INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Adverse Drug Reactions Associated with Cancer Immunotherapy: Mechanisms, Clinical Spectrum, and Management Strategies

J. S. Venkatesh[1*], Dr. Santosh Uttangi[2], Gauthamvishnu V. L.[3], Jerin Rajan[4], K. G. Apeksha[5], Kushal Jain[6]

[1] *Professor, S.C.S College of Pharmacy, Harapanahalli.*
[2] *Assistant Professor, S.C.S College of Pharmacy, Harapanahalli.*
[3,4,5,6] *Pharm D Interns, S.C.S College of Pharmacy, Harapanahalli.*

ARTICLE INFO

Published: 18 Nov 2026
Keywords:
Cancer immunotherapy, immune checkpoint inhibitors, immune-related adverse events, adverse drug reactions, PD-1, PD-L1, CTLA-4, pharmacovigilance, immunotherapy toxicity
DOI:
10.5281/zenodo.24334413

ABSTRACT

Background: Cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), has substantially changed the treatment of advanced malignancies. By blocking inhibitory immune pathways such as programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), these agents enhance antitumour immune activity. However, the same immune activation can produce inflammatory toxicities known as immune-related adverse events (irAEs), which may involve almost any organ system. Objective: To review the mechanisms, clinical spectrum, risk factors, diagnosis, management, and long-term considerations associated with adverse drug reactions caused by cancer immunotherapy, with emphasis on evidence from original clinical, observational, translational, and pharmacovigilance studies. Methods: A narrative literature review incorporating elements of systematic search methodology was conducted. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for original research articles published between January 2010 and August 2026. Results: Clinical studies demonstrate that irAEs can affect the skin, gastrointestinal tract, liver, endocrine organs, lungs, kidneys, cardiovascular system, nervous system, and musculoskeletal system. Toxicity varies according to the checkpoint pathway targeted, treatment regimen, cancer type, and patient characteristics. Combination CTLA-4/PD-1 blockade is generally associated with a broader and more frequent toxicity profile than monotherapy. Gastrointestinal toxicity, endocrinopathies, pneumonitis, myocarditis, nephrotoxicity, and neurological toxicity may require treatment interruption or immunosuppressive therapy.

***Corresponding Author:** J. S. Venkatesh
Address: Professor, S.C.S College of Pharmacy, Harapanahalli
Email ✉: jerinrajan0205@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Emerging research indicates that T-cell phenotypes and gut microbiome composition may contribute to susceptibility to irAEs. Management generally involves early recognition, exclusion of alternative causes, interruption of immunotherapy according to severity, corticosteroid therapy for clinically significant inflammatory toxicity, and organ-specific immunomodulation for steroid-refractory disease. Conclusion: Adverse drug reactions associated with cancer immunotherapy represent a clinically heterogeneous group of toxicities requiring multidisciplinary recognition and management. Increasing evidence from prospective cohorts, real-world studies, and biomarker investigations is improving understanding of their mechanisms and risk factors. Continued research is required to identify reliable predictive biomarkers, optimize immunosuppression, and establish safer strategies for immunotherapy rechallenge.

INTRODUCTION

Cancer immunotherapy has become an important component of modern oncology. Immune checkpoint inhibitors (ICIs), including antibodies directed against PD-1, PD-L1, and CTLA-4, enhance antitumour immunity by removing inhibitory signals that normally restrain T-cell activation. Their expanding use has resulted in durable responses across multiple malignancies but has also introduced a distinctive spectrum of drug-related toxicities. Unlike conventional chemotherapy-associated adverse effects, immune-related adverse events (irAEs) are generally associated with excessive or dysregulated immune activation. In a prospective French REISAMIC registry study, 380 of 1187 patients developed at least one irAE, demonstrating the substantial burden of clinically relevant immune toxicity in routine practice. Severe events may occur early and can occasionally result in permanent organ dysfunction or death.[1]

The pathogenesis of irAEs is multifactorial. Clinical and translational studies have demonstrated associations between irAEs and alterations in T-cell populations, including Th17 cells, Th1 cells, regulatory T cells, and activated CD8-positive T cells.[2] Prospective microbiome studies have additionally demonstrated associations between specific intestinal microbial patterns and the subsequent development of irAEs.[3,4] These findings suggest that susceptibility to immunotherapy toxicity is influenced by both systemic immune characteristics and host-microbiome interactions.

Gastrointestinal toxicity may present as diarrhoea and colitis, particularly with combination checkpoint blockade.[5] The clinical presentation of irAEs is highly heterogeneous. Dermatological manifestations may include pruritus, rash, eczema, lichenoid disorders, vitiligo, and other inflammatory dermatoses.[6] Endocrine toxicity includes thyroid dysfunction, hypophysitis, adrenal insufficiency, and immune-mediated diabetes. [7,8] Less frequent but potentially life-threatening complications include pneumonitis, myocarditis, nephritis, encephalitis, neuropathies, and neuromuscular syndromes. [9-15]

Because irAEs may resemble infection, disease progression, conventional drug toxicity, or other autoimmune diseases, timely diagnosis requires clinical suspicion and appropriate investigations. Severe toxicity may require corticosteroids and additional immunosuppressive treatment. [16,17] At the same time, excessive immunosuppression may complicate cancer management, making individualized treatment important.

Rechallenge after an irAE is another emerging clinical issue. An observational VigiBase study published in 2020 identified 452 informative ICI rechallenge cases and reported recurrence of the same irAE in 130 cases (28.8%).[18] These findings emphasize the need to balance cancer-control considerations against the possibility of recurrent immune toxicity.

Therefore, this review summarizes current evidence regarding the mechanisms, clinical spectrum, diagnosis, management, and long-term considerations of adverse drug reactions associated with cancer immunotherapy, with emphasis on findings from original research studies.

MATERIALS AND METHODS

Literature Search

A narrative literature review was conducted to examine adverse drug reactions associated with cancer immunotherapy, with particular emphasis on immune checkpoint inhibitors. PubMed/Medline, Scopus, Web of Science, and Google Scholar were searched for

relevant literature published between January 2010 and August 2026. The search used combinations of terms related to cancer immunotherapy, immune checkpoint inhibitors, CTLA-4 inhibitors, toxicity mechanisms, risk factors, etc.

Eligibility Criteria

Inclusion criteria:

1. Evaluated patients receiving cancer immunotherapy or immune checkpoint inhibitors;
2. Reported immune-related adverse events, adverse drug reactions, mechanisms, risk factors, diagnosis, treatment, outcomes, or rechallenge;
3. Were prospective or retrospective clinical studies, cohort studies, translational investigations, or pharmacovigilance studies.

Exclusion criteria:

1. Review articles were excluded.
2. Unavailable full text.

Data Extraction and Analysis

Information extracted from eligible studies included study design, population, cancer type, ICI regimen, type and frequency of irAEs, severity, time to onset, risk factors, diagnostic investigations, treatment, clinical outcomes, and rechallenge outcomes. The retrieved evidence was organized into the following thematic categories:

1. Mechanisms and clinical spectrum of immunotherapy-associated toxicity
2. Organ-specific adverse reactions
3. Diagnosis and management
4. Rechallenge and long-term monitoring, biomarkers and pharmacovigilance.

RESULTS

Mechanisms and clinical spectrum of Immune-Related Adverse Reactions

The biological mechanisms underlying irAEs remain incompletely defined. Available original research supports several interacting mechanisms, including excessive T-cell activation, loss of peripheral immune tolerance, activation of autoreactive lymphocytes, inflammatory cytokine production, autoantibody development, and alterations in the intestinal microbiome. [2-4]

A T-cell profiling study involving patients treated with anti-PD-1 therapy identified distinct immunological patterns associated with severe irAEs. Patients developing severe toxicity demonstrated differences in Th17/Th1 activity, regulatory T-cell responses, and proliferating PD-1-positive CD8-positive T cells.[2] These observations suggest that different organ toxicities may arise from partially distinct immune pathways rather than from a single mechanism.

Endocrine toxicity has also been associated with pre-existing or treatment-emergent autoantibodies. In a prospective study of 60 patients receiving ICIs, endocrine adverse events occurred in 23.3%; the presence of endocrine-specific antibodies was significantly associated with endocrine toxicity.[7] This supports a potential role for pre-existing immune autoreactivity in some patients.

The intestinal microbiome may additionally modify immune activation. A prospective study of 27 patients with metastatic melanoma found that distinct microbiome clusters were associated with substantially different risks of developing irAEs.[3] A larger prospective study involving 195 patients and 497 stool samples found higher abundance of pathobionts and reductions in Ruminococcaceae among patients who developed severe irAEs.[4]

These findings indicate that irAE development is probably influenced by interactions among treatment characteristics, host immunity, autoimmunity, and microbial ecology.

