Immune checkpoint inhibitor induced lichenoid reactions: A systematic review of characteristics and treatment outcomes

To the Editor: The use of immune checkpoint inhibitors (ICIs) as a method of cancer management has increased due to the efficacy; with the increased use of ICIs, there have been increased reports of immune-related adverse events. Lichenoid reactions (LRs) have been reported as specific cutaneous immune-related adverse events of ICIs.[1] LRs are uncommon skin rashes that share many features with idiopathic lichen planus.[2] This systematic review aimed to summarize reports of

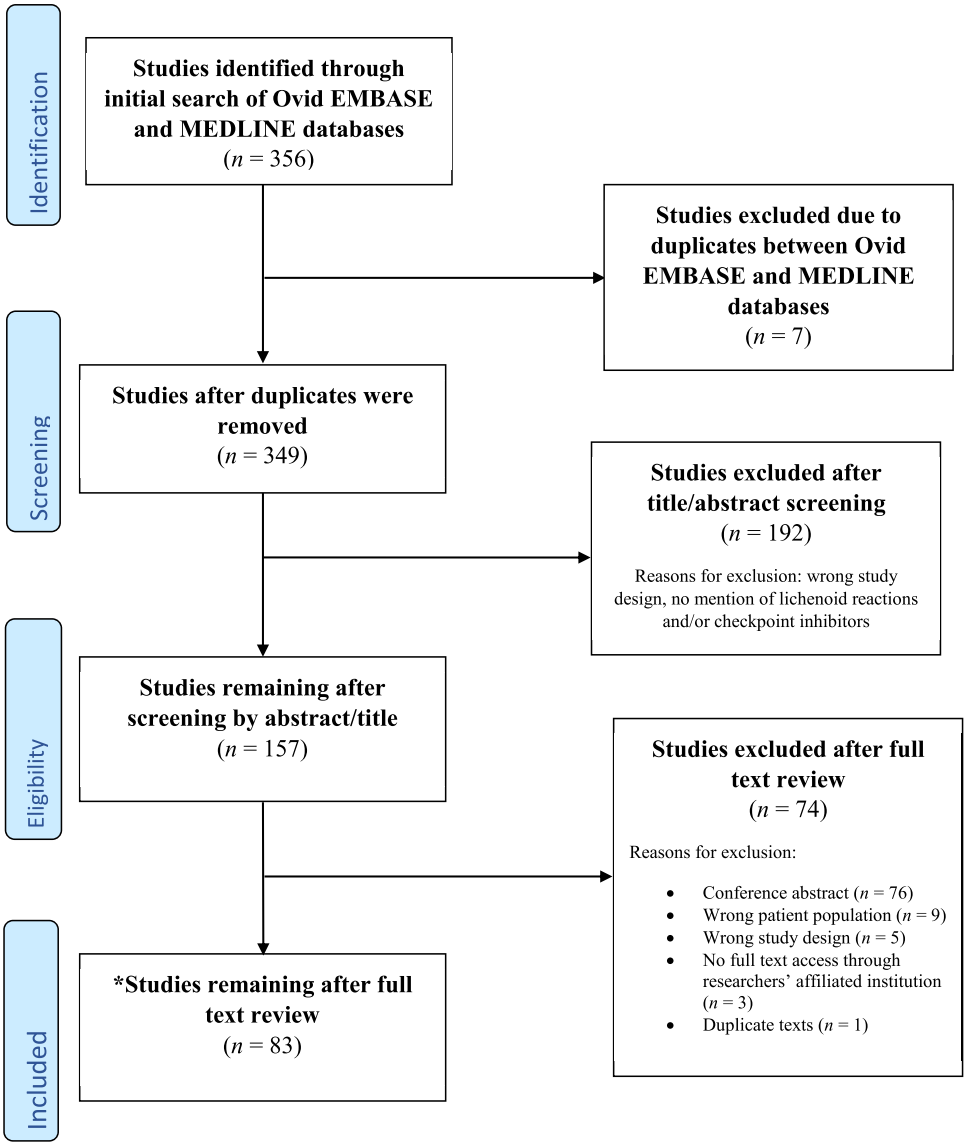

Fig 1. The selection process for study inclusion. *The criteria for study inclusion were as follows: (1) documented patient(s) who were diagnosed with lichenoid reaction; (2) studies that were observational or experimental, including case reports, case series, or retrospective and prospective cohort studies, or randomized controlled trials; and (3) patients on checkpoint inhibitors. Histologic diagnosis was not required for inclusion.

