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Long-term mortality outcomes among immunotherapy recipients treated with dupilumab for the management of cutaneous immune-related adverse events

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ABSTRACT

Background Dupilumab has been added to National Cancer Comprehensive Network guidelines as a therapeutic strategy for managing certain cutaneous immune-related adverse events (cirAEs) from immune checkpoint blockade (ICB). However, little is known about the implications of dupilumab for cancer outcomes in this population. In this multi-institutional study, we evaluate the impact of dupilumab treatment on survival among ICB recipients.

Methods We conducted a multi-institutional retrospective cohort study of ICB recipients from the Mass General Brigham Healthcare System and Dana-Farber Cancer Institute. The dupilumab group was compared with two control groups who did not receive dupilumab: with and without cirAEs (control groups 1 and 2, respectively) that were 1:2 matched on sex, race, age at ICB initiation, Charlson Comorbidity Score, year of ICB initiation, and ICB type. Manual chart review was performed to obtain cirAE characteristics, systemic glucocorticoid use, dupilumab treatment, vital status, and last contact date. Time-varying multivariable Cox proportional hazards regressions were used to evaluate the impact of dupilumab on overall survival, adjusted for sex, race, age at ICB initiation, ICB type, Charlson Comorbidity Index score, cancer type, cancer stage at ICB initiation, and systemic glucocorticoid use.

Results A total of 53 cirAE patients treated with dupilumab were compared with two control groups of 106 patients each. Most patients receiving dupilumab demonstrated either complete or partial resolution of their cirAE (88.7%). In multivariable modeling, the overall survival of the dupilumab group was not significantly different from control group 1 (HR=0.74, 95% CI: 0.35 to 1.60, p=0.5) or control group 2 (HR=0.70, 95% CI: 0.32 to 1.51, p=0.4). However, the use of systemic glucocorticoids within 2 years after ICB initiation was associated with poorer overall survival when comparing the dupilumab group to control group 1 (HR=2.03, 95% CI: 1.04 to 3.96, p=0.039) and control group 2 (HR=2.21, 95% CI: 1.25 to 3.91, p=0.006).

Conclusions This study suggests that dupilumab is an effective therapy for recalcitrant cirAEs and does not adversely impact mortality. Due to the observed detrimental effects of systemic glucocorticoid therapy, this study suggests the need to shift away from systemic glucocorticoid immunosuppression and toward targeted immune modulators for irAE management, though prospective randomized trials are necessary to investigate this.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current guidelines recommend the use of dupilumab in the treatment of certain moderate to severe cutaneous immune-related adverse events (cirAE) and systemic glucocorticoids for others. Previous studies have shown dupilumab to be effective for steroid-refractory cirAEs; however, the impact of dupilumab on survival outcomes among recipients of immune checkpoint blockade (ICB) remains understudied.

WHAT THIS STUDY ADDS

⇒ This study concludes that dupilumab is an effective modality to treat cirAEs, with 88.7% of patients responding to treatment. Additionally, this study demonstrates a 206-day average delay from cirAE onset to dupilumab treatment, suggesting the need for more timely consideration of this therapeutic option. Finally, our results demonstrated that dupilumab does not increase mortality among ICB recipients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study suggest that the use of dupilumab in the treatment of cirAEs is effective and does not adversely impact mortality in the cancer population. Based on these findings, clinicians should consider dupilumab treatment for cirAEs in the appropriate clinical setting. Moreover, this study provides further evidence for the use of targeted immune modulators as preferred over more commonly used broad-based glucocorticoid immunosuppression for the management of immune-related adverse events in the setting of ICB.

INTRODUCTION

Immune checkpoint blockade (ICB) therapy has revolutionized cancer treatment but is associated with morbid and potentially life-threatening toxicities known as immune-related adverse events (irAEs). Of these, cutaneous irAEs (cirAEs) are the most common, occurring in up to 40% of ICB recipients. Current National Cancer Comprehensive Network (NCCN) version 1.2024 guidelines for the management of cirAEs of different morphologies range from the use of topical steroids and oral antihistamines for low-grade eruptions to holding immunotherapy and initiating high-dose systemic immunosuppressive agents, typically systemic glucocorticoid therapy, for high-grade eruptions.[1] Though there is not yet consensus regarding the use of systemic immunosuppression in patients receiving ICB treatment for cancer care,[2–4] there is a growing body of evidence suggesting that the use of systemic glucocorticoids in ICB-treated patients is detrimental to survival outcomes,[5 6] especially early in the course of ICB therapy.[7] In response to this concern, increasing attention has been given to considering more targeted immune-modulating approaches for the management of irAEs[8], which are hypothesized to be less likely to blunt the antitumor effect of ICB therapy than broader systemic glucocorticoid immunosuppression.

Evidence of this approach notes the recent inclusion of dupilumab, currently approved by the US Food and Drug Administration for the management of atopic dermatitis and prurigo nodularis, in the NCCN guidelines for the management of certain cirAEs. Dupilumab is a monoclonal antibody that inhibits interleukin 4 (IL-4) and interleukin 13 (IL-13) cytokine signaling and prevents the release of downstream IgE, which plays an important role in immune-mediated allergic processes, primarily in the type 2 inflammatory pathway.[9 10] Though these guidelines propose the use of dupilumab for the management of moderate to severe bullous eruptions and severe pruritus in the setting of ICB therapy,[1] it has been rapidly adopted as an off-label therapeutic strategy across a wide range of cirAEs. However, though several recent studies have demonstrated the efficacy of dupilumab in the management of several specific morphologies of cirAEs, these have been limited to case reports[11–14] and single institutional cohorts[8 15 16] without inclusion of comparator populations and long-term follow-up to evaluate the specific impact of dupilumab on ICB outcomes. As a result, there are no available data on the long-term impact of dupilumab on mortality among ICB recipients.

In this multi-institutional retrospective cohort study, our primary aim is to evaluate overall survival outcomes among ICB recipients treated with dupilumab. Our secondary aim includes evaluating the efficacy of dupilumab in the management of cirAEs. To our knowledge, this is the largest cohort of ICB recipients treated with dupilumab to date and the first to explicitly evaluate survival outcomes by comparison to robust non-dupilumab treated comparator populations of ICB recipients.

METHODS

We conducted a multi-institutional retrospective cohort study of ICB recipients who received dupilumab therapy for the management of cirAEs between September 27, 2017, and December 8, 2023, at the Mass General Brigham Healthcare System and the Dana-Farber Cancer Institute (MGBD). Figure 1 presents the population included in this study. We extracted patient demographic and medical history information from the MGBD Research Patient Data Registry[17] and the Enterprise Data Warehouse[18] using the same approaches as in our recently published studies[19–21] and in alignment with the published guidelines on defining cirAEs.[22] Manual chart review was conducted to extract cirAE characteristics (cirAE status—yes or no, cirAE onset date, cirAE morphology, and cirAE severity), dupilumab variables (dupilumab status—yes or no, dupilumab indication, dupilumab start and end date, treatments before dupilumab initiation, and dupilumab response), immunosuppression variables (systemic glucocorticoid use—yes or no, start date, and indication within 24 months after ICB initiation), absolute eosinophil count before and after dupilumab start, and patient outcomes (vital status, and date of last contact). Due to the heterogeneity in causes for ICB discontinuation (eg, treatment failure, irAEs, and patient death) and the difficulty in assessing this variable (eg, immunotherapy duration recommendations vary considerably over time and by cancer indication), we defined ICB interruption as "discontinuation" if a patient received less than 3 cycles of treatment, "pause" if a patient missed or delayed at least two cycles within 1 year of ICB initiation, and "continuation" otherwise. We chose three cycles as the cut-off as this number of treatment cycles has been shown to be minimally necessary to provide a clinical benefit.[23 24]

Manual chart review to identify cirAEs was conducted in accordance with our previously published approaches.[19–21] Briefly, a likelihood score between one to four was assigned to each cutaneous eruption in the setting of ICB use, with 1 representing that the eruption is highly unlikely to be secondary to ICB treatment and 4 representing that the eruption is highly likely to be secondary to ICB treatment. Cutaneous eruptions with a likelihood score of 3 or 4 were considered as cirAEs in this study.

High-dose systemic glucocorticoid use was defined as treatment with a glucocorticoid of 10 mg prednisone equivalent daily for at least seven consecutive days, which is consistent with prior literature.[25] Reasons for high-dose systemic glucocorticoid use were classified into four groups: cirAEs, other irAEs, cancer palliation, and other. The other irAEs group included patients who received systemic glucocorticoids for managing other non-cutaneous irAEs, such as colitis.

CirAE severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[26] CirAE morphology was documented based on clinical and histologic confirmation, whenever available. If histologic confirmation was not available, the morphology was documented based on clinical assessment by the dermatology

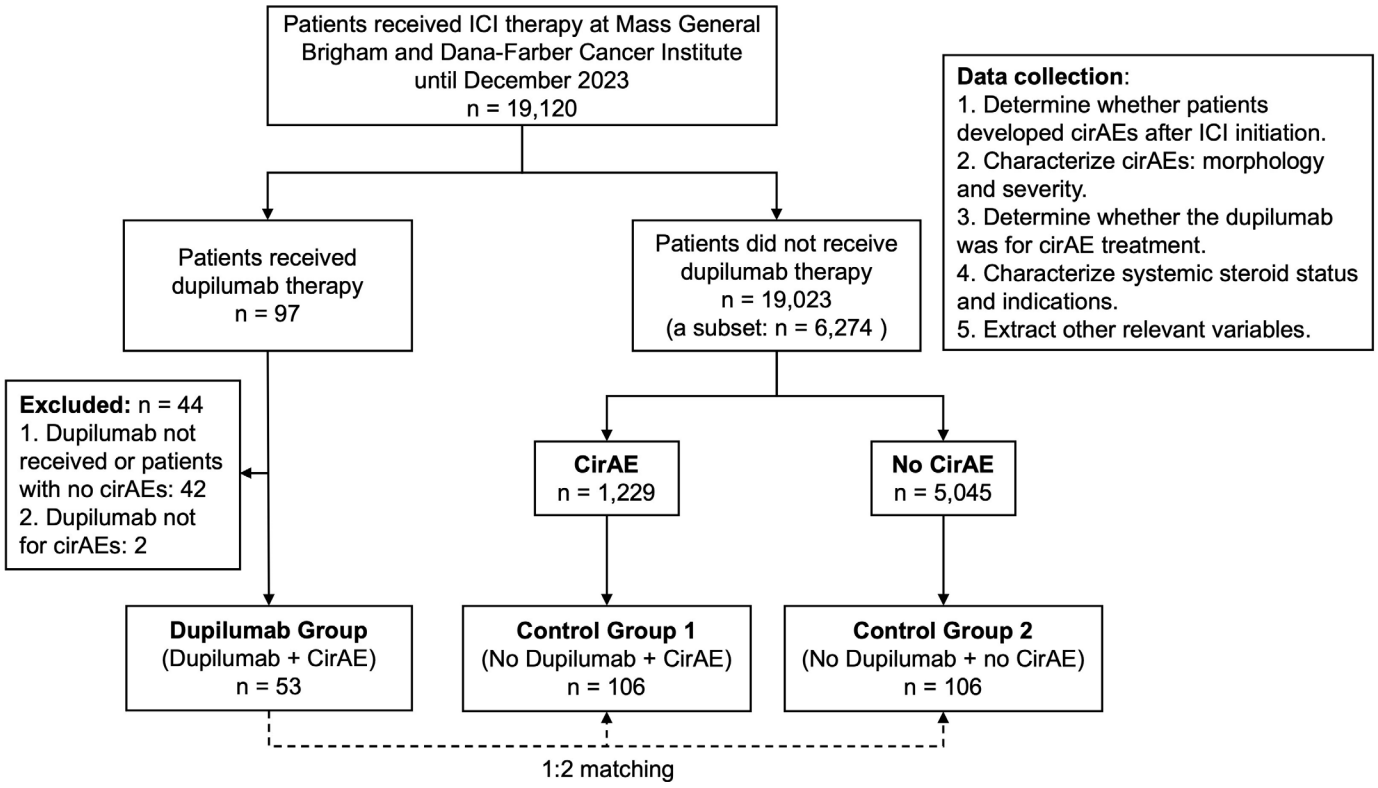

Figure 1 The study population and data collection. This study identified all ICB recipients who developed cirAEs and received dupilumab for managing cirAEs as the case group (the dupilumab group). To demonstrate the robustness of this study, the dupilumab group was compared with two control groups that were identified using 1:2 matching based on sex, race, age at ICB initiation, Charlson Comorbidity Score, year of ICB start, and ICB type. The first control group included 106 ICB recipients who developed cirAEs and were not treated with dupilumab; the second control group included 106 ICB recipients who did not experience cirAEs and were not treated with dupilumab. CirAE, cutaneous immune-related adverse event; ICB, immune checkpoint blockade.

team. Response to dupilumab was measured by comparing the CTCAE grade of the cirAE before and after the use of dupilumab. Patients whose cirAE became grade 0 were considered complete responders. Patients whose cirAE became grade 1 were considered partial responders. Both complete responders and partial responders were categorized as responders.

Patients who did not ultimately receive dupilumab treatment or who were given dupilumab for treatment of a condition besides a cirAE were excluded from the study population. The retained ICB recipients who were treated with dupilumab for management of cirAEs (dupilumab group) were then compared with two control groups that were identified by 1:2 best matching based on sex, race, age at ICB initiation, Charlson Comorbidity Score (CCS), year of ICB start, and ICB type using the "matchControls" function in the R package e1071 V.1.7-14. The first control group included ICB recipients who developed cirAEs but were not treated with dupilumab (control group 1). The second group included ICB recipients who did not experience cirAEs and were not treated with dupilumab (control group 2). Because the development of cirAEs has been associated with improved survival in the setting of ICB therapy,[19 25 27] we controlled for the presence of cirAEs by matching with patients who developed cirAEs but did not use dupilumab (control group 1). The second control group was used to examine the impact of dupilumab on overall survival independent of the presence of cirAEs.

We used Pearson's χ^2 test for categorical variables and t-test for continuous variables to compare groups. We used an alpha of 0.05 as the significance threshold. To account for immortal time bias,[28] we performed time-varying Cox proportional hazards modeling, adjusting for sex, race, age at ICB initiation, ICB type, CCS, cancer type, cancer stage at ICB initiation, and systemic glucocorticoid use within 2 years after ICB initiation. Both dupilumab and high-dose systemic glucocorticoid use were considered as time-varying covariates. We also conducted sensitivity analyses by additionally adjusting for ICB interruption and duration status. The proportional hazards assumption was examined using the "cox.zph" function in the R package survival V.3.5-7. All statistical analyses were conducted in R V.4.3.2.

RESULTS

A total of 53 ICB recipients who received dupilumab for the management of cirAEs were included and were matched to 106 ICB recipients with cirAEs but no

Table 1 Characteristics of the study population

	Dupilumab (N=53)	Control 1 (N=106)	Control 2 (N=106)	P value 1*	P value 2*
Mortality status					
Alive	43 (81.1%)	69 (65.1%)	47 (44.3%)	0.057	<0.001
Dead	10 (18.9%)	37 (34.9%)	59 (55.7%)		
Follow-up duration, days					
Median (Q1, Q3)	961 (531, 1240)	718 (432, 1090)	416 (185, 791)	0.114	<0.001
Sex					
Female	18 (34.0%)	35 (33.0%)	35 (33.0%)	>0.9	>0.9
Male	35 (66.0%)	71 (67.0%)	71 (67.0%)		
Race					
White	47 (88.7%)	99 (93.4%)	101 (95.3%)	0.474	0.224
Other/unavailable	6 (11.3%)	7 (6.6%)	5 (4.7%)		
Age at ICB initiation, years					
Median (Q1, Q3)	67 (61, 75)	66 (61, 74)	67.5 (62, 74)	0.360	0.848
Year of ICB initiation					
<2018	2 (3.8%)	5 (4.7%)	5 (4.7%)	>0.9	>0.9
2018	5 (9.4%)	12 (11.3%)	10 (9.4%)		
2019	5 (9.4%)	9 (8.5%)	9 (8.5%)		
2020	14 (26.4%)	28 (26.4%)	28 (26.4%)		
2021	12 (22.6%)	21 (19.8%)	24 (22.6%)		
2022	12 (22.6%)	25 (23.6%)	24 (22.6%)		
2023	3 (5.7%)	6 (5.7%)	6 (5.7%)		
ICB type†					
Combination	18 (34.0%)	38 (35.8%)	29 (27.4%)	>0.9	0.499
PD-1/PD-L1	35 (66.0%)	68 (64.2%)	77 (72.6%)		
CCS					
Median (Q1, Q3)	1 (0, 3)	2 (0, 3)	2 (1, 3)	0.197	0.023
Cancer stage at ICB‡					
IV	37 (69.8%)	74 (69.8%)	85 (80.2%)	0.292	0.341
III	11 (20.8%)	28 (26.4%)	14 (13.2%)		
Other	5 (9.4%)	4 (3.8%)	7 (6.6%)		
Cancer type					
Melanoma	13 (24.5%)	50 (47.2%)	30 (28.3%)	0.013	0.887
Genitourinary	16 (30.2%)	28 (26.4%)	29 (27.4%)		
Head and neck	8 (15.1%)	8 (7.5%)	13 (12.3%)		
Thoracic	8 (15.1%)	16 (15.1%)	21 (19.8%)		
Other	8 (15.1%)	4 (3.8%)	13 (12.3%)		
Systemic glucocorticoids use within 2 years of ICB start§					
Yes	38 (71.7%)	64 (60.4%)	51 (48.1%)	0.220	0.008
No	15 (28.3%)	42 (39.6%)	55 (51.9%)		
Systemic glucocorticoid reason§					
CirAEs	26 (49.1%)	12 (11.3%)	0 (0%)	<0.001	<0.001
Other irAEs¶	10 (18.9%)	42 (39.6%)	28 (26.4%)		
Cancer palliation	2 (3.8%)	7 (6.6%)	12 (11.3%)		

Continued

Table 1 Continued

	Dupilumab (N=53)	Control 1 (N=106)	Control 2 (N=106)	P value 1*	P value 2*
Other	0 (0%)	3 (2.8%)	11 (10.4%)		
ICB to systemic glucocorticoid§, days					
Median (Q1, Q3)	253 (74, 518)	140 (67.8, 267)	168 (47.5, 263)	0.046	0.010

*P value 1: comparison between the dupilumab group and the control 1 group. P value 2: comparison between the dupilumab group and the control 2 group.
†Combination therapy of CTLA-4 and PD-1/PD-L1.
‡Other includes the cases where the corresponding cancers were not staged based on AJCC criteria.
§For these variables, we consider the systemic glucocorticoid use within 2 years after the initiation of ICB therapy.
¶See detailed list of Other irAEs in online supplemental table S6.
AJCC, American Joint Committee on Cancer; CCS, Charlson Comorbidity Score; cirAEs, cutaneous irAEs; CTLA-4, Cytotoxic T-Lymphocyte Associated Protein 4; ICB, immune checkpoint blockade; irAEs, immune-related adverse events; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Q1, the first quartile; Q3, the third quartile.

dupilumab treatment and 106 ICB recipients without cirAEs and without dupilumab therapy (figure 1). The characteristics of the dupilumab group and the two control groups are presented in table 1. Comparing the dupilumab group and the control group 1, there were no significant differences in mortality status, follow-up duration, sex, race, age at ICB initiation, year of ICB initiation, ICB type, CCS, cancer stage at ICB initiation, and high-dose systemic glucocorticoid use within 2 years after initiation of ICB therapy (p>0.05). Comparing the dupilumab group and the control group 2, there were significant differences in mortality status (18.9% vs 55.7%, p<0.001), follow-up duration (median: 961 vs 416 days, p<0.001), CCS (median: 1 vs 2, p=0.023), and high-dose systemic glucocorticoid use within 2 years after initiation of ICB therapy (71.7% vs 48.1%, p=0.008). Among the 38 patients who received high-dose systemic glucocorticoids within 2 years after initiation of ICB therapy in the dupilumab group, 81.6% (31 patients) received systemic glucocorticoids before dupilumab treatment to manage either cutaneous irAEs (24 patients) or non-cutaneous irAEs (7 patients). The remaining 18.4% (seven patients) who were treated with high-dose systemic glucocorticoids received it after initiating dupilumab therapy, for the management of either cutaneous irAEs (three patients), non-cutaneous irAEs (one patient), cerebral edema from brain metastases (two patients), or worsening pre-existing cough (one patient). All patients started on dupilumab after ICB initiation. However, some patients received dupilumab while on ICB (26/53) while the remainder (27/53) received dupilumab after stopping ICB, defined as ≥42 days from final ICB infusion.

Among the dupilumab group, 30.2% (16/53) of patients developed an initial cirAE presentation before a subsequent cirAE for which treatment with dupilumab was indicated. Among these 16 patients, dupilumab-treated cirAEs had more morphologic specificity (eight patients from unspecific rash to eczematous dermatitis, lichenoid dermatitis, or bullous pemphigoid; four patients from pruritus to eczematous dermatitis or lichenoid dermatitis; three patients from maculopapular eruption to bullous pemphigoid or sclerodermoid reaction with morphea-profunda; and one patient from lichenoid dermatitis to lichenoid dermatitis and bullous pemphigoid) and the grade was higher (greater than grade 1: 98.1% vs 75.5%, p=0.003) by comparison to the first cirAE presentation. Table 2 presents the cirAE severity and morphologies. Moreover, compared with control group 1, the first cirAE presentation for the dupilumab group was more severe (greater than grade 1: 75.5% vs 50.9%, p=0.012). Among all 53 dupilumab-treated patients, 22 (41.5%) had eczematous dermatitis, 14 (26.4%) had bullous pemphigoid, 7 (13.2%) had lichenoid dermatitis, 5 (9.4%) had maculopapular drug eruptions, 3 (5.7%) had mixed morphology (which consisted of lichenoid dermatitis/maculopapular drug eruption, lichenoid dermatitis/bullous pemphigoid, and lichenoid dermatitis/eczematous dermatitis), and 2 (3.8%) had other morphologies (radiation-induced ICB exacerbated morphea and sclerodermoid reaction with morphea profunda) (table 2). The median time from ICB start to first cirAE onset was 63 vs 54.5 days (p=0.395) for dupilumab and control group 1 cohorts, respectively. Online supplemental table S2 presents the median time from ICB start to the first cirAE stratified by morphology. The median duration from ICB start to the onset of dupilumab-treated cirAEs and to the initiation of dupilumab treatment was 146 and 352 days, respectively. The median duration of dupilumab treatment was 230 days.

Of the 53 patients treated with dupilumab, 33 (62.3%) were complete responders, 14 (26.4%) were partial responders, and 6 (11.3%) were non-responders (online supplemental table S3). Among single morphologies of cirAEs that were treated with dupilumab, complete response was highest for maculopapular drug eruptions (80%), followed by eczematous eruptions (63.6%). Non-response was highest for bullous pemphigoid (21.4%). All patients with lichenoid eruptions and other eruptions in this cohort had either a complete response or partial response to dupilumab. Therefore, the response rate to dupilumab treatment was 88.7% (47/53). There was a

Table 2 Severity and morphology of cirAEs and eosinophil count

	Dupilumab (N=53)	Control 1 (N=106)	P value
Severity of the first cirAE			
1	13 (24.5%)	52 (49.1%)	0.012
2	32 (60.4%)	43 (40.6%)	
3	8 (15.1%)	11 (10.4%)	
Severity of the dupilumab-treated cirAE			
1	1 (1.9%)	N/A	
2	42 (79.2%)	N/A	
3	10 (18.9%)	N/A	
Morphology of the first cirAE			
Eczematous dermatitis	15 (28.3%)	7 (6.6%)	<0.001
Bullous pemphigoid	10 (18.9%)	3 (2.8%)	
Maculopapular eruption	8 (15.1%)	27 (25.5%)	
Lichenoid dermatitis	5 (9.4%)	7 (6.6%)	
Lichenoid dermatitis, eczematous dermatitis	1 (1.9%)	0 (0%)	
Lichenoid dermatitis, maculopapular eruption	1 (1.9%)	0 (0%)	
Radiation induced morphea ICB exacerbated	1 (1.9%)	0 (0%)	
Pruritus	4 (7.5%)	16 (15.1%)	
Psoriasiform eruption	0 (0%)	6 (5.7%)	
Vitiligo	0 (0%)	7 (6.6%)	
Rash, NOS	8 (15.1%)	33 (31.1%)	
Morphology of the dupilumab-treