

# Increased rates of immunosuppressive treatment and hospitalization after checkpoint inhibitor therapy in cancer patients with autoimmune disease

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## ABSTRACT

**Background** Immune checkpoint inhibitors (ICIs) are important new therapeutic options for the treatment of malignancy. Existing data on the relative safety of ICI treatment in patients with pre-existing autoimmune disease (AID) are limited.

**Methods** In this retrospective study utilizing an oncology medical claims database, we determined the rates of treatment with immunosuppressive agents and hospitalization within 180 days of treatment with ICIs (pembrolizumab, nivolumab, and ipilimumab) in patients both with and without AID. Patients had diagnoses of either malignant melanoma or lung cancer. Immunosuppressive agents evaluated included oral prednisone and intravenous methylprednisolone.

**Results** 124 cancer patients with AID and 1896 cancer patients without AID met inclusion criteria for oral prednisone analysis, while 284 patients with AID and 3230 patients without AID met inclusion criteria for all other analyzes. Following treatment with PD-1 inhibitors, rates of treatment with both oral prednisone and intravenous methylprednisolone within 180 days of ICI treatment were significantly increased in the AID group relative to the control group (oral prednisone: 16.7% treatment in AID vs 8.3% in non-AID,  $p=0.0048$ ; intravenous methylprednisolone: 8.4% treatment in AID vs 3.7% in non-AID,  $p=0.0012$ ). Rates of hospitalization were significantly increased in melanoma patients with AID relative to melanoma patients without AID following treatment with PD-1 inhibitors (24.1% in AID vs 5.8% in non-AID,  $p<0.0001$ ).

**Conclusion** Cancer patients with AID have higher rates of hospitalization and treatment with immunosuppressive agents following treatment with ICI therapy compared with patients with no AID. This suggests that patients with AID may have increased toxicity risk while being treated with checkpoint inhibitor therapy. Further prospective clinical trials are needed to determine safety.

## INTRODUCTION

Immune checkpoint inhibitors (ICIs), including the CTLA-4 inhibitor ipilimumab and PD-1 inhibitors nivolumab and pembrolizumab, are now first-line therapy for a variety of locally-advanced and metastatic

malignancies. These potent immune-modulating agents are associated with serious and potentially fatal immune-related adverse events (irAEs).<sup>1</sup> Therefore, caution is warranted when considering ICI therapy in patients with potentially complicating pre-existing conditions, including patients with autoimmune disease (AID).

Approximately 15% to 30% patients treated with ICI monotherapy and significantly higher percentage (>50%) of patients treated with dual ICI therapy develop  $\geq 3$  grade irAEs.<sup>2</sup> irAEs can affect nearly every organ system, though most commonly involve the gastrointestinal (GI) tract, the endocrine system, lung, skin, and liver.<sup>4</sup> It is hypothesized that patients with a genetic predisposition or a pre-existing AID are at higher risk for irAEs.<sup>5</sup> In the setting of safety concerns and a paucity of data regarding ICI use in patients with pre-existing AID, these patients were excluded from early clinical trials that have served as the foundation for Food and Drug Administration approval and clinical use. It is estimated that AIDs affect at least 10% of the general population (with recent estimates in cancer patients high as of 13% to 25%).<sup>6</sup>

A number of retrospective studies have examined the safety and efficacy of using checkpoint inhibitors in patients with AID, with mixed results concerning the relative safety of ICIs in patients with pre-existing AID. Several studies suggested that immune toxicities in these patients were common but comparable to rates in patients without AID, with 23% to 50% of patients developing AID flares and 29% to 42% developing irAEs.<sup>7–12</sup> irAEs in these studies were generally manageable with immunosuppression but severe or fatal reactions did occur, though infrequently. One large multicenter study directly compared rates of GI adverse events in patients

with pre-existing inflammatory bowel disease (IBD) versus non-IBD controls, finding significantly higher rates of GI adverse events in patients with pre-existing IBD (41% vs 11%), including 21% of patients with IBD experiencing grade 3 or 4 diarrhea and 4% experiencing colonic perforation.<sup>13</sup> These data suggest that while toxicity risk for patients with AID might not be dramatically increased, certain subgroups may be at increased risk, and further data on this question is warranted.

To contribute to this expanding literature on the safety of ICIs in patients with pre-existing AID, we conducted a retrospective analysis of a large claims database to assess toxicity-related interventions occurring subsequent to ICI treatment in patients both with and without AID. We compared rates of immunosuppressant use and hospitalization following checkpoint inhibitor treatment in 284 patients with lung cancer or advanced melanoma and pre-existing AID compared with 3230 control patients with a diagnosis of either lung cancer or melanoma without a diagnosis of AID.