Table I. Summary of case reports of lichenoid reactions as a checkpoint inhibitor therapy adverse drug reaction*

Drug class	Drug name (specific drug cases/total cases in review)	Indication	Mean latency period, mo (*n*)	Drug discontinuation (*n*)	Resolution	Treatment	Mean resolution period, d (*n*)	Medications prescribed for the original indication	Recurrence of LR?	Naranjo score (interpretation)
PD-1 inhibitor (165)	Nivolumab: 72% (119/165)	Melanoma: 41% (49/119) Renal cell carcinoma: 23% (27/119) Non−small cell lung cancer: 16% (19/119) Lung cancer: 7% (8/119) Squamous cell carcinoma: 5% (6/119) Breast cancer: 2% (2/119) Glioblastoma: 2% (2/119) Lymphoma: 2% (2/119) Bladder cancer: 1% (1/119) Gastric cancer: 1% (1/119) Multiple myeloma: 1% (1/119) Pancreatic cancer: 1% (1/119)	5.6 (104)	Y: 23% (27/119) N: 35% (42/119) NR: 42% (50/119)	CoR: 43% (51/119) PR: 7% (8/119) NoR: 2% (2/119) NR: 49% (58/119)	Corticosteroids: 49% (25/51) Withdrawal and corticosteroids: 31% (16/51) Withdrawal only: 8% (4/51) Calcineurin inhibitor: 4% (2/51) Phototherapy: 4% (2/51) Retinoid: 2% (1/51) No treatment: 2% (1/51) Corticosteroids: 38% (3/8) Withdrawal and corticosteroids: 25% (2/8) No treatment: 25% (2/8) NR: 13% (1/8) Withdrawal and corticosteroids: 50% (1/2) Withdrawal and Retinoid: 50% (1/2) Corticosteroids: 2% (1/58) NR: 98% (57/58)	61.8 (23) 14 (1) NA NA	Unchanged: 23% (27/119) Methotrexate: 1% (1/119) Dabrafenib and trametinib: 1% (1/119) Docetaxel: 1% (1/119) NR: 75% (89/119)	Y: 2% (2/119) N: 13% (15/119) NR: 86% (102/119)	5.1 (probable)
	Pembrolizumab: 28% (46/165)	Melanoma: 54% (25/46) Non−small cell lung cancer: 22% (10/46) Breast cancer: 7% (3/46) Squamous cell carcinoma: 7% (3/46) Urothelial carcinoma: 4% (2/46) Invasive thymoma: 2% (1/46) Merkel cell carcinoma: 2% (1/46) Metastasis of unknown primary: 2% (1/46)	3.7 (19)	Y: 41% (19/46) N: 35% (16/46) NR: 24% (11/46)	CoR: 67% (31/46) PR: 9% (4/46) NoR: 7% (3/46) NR: 17% (8/46)	Withdrawal and corticosteroids: 42% (13/31) Corticosteroids: 42% (13/31) Withdrawal with retinoid: 6% (2/31) No treatment: 3% (1/31) Methotrexate: 3% (1/31) Withdrawal with methotrexate: 3% (1/31) Withdrawal and corticosteroids: 25% (1/4) Corticosteroids: 75% (3/4) Withdrawal and corticosteroids: 67% (2/3) Methotrexate: 33% (1/3) NR: 100% (8/8)	100.1 (23) NR (4) NA NA	Unchanged: 35% (16/30) Discontinued treatment: 11% (5/30) Ipilimumab + nivolumab combination: 2% (1/31) Dabrafenib and trametinib: 2% (1/30) NR: 48% (22/30)	Y: 4% (2/46) N: 31% (14/46) NR: 65% (30/46)	5.4 (probable)

PD-L1 inhibitor (13)	Atezolizumab: 62% (8/13)	Renal cell carcinoma: 50% (4/8) Non−small cell lung cancer: 38% (3/8) Adenocarcinoma of the esophagus: 13% (1/8)	5.3 (8)	Y: 38% (3/8) N: 38% (3/8) NR: 25% (2/8)	CoR: 75% (6/8) NoR: 13% (1/8) NR: 13% (1/8)	Withdrawal and corticosteroids: 50% (3/6) Corticosteroids: 50% (3/6) Corticosteroids: 100% (1/1) NR: 100% (1/1)	150 (1) NA NA	NR: 100% (8/8)	N: 13% (1/8) NR: 88% (7/8)	4.75 (possible)
	Avelumab: 23% (3/13)	Merkel cell carcinoma: 33% (1/3) Renal cell carcinoma: 33% (1/3) Urothelial carcinoma: 33% (1/3)	2.5 (3)	N: 100% (3/3)	CoR: 33% (1/3) PR: 33% (1/3) NR: 33% (1/3)	Corticosteroids: 100% (1/3) Cryotherapy: 100% (1/3) Corticosteroids: 100% (1/3)	21 (1) NR (1) NA	Unchanged: 66.7% (2/3) NR: 33.3% (1/3)	Y: 66.7% (2/3) NR: 33.3% (1/3)	5 (probable)
	Durvalumab: 15% (2/13)	Squamous cell carcinoma: 50% (1/2) Non−small cell lung cancer: 50% (1/2)	15 (2)	Y: 50% (1/2) NR: 50% (1/2)	CoR: 100% (2/2)	Withdrawal and corticosteroids: 100% (1/2) Corticosteroids: 100% (1/2)	NR (2)	NR: 100% (2/2)	NR: 100% (2/2)	6.5 (probable)
CTLA-4 inhibitor (5)	Ipilimumab: 80% (4/5)	Melanoma: 100% (4/4)	3.5 (4)	Y: 25% (1/4) N: 50% (2/4) NR: 25% (1/4)	CoR: 50% (2/4) NR: 50% (2/4)	Withdrawal and corticosteroids: 50% (1/2) Corticosteroids: 50% (1/2) NR: 100% (2/2)	NR (2) NA	Unchanged: 25% (1/4) NR: 75% (3/4)	N: 25% (1/4) NR: 75% (3/4)	4 (possible)
	Tremelimumab: 20% (1/5)	Renal cell carcinoma: 100% (1/1)	NR (1)	N: 100% (1/1)	NoR: 100% (1/1)	Corticosteroids: 100% (1/1)	NA	Unchanged: 100% (1/1)	NR: 100% (1/1)	3 (possible)

Continued

Table I. Cont'd

Drug class	Drug name (specific drug cases/total cases in review)	Indication	Mean latency period, mo (*n*)	Drug discontinuation (*n*)	Resolution	Treatment	Mean resolution period, d (*n*)	Medications prescribed for the original indication	Recurrence of LR?	Naranjo score (interpretation)
Combination therapy (11)	Nivolumab and ipilimumab: 45% (5/11)	Melanoma: 60% (3/5) Non—small cell lung cancer: 40% (2/5)	2.6 (5)	N: 80% (4/5) NR: 20% (1/5)	CoR: 80% (4/5) NR: 20% (1/5)	Corticosteroids: 100% (4/4) NR: 100% (1/1)	NR (1) NR (1)	Unchanged: 80% (4/5) NR: 20% (1/5)	NR: 100% (5/5)	4.6 (possible)
	Ipilimumab and pembrolizumab: 18% (2/11)	Melanoma: 100% (2/2)	0.9 (2)	NR: 100% (2/2)	CoR: 50% (1/2) PR: 50% (1/2)	Corticosteroids: 100% (1/1) Corticosteroids: 100% (1/1)	NR (1) NR (1)	Unchanged: 50% (1/2) NR: 50% (1/2)	N: 100% (2/2)	4 (possible)
	Nivolumab and bevacizumab: 9% (1/11)	Non—small cell lung cancer: 100% (1/1)	1.5 (1)	N: 100% (1/1)	CoR: 100% (1/1)	Corticosteroids: 100% (1/1)	NR (1)	Unchanged: 100% (1/1)	NR: 100% (2/2)	4 (possible)
	Nivolumab and mogamulizaumab: 9% (1/11)	Non—small cell lung cancer: 100% (1/1)	3.3 (1)	NR: 100% (1/1)	NR: 100% (1/1)	NR: 100% (1/1)	NR (1)	NR: 100% (1/1)	NR: 100% (1/1)	7 (probable)
	Nivolumab and Pembrolizumab: 9% (1/11)	Melanoma: 100% (1/1)	4.7 (1)	NR: 100% (1/1)	NR: 100% (1/1)	NR: 100% (1/1)	NR (1)	NR: 100% (1/1)	NR: 100% (1/1)	4 (possible)
	Tislelizumab and sitravatinib: 9% (1/11)	Non—small cell lung cancer: 100% (1/1)	1.5 (1)	NR: 100% (1/1)	CoR: 100% (1/1)	Corticosteroids: 100% (1/1)	14 (1)	NR: 100% (1/1)	NR: 100% (1/1)	4 (possible)

CoR, Complete resolution; *LR*, lichenoid reaction; *N*, no; *NA*, not applicable; *NoR*, no response; *NR*, not reported; *PR*, partial resolution; *Y*, yes.

*Additional details regarding patient demographics and comorbidities are listed in Supplementary Table II (available via Mendeley at https://doi.org/10.17632/w7x25j7f5f.1).

ICI-induced LRs, offending drugs, and treatment outcomes.

EMBASE and MEDLINE databases were searched on April 16, 2021, per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using the key words "Lichen*" along with "PD-1*" or "PD-L1*" or "CTLA-4*." In total, 83 studies were included (64 case reports, 11 case series, 6 retrospective cohort studies, and 2 prospective cohort studies), representing 194 patients (mean age, 64.7 years; male, 52.1%) and 4 drug classes (Fig 1). Drug classes included PD-1 inhibitors (85.1%, $n = 165/194$), PD-L1 inhibitors (6.7%, $n = 13/194$), CTLA-4 inhibitors (2.6%, $n = 5/194$), and combination therapy (5.7%, $n = 11/194$). Nivolumab (61.3%, $n = 119/194$), a PD-1 inhibitor, was the most prescribed ICI resulting in LR (Table I).

Data showed that the mean onset of LR for nivolumab was 5.6 months ($n = 104$), and 51 (43%) of the 119 patients receiving treatment with nivolumab achieved complete resolution (CoR) within 61.8 days ($n = 23$). Of these 51 patients, CoR was achieved with corticosteroids in 25 (49%) patients, drug withdrawal with corticosteroids in 16 (31.0%), and drug withdrawal alone in 4 (8.0%); other treatment modalities were used in 8 patients (Table I). The mean onset of LR for pembrolizumab (23.7%, $n = 46/194$) was 3.7 months, and 31 (67%) of the 46 patients achieved CoR within 100.1 days. Of these 31 patients, CoR was achieved with corticosteroids in 13 (42%) patients and drug withdrawal with corticosteroids in 13 (42%) patients; other treatment modalities were used in 5 patients (Table I). The mean onset of LR for atezolizumab (4.1%, $n = 8/194$) was 161 days ($n = 8$), and 6 (75%) of the 8 patients achieved CoR, with a mean resolution period of 150 days. Of these 6 patients, CoR was achieved with corticosteroids in 3 (50%) patients and drug withdrawal with corticosteroids in 3 (50%) patients.

The relationship between LRs and classic lichen planus remains unclear. Both share common histologic features, including subepidermal band-like cytotoxic lymphocyte infiltration and apoptosis of basal keratinocytes; to distinguish between them, clinical and histologic correlation is recommended.[2] Although mechanisms of LRs remain unclear, it is believed that T cells, dendritic cells, keratinocytes, and endothelial cells trigger an inflammatory reaction cascade (eg, L-selectin, major histocompatibility complex class II, intercellular adhesion molecules) that ultimately leads to LRs.[3] This is reinforced by observations that PD-1 inhibitors, due to unclear causes, frequently cause adverse cutaneous reactions, supporting claims that PD-1/PD-L1 interaction is necessary to preserve epidermal integrity during inflammatory skin reactions.[4]

Limitations of this systematic review include the small sample sizes, lack of high-quality randomized controlled trials, and lack of follow-up data. Additionally, the confirmation of ICI-induced LR in all included cases is challenging to determine. However, LR histology was confirmed by biopsy in 124 (63.9%) of the 194 patients. In addition, the mean Naranjo score was 5, which suggests a "probable" association between the suspected drug and LRs.[5] Despite these limitations, our findings provide essential conclusions to guide LR management, showing that 99 (51%) of the 194 patients with ICI-induced LR achieved CoR with drug withdrawal and corticosteroids (topical or oral) or corticosteroids (topical or oral) alone.

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Conflicts of interest

None disclosed.

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