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Review

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Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study

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Abstract

In recent years the use of immunomodulating therapy to treat various cancers has been on the rise. Three checkpoint inhibitors have been approved by the Food and Drug Administration (ipilimumab, pembrolizumab and nivolumab). The use of these drugs comes with serious adverse events related to excessive immune activation, collectively known as immune-related adverse events (irAEs). We conducted a system-based review of 139 case reports/case series that have described these adverse events between January 2016 and April 2018, found in the PubMed database. There was a broad spectrum of presentations, doses and checkpoint inhibitors used. The most common check point inhibitor observed in our literature review was nivolumab. The most common adverse effects encountered were colitis (14/139), hepatitis (11/139), adrenocorticotropic hormone insufficiency (12/139), hypothyroidism (7/139), type 1 diabetes (22/139), acute kidney injury (16/139) and myocarditis (10/139). The treatment most commonly consisted of cessation of the immune checkpoint inhibitor, initiation of steroids and supportive therapy. This approach provided a complete resolution in a majority of cases; however, there were many that developed long-term adverse events with deaths reported in a few cases. The endocrine system was the mostly commonly affected with the development of type 1 diabetes mellitus or diabetic ketoacidosis being the most frequently reported adverse events. While immunomodulating therapy is a significant advance in the management of various malignancies, it is capable of serious adverse effects. Because the majority of the cases developed pancreatic dysfunction within five cycles of therapy, in addition to the evaluation of other systems, pancreatic function should be closely monitored to minimize adverse impact on patients.

Keywords: Immunomodulating therapy; Programmed cell death inhibitors; Ipilimumab; Pembrolizumab; Nivolumab; Immunotherapy side effects

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Introduction

The increased use of immune modulating therapy has advanced our understating of the role of immune system in cancer destruction. Immunotherapy is being increasingly utilized to provide individualized treatment for certain cancers. The majority of tumors have genetic and epigenetic alterations that result in diverse antigen expression that can alter the host immune system response. The immune system has the inherent ability to distinguish self from non-self and can typically mount an attack on the non-self tissue such as cancer cells [1, 2]. T cells are a part of this system and their activation and interaction with the immune system and non-self tissue are important [3]. This process is regulated by stimulatory, co-stimulatory, and inhibitory (checkpoint) signals [4-6]. In addition, there are multiple immunomodulators that target T-cell activation [7]. Among the most promising approaches for this is the blockade of immune checkpoints [8]. Immune checkpoints are inhibitory pathways that keep the immune system in check in order to maintain self-tolerance and prevent autoimmunity [3, 8]. Immune checkpoint blockade by various immune-modulating therapies ultimately results in immune activation against tumor cells [8].

Thus far, there have been three immunotherapy drugs that have been approved by the Food and Drug Administration (FDA) [9, 10]. These include ipilimumab, pembrolizumab and nivolumab. Ipilimumab is a monoclonal antibody (mAb) that blocks T-cell activation checkpoint inhibitor called cytotoxic T-lymphocyte antigen 4 (CTLA-4) [9]. Pembrolizumab and nivolumab are immunoglobulin G4 (IgG4) mAb that regulates T-cell activation by blocking programmed cell death protein 1

(PD-1) [10]. These immunotherapy medications are currently used to treat multiple cancers including melanoma, non-small-cell lung carcinoma (NSCLC), glioblastoma, mesothelioma, large-cell lung cancer and renal cell carcinoma [2, 11, 12].

Despite impressive survival benefits through the use of immunotherapy in patients with melanoma and NSCLC, its use can be hampered by occurrence of serious adverse events related to excessive immune activation, collectively named as immune-related adverse events (irAEs) [3]. This over-activation can potentially affect multiple organ systems including the gastrointestinal tract, kidneys, nervous system, liver, eyes, skin, pancreas and endocrine system [8-12]. Many of the conditions can be life-threatening calling for discontinuation of treatment, long-term corticosteroids and at times anti-tumor necrosis factor therapy [13].

While isolated case reports have highlighted irAE, a systematic review of these complications is not readily available. In this study, we present the adverse side effects associated with immunotherapy, patient characteristics, possible predisposing factors, presentation, management and clinical outcomes of these irAEs.

Literature Search

A PubMed and manual bibliography search was performed between January 2016 and April 2018. We have decided to conduct our review between these dates as the most recent FDA approval was received in September 2015 for the combination of ipilimumab and nivolumab in patients with advanced melanoma [9]. This way the timeline would include the use of all the immunomodulators thus avoiding the chance for bias. Broad-based search terms were used such as cancer, adverse or harmful events, checkpoint, and immune therapy to name a few. Screening of eligible publications was carried out independently based on organ system. Keywords used were nivolumab, pembrolizumab, ipilimumab, adrenal, thyroid, diabetes, gastrointestinal, pancreas, renal, kidney, cardiac, myocarditis, colitis and diabetic ketoacidosis (DKA) to name a few. The abstracts were screened and full text of articles was reviewed. The patients who received FDA-approved checkpoint inhibitors such as ipilimumab, pembrolizumab and nivolumab were considered whether they received the treatment in a clinical trial or as part of standard of care.

We defined irAEs as all adverse events reported after treatment with immune inhibitors, which were not present prior to the initiation of treatment. A wide range of affected organ systems were included, like endocrine, gastrointestinal, pulmonary, cardiac and renal systems. We did not collect irAEs involving dermal, genitourinary, hematopoietic, musculoskeletal or nervous system.

The data gathered from the cases included the immunoinhibitor used, adverse effect, patients' age, dose, presentation, specific lab findings pertinent to the organ system, and the outcome. To evaluate the quality of case reports, we used the guidelines for publishing adverse events recommended by International Society of Pharmacovigilance (ISoP) and International Society for Pharmacoepidemiology (ISPE). The case reports were assessed based on the adequate description of the patient (past medical history, demographics, and laboratory abnormalities), the relevance of the title to reported information, and the description of the adverse event and its outcome. Only original reports were included.

Our study has several limitations. We did not analyze individual patient data and thus this review is subject to the quality of case reports. Many case reports did not include the grading of severity of irAEs, and thus were not reported and analyzed by us.

Literature Review

There were over 3,000 unique citations generated and initially reviewed. A total of 101 publications were included and reviewed. These publications reported a total of 139 cases in which irAEs were discussed. These cases were broken down based on the presenting/underlying adverse events of the patients. Tables 1-5 summarize adverse events and treatment outcomes of checkpoint blockade therapy as they relate to the gastrointestinal, endocrine, cardiac, pulmonary and renal systems.

Gastrointestinal system

A total of 46 cases involving the gastrointestinal tract were identified. There were 21 cases involving the luminal digestive tract, 13 involving the liver, six involving the biliary tract and six involving the pancreas (Table 1) [14-52].

Endocrine system

There were a total of 54 cases of immunomodulators causing adverse effects of the endocrine system. There were 14 cases involving the adrenal gland, 17 cases involving the thyroid, 22 cases involving the pancreas and one case involving the parathyroid. The 54 case reports were reviewed in detail with results shown in Table 2 [53-94].

Cardiac system

Seventeen cases of cardiac toxicity from immune checkpoint inhibitors were reported in PubMed between January 2016 and April 2018. The cases are illustrated in Table 3 below [95-102].

Pulmonary system

There were a total of five cases found of immunomodulators adversely affecting the pulmonary system as shown in Table 4 [103, 104, 105].

Renal system

A total of 18 renal cases were initially found in the search pa-

Table 1. Summary of Reported IrAEs Involving Gastrointestinal System: UDCA, ENBD

References	Presentation	Number of cases	Age (mean)	Immune checkpoint inhibitors (number of cases)	Doses (mean)	Treatment (outcome)
			Tubular gastrointestinal tract			
[14-27]	Enterocolitis/ enteritis/colitis	14	32 - 85 (65)	Pembrolizumab-3, nivolumab-11	1 - 19 (13)	Prednisone/infliximab/mesalazine/ budesonide, improved
[28, 29]	Intestinal perforation	2	73, 65	Nivolumab-2	3, 3	Surgical intervention, improved
[30]	Intestinal pseudo-obstruction	1	62	Nivolumab	14	Prednisone, improved
[31]	Esophagitis and gastritis	1	93	Nivolumab	6 mo.	Prednisone, improved
[32]	Hemorrhagic gastritis	1	77	Nivolumab	10	Prednisolone, improved
[33]	Oral mucositis, esophagitis	1	69	Pembrolizumab	14	Methylprednisolone, prednisone, improved
[34]	Intra-abdominal abscess	1	49	Pembrolizumab	5	Abscess drainage, antibiotics, adalimumab, improved
			Liver			
[35-42]	Hepatitis	11	42 - 80 (61)	Pembrolizumab-5, nivolumab-6	1 - 17 (5)	Methylprednisolone/corticosteroids/ prednisone/UDCA/mycophenolate, improved
[40]	Vanishing bile duct syndrome	1	49	Pembrolizumab	1	Prednisolone, UDCA, mycophenolate
[43]	Acute liver failure	1	60	Pembrolizumab	1	Prednisone/deceased
			Biliary tract			
[44-46]	Cholangitis	5	64 - 82 (75)	Nivolumab-5	4 - 12 (8)	Methylprednisolone/UDCA/ stent/prednisone, improved
[47]	Cholecystitis	1	63	Nivolumab	5	stent, ENBD, antibiotics, steroids
			Pancreas			
[48-52]	Pancreatitis	6	43 - 76 (57)	Pembrolizumab-2, nivolumab-4	2 - 19 (7)	Prednisone/duodenal stent/ pancreaticoduodectomy/pancreatic enzymes/dexamethasone, improved

UDCA: ursodeoxycholic acid; ENBD: endoscopic naso-biliary drainage.

rameters outlined in the methods section. One case was discarded from analysis when the renal function improved after discontinuation of proton pump inhibitors. Therefore a total of 17 cases were reviewed. The detailed results are presented in Table 5 [106-113].

Discussion

With an increased use of immune checkpoint inhibitors it has become more important to understand irAEs and the potential benefit of monitoring patients receiving these therapies. With the advancing interest and research into this new class of medication its use will likely increase in various types of malignancies. While many of the adverse events were well established during the clinical trials, new manifestations are now being reported. Many of the cases report the appearance of autoantibodies; however, the exact mechanism by which immunomodulating therapies induce the development of autoantibodies is not well understood.

Gastrointestinal system

The incidence of enterocolitis with PD-1 inhibitors can be as high as 30% [14]. It is important to note that this seemed to occur with as little as one dose of PD-1 inhibitor to as many as 70 doses. Therefore, providers should be tuned into this side effect at any point in the course of therapy. Other gastrointestinal adverse reactions included mucositis, esophagitis, and gastritis with some patients even developing hemorrhagic gastritis (Table 1). Less commonly reported were two cases of intestinal perforation and one case of intestinal pseudo-obstruction. Overall, nivolumab was involved in 16/21 cases, the doses ranged from 1 - 19 and the intervention for the cases consisted of stopping the treatment and administering steroids. Interestingly, there was a reported case of colitis with ipilimumab and secondary switching to pembrolizumab with no resultant

Table 2. Summary of Reported IrAEs Involving Endocrine System: TSH, TPO Antibodies, TgAb, N/A, GAD, ACTH, DM, and DKA

References	Presentation	Number of cases	Age (mean)	Immune checkpoint inhibitors (number of cases)	Doses (mean)	Labs (number of cases)			Treatments (outcome)
				Adrenal					
						Cortisol		ACTH	
[53-63]	ACTH insufficiency	12	39 - 83 (60)	Nivolumab-8, nivolumab/ipilimumab-4	2 - 13 (9)	Low-11 High-1		Low-11 High-1	Hydrocortisone, life long
[64, 65]	Primary adrenal insufficiency	2	43, 55	Pembrolizumab-1, nivolumab-1	4, 10	Low-2		High-2	Hydrocortisone with fludrocortisone, life long
				Thyroid					
						Free T4	TSH	Antibodies	
[61, 65-69]	Thyroiditis followed by hypothyroidism	7	46 - 73 (59)	Pembrolizumab-1, nivolumab-1, nivolumab/ipilimumab-5	1 - 8 (3)	Low-7	High-7	Negative-2, TPO/TgAb-2, TgAb-1, N/A-2	Levothyroxine, life long
[70]	Hypophysitis with central hypothyroidism	1	77	Nivolumab/ipilimumab	5	Low	Low	N/A	Levothyroxine/ steroids, life long
[53, 58, 59]	Hypophysitis with primary hypothyroidism	3	54 - 83 (66)	Nivolumab-3	5 - 11 (7)	Low-3	High-3	TPO/TgAb-1, TPO-1, N/A-1	Levothyroxine, life long
[71]	Myxedema crisis	1	53	Nivolumab	N/A	Low	High	N/A	Levothyroxine, life long
[72, 73]	Primary hypothyroidism	2	62, 63	Nivolumab-2	2, 1	Low-1, N/A-1	High-1, WNL-1	TPO/TgAb-1, TPO-1	Levothyroxine, life long
[74]	Thyroid storm	1	24	Nivolumab/ipilimumab	2	High	Low	Negative	Symptomatic treatment and hydrocortisone followed by prednisone
[62]	Thyroiditis followed by central hypothyroidism from hypophysitis	1	53	Nivolumab/ipilimumab	3	Low	Low	Negative	Levothyroxine, life long
[75]	Thyrotoxicosis from thyroiditis	1	55	Nivolumab	2	High	Low	TgAb	Symptomatic treatment
				Pancreas					
						HbA1c (mean)		Anti-GAD antibodies	
[66, 76-80]	Acute type 1 DM	6	58 - 73 (79)	Pembrolizumab-2, pembrolizumab/ipilimumab-1, nivolumab-3	1 - 17 (8)	6.3 - 9.7 (6.6)		Negative-3, positive-3	Insulin injections, insulin dependent
[69, 73, 81-94]	DKA	16	34 - 80 (61)	Pembrolizumab-2, pembrolizumab/ipilimumab-2, nivolumab-8, nivolumab/ipilimumab-4	1 - 20 (6)	6.5 - 10.7 (7.9)		Positive-8, negative-8	Insulin drip followed by multiple insulin injections, insulin dependent
				Parathyroid					
						Calcium		Parathyroid hormone	
[67]	Primary hypoparathyroidism	1	73	Nivolumab/ipilimumab	2	Low		Undetectable	Calcium and vitamin D, long-term calcium and vitamin D supplement

TSH: thyroid-stimulating hormone; TPO: thyroid peroxidase; TgAb: thyroglobulin antibodies; N/A: not available; GAD: glutamic acid decarboxylase; ACTH: adrenocorticotropic hormone; DM: diabetes mellitus; DKA: diabetic ketoacidosis.

Table 3. Summary of Reported IrAEs Involving Cardiovascular System: EF

References	Presentation	Number of cases	Age (mean)	Immune checkpoint inhibitors (number of cases)	Doses (mean)	Labs		Treatments (outcome)
						Cardiac enzyme elevation	EF reduction	
[95-99]	Myocarditis	10	49 - 80 (62)	Nivolumab-2, ipilimumab-5, nivolumab/ipilimumab-4	1 - 10 (3)	Yes-6, no-2, N/A-2	Yes-6, no-2, N/A-2	Cardioversion/steroids/infliximab/pacemaker/beta blockers/diuretics, death-6, EF improved-4
[98, 100]	Cardiac arrest	2	63, 88	Pembrolizumab-1, nivolumab-1	4, 3	Yes-2	Yes-1, N/A-1	Steroids/pacemaker, death-1, clinically improved-1
[98]	Heart failure	1	81	Ipilimumab	3	No	Yes	Diuretics, EF did not improve
[101]	Temponade	1	64	Nivolumab	9	No	N/A	Pericardiocentesis, improved
[98]	Myocardial fibrosis	1	61	Ipilimumab	2	N/A	N/A	Steroids, death
[102]	Cardiac allograft rejection	1	49	Nivolumab	1	Yes	Yes	Steroids/dobutamine, EF improved
[98]	Cardiomyopathy	1	68	Ipilimumab	4	N/A	Yes	Diuretics/ACE inhibitors/beta blocker, EF, improved

EF: ejection fraction.

Table 4. Summary of Reported IrAEs Involving Pulmonary System

References	Presentation	Number of cases	Age (mean)	Immune checkpoint inhibitors (number of cases)	Doses (mean)	Treatments (outcome)
[103, 103]	Pneumonitis	3	72 - 83 (76)	Nivolumab-3	1 - 8 (4)	Methylprednisolone
[104]	Infusion reaction	1	68	Nivolumab	2	Methylprednisolone
[105]	Acute fibrinous and organizing pneumonia	1	68	Nivolumab	10	Methylprednisolone

Table 5. Summary of Reported IrAEs Involving Renal System: AKI

References	Presentation	Number of cases	Age (mean)	Immune checkpoint inhibitors (number of cases)	Doses (mean)	Labs		Treatments (outcome)
						Urine studies	Biopsy	
[106-113]	AKI	16	43 - 78 (67)	Pembrolizumab-5, nivolumab-6, ipilimumab-1, nivolumab/ipilimumab-3, pembrolizumab/nivolumab-1	2 - 5 (3)	Proteinuria-6, hematuria-3, WBC casts-3, granular casts-2, eosinophils-2, normal-1, N/A-2	Interstitial nephritis-10, tubular-interstitial injury-3, IgA nephropathy-1, minimal change disease-1, acute post-infectious glomerulonephritis-1	Steroids, improved AKI-15, hemodialysis-1
[111]	Nephrotic syndrome	1	45	Ipilimumab	4	Proteinuria	Minimal change disease	Corticosteroids, proteinuria improved

AKI: acute kidney injury.

serious toxicities, which indicates that there may be leeway in switching between immunotherapeutic classes, if there is intolerance to one class [15].

There were 13 case reports describing liver injury, which all consisted of hepatitis, with one case of a patient presenting with vanishing bile duct syndrome. The patients all presented with elevated transaminases and the few patients who got a liver biopsy showed non-specific findings such as steatohepatitis, portal inflammation, and/or bile duct injury. The case reports were equally associated with either pembrolizumab or nivolumab, with four of them using a combination of ipilimumab (a CTLA-4 inhibitor). Most cases were reported after only a few doses of PD-1 inhibitor, and many improved with steroids and ursodeoxycholic acid (UDCA) (Table 1).

There were six reported cases of biliary tract abnormalities all comprising of cholangitis, which occurred after four to 12 doses (Table 1). Nivolumab was the only immunomodulator to have caused this reaction with no reported cases of biliary tract dysfunction due to either pembrolizumab or ipilimumab (Table 1). These patients presented with elevated transaminases and computer tomography (CT) scan showing extrahepatic bile duct dilation. Treatment entailed steroids, antibiotics, UDCA and biliary stents in some cases.

There were six reported cases of pancreatitis. The cases were associated with pembrolizumab (two cases) and nivolumab (four cases) (Table 1). The treatment for these patients consisted of steroids with a few requiring stents and one requiring a pancreaticoduodenectomy. There was one case report of a patient who developed pancreatic exocrine insufficiency that required life-time pancreatic enzyme replacement therapy [51].

Out of the 46 cases reviewed, the most common adverse effect of the gastroenterology system was enterocolitis (14/46) followed by hepatitis (11/46). Nivolumab was the most common immunotherapy seen in this organ system (32/46). The discontinuation of the immunotherapy and prednisone was the most common treatment with the majority of patients having resolution of their symptoms. The side effect of these medications does not seem to be dose-specific as there were cases of adverse events from patients only receiving one dose all the way up to 19 doses.

Endocrine system

There were a total of 54 cases involving the endocrine system (Table 2). The pancreas was the most common organ to be affected which resulted in either presenting as type 1 diabetes mellitus or DKA (22 cases) followed by thyroiditis (17 cases), primary and secondary adrenal insufficiency (14 cases) and parathyroid dysfunction (one case).

Among the 14 cases of adrenal insufficiency reported in PubMed, 12 of them were associated with nivolumab therapy either alone or in combination with ipilimumab. The patients developed hypophysitis with five of these patients with magnetic resonance imaging images showing pituitary changes. Primary adrenal insufficiency was found in only two out of the 14 cases. The patients were all treated with oral hydrocortisone and/or fludrocortisone as needed with some requiring long-term treatment even after cessation of the drugs.

There were a total of 17 cases of thyroid dysfunction related to immune checkpoint inhibitors (Table 2). There were 13 cases that developed primary hypothyroidism after the development of thyroiditis. Central hypothyroidism due to damage to the adrenal gland and a resultant decrease in thyroid stimulating hormone (TSH) was found in two cases [62, 70]. Development of thyroid dysfunction mostly within first three doses of PD-1 inhibitor therapy was an interesting and significant finding as in most previously discussed endocrine and gastrointestinal findings there did not seem to be a correlation between doses and occurrence of disease. Out of the 17 cases 12 of them reported on the presence or absence of antithyroid antibodies (Table 2). Out of the 12 cases there were eight cases that were positive for antithyroid antibodies such as thyroid peroxidase (TPO) antibodies and/or thyroglobulin antibodies (TgAb). This shows that although not all of the cases are positive for antithyroid antibodies, the presence of them could help in making the diagnosis. Nivolumab therapy either alone or in combination with ipilimumab was the most common cause for thyroid toxicity (16/17 cases).

There were a total of 22 cases of pancreatic dysfunction in the form of type 1 diabetes mellitus or DKA. There were four patients who presented with acute type 1 diabetes mellitus and two who presented with fulminant type 1 diabetes mellitus. The most common presentation was DKA affecting 16 out of the 22 cases (Table 2). This highlights that the pathophysiology of this immune toxicity is likely acute. DKA as the first presenting symptom should also alert the clinician about the high mortality of this adverse event. Twelve of these 16 cases occurred within the first five cycles of PD-1 therapy, which was a significant finding as this is the only adverse reaction that has shown to be caused consistently by low doses. Twelve of these 16 patients were on nivolumab therapy either alone (8/12) or in combination with ipilimumab (4/12). Pembrolizumab was the treatment regimen in four of these cases with two of the four cases on combination therapy with ipilimumab.

A single case of parathyroid dysfunction was reported on nivolumab/ipilimumab combination therapy after two doses. The patient presented with low calcium and an undetectable parathyroid hormone (PTH) level. The patient was started on calcium and vitamin D supplements.

Overall, multiple endocrine adverse effects were noted with immunomodulating therapy. Clinicians must be tuned into these adverse events in order to minimize morbidity and mortality.

Cardiovascular system

Cardiac toxicities were mainly related to myocardium and electrical conduction system amongst all reported cases (Table 3). Clinical presentation is variable and includes heart failure, atrio-ventricular nodal conduction abnormalities and other arrhythmia. Cardiac adverse effect from immune checkpoint inhibitors is rare but it could be severe. Out of 17 reported cases six patients died mainly secondary to cardiac arrest due to ventricular tachycardia and ventricular fibrillation [95, 96,

98, 100]. The timing from the start of the medication to the development of cardiac toxicities was variable ranging from 12 days to 31 weeks, although the two patients who received combination immune checkpoint inhibitors, ipilimumab and nivolumab, developed fatal cardiac arrhythmia within two weeks of treatment [96, 99]. Nine cases have shown elevated troponin level [96, 98]. Out of them three patients had ST changes, which include ST depression in two patients and ST elevation in one patient [96, 98]. Coronary angiography was done which ruled out coronary artery disease with ST segment changes in one patient and remaining two had endomyocardial biopsy, which showed myocarditis. Of the 12 cases that reported ejection fraction there were 10 which showed decreased ejection fraction compared to baseline before immunotherapy as seen on transthoracic echocardiogram.

Corticosteroids were given most commonly for the management strategy. However, corticosteroid use for management has not demonstrated a complete efficacy as four out of 10 patients who had fatal adverse effect were given corticosteroids early in the treatment and showed benefit. The other four did not improve as steroid therapy was delayed. Corticosteroids helped to improve autoimmune myocarditis; however, duration of treatment is unknown. Journal of Immunotherapy reported a case of smoldering myocarditis [114]. The patient received corticosteroids early in the management and tapered over a month but still it was not fully effective [99].

The exact pathophysiology to cause adverse cardiac events is unknown. A recently published animal (mouse model) study demonstrated a critical role of PD-L1 in controlling autoimmune heart and lung diseases [114]. Another study published in Nature Medicine reported that mice deficient in the PD-1 immuno-inhibitory co-receptor develop autoimmune dilated cardiomyopathy with production of high titer autoantibodies against a heart specific protein [115]. Finally, another study revealed that PD-1 deficiency results in development of fatal myocarditis in mice [116]. In this study a biopsy of the myocardium was performed which showed diffuse infiltration of $CD4^+$ and $CD8^+$ T cells and myeloid cells and there was a high titer of auto-antibodies against cardiac myosin [116]. CTLA-4 ablation also enhances cardio-pathogenicity reported in study published in circulation research with research showing that PD-1, PD-L1 and CTLA-4 play a role in preventing autoimmune myocarditis [117].

Cardiac events are the source of morbidity and mortality. More research is needed to develop prevention protocol to avoid life-threatening cardiac adverse events with use of immune check point inhibitors. Troponin was studied as a biomarker of cardiac damage to predict myocarditis yet the efficacy of troponin is not yet proven [118].

Pulmonary system

The development of interstitial lung disease (ILD) was mostly observed after the first few rounds of PD-1 inhibitor treatment (Table 4). Interestingly the patients affected in all the cases reported were of Japanese descent although the reason for this is unknown. The mechanisms of toxicity include infusion-related reaction, immune-related adverse reaction and immunosuppression. It encompasses non-specific interstitial pneumonia, organizing pneumonia, diffuse alveolar damage and acute fibrinous organizing pneumonia. Management depended on the pathophysiology of pulmonary involvement; it included stopping infusions, routine laboratory, radiology, bronchoscopy, lung cultures and autoimmune serology. Steroids are mainstay for treatment of ILDs, which showed good response in all of the patients.

Renal system

Out of the 18 cases found of renal dysfunction as a result of checkpoint blockade therapy the most common side effect seen was acute interstitial nephritis, which responded well to treatment with steroids and discontinuation of the drugs (Table 5). Minimal change disease was noted in two out of 17 cases, one of which was due to PD-1 inhibitor, and the other a CTLA-4 inhibitor, both of which improved significantly with holding medication and treatment with steroids.

Immunoglobulin A (IgA) nephropathy was noted in one case on treatment with PD-1 inhibitor therapy, which again responded to holding medication and treatment with steroids. It is important to mention that IgA nephropathy is the most common form of glomerulonephritis worldwide. While IgA nephropathy was reported in conjunction, it might have not been related to immunotherapy and could have been an incidental finding.

Conclusions

Immune checkpoint inhibitors have recently changed the dynamics for treatment of solid tumors with their use becoming more common in the treatment of various malignancies. We found that these drugs can cause multiple adverse effects that increase morbidity and mortality. Therefore, it is important to have a high index of suspicion for these irAEs, as they can be life-threatening. The diagnosis of these side effects, however, should always be accompanied by an extensive work-up to rule out the more common cause of various diseases before attributing the cause to immune checkpoint inhibitors. These work-ups will be dependent on the patient's symptoms and the organ affected. There are no established criteria for monitoring patients for these adverse events. The use of monitoring potential side effects of the treatments can be conducted on a case-by-case basis.

Statement of Ethics

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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