Overall Clinical Spectrum

The clinical spectrum of irAEs ranges from mild, self-limiting cutaneous or endocrine abnormalities to severe organ-threatening disease.

In the French REISAMIC registry, 380 of 1187 patients developed clinically significant irAEs.[1] Very severe grade IV-V events were associated with poorer baseline performance status and higher neutrophil-to-lymphocyte ratios, while pulmonary toxicity, particularly pneumonitis, was prominent among fatal events.[1]

IrAEs may occur during treatment, shortly after treatment initiation, or after prolonged exposure. Their timing varies according to the affected organ. Cardiovascular toxicity may occur relatively early, whereas endocrine abnormalities and some delayed toxicities can appear later. [7,9]

Table 1: Major Organ-Specific Adverse Drug Reactions Associated with Immune Checkpoint Inhibitors

Organ system	Common/Important manifestations	Evidence from original studies
Skin	Rash, pruritus, eczema, vitiligo, lichenoid eruptions, pemphigoid	Cutaneous toxicity occurred in approximately 25% in a large population-level cohort.[19]
Gastrointestinal	Diarrhoea, Colitis, Enterocolitis	Colitis occurred in 8.6% overall, 3.2% with anti-PD-1 monotherapy and 24.4% with combination therapy.[5]
Liver	Hepatitis, Aminotransferase elevation	High-grade hepatitis occurred in 294 patients in a multicentre cohort of ICI-treated patients. [11]
Endocrine	Hypothyroidism, Thyrotoxicosis, Hypophysitis, Diabetes	Endocrine toxicity occurred in 23.3% in a prospective biomarker study.[7]
Lung	Pneumonitis	Pneumonitis occurred in 6.4% of 654 ICI-treated patients in one retrospective cohort. [10]
Heart	Myocarditis, Arrhythmia, Heart failure	ICI-associated myocarditis occurred in 1.14% in an 8-centre registry.[9]
Kidney	AKI, Acute interstitial nephritis	Renal toxicity has been demonstrated in real-world ICI cohorts. [12,13]
Nervous system	Neuropathy, Encephalitis, Myasthenia gravis, Meningitis	Neurological events occurred in 1.72% of 3137 ICI-treated patients in one cohort.[14]
Musculoskeletal	Arthritis, Myositis, Inflammatory syndromes	Musculoskeletal toxicity is reported among clinically relevant irAEs. [1,2]

Cutaneous Adverse Drug Reactions

Cutaneous toxicity is among the most frequently observed manifestations of ICI therapy. In a United States population-level analysis involving 8,637 ICI-treated patients and matched controls, the overall incidence of cutaneous irAEs was 25.1%.[19] The most frequently observed diagnoses included rash or nonspecific eruption, drug eruption, pruritus, mucositis, vitiligo, lichen planus, pemphigoid, and Grover disease.[19]

Another institutional study of 1,857 anti-PD-1-treated patients found that 13.0% developed one of 11 prespecified cutaneous adverse events, with pruritus and eczema among the most frequently observed manifestations.[6]

Most cutaneous reactions are manageable, but severe blistering disorders and extensive inflammatory eruptions require early dermatological evaluation and discontinuation of the suspected ICI when clinically indicated.

Gastrointestinal Adverse Drug Reactions

ICI-associated gastrointestinal toxicity commonly presents with diarrhoea and colitis. In a multicentre cohort of 1261 patients treated with anti-PD-1-based regimens, 109 patients developed clinically significant colitis.[5] The incidence was 3.2% among patients receiving anti-PD-1 monotherapy compared with 24.4% among those receiving combined ipilimumab and nivolumab/pembrolizumab.[5]

Combination therapy was also associated with earlier onset, higher corticosteroid requirements, and longer steroid tapering.[5]

Patients with significant diarrhoea require evaluation for infectious causes, inflammatory bowel disease-like pathology, and other alternative diagnoses. Endoscopy and biopsy may be necessary in persistent or severe disease.

