visual disturbance OR ▶ Fatigue/mood alteration BUT haemodynamically stable, no electrolyte disturbance	▶ 'Stress-dose' at 2×/3× maintenance (prednisone, 7.5 mg daily; hydrocortisone, 20 mg morning, 10 mg afternoon)
Hypophysitis **prevalence**[8 10–13 19 29–31]: Anti-PD-(L)1: <1% Anti-CTLA-4: ≤10%–17% Anti-PD-1+anti-CTLA-4: 9%	▶ Fatigue ▶ Headache ▶ Nausea ▶ Vision changes ▶ Confusion ▶ Polyuria ▶ Anorexia	▶ Visual field assessment ▶ Pituitary axis labs: 09:00 hour cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/free T4 ▶ CNS imaging – CT head – MRI brain (pituitary protocol if available) ▶ Endocrinology referral ▶ Consider neurology consult if needed for pain relief beyond NSAIDs/ paracetamol	Grade 3/4: severe mass effect symptoms: ▶ Severe headache, any visual disturbance OR ▶ Severe hypoadrenalism (ie, hypotension, severe electrolyte disturbance)	▶ Intravenous (methyl)prednisolone 1–2 mg/kg ▶ Start after sending pituitary assessment labs ▶ Analgesia as needed for headache
			Grade 2: moderate symptoms: ▶ Headache but no visual disturbance OR ▶ Fatigue/mood alteration BUT haemodynamically stable, no electrolyte disturbance	▶ Consider: – Cortisol and/or thyroid replacement – Oral prednisolone 0.5–1 mg/kg once daily (start after sending labs for pituitary axis assessment) with oncology input