## METHODS

### Database characteristics

The Decision Resources Group database is a patient database containing a combination of claims data, electronic health record data (inpatient and outpatient), and pharmacy/drug data collected from community and academic settings throughout the USA, originally assembled for commercial purposes by the Decision Resources Group. Patient information was deidentified and the data was offered for research use. The database was separated into cancer diagnosis groups based on the International Classification of Diseases (ICD)9/10 codes and included patients with malignant melanoma and lung cancer. In this analysis, we included melanoma and lung cancer patients with at least one claim for immunotherapy use within the claims database from March 2010 to April 2017.

### Inclusion criteria: medical claims analysis

Medical and pharmaceutical claims for patients with either lung cancer or melanoma who had at least one claim in the data set for treatment with ipilimumab, pembrolizumab, or nivolumab were identified. We excluded individuals with a lack of complete claims for the time period of analysis. Patients with at least one claim 60 days prior to their earliest ICI treatment and with at least one claim 180 days following their latest ICI treatment, were included for further analysis. Across all checkpoint inhibitors and both cancer types, 17.8% of the patients who had at least one claim in the database for any ICI were used for Medical Claims Analysis after the application of inclusion criteria.

### Inclusion criteria: medical-pharmacy claims analysis

Oral prednisone analysis involved use of pharmacy claims in addition to medical claims, so inclusion criteria were distinct from analyzes solely involving medical claims.

For each patient, an immunotherapy period pharmacy overlap (IPO) quantity was calculated using this equation:

$IPO = ND_p / ND_i$  in which  $ND_p$  = the total number of days between the earliest pharmacy claim date and the latest pharmacy claim date in the database that were within the immunotherapy time period, and  $ND_i$  = the total number of days within the immunotherapy time period. Patients with pharmacy claims both before and following the immunotherapy time period would have an IPO value of 1. Patients with IPO values  $>0.4$  were included for further analysis. This quantity was selected based on an analysis that compared IPO values to rates of treatment with oral prednisone following checkpoint inhibitor therapy, finding a marked decline in the rates of oral prednisone claims across all patients following ICI therapy once IPO values were  $<0.4$ . Across all checkpoint inhibitors and both cancer types, 10.3% of patients within the database were considered for medical-pharmacy claims analysis after the application of inclusion criteria.

Due to the use of distinct inclusion criteria, the patient population in medical-pharmacy claims analysis that was used to calculate rates of oral prednisone use after checkpoint inhibitor therapy was distinct from the patient population included in medical claims analysis that was used to calculate rates of both methylprednisolone infusions and hospitalizations. Specific codes to identify interventions can be found in supplementary data (online supplemental table 1).

For both analyses, patients were included regardless of whether they were treated with any form of immunosuppression prior to beginning ICI therapy.

### Identification of patient and treatment groups

Patients with AID who also received immunotherapy were identified by ICD9/ICD10 diagnosis codes (online supplemental table 2) associated with AIDs. If a patient had a single claim within the database with a diagnosis code affiliated with a particular AID, they were assumed to have this condition. Patients treated with combination ICI therapy were defined as having ipilimumab and nivolumab claim dates within 30 days of each other at least once.