Corticosteroids are commonly used for clinically significant immune-mediated colitis. In a multicentre cohort of 127 patients with corticosteroid-refractory

ICI enterocolitis treated with infliximab, corticosteroid-free clinical remission was achieved in 41.2% at 12 weeks and 50.9% at 26 weeks.[16]

Vedolizumab has also been investigated in steroid- or infliximab-refractory disease. In a multicentre study of 28 patients, 24 patients achieved sustained clinical remission following vedolizumab treatment.[17]

Hepatic Adverse Drug Reactions

ICI-associated hepatitis is generally characterized by elevation of aminotransferases after exclusion of alternative causes of liver injury. In a multicentre retrospective cohort, 294 patients developed grade 3-4 ICI hepatitis among more than 10,000 ICI-treated patients.[11]

Among these patients, 166 were hospitalized and 128 were managed without hospitalization. Hospitalized patients had higher aminotransferase levels and were more likely to develop grade 4 injury and steroid-refractory hepatitis.[11]

The study demonstrated that CTCAE grading may not always correspond directly to the severity of liver injury when evaluated using drug-induced liver injury criteria.[11] This highlights the importance of interpreting biochemical abnormalities together with bilirubin levels, symptoms, alternative diagnoses, and clinical status.

Endocrine Adverse Drug Reactions

Endocrine toxicities include thyroid dysfunction, hypophysitis, adrenal insufficiency, and insulin-deficient diabetes.

In a prospective study of 60 ICI-treated patients, endocrine adverse events occurred in 14 patients (23.3%). Hypothyroidism occurred in 20% and hypophysitis in 3.33%.[7] The presence of endocrine-specific autoantibodies was associated with endocrine toxicity.[7]

A real-world melanoma cohort of 140 patients reported endocrine adverse events in 29%, with thyroid disorders being the most frequent manifestation.[8]

ICI-associated diabetes is less common but can be clinically severe. Patients may present with abrupt hyperglycaemia or diabetic ketoacidosis and may require permanent insulin therapy. Consequently, glucose monitoring during ICI therapy is important, particularly when symptoms suggest new metabolic dysfunction.

Pulmonary Adverse Drug Reactions

Pneumonitis is an important potentially life-threatening pulmonary toxicity. In a retrospective cohort of 654 ICI-treated patients, 42 patients developed pneumonitis, corresponding to an incidence of 6.4%.[10] Among affected patients, 81% had grade ≥2 pneumonitis, 45% required hospital admission, and 10% required intensive care.[10]

Diagnosis requires exclusion of infectious pneumonia, tumour progression, pulmonary oedema, radiation pneumonitis, and other causes. Chest computed tomography is particularly useful for characterization of radiological patterns.

The French REISAMIC study also identified pulmonary toxicity, particularly pneumonitis, among important contributors to fatal very severe irAEs.[1]

Cardiovascular Adverse Drug Reactions

Cardiovascular irAEs are uncommon but potentially fatal. Myocarditis is the most clinically important manifestation.

An 8-centre registry identified 35 cases of ICI-associated myocarditis and compared them with 105 ICI-treated controls.[9] The prevalence was 1.14%, with a median onset of 34 days after ICI initiation.[9] Major adverse cardiac events occurred in 46% of patients, and combination ICI therapy was more common among myocarditis cases than controls.[9]

Troponin elevation was associated with adverse outcomes, emphasizing the importance of cardiac biomarker assessment when myocarditis is suspected.[9]

Because symptoms may be nonspecific, including fatigue, dyspnoea, chest discomfort, palpitations, or syncope, early ECG and cardiac biomarker testing are important when clinically indicated.

Renal Adverse Drug Reactions

Renal toxicity associated with ICIs commonly manifests as acute kidney injury, often related to immune-mediated tubulointerstitial nephritis.

A retrospective cohort study from the Princess Margaret Cancer Centre evaluated patients receiving ipilimumab, nivolumab, or pembrolizumab and investigated the incidence, risk factors, and outcomes of ICI-associated acute kidney injury.[12]

A separate real-world cohort identified baseline kidney function and concomitant medications as clinically relevant factors associated with sustained kidney injury.[13]

Evaluation of a patient with rising serum creatinine should therefore include assessment of volume status, concomitant nephrotoxic medications, infection, obstruction, disease progression, and other causes of acute kidney injury before attributing the abnormality to ICI therapy.