Continued

Table 2 Continued

IMAR*	Possible presenting signs/symptoms	Recommended workup	Grade†	Management
Hypothyroidism prevalence[6–8 10 11 29 31]: Anti-PD-(L)1: 5%–9% Anti-CTLA-4: <1% Anti-PD-1+anti-CTLA-4: 22%	► Fatigue ► Constipation ► Weight gain ► Hair loss ► Cold intolerance ► Depression	► Thyroid function (free T4, TSH) ► Assess for adrenal insufficiency, which may be concurrent	Grade 4: life-threatening consequences; urgent intervention required	► Start standard thyroid replacement therapy: initial dose can be the full dose (1.6 µg/kg) in young, healthy patients, but a reduced dose of 25–50 µg should be initiated in elderly patients with known cardiovascular disease
			Grade 3: severe symptoms; limiting self-care ADL; hospitalisation indicated	
			Grade 2: symptomatic; thyroid replacement indicated; limiting instrumental ADL	
Hyperthyroidism prevalence[6–8 10 28 29 31]: Anti-PD-(L)1: 1%–5% Anti-CTLA-4: <1% Anti-PD-1+anti-CTLA-4: 8%	► Weight loss ► Palpitations ► Heat intolerance ► Tremors ► Anxiety ► Diarrhoea	► Thyroid function (free T4, TSH)		
			Grade 4: life-threatening consequences; urgent intervention required	► Follow standard therapy for hyperthyroidism ► Thyroiditis is self-limiting and has two phases: – In the hyperthyroid phase, patients may benefit from beta-blockers if symptomatic (eg, atenolol 25–50 mg daily, titrate for HR<90 if BP allows)
			Grade 3: severe symptoms; limiting self-care ADL; hospitalisation indicated	
			Grade 2: symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	
Pneumonitis prevalence (most common lung toxicity)[6–8 10 17 28–31]: Anti-PD-(L)1:<1%–4% Severe: 1%–2% Anti-CTLA-4: <1% Anti-PD-1+anti-CTLA-4: 6%	► Dyspnoea ► Fatigue ► Chills ► Weakness ► Cough ► Headache	► History including travel, allergy, infections ► Blood tests (CBC/UEC/LFTs/TFTs/Ca/ESR/CRP) ► CXR ► CT angiogram ► Respiratory/pulmonology review ► Consider: – Sputum sample and screening for infections	Grade 3/4: severe new symptoms; limiting self-care ADL; new/worsening hypoxia; life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	► Admit to hospital ► Cover with empirical antibiotics ► Intravenous (methyl)prednisolone 1–2 mg/kg/day ► Discuss need for escalation/ventilation
			Grade 2: symptomatic mild/moderate (cough, dyspnoea, chest pain); no hypoxia; vitals normal	► Start antibiotics if infection suspected based on fever, CRP, neutrophils ► Intravenous (methyl)prednisolone 1–2 mg/kg/day and/or oral dosing
Hepatitis prevalence[6–8 10 28 29 31]: Anti-PD-(L)1: <1%–2% Anti-CTLA-4: 11% Anti-PD-1+anti-CTLA-4: 13%	► Jaundice of skin or sclera ► Nausea ► Vomiting ► Abdominal pain ► Fatigue ► Dark urine ► Anorexia	► Metabolic panel or hepatic function panel ► Hepatitis A/B/C serology if not done previously ► Consider: – Ultrasound – CT abdomen/pelvis	Grade 3/4: AST, ALT>5× ULN; total bilirubin>3× ULN	► Start prednisone 1–2 mg/kg/day
			Grade 2: AST, ALT>3 to ≤5× ULN; total bilirubin>1.5 to ≤3× ULN	► Start prednisone 0.5–1 mg/kg/day (or equivalent dose of methylprednisolone)
Encephalitis prevalence[6–8 10 28 31]: Anti-PD-(L)1: <1% Anti-CTLA-4: <1% Anti-PD-1+anti-CTLA-4: <1%	► Confusion ► Altered behaviour ► Headache ► Seizures ► Short-term memory loss ► Depressed level of consciousness ► Focal weakness ► Speech abnormality	► Blood tests: metabolic panel, CBC, ESR, CRP, ANCA (if suspect vasculitis process), morning cortisol, ACTH, thyroid panel including TPO and thyroglobulin ► MRI brain with and without contrast ► Lumbar puncture (cell count, check for HSV/other viral PCRs, oligoclonal bands, check for autoimmune encephalopathy) ► EEG (subclinical seizures)	Grade 3/4: severe, limiting self-care and aids warranted Grade 2: moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)	► Inform oncology team so that ICI can be withheld, intravenous acyclovir until PCR proven negative ► Trial of methylprednisolone 1–2 mg/kg ► Severe/progressing symptoms or oligoclonal bands: – Pulse corticosteroids (methylprednisolone 1 g intravenous daily 3–5 days) plus IVIG 2 g/kg over 5 days
Nephritis prevalence[6 7 10 28 29]: Anti-PD-(L)1:<1%–1% Anti-CTLA-4: <1% Anti-PD-1+anti-CTLA-4: 2%	► Oliguria ► Haematuria ► Peripheral oedema ► Anorexia	► Ask patient about urination frequency ► Review hydration status and medications ► Urine test/culture if symptoms of urinary tract infection ► Dipstick urine and send for protein assessment UPCR ► Renal ultrasound±Doppler if obstruction suspected ► Proteinuria: 24 hours collection or UPCR ► Haematuria: phase contrast microscopy and glomerulonephritis screen	Grade 4: creatinine>6× ULN	► Admit patient for monitoring/fluid balance ► Repeat creatinine every 24 hours ► If worsening or severe renal failure, intravenous (methyl)prednisolone 1–2 mg/kg
			Grade 3: creatinine>3× baseline or >3–6× ULN	

Continued

Table 2 Continued

IMAR*	Possible presenting signs/ symptoms	Recommended workup	Grade†	Management
			Grade 2: creatinine>1.5–3× baseline or >1.5–3× ULN	► Hydration ► Review creatinine
Pancreatitis prevalence[6–8 28 31]: Anti-PD-(L)1: <1% Anti-CTLA-4: 1.3% Anti-PD-1+anti-CTLA-4: <1%	► Abdominal pain ► Nausea ► Vomiting	► Metabolic panel ► Pancreatic enzymes (amylase, lipase) ► Consider CT abdomen/pelvis	Grade 4: life-threatening consequences; urgent intervention indicated	► Intravenous (methyl)prednisolone 1–2 mg/kg for grade 3 or greater toxicity
			Grade 3: severe pain; vomiting; medical intervention indicated	
			Grade 2: elevated enzymes or radiographic findings only	
Peripheral motor and sensory neuropathy prevalence[28]: Anti-PD-(L)1:<1% Anti-PD-1+anti-CTLA-4: <1%	► Numbness ► Paraesthesias with or without pain ► Sensory ataxia ► Hyporeflexia or areflexia	► Neurology referral	Grade 4: life-threatening consequences; urgent intervention indicated	► Start 1–2 mg/kg/day methylprednisolone equivalents intravenous
			Grade 3: severe symptoms; limiting self-care ADL	
			Grade 2: moderate symptoms; limiting instrumental ADL	► Treatment to be guided by neurology
Myocarditis, pericarditis, arrhythmias prevalence (all cardiac toxicities)[10–12 14 29 30]: Anti-PD-(L)1: <1%–5% Anti-PD-1+anti-CTLA-4: <1%	► Dyspnoea ► Chest pain ► Arrhythmia ► Pleural effusion ► Fatigue ► Palpitations ► Weakness ► Dizziness ► Nausea ► Vomiting	► ECG, telemetry monitoring ► CBC ► Troponin, CK, CRP ► B-type natriuretic peptide ► CXR ► Echocardiogram ► Cardiology referral	Grade 4: moderate-to-severe decompensation, intravenous medication or intervention required, life-threatening conditions	► 1–2 mg/kg of prednisone initiated rapidly (oral or intravenous depending on symptoms) ► Admit to hospital ► Manage symptoms with cardiology consultation ► Transfer to coronary care if elevated troponin/conduction abnormalities
			Grade 3: moderately abnormal testing or symptoms with mild activity	
			Grade 2: abnormal screening tests with mild symptoms	
Uveitis prevalence[12]: Any ICI: <1%	► Blurred vision ► Change in colour vision ► Photophobia ► Distortion ► Scotomas ► Visual field changes ► Double vision ► Tenderness ► Pain with eye movement ► Eyelid swelling ► Proptosis	► Ophthalmology referral (urgent for anterior uveitis with 1+ or greater cells) ► Vision testing by/under guidance of ophthalmology: – Visual acuity (each eye) – Colour vision – Pupil size/shape/reactivity – Red reflex – Fundoscopic examination	Grade 4: best-corrected visual acuity of 20/200 or worse in the affected eye	► Treatment to be guided by ophthalmology ► To include ophthalmic/systemic prednisone/methylprednisolone
			Grade 3: anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	
			Grade 2: anterior uveitis with 1+ or 2+ cells	

G1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated.
G2: moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
G3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
G4: life-threatening consequences; urgent intervention indicated.
*Prevalence of IMARs is for any-grade IMARs.
†CTCAE grade definitions[18].
ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ALT, alanine aminotransferase; ANCA, antineutrophil cytoplasmic antibodies; AST, aspartate aminotransferase; BSA, body surface area; CBC, complete blood count; CK, creatine kinase; CNS, central nervous system; CRP, C reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte antigen-4; CXR, chest X-ray (roentgenogram); ECG, electrocardiogram; EEG, electroencephalography; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; ICI, immune checkpoint inhibitor; ICU, intensive care unit; IMAR, immune-mediated adverse reaction; IVIG, intravenous immunoglobulin; LFT, liver function test; NSAID, non-steroidal anti-inflammatory drug; PCR, polymerase chain reaction; PD-1, programmed death-1; PD-L1, programmed death ligand 1; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TPO, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine; ULN, upper limit of normal; UPCR, urine protein/creatinine ratio.

to melanoma, could also be responsible for the patient's signs and symptoms.

Given that the patient misconstrued her therapy as 'chemo', she may not have been appropriately counselled about the nature of her treatment and how to recognise and report IMARs, potentially delaying effective intervention.

Vignette 2: ICI-associated pneumonitis

A man aged 35 years came into the ED with a dry cough, worsening dyspnoea and chest pain but without fever. Patient history indicated that he was diagnosed with melanoma and was on anti-PD-1 therapy. As part of the initial workup, nasal swabs were tested for viral pathogens and pan-culture and sensitivity performed on blood, urine and sputum, all of which were negative. Further diagnostic workup included pulse oximetry and cross-sectional CT.[17]

More than one lobe of the lung and 45% of lung parenchyma were involved, with findings including ground-glass opacities. Bronchoscopy with bronchoalveolar lavage (BAL) was performed, and the BAL fluid showed lymphocytosis (a sign consistent with ICI-induced pneumonitis). No lung biopsy was performed to confirm pathology.[17] Empirical antibiotics were instituted before pan-culture and sensitivity results were available and discontinued when these tests returned normal.

Based on the lack of infectious disease, the CT and bronchoscopy results and a history of ICI treatment for melanoma, a diagnosis of ICI-induced pneumonitis was made. The patient was treated with prednisone 1 mg/kg/day and admitted to hospital, where he experienced rapid improvement in symptoms after 3 days and was later discharged. On improvement of the patient's symptoms to grade 1, the corticosteroid therapy was tapered by 5–10 mg/week over 4–6 weeks and ICI therapy reinstated. This case, which is consistent with grade 2 ICI-induced pneumonitis, illustrates the importance of ruling out infectious causes and establishing a diagnosis in a timely manner to allow prompt institution of effective treatment.[17] Mild symptoms may be managed as an outpatient and bronchoscopy may be delayed and used if patients fail to respond to initial management with new or worsening infiltrates. Cancer progression, alveolar haemorrhage, radiation pneumonitis and pneumonia may mimic immune-mediated pneumonitis.

Taken together, the case vignettes underscore the importance of early IMAR recognition with appropriate evaluation, therapy and triage for further inpatient versus outpatient management to decrease morbidity for this patient population.[12] IMARs of ICIs may present similarly to adverse events associated with chemotherapy or targeted therapies, but they require different management.[12] Management of IMARs is also dependent on the severity of symptoms, as shown for these two case vignettes reflecting contemporary clinical practice guidelines.[12–14] Although the index of clinical suspicion for IMARs may be elevated in a patient receiving ICIs, it is important to underscore the fact that other, potentially more common, aetiologies often must be ruled out. These include infection, effects of other medications and malignant transformation or metastasis.

Objectives

The goals of this review are to provide ED physicians with (1) information concerning key IMARs of ICIs (including their differential diagnosis, frequency, presentation, time of onset), focusing on common IMARs as well as less common but potentially life-threatening IMARs and (2) consensus recommendations and tools to identify and manage these IMARs in an ED or urgent-care setting.

To address these goals, we conducted a 5-year English-language literature search of PubMed using title and abstract terms including 'immunotherapy', 'checkpoint', 'CTLA-4', 'PD-1/PD-L1' (with abbreviations also spelled out) and individual ICI names. Selected articles were manually searched to identify important, previously published reports. To enrich the output, we searched online medical-information portals, including educational videos, and identified recent consensus clinical practice guidelines issued by major cancer and other patient care professional societies. US full prescribing information and other educational materials from life sciences companies for selected ICIs were also reviewed. Finally, websites for the ICIs were searched for educational guidelines to manage IMARs.

RECOGNITION OF IMARS

Frequency and presentation of IMARs in the ED

The frequency and timing of IMARs differ between ICIs, dosing schedule and regimen and cancer type. Current grading and tracking of IMARs rely on the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE V.5.0), in which adverse events are rated from grade 1 to 5, corresponding to mild, moderate, severe, life-threatening and death, respectively.[18] Grade 2 or higher toxicity is generally correlated with the need for medical intervention. [13]

A higher-grade toxicity usually requires more urgent medical intervention.[13 18] CTLA-4 inhibitors, such as ipilimumab, are associated with more frequent and severe (higher grade) IMARs than PD-1/PD-L1 inhibitor monotherapy.[12] Combination therapy with two ICIs is associated with both earlier IMAR onset and noticeably higher levels of immune-related toxicity than either one alone (figure 1).[2 14 19] In patients receiving nivolumab and ipilimumab in combination (for melanoma, RCC or MSI-H/dMMR CRC, respectively), 96%, 93% and 73% of patients had treatment-related adverse events, of which 55%, 46% and 32% (respectively) were grade 3 or higher.[20–22] An increased frequency of adverse events may also be seen when ICIs are administered sequentially.[14]

Overall, the most frequent IMARs are those affecting the skin, endocrine system, GI tract and lungs.[2 12 14 23] More rarely, neurologic, ocular, cardiovascular, haematologic and renal IMARs can occur.[12] In some cases, these less common toxicities may be life-threatening and therefore require prompt diagnosis and treatment, particularly because initial presentation may be mild, with non-specific symptoms such as fatigue, headache and electrolyte disturbance.[12] IMARs related to ICIs may present similarly to those related to chemotherapy (eg, diarrhoea and colitis), but may have different underlying causes and therefore require different diagnostic procedures, additional workup and different management.[12 24]

For instance, intestinal perforation may present as abdominal pain[25]; pneumonitis and myocarditis as complaints of shortness of breath[14]; myositis, Guillain-Barré syndrome, adrenal crisis, myocarditis, myasthenia gravis and diabetes as weakness/fatigue[14]; encephalitis and adrenal or thyroid crisis as confusion[14] and uveitis and hypophysitis as vision changes.[14]

Time of onset

While they may occur with the first dose, IMARs related to ICIs most often occur after several infusions and may worsen later in therapy or after treatment discontinuation. IMARs have been documented as late as 1 year after treatment discontinuation.[13] Immune-related toxicity risk generally progresses over time,

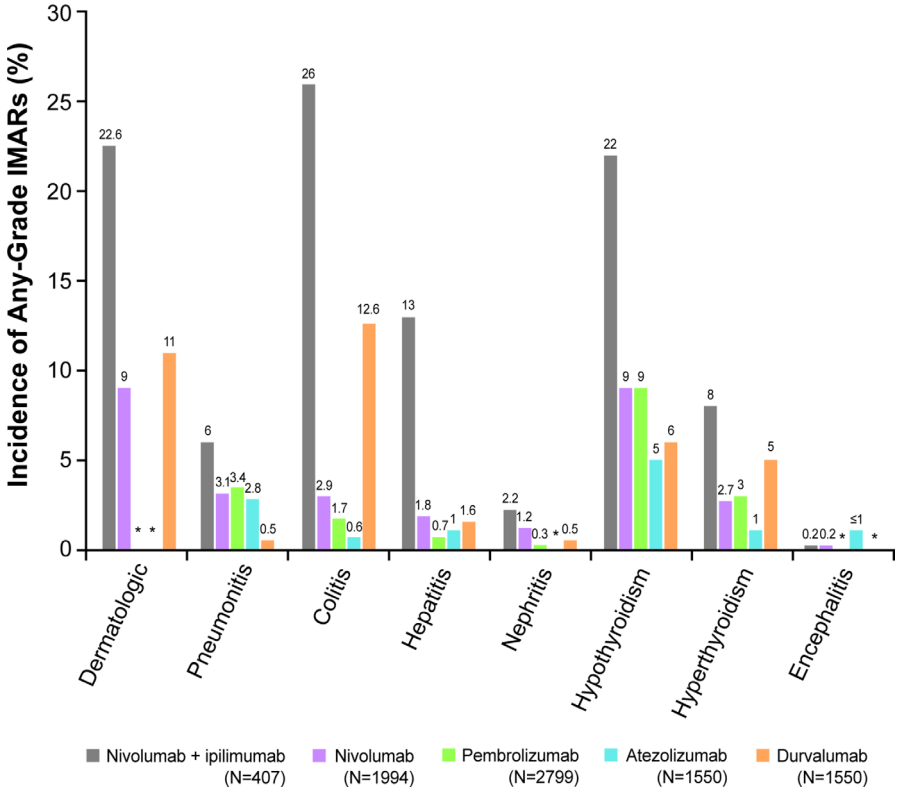

Figure 1 Frequency of IMARs following ICI treatment.[2 7 8 10 11 14 19 28–31] *Data not available. ICI, immune checkpoint inhibitor; IMAR, immune-mediated adverse reaction.

as some IMARs appear to require the generation of an immune response to the ICI. This is in contrast to chemotherapy, where adverse events typically occur early and repetitively in the treatment course.[12] Figure 2A shows the median (range) time of appearance of IMARs with anti-PD-1/PD-L1 treatment.[7 8 11] Median time to onset of IMARs with anti-PD-1/PD-L1 antibodies is typically between 1 and 6 months; however, IMARs again may present as late as 41 months after treatment initiation.[7 8 11] For ipilimumab (anti-CTLA-4), dermatologic IMARs typically present after 2–3 weeks of treatment, while GI and hepatic IMARs appear after 6–7 weeks and some endocrinopathies can appear 9 weeks or later after immunotherapy (figure 2B)[26]

MANAGEMENT OF IMARS

Because of the prolonged kinetics of ICIs, it is vital that patients presenting to the ED have oncology follow-up within 1–3 days after discharge. Toxicities may continue to evolve over days and weeks,

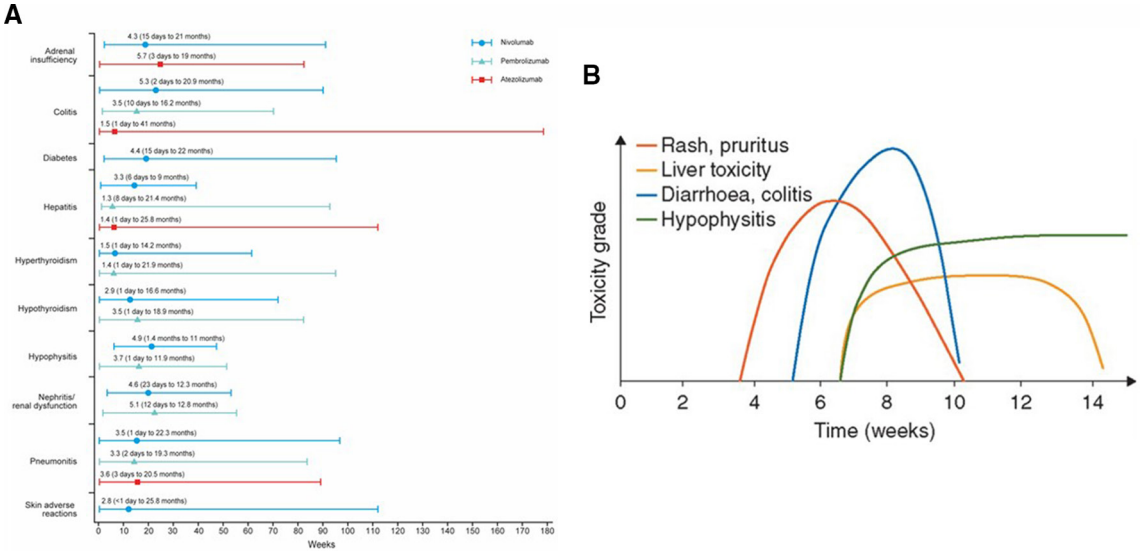

Figure 2 Kinetics of appearance of IMARs.[2 7 8 11 14 19 26 45] (A) Median (range) IMAR symptom onset (months) following PD-1/PD-L1 inhibitor treatment across FDA-approved tumour types. (B) Timing of IMAR occurrence by toxicity grade following ipilimumab inhibitor treatment in melanoma. Figure 2B reprinted with permission from the *Journal of Clinical Oncology*. FDA, US Food and Drug Administration; IMAR, immune-mediated adverse reaction; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

from mild to severe, and may be associated with new organ dysfunction.[13] Table 2 describes the potential signs and symptoms, evaluations and immediate intervention recommended for management of key IMARs, including the most common ICI-associated IMARs, along with less common but serious and potentially life-threatening toxicities. Table 2 includes additional testing to consider whenever the differential diagnosis remains unclear. High-dose steroids are often used as a first attempt at symptom control, with long tapers occurring over at least 4 weeks,[13 14] in contrast with other immune-mediated events unrelated to immuno-oncology (I-O) therapy[27]; patients presenting to the ED may have already commenced steroidal therapy prescribed by their oncology team. Subsequent management strategies are therefore included in table 2 to provide guidance when treating these patients.

Identifying patients receiving ICI therapy

Because of the multitude of medications used in patients with cancer, it is important to inquire about the type of treatment patients are on (eg, immunotherapy, chemotherapy, targeted therapy), and determine which specific ICI(s) (eg, nivolumab, ipilimumab, pembrolizumab, atezolizumab, durvalumab, avelumab) patients are receiving. Patients will have received education on their treatment from their oncology team but may not distinguish immunotherapy from other types of anticancer therapy.[13 14] Consider asking to see an alert card or other information the patient may have been provided. Alert cards contain information about symptoms of key IMARs and oncologist contact details (certain alert cards may contain QR codes allowing access to management guidelines).[32]

Furthermore, it is important to be aware of the potential delay in presentation of IMARs. Consider inquiring about the nature of ongoing and past treatment(s) in patients with a recent history of cancer.[13 33] New agents are continuing to be developed that will add to both benefit and risk for oncology patients, including the possibility of new toxicities as these agents impact other immune regulatory receptors or molecules.

Reassure patients that IMARs are generally manageable, and that interrupted ICI treatment may be reinitiated at their oncologist's discretion.[12 13]

Guidelines and other management tools

Various resources are available to ED clinicians. Guidelines and management tools are outlined below. In some cases, education may be provided by local oncologists and oncology nurses who are familiar with immunotherapy and related IMARs.[33]

Multidisciplinary guidance reflecting broad-based perspectives have been issued to guide clinicians on how to recognise, report and manage organ-specific toxicities related to immunotherapy. To date, guidelines have been published by the European Society of Medical Oncology,[13] the Society for Immunotherapy of Cancer[12] and other health authorities.[24] These guidelines focus on the recognition and management of a wide array of IMARs, including asymptomatic or mild cases not discussed in this review. The guidelines also provide recommendations for additional evaluations, interrupting or permanently discontinuing ICI treatment and dosing of corticosteroid therapy.[12–14]

A variety of educational tools and resources to improve understanding of IMARs associated with I-O agents are available as well. Two continuing medical education videos by Healio[34] and Medscape[35] provide ED clinicians with valuable information on the identification and management of IMARs in patients with cancer. Furthermore, an education project review developed by the Association of Community Cancer Centers addresses real-world experiences and practical concerns with I-O delivery.[33] Additional information on immunotherapy and IMARs in patients has also been developed by UpToDate,[36] Access Medicine[37] and the Oncology Nursing Society,[38] including a speed talk video on ICIs.[39] An interactive management tool is available from Clinical Care Options.[40]

Life science companies that manufacture and/or market ICIs have also developed educational tools to recognise and manage IMARs. These tools and management guides provide detailed information concerning the incidence of specific IMARs in the clinical trial setting. Moreover, these tools inform decisions about interrupting or permanently discontinuing I-O agents and instruct on the use of corticosteroids to mitigate each type of IMAR:

- BAVENCIO (avelumab) safety information.[41]
- IMFINZI (durvalumab) IMAR handbook.[29]
- KEYTRUDA (pembrolizumab) management of IMARs.[30]
- OPDIVO (nivolumab) digital safety tool and IMAR management guide.[42]
- OPDIVO (nivolumab) IMAR management guide.[28]
- TECENTRIQ (atezolizumab) management of IMARs.[31]
- YERVOY (ipilimumab) management of IMARs.[43]

A number of tools to improve the flow of care for patients receiving ICIs have also been developed, including the tagging of electronic medical records. The electronic medical record environment alerts providers with popup flags when patients on ICIs first present to a new healthcare environment (ie, admitted to the hospital or the ED). These flags offer both an immediate alert regarding the unique IMAR spectrum experienced by the patient and links to additional information. ED teams may consider liaising with their local oncology team(s) to put similar measures in place. Standardised nursing assessment flow charts for IMAR assessment and documentation may also help healthcare providers in diagnosing IMARs, particularly because patients may not indicate that they are experiencing symptoms if they do not consider them relevant.[44] Updating institutional telephone triage guidelines to better respond to patients receiving immunotherapy calling with concerns about side effects can aid optimal management of IMARs as well.[24]

Communication with the oncology team

It is extremely important for the patient's oncology team to be informed about any new or worsening symptoms, ED visits, interventions or changes to their treatment. Encourage patients to report these to their oncology team as quickly as possible. Where possible, alert the oncology team directly in case the patient fails to do so, particularly for symptomatic IMARs, so that the patient's oncologist can inform the patient about their diagnosis and potential need to discontinue ICI therapy. Moreover, relay any admission to the on-call oncologist for that patient. Institutions may want to consider a single institution-based telephone triage system providing support for non-specialist healthcare professionals such as the one currently being assessed at Smilow Cancer Hospital at Yale New Haven Hospital, New Haven, Connecticut, USA, for times when the patient's usual team is not available and advice is required. However, even if immediate management advice is not required, follow-up and monitoring of the patient is crucial because toxicities may continue to evolve.

CONCLUSIONS

Early recognition and prompt, appropriate treatment of IMARs arising from ICIs increases the likelihood of resolving IMARs. This review increases ED providers' awareness of potential IMARs related to ICI treatment. It also provides resources on

how these IMARs differ from those related to chemotherapy, as well as a variety of tools and guidelines that can assist ED providers in effective assessment and management of IMARs. It is important to be aware that IMARs can develop or worsen at any time during treatment, even once ICI treatment has been discontinued. Most significantly, open communication between patients, ED providers and the patient's oncologist is imperative to ensure optimal management of IMARs in the ED.

Contributors All authors reviewed and approved the manuscript.

Funding Medical writing support was provided by Jason Hoffman, and editorial support was provided by Jay Rathi, both of Spark Medica, supported by Bristol-Myers Squibb according to Good Publication Practice guidelines (no grant number).

Competing interests JV-U reports consulting fees from Bristol-Myers Squibb. No other authors have commercial, financial or other relationships in any way related to the subject of this article to disclose, per ICMJE conflict of interest guidelines. Outside the submitted work, GD reports clinical trial support from Bristol-Myers Squibb, Nektar, Regeneron, Viralytics, Dynavax, OncoSec and Merck. DK reports personal fees and non-financial support from Bristol-Myers Squibb.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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