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

David Andrew Bender ,[1] Samuel P Heilbroner,[1] Tony J C Wang,[1,2] Catherine A Shu,[2,3] Brigham Hyde,[4] Catherine Spina,[1,2] Simon K Cheng[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Simon K Cheng;
sc3225@cumc.columbia.edu

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).[1] 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 ≥3 grade irAEs.[2] irAEs can affect nearly every organ system,[3] though most commonly involve the gastrointestinal (GI) tract, the endocrine system, lung, skin, and liver.[4] It is hypothesized that patients with a genetic predisposition or a pre-existing AID are at higher risk for irAEs.[5] 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 effect at least 10% of the general population (with recent estimates in cancer patients high as of 13% to 25%).[6]

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.[7–12] 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.[13] 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 ipilumumab, 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 χ^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

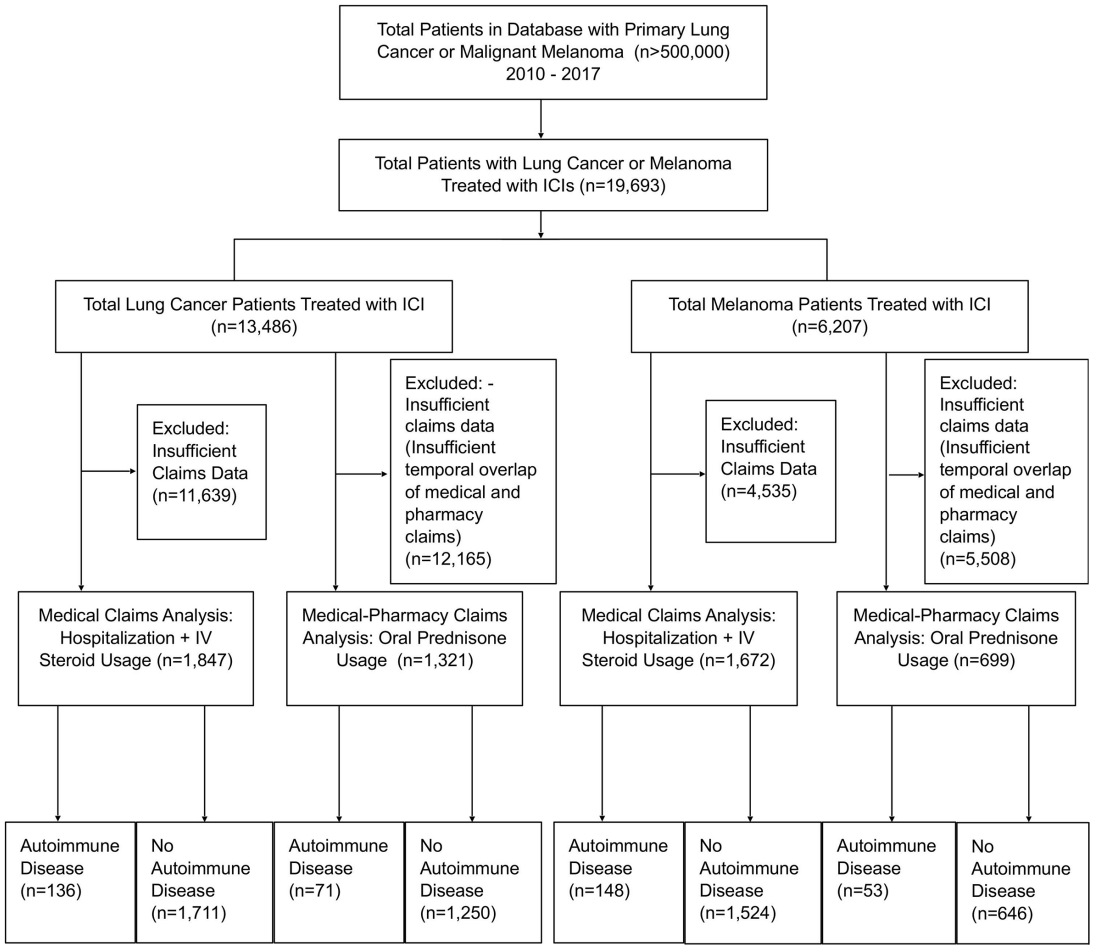

Figure 1 Database flow chart. Patients were excluded from further analysis solely based on criteria related to the completeness of their data set as described in Methods section. ICI, immune checkpoint inhibitor; IV, intravenous.

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.[9] 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,[4] our data could be interpreted as

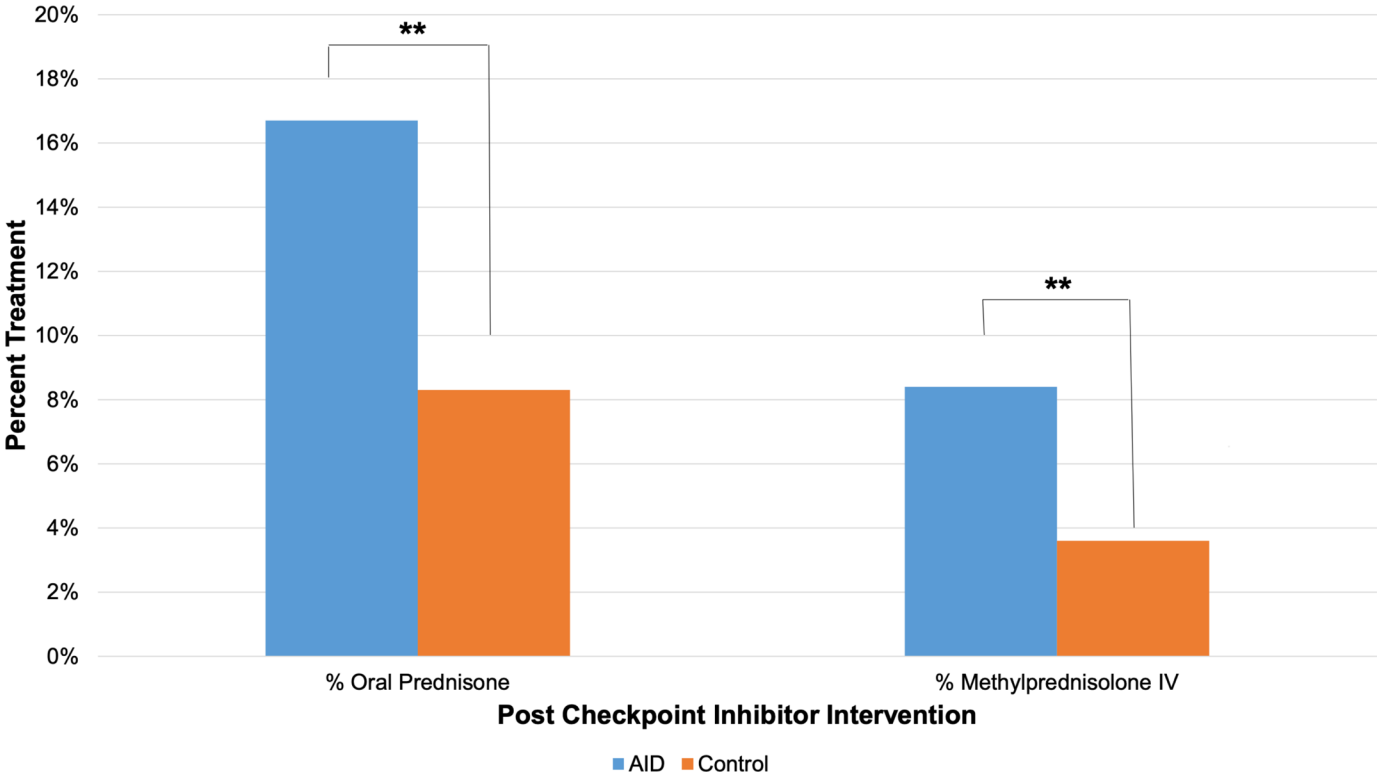

Figure 2 Increased rates of treatment with systemic immunosuppression following treatment with PD-1 inhibitors in patients with AID. Patients received corticosteroid treatment within 180 days of receiving immune checkpoint inhibitor treatment. ** is indicative of p<0.01. AID, autoimmune disease.

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,[8] 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.[9]

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.[13] 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.[7–12] 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.[9] 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.[8] 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.

Author affiliations
[1]Department of Radiation Oncology, Vagelos College of Physicians & Surgeons, Columbia University Irving Medical Center, New York City, New York, USA
[2]Herbert Irving Comprehensive Cancer Center, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York City, New York, USA
[3]Department of Internal Medicine, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York City, New York, USA
[4]Eversana, New York City, New York, USA

Twitter Catherine Spina @Katie_Spina and Simon K Cheng @drdrcheng

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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).

ORCID iD

David Andrew Bender http://orcid.org/0000-0002-1709-4774

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