Neurological and Musculoskeletal Adverse Drug Reactions

Neurological irAEs are relatively uncommon but can cause substantial morbidity. In a retrospective cohort of 3137 ICI-treated patients, 54 neurological adverse events were identified, corresponding to 1.72% of patients; 0.8% were grade 3-4.[14]

The neurological spectrum includes peripheral neuropathies, myasthenia gravis, encephalitis, meningitis, myelitis, and other inflammatory neurological syndromes.

A nationwide multicentre Italian cohort of 66 patients with neurological irAEs found peripheral nervous system involvement in 73%, central nervous system involvement in 21%, and combined involvement in 6%.[15] The study also demonstrated that some neurological toxicities may become chronic rather than resolving completely after initial treatment.[15]

Musculoskeletal toxicity may include inflammatory arthritis, myositis, myalgia, and overlapping neuromuscular syndromes.

Diagnosis and Severity Assessment

Diagnosis of irAEs is primarily clinical and requires temporal association with immunotherapy combined with exclusion of alternative causes.

Assessment should consider:

- Time since ICI initiation;
- Type and combination of ICI therapy;
- Severity and progression of symptoms;
- Baseline organ function;
- Concomitant medications;
- Infection;
- Malignancy progression;
- Pre-existing autoimmune disease;
- Laboratory investigations;
- Organ-specific imaging and functional tests.

The Common Terminology Criteria for Adverse Events (CTCAE) are commonly used to classify toxicity severity. However, organ-specific investigations may provide additional information beyond numerical grading, as demonstrated in ICI-associated hepatitis.[11]

Early identification is particularly important because severe irAEs can progress rapidly. The REISAMIC registry demonstrated that very severe events tended to occur earlier than less severe events and were associated with poorer baseline performance status and higher neutrophil-to-lymphocyte ratio.[1]

Management Strategies

Management depends on the affected organ, clinical severity, and response to initial therapy. Consensus guidelines from oncology and immunotherapy societies provide organ-specific assessment and treatment algorithms; these recommendations should be applied alongside individual clinical judgment.[22]

General Management

The initial approach generally includes:

1. Recognition of the suspected irAE;
2. Assessment of severity;
3. Exclusion of alternative causes;
4. Temporary interruption of ICI therapy when clinically indicated;
5. Organ-specific supportive treatment;
6. Corticosteroids for significant inflammatory toxicity;

7. Escalation to additional immunosuppression for steroid-refractory disease; and
8. Long-term monitoring for recurrence or persistent dysfunction.

In general, treatment decisions are guided by toxicity grade and the organ involved. Mild events may be managed with symptomatic treatment and close monitoring, whereas clinically significant events commonly require temporary withholding of ICI therapy and consideration of systemic corticosteroids. Severe or life-threatening events require urgent specialist assessment and may require hospital admission and permanent discontinuation of the ICI. The specific approach differs by organ system; for example, suspected myocarditis, severe pneumonitis, and neurological toxicity warrant urgent evaluation. These are broad principles, not a substitute for organ-specific protocols.[22]

Corticosteroid Therapy

Corticosteroids remain the principal immunosuppressive treatment for many clinically significant irAEs. Their use is supported by multiple original cohorts demonstrating improvement in inflammatory toxicities.

In ICI-associated myocarditis, 89% of patients in the multicentre registry received corticosteroids, while lower steroid doses were associated with greater residual troponin elevation and higher rates of major adverse cardiac events.[9]

For gastrointestinal toxicity, corticosteroid therapy is frequently used as initial treatment, with infliximab or vedolizumab used in steroid-refractory disease. [16,17]

Biological and Other Immunosuppressive Therapy

Infliximab has been evaluated for corticosteroid-refractory ICI enterocolitis. In the six-centre cohort of 127 patients, fewer than half achieved corticosteroid-free remission at 12 weeks.[16]

Vedolizumab provides a gut-selective alternative. In the 28-patient multicentre study, sustained clinical remission was achieved in 86% of patients.[17]

For highly refractory gastrointestinal toxicity, additional immunosuppressive approaches have been reported in smaller cohorts, although evidence remains limited and treatment decisions require specialist involvement.

Rechallenge and Long-Term Monitoring

Rechallenge refers to resumption of ICI therapy after resolution or improvement of an irAE.

An updated WHO VigiBase observational pharmacovigilance study identified 1,016 informative rechallenge cases and found recurrence of the same irAE in 323 cases, corresponding to 31.8%.[20] Recurrence varied according to the type of irAE.[20]

The earlier VigiBase study also demonstrated that a substantial proportion of patients experienced recurrent or new irAEs following rechallenge.[18]

Specific organ toxicity may influence rechallenge decisions. In a retrospective cohort of melanoma patients who recovered from grade 3-4 ICI hepatitis, 31 of 102 patients were rechallenged.[21] Fifteen developed an irAE of any grade, but only six required permanent discontinuation because of toxicity.[21]

Therefore, rechallenge should be individualized according to the original toxicity, severity, degree of recovery, cancer status, available alternative therapies, and patient preferences.

Long-term follow-up is particularly important for endocrine, neurological, renal, pulmonary, and cardiovascular toxicities because some effects may persist after ICI discontinuation.

Pharmacovigilance and Emerging Predictive Biomarkers

Traditional clinical trials may underestimate rare and delayed toxicities because of restricted eligibility criteria and limited follow-up. Pharmacovigilance databases therefore provide an important complementary source of safety information.

The VigiBase rechallenge studies demonstrate how international spontaneous reports can identify patterns of recurrent toxicity after ICI re-exposure.[18,20] Similarly, FAERS-based studies have identified neurological and organ-specific safety signals associated with checkpoint inhibitors.

Biomarker research is moving toward individualized prediction. T-cell profiling has identified immune phenotypes associated with severe irAEs.[2] Endocrine

autoantibodies may identify patients at increased risk of endocrine toxicity.[7] Microbiome studies have identified microbial signatures associated with irAE development and severity. [3,4]

However, these biomarkers remain investigational. Their clinical utility requires validation in larger, diverse prospective cohorts before routine implementation.

DISCUSSION

Cancer immunotherapy has introduced a fundamentally different pattern of adverse drug reactions compared with conventional anticancer treatment. Rather than primarily reflecting direct cytotoxicity, many irAEs appear to result from immune dysregulation following removal of inhibitory immune checkpoints. [1,2]

The available original research indicates that toxicity is heterogeneous. Combination checkpoint blockade generally produces greater immune activation and consequently greater toxicity. This was particularly evident in gastrointestinal toxicity, where colitis occurred in 24.4% of patients receiving combination therapy compared with 3.2% receiving anti-PD-1 monotherapy in a multicentre cohort.[5] Similar differences have been observed across other organ systems.

The mechanisms underlying this heterogeneity are increasingly being investigated. T-cell profiling suggests that severe irAEs can be separated into immunologically distinct patterns involving Th17, TNF-related, CD8-positive T-cell, and regulatory T-cell pathways. [2] This finding is important because it suggests that future management may move from generalized immunosuppression toward toxicity-specific interventions.

The gut microbiome is another emerging area. Prospective studies have demonstrated associations between microbial composition and irAE risk. [3,4] The 2025 prospective cohort involving 195 patients found increased pathobiont abundance and decreased Ruminococcaceae among patients who developed severe irAEs.[4] Nevertheless, these associations do not establish causation, and microbiome-based prediction is not yet ready for routine clinical use.

Organ-specific studies demonstrate substantial variation in clinical severity. Cutaneous reactions are frequent but are often manageable,[6] whereas myocarditis is uncommon but associated with a high risk of major cardiovascular events.[9] Pneumonitis similarly requires early recognition because severe cases may require hospitalization or intensive care.[10] Neurological irAEs are less common but may become chronic and cause persistent neurological disability. [14,15]

The management evidence is also uneven. Gastrointestinal toxicity has generated several clinical cohorts evaluating infliximab and vedolizumab. [16,17] By contrast, evidence for rare neurological, cardiac, and other severe toxicities frequently comes from smaller cohorts. This difference highlights the need for multicentre registries and prospective studies.

Another important issue is whether immunosuppression compromises anticancer efficacy. The relationship between irAEs, corticosteroid exposure, and tumour response remains complex and may vary according to indication, timing, steroid dose, and underlying cancer. Consequently, treatment decisions should focus on controlling potentially dangerous inflammation while minimizing unnecessary interruption of effective cancer therapy.

Rechallenge represents one of the most clinically difficult decisions. The updated VigiBase analysis demonstrated a 31.8% recurrence rate of the same irAE following rechallenge.[20] However, recurrence risk varies according to the initial organ system. The hepatitis-specific cohort also demonstrated that rechallenge was possible in selected patients after recovery from high-grade hepatitis, although recurrent hepatitis remained an important reason for discontinuation.[21]

This review has limitations. It is a narrative synthesis and did not use a formal systematic-review workflow, predefined risk-of-bias assessment, or quantitative meta-analysis. The included studies differ in design, patient populations, cancer types, ICI regimens, toxicity definitions, and follow-up duration, which limits direct comparison of reported incidence estimates. Pharmacovigilance databases are also subject to underreporting, reporting bias, and incomplete clinical

information. Accordingly, the findings should be interpreted in light of these limitations.

Overall, current evidence supports a multidisciplinary model involving oncologists, pharmacists, organ-specific specialists, and other healthcare professionals. Pharmacists can contribute through medication reconciliation, identification of alternative causes of organ dysfunction, monitoring for corticosteroid-related complications, assessment of drug interactions, patient education, and pharmacovigilance reporting.

CONCLUSION

Adverse drug reactions associated with cancer immunotherapy constitute a diverse spectrum of immune-mediated toxicities involving virtually every organ system. Original clinical and translational studies demonstrate important differences in incidence, timing, severity, and outcomes according to ICI regimen and affected organ.

Evidence from T-cell, endocrine autoantibody, microbiome, and pharmacovigilance studies suggests that irAE susceptibility is influenced by multiple biological and clinical factors. Early recognition, appropriate diagnostic evaluation, severity assessment, and timely immunosuppressive treatment remain central to minimizing morbidity.

Future research should prioritize validated predictive biomarkers, standardized definitions, prospective multicentre registries, organ-specific treatment studies, and safer strategies for ICI rechallenge. Improved integration of clinical pharmacy and pharmacovigilance services may further strengthen the detection and management of immunotherapy-associated adverse drug reactions.

Acknowledgments

The authors acknowledge the contributions of the Department of Pharmacy Practice and the clinical departments involved in the management of patients receiving cancer immunotherapy.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No specific funding was received for the preparation of this review.

REFERENCES

1. Ruste V, Goldschmidt V, Laparra A, Messayke S, Danlos FX, Romano-Martin P, et al. The determinants of very severe immune-related adverse events associated with immune checkpoint inhibitors: a prospective study of the French REISAMIC registry. Eur J Cancer. 2021;158:217-224. doi:10.1016/j.ejca.2021.08.048.
2. Kim KH, Hur JY, Cho J, Ku BM, Koh J, et al. Immune-related adverse events are clustered into distinct subtypes by T-cell profiling before and early after anti-PD-1 treatment. Oncoimmunology. 2020;9 (1):1722023. doi:10.1080/2162402X.2020.1722023.
3. Usyk M, Pandey A, Hayes RB, Moran U, Pavlick A, Osman I, et al. Bacteroides vulgatus and Bacteroides dorei predict immune-related adverse events in immune checkpoint blockade treatment of metastatic melanoma. Genome Med. 2021;13:160. doi:10.1186/s13073-021-00974-z.
4. Verheijden RJ, van Eijs MJM, Paganelli FL, Viveen MC, Rogers MRC, Top J, et al. Gut microbiome and immune checkpoint inhibitor toxicity. Eur J Cancer. 2025;216:115221. doi:10.1016/j.ejca.2025.115221.
5. Wang DY, Mooradian MJ, Kim DW, Shah NJ, Fenton SE, Conry RM, et al. Clinical characterization of colitis arising from anti-PD-1 based therapy. Oncoimmunology. 2019;8 (1):e1524695. doi:10.1080/2162402X.2018.1524695.
6. Le TK, Kaul S, Cappelli LC, Naidoo J, Semenov YR, Kwatra SG. Cutaneous adverse events of immune checkpoint inhibitor therapy: incidence and types of reactive dermatoses. J Dermatolog Treat. 2022;33 (3):1691-1695. doi:10.1080/09546634.2021.1898529.
7. Labadzhyan A, Wentzel K, Hamid O, Chow K, Kim S, Piro L, et al. Endocrine autoantibodies determine immune checkpoint inhibitor-induced endocrinopathy: a prospective study. J Clin

Endocrinol Metab. 2022;107 (7):1976-1982. doi:10.1210/clinem/dgac161.

8. Karhapää H, Mäkelä S, Laurén H, Jaakkola M, Schalin-Jäntti C, Hernberg M. Immune checkpoint inhibitors, endocrine adverse events, and outcomes of melanoma. Endocr Connect. 2022;11 (2). doi:10.1530/EC-21-0562.
9. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol. 2018;71 (16):1755-1764. doi:10.1016/j.jacc.2018.02.037.
10. Banavasi H, Kim S, Alkassis S, Daoud A, Laktineh A, Nagasaka M, et al. Immune checkpoint inhibitor-induced pneumonitis: incidence, clinical characteristics, and outcomes. Hematol Oncol Stem Cell Ther. 2023;16 (2):144-150. doi:10.1016/j.hemonc.2021.09.005.
11. Li M, Wong D, Sack JS, Vogel AS, Hodi FS, Fong L, et al. Outcomes of high-grade immune checkpoint inhibitor hepatitis in hospitalized and non-hospitalized patients. Clin Gastroenterol Hepatol. 2024;22 (7):1444-1452.e4. doi:10.1016/j.cgh.2024.02.006.
12. Meraz-Muñoz A, Amir E, Ng P, Avila-Casado C, Ragobar C, Chan C, et al. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. J Immunother Cancer. 2020;8. doi:10.1136/jitc-2019-000467.
13. Panich J, et al. Cohort study on immune checkpoint inhibitor-associated acute kidney injury: incidence, risk factors, and management strategies. J Oncol Pharm Pract. 2024;30 (2):286–294. doi:10.1177/10781552231171078.
14. Hunting JC, Faucheux AT, Price SN, Elko CA, Quattlebaum A, Bloomer C, et al. Patterns of neurological adverse events among a retrospective cohort of patients receiving immune checkpoint inhibitors. Immunotherapy. 2024;16 (6):381-390. doi:10.2217/imt-2023-0273.
15. Rossi S, Farina A, Malvaso A, Dinoto A, Fionda L, Cornacchini S, et al. Clinical course of neurologic adverse events associated with immune checkpoint inhibitors: focus on chronic toxicities. Neurol Neuroimmunol Neuroinflamm. 2024;11 (6). doi:10.1212/NXI.0000000000200314.
16. Alexander JL, Ibraheim H, Sheth B, Little J, Khan MS, Richards C, et al. Clinical outcomes of patients with corticosteroid refractory immune checkpoint inhibitor-induced enterocolitis treated with infliximab. J Immunother Cancer. 2021;9. doi:10.1136/jitc-2021-002742.
17. Abu-Sbeih H, Ali FS, Alsaadi D, Jennings J, Luo W, Gong Z, et al. Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor-induced colitis: a multi-center study. J Immunother Cancer. 2018;6:142. doi:10.1186/s40425-018-0461-4.
18. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. JAMA Oncol. 2020;6 (6):865–871. doi:10.1001/jamaoncol.2020.0726.
19. Wongvibulsin S, Pahalyants V, Kalinich M, Murphy W, Yu KH, Wang F, et al. Epidemiology and risk factors for the development of cutaneous toxicities in patients treated with immune-checkpoint inhibitors: a United States population-level analysis. J Am Acad Dermatol. 2022;86 (3):563–572. doi:10.1016/j.jaad.2021.03.094.
20. L'Orphelin JM, Da Silva A, Cabon J, Alexandre J, Dolladille C. Immune checkpoint inhibitor rechallenge after immune-related adverse events: a retrospective study from VigiBase update in 2024 looking for emergent safety signals. BMJ Open. 2024;14. doi:10.1136/bmjopen-2024-091708.
21. Li M, Sack JS, Rahma OE, Hodi FS, Zucker SD, Grover S. Outcomes following resumption of immune checkpoint inhibitor therapy after high-grade immune-mediated hepatitis. Cancer. 2020;126 (23):5088–5097. doi:10.1002/cncr.33165.
22. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann

Oncol. 2022;33 (12):1217-1238. doi:10.1016/ j.annonc.2022.10.001.

HOW TO CITE: J. S. Venkatesh, Dr. Santosh Uttangi, Gauthamvishnu V. L., Jerin Rajan, K. *G. Apeksha*, Kushal Jain, Adverse Drug Reactions Associated with Cancer Immunotherapy: Mechanisms, Clinical Spectrum, and Management Strategies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 3031-3041. https://doi.org/10.5281/zenodo.24334413