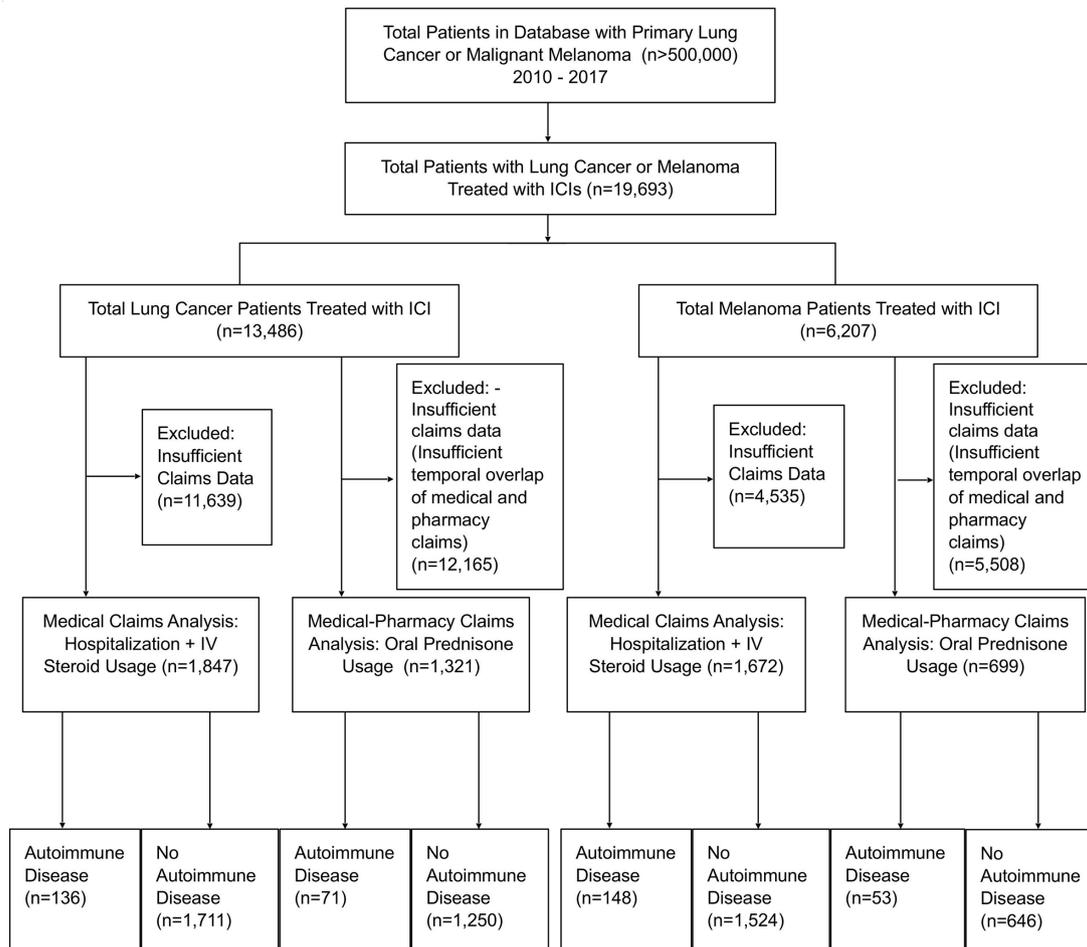
### Primary analysis and statistics

In the absence of actual dates of service, dates of claims payment were used as a proxy for dates of service. For each patient receiving ICI, it was determined whether they received each intervention at least once within 180 days after any ICI treatment date. Proportions were compared with the N-1  $\chi^2$  test. All analyses were performed using MATLAB software (Mathworks, Natick, Massachusetts, USA).

## RESULTS

### Patient population

We identified 19,693 patients diagnosed with either lung cancer or melanoma that received at least one



**Figure 1** Database flow chart. Patients were excluded from further analysis solely based on criteria related to the completeness of their data set as described in Methods section. ICI, immune checkpoint inhibitor; IV, intravenous.

cycle of ICI therapy (nivolumab, pembrolizumab, or ipilimumab). A total of 1847 patients with lung cancer met inclusion criteria for medical claims analysis, and 1321 patients with lung cancer met inclusion criteria for medical-pharmacy claims analysis. A total of 1672 patients with melanoma met inclusion criteria for medical claims analysis, and 699 patients with melanoma met inclusion criteria for medical-pharmacy claims analysis (figure 1).

Patient characteristics for the subset of patients used for medical claims analysis and medical-pharmacy claims analysis are summarized within table 1A and B. Overall, 8.1% of patients in the medical claims analysis subset and 6.1% of the patients in the medical-pharmacy claims analysis subset had at least one AID. Median ICI infusions were higher for PD-1 inhibitors than ipilimumab, ranging from two to five infusions depending on subgroup for PD-1 inhibitors versus one in each subgroup for ipilimumab. Ipilimumab was not analyzed for lung cancer patients, given that it was not approved for lung cancer during this time frame. Given our inclusion criteria, all patients had a set follow-up period of 180 days after the last ICI administration.

### Post-ICI interventions

Melanoma and lung patients with an AID were approximately twice as likely as patients without AID to have received oral prednisone following treatment with PD-1 inhibitors (16.7% vs 8.6%,  $p=0.0048$ ; figure 2), while patients with AID were 2.3 times as likely to receive intravenous methylprednisolone following PD-1 inhibitor therapy (8.4% vs, 3.7%  $p=0.0012$ ). Overall, patients were less likely to receive intravenous methylprednisolone relative to oral prednisone.

Subset analyzes of patients based on cancer type and immunosuppressant use suggested trends for increased rates in oral prednisone and intravenous methylprednisolone treatment across all subgroups for patients with AID. There was a statistically significant increase in oral prednisone use for the melanoma-PD-1 inhibitors group (relative risk (RR)=2.9,  $p=0.03$ ). There was also an increase in intravenous methylprednisolone use for the lung cancer-PD-1 inhibitors group (RR=2.2,  $p=0.0004$ ) (table 2).

For patients receiving intravenous methylprednisolone across all cancers and checkpoint inhibitors (109 total patients), the median number of days from the date of

**Table 1A** Patient characteristics in medical claims analysis

	Melanoma	Lung cancer	Autoimmune disease	No autoimmune disease
Total patients	1672	1847	284	3230
Average age	62.9	67.1	65.6	65.1
%Female	34.8	50.2	50.0	42.2
%Nivolumab	13.0	96.2	53.9	57.0
%Pembrolizumab	18.9	3.8	13.0	10.8
%Ipilimumab	68.1	N/A	33.1	32.2
%Ipilimumab-nivolumab combo	2.45	N/A	2.5	1.3
Median # ICI infusions, PD-1 Inhibitors	2	4	3	3
Median # ICI infusions, ipilimumab	1	N/A	1	1

**Table 1B** Patient characteristics in medical-pharmacy claims analysis

	Melanoma	Lung cancer	Autoimmune disease	No autoimmune disease
Total patients	699	1321	124	1896
Average age	62.6	67.0	65.4	65.5
%Female	35.1	48.9	47.6	43.9
%Nivolumab	21.9	89.8	63.7	66.5
%Pembrolizumab	27.9	10.2	13.7	16.5
%Ipilimumab	50.2	N/A	22.6	17.0
%Ipilimumab-nivolumab combo	7.2	N/A	5.7	2.3
Median # ICI infusions, PD-1 inhibitors	2	5	4	4
Median # ICI Infusions, Ipilimumab	1	N/A	1	1

ICI, immune checkpoint inhibitors.

first checkpoint inhibitor treatment to the date of the earliest intravenous methylprednisolone infusion was 79 days. Following intravenous methylprednisolone infusion, 68.9% of patients did not receive another treatment with the same checkpoint inhibitor.

In addition to corticosteroid use, we evaluated the rates of hospitalization in patients within 180 days after any treatment with checkpoint inhibitors (table 3). Patients with melanoma and AID who received PD-1 inhibitors had a significantly increased risk of hospitalization relative to patients with melanoma without AID following checkpoint inhibitor therapy (RR=4.2,  $p<0.0001$ ). Rates of hospitalization after treatment with ICIs were increased for patients with AID across all subgroups. Hospitalization was correlated with stopping ICI therapy. In all, 85.4% of patients who were hospitalized following ICI therapy did not receive the same ICI treatment after the hospitalization. However, a causal relationship cannot be determined from these data. Rates of treatment with corticosteroids and hospitalization following treatment with ICIs was not uniform across autoimmune conditions, though limited data for individual conditions limits the interpretation of this data (online supplemental table 3).

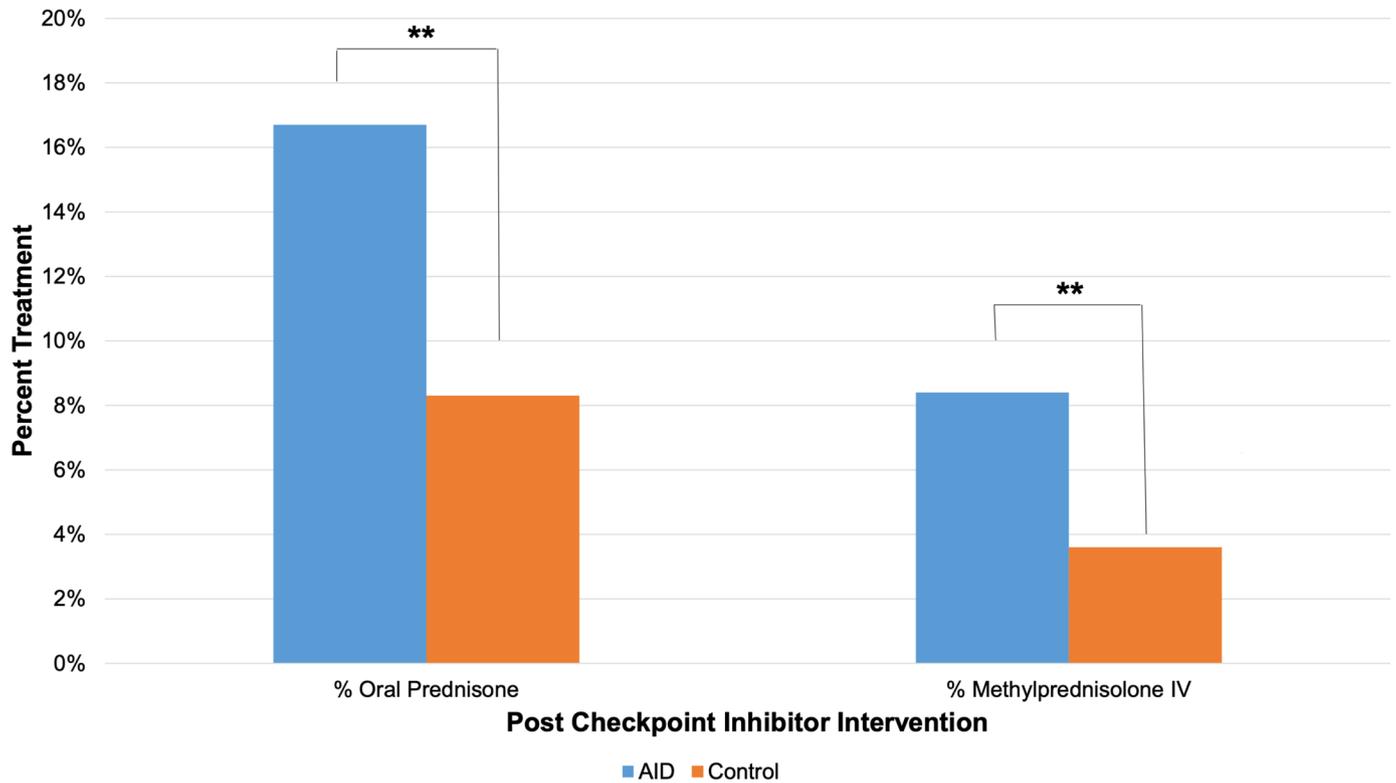
Ipilimumab-nivolumab combination ICI therapy has been shown to have a higher risk of irAEs than ICI monotherapy.<sup>9</sup> We found a significant increase in the rate of hospitalizations following combination ICI therapy in

melanoma patients with AIDs compared with non-AID patients (RR 4.4,  $p=0.0234$ ; table 3). There were trends for increased rates of intravenous methylprednisolone use and oral prednisone use in melanoma patients treated with combination therapy with AID relative to patients with no AID (tables 2–3).

## DISCUSSION

To our knowledge, this is the largest study evaluating the toxicity of ICI therapy in cancer patients with AIDs and comparing with patients with no AID. This also the first to use a large medical-pharmacy claims data set from numerous facilities. Here, we demonstrate a significant association of increased corticosteroid treatment and hospitalization rates following ICI therapy in cancer patients with AID compared with patients without AID.

Due to the intervention-based nature of medical claims data, we employed steroid use as proxy measurements of clinical irAEs that plausibly represent clinical responses to ICI toxicity, though this represents a ceiling on the rate of irAEs as steroids could plausibly be used for alternative purposes. Because intravenous corticosteroids are more likely to be used in the context of more serious toxicities and oral corticosteroid treatment more likely used for moderate toxicity,<sup>4</sup> our data could be interpreted as



**Figure 2** Increased rates of treatment with systemic immunosuppression following treatment with PD-1 inhibitors in patients with AID. Patients received corticosteroid treatment within 180 days of receiving immune checkpoint inhibitor treatment. \*\* is indicative of  $p < 0.01$ . AID, autoimmune disease.

approximations of moderate and severe irAEs for rates of oral steroids and intravenous steroids, respectively.

Rates of corticosteroid use following treatment with PD-1 inhibitors in our study are similar to previous clinical studies that used clinical records alone. In a prior study that determined rates of treatment with prednisone for PD-1 therapy toxicity in patients with AID and NSCLC, 14.3% of patients (8/56) were treated

with prednisone following treatment,<sup>8</sup> compared with 14.1% of patients with AID with all types of lung cancer treated with PD-1 inhibitors in our study (10/71). In a study of the toxicity profile of PD-1 inhibitors in patients with advanced melanoma, 38% of patients (20/52) experienced a reaction requiring immunosuppression, compared with 24% of patients (6/25) requiring oral prednisone in our study.<sup>9</sup>

**Table 2** Rates of corticosteroid treatment after ICI treatment across cancer type, ICI and AID\*†

	Oral prednisone		Intravenous methylprednisolone	
	AID	No AID	AID	No AID
Melanoma PD-1 inhibitors	24.0%* (6/25) (RR=2.4)	9.9% (32/323)	1.9% (1/54)(RR=1.3)	1.5% (7/480)
Lung cancer PD-1 inhibitors	14.1% (10/71) (RR=1.7)	8.3% (104/1250)	11.0%*** (15/136) (RR=2.6)	4.3% (74/1711)
All cancers PD-1 inhibitors	16.7%** (16/96) (RR=1.9)	8.6% (131/1573)	8.4%** (16/190) (RR=2.3)	3.7% (81/2191)
Melanoma ipilimumab	10.7% (3/28) (RR=2.14)	5.0% (16/323)	2.1% (2/94) (RR=1.6)	1.3% (14/1039)
Melanoma ipilimumab-nivolumab combo	14.3% (1/7) (RR=1.2)	11.6% (5/43)	14.3% (1/7) (RR=2.9)	4.9% (2/41)

\*Values with \* were significantly different at  $p < 0.05$  when comparing AID versus non-AID patients within particular subgroups, values with \*\* were significant at  $p < 0.01$ , and values with \*\*\* were significant at  $p < 0.001$ .

†The patient populations for prednisone and methylprednisolone are not identical because the separate analyses required distinct inclusion criteria (see Methods).

AID, autoimmune disease; ICI, immune checkpoint inhibitor; RR, relative risk.

**Table 3** Rates of hospitalization after ICI treatment across cancer type, ICI, and AID\*

	Hospitalization	
	AID	No AID
Melanoma PD-1 inhibitors	24.1%*** (13/54) (RR=4.2)	5.8% (28/480)
Lung cancer PD-1 inhibitors	38.2% (52/136) (RR=1.2)	32.5% (556/1711)
All cancers PD-1 inhibitors	34.2%* (65/190) (RR=1.3)	26.1% (572/2191)
Melanoma ipilimumab	10.6% (10/94) (RR=1.5)	6.9% (72/1039)
Melanoma ipilimumab-nivolumab combo	42.9%* (3/7) (RR=4.4)	9.8% (4/41)

\*Values with \* were significantly different at  $p < 0.05$  when comparing AID versus non-AID patients within particular subgroups, values with \*\*\* were significant at  $p < 0.001$ . AID, autoimmune disease; ICI, immune checkpoint inhibitor.

Similar to a single study comparing toxicity in a group of AID patients to non-AID controls, our study found increased rates of both oral and intravenous steroid use following treatment with ICIs.<sup>13</sup> This previous study specifically evaluated patients with IBD. Our results support increased toxicity risk for patients with AID, but limited sample size for individual diseases prevent subgroup analyzes at the level of specific conditions. It is likely that both the severity of the disease and certain conditions—for example, IBD—place patients at varying degrees of increased risk. Several other retrospective series of AID patients do not compare the toxicity rates with non-AID patients, so it is unclear in these studies if the treatment toxicities are notably worse in patients with AID.<sup>7–12</sup> Of note, the rates of steroid use in AID patients in our study are comparable to these studies. However, caution should be applied when comparing rates of steroid use in this study to irAE rates more generally. Missing interventions may have arisen from incomplete data collection, and some irAEs may not be treated with systemic steroids at all. Similar to the study of patients with IBD, our study supports that patients with AID have increased toxicity risk and provided an estimate of this risk, but it is not suggestive of AID being a clear contraindication to treatment.

An unexpected result of our study is that there were lower rates of corticosteroid treatment and hospitalization in patients with AID following treatment with ipilimumab relative to PD-1 inhibitors (tables 2 and 3), despite the fact that ipilimumab has been shown to be more toxic than PD-1 inhibitors in previous studies.<sup>9</sup> One potential explanation is that prior knowledge of the toxicity of ipilimumab caused increased hesitation from medical providers when prescribing and continuing ipilimumab, leading to fewer cycles of treatment and ultimately less toxicity. This is consistent with our data, as ipilimumab had the lowest median number of infusions per patient across all checkpoint inhibitors at 1.

Several methodological limitations must be taken into account when interpreting our results. Retrospective analysis of medical claims data does not indicate causation. It is possible that the interventions used in this study as indications of toxicity were not in fact driven by checkpoint inhibitor toxicity, but from another cause, such as cancer morbidity. This is particularly relevant when interpreting the hospitalization results, given that overall rates of hospitalization following checkpoint inhibitor therapy were much higher among lung cancer patients relative to advanced melanoma patients despite the fact that rates of corticosteroid use were similar across cancer type. Our analysis also did not distinguish patients with active AID from inactive AID, and in previous studies of patients with AID receiving ICI treatment the majority of patients did not have active disease.<sup>8</sup> Similarly, our results may not be generalizable to patients with active AID.

Our inclusion criteria led to the exclusion of numerous patients within the database, which is typical for large claims-based analysis such as Surveillance, Epidemiology, and End Results (SEER)-Medicare. Because these criteria were solely based on measures of completeness of the data set for individual patients, it is unlikely to skew comparisons across groups, but may lead to the exclusion of patients who were deceased prior to 180 days following their final ICI infusion. The database used had limited survival data, rendering it impossible to discern whether a lack of medical claims during the period following therapy was due to missing data from the database or from patient mortality. Because of this, our exclusion criteria for medical claims analysis included the requirement that the patient had at least a single claim 180 days following the final administration of immunotherapy, implying that the patient survived throughout this period. While this criterion reduces the likelihood of false negatives due to missing data, it also ensures that patients who did not survive during this time period—potentially as a result of fatal treatment-related toxicity—are not included within our analysis.

In summary, our findings suggest an association of increased toxicity risk for AID patients being treated with ICIs compared with patients with no AID. This is consistent with a cooperative effect between AID and ICI, and AID patients should be monitored carefully for immune-related toxicities. Higher levels of evidence with prospective clinical trials are needed to determine the immune-related toxicity profile and safety.

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**Contributors** DAB, CAS, SPH, CS, BH, TJCW, and SKC performed initial study planning and hypothesis creation. DAB performed data analysis. DAB drafted the initial manuscript. DAB, CAS, SPH, CS, BH, TJCW, and SKC revised and approved the final study manuscript.

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**Competing interests** CAS reports personal fees from Genentech, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, outside the submitted work. TJCW reports personal fees and non-financial support from AbbVie, personal fees from AstraZeneca, personal fees from Cancer Panels, personal fees from Doximity, personal fees and non-financial support from Elekta, personal fees and non-financial support from Merck, personal fees and non-financial support from Novocure, personal fees and non-financial support from RTOG Foundation, personal fees from Rutgers, personal fees from University of Iowa, personal fees from Wolters Kluwer, outside the submitted work. BH is an employee of Eversana. SKC reports personal fees and non-financial support from AbbVie and Sanofi, outside of the submitted work.

**Patient consent for publication** Not required.

**Ethics approval** The data utilized in this study was fully deidentified and offered for academic use by Decision Resources Group (Burlington, Massachusetts), a healthcare data analysis company.

**Provenance and peer review** Not commissioned; externally peer-reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. The data used in this study is deidentified medical claims data offered for academic use from a third party, the Decision Resources Group (855-380-4850).

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**Supplemental Tables/eTables****eTable 1A: Intervention HCPCS/CPT Codes**

Intervention	HCPCS/CPT Codes
Ipilimumab infusion	J9228/C9284
Nivolumab infusion	J9299/C9453
Pembrolizumab infusion	J9271/C9027
Methylprednisolone infusion	J2920/J2930
Hospitalization	99221-99223/99234-99236/99218-99220

**eTable 1B: Oral Prednisone NDC Code Stems**

545693043	500902403	332610352	105440125	551544926	619190373	591150140	504364326
500900095	500902532	332610780	105440274	551544938	619190404	591150141	504364324
500900096	500902608	532170255	105440473	551544946	619190235	597460171	504364325
500900099	500902786	532170288	105440538	551544949	619190226	597460172	504361720
500900100	500902789	532170292	105440913	551544950	619190342	597460173	707860172
500900101	500902804	606870122	105440914	551544954	619190995	597460175	504361750
500900093	500902822	606870134	105440915	551544965	619190321	683870240	1431410
500900094	545690330	606870145	636291579	681510820	682583013	683870241	1439741
500900097	545690331	433530657	636291587	581180018	663360094	353560674	1431425
500900098	545690332	433530819	636291605	581184728	663360058	499990008	1431473
500900102	545690333	675440399	636294562	581185338	663360219	499990110	1431475
500900439	545693302	126340188	636294658	581189738	663360428	353560673	1431477

500901001	545694026	126340184	636295250	581180027	604290130	499990028	1439738
500901002	545693413	178563722	636296621	581185442	604290131	353560677	1439739
500901455	545695840	105440508	636296659	556950013	604290132	353560818	1439740
500901989	5915052	105440509	636297335	556950014	765191048	353560819	540017
500901990	5915442	105440045	636297388	556950015	529590126	557000049	540018
500901991	5915443	105440046	4636141	556950024	529590127	557000072	540019
500902136	332610129	105440048	4636155	619190326	529590220	557000203	543722
500902402	332610351	105440093	708820117	619190365	591150139	557000208	544728
557000209	6151542	430630472	687887372	216950764	493490725	705180306	544741
4408165	6152513	430630590	687889177	216950765	493490997	705180307	544742
4408167	6153593	430630608	687889178	672960140	521250034	705180242	548724
762370227	6156516	430630610	687889179	672960600	521250054	705180473	548739
762370228	516550320	430630643	687881473	672960602	521250150	705180632	548740
637390518	516550410	430630644	687889513	672960247	521250255	705180800	
637390519	6035335	430630703	687889503	672960974	521250522	548722	
637390520	6035336	458020303	687889551	672961032	521250555	484330321	
637390588	6035337	458020733	687889309	672961194	521250366	607600629	
511380144	6035338	548680258	631870020	672961203	521250775	165900373	
511380145	6035339	548680836	631870037	242360205	242360418	165900624	
511380146	430630097	548680908	631870066	493490059	521250957	425490647	
511380147	552890330	548681119	631870085	493490550	521250996	165900326	
458650638	552890352	548681183	631870243	493490607	617860049	165900365	
458650670	552890373	548684095	631870300	493490717	242360107	538080399	

661160485	552890438	548684096	631870807	493490783	242360405	538080540	
534890138	430630109	548685213	216950305	493490856	617860538	538080542	
534890139	430630415	548685230	216950306	242360217	705180073	538080543	
534890140	430630426	687886414	216950307	242360248	705180205	538080560	
6150536	430630432	687886440	216950580	242360625	705180305	647251473	

**eTable 2: ICD9/10 Codes Used in Autoimmune Disease Identification**

<b>Disease</b>	<b>ICD9/10 Codes</b>
Alopecia areata	70401/L63
Autoimmune hemolytic anemia	2830/D591
Autoimmune hepatitis	57142/K754
Crohn's Disease	555/K50
Discoid lupus	6954/L93
Graves's Disease	2420/E05
Hashimoto's thyroiditis	2452E063
Idiopathic pulmonary fibrosis	51631/J84112
Multiple sclerosis	340/G35
Myasthenia gravis	358/G70
Polymyalgica Rheumatica	725/M353
Psoriasis	696/L40
Psoriatic arthritis	6960L4050
Rheumatic fever	390/I00/I01

Rheumatoid arthritis	7140/M06
Scleroderma	7010/L940
Seronegative arthritis	7140/M060
Sjögren syndrome	7102/M350
Systemic lupus erythematosus	7100/M32
Ulcerative colitis	556/K51
Vasculitis	4476/I776/L959

**eTable 3: Results Summary by Autoimmune Disease**

Disease	Prednisone	IV Methylprednisolone	Hospitalization
Autoimmune Hemolytic Anemia	0% (0/1)	0% (0/6)	33.3% (2/6)
Autoimmune Hepatitis	100% (1/1)	23.1% (3/13)	38.5% (5/13)
Crohn's Disease	0% (0/3)	14.3% (1/7)	14.3% (1/7)
Discoid Lupus	0% (0/2)	N/A (0/0)	N/A (0/0)
Grave's Disease	14.8% (4/27)	2.5% (1/40)	25.0% (10/40)
Hashimoto's Thyroiditis	22.2% (2/9)	6.7% (1/15)	33.3% (5/15)
Idiopathic Pulmonary Fibrosis	0% (0/2)	60.0% (3/5)	40.0% (2/5)
Multiple Sclerosis	0% (0/3)	0% (0/7)	42.9% (3/7)
Myasthenia Gravis	0% (0/1)	16.7% (1/6)	50.0% (3/6)
Polymyalgia Rheumatica	0% (0/2)	0% (0/9)	33.3% (3/9)
Psoriasis	25.0% (4/16)	8.7% (2/23)	13.0% (3/23)

Psoriatic Arthritis	0% (0/2)	N/A (0/0)	N/A (0/0)
Rheumatoid Arthritis	16.7% (4/24)	6.7% (2/30)	50.0% (15/30)
Rheumatic Fever	0% (0/2)	0% (0/1)	0% (0/1)
Scleroderma	N/A (0/0)	0% (0/1)	100% (1/1)
Seronegative Arthritis	25.0% (4/16)	7.1% (2/28)	46.4% (13/28)
Sjogren's Syndrome	33.3% (1/3)	0% (0/7)	57.1% (4/7)
Systemic Lupus	0% (0/4)	0% (0/3)	0% (0/3)
Ulcerative Colitis	28.6% (2/7)	8.3% (2/24)	54.2% (13/24)
Vasculitis	N/A (0/0)	0% (0/2)	100.0% (2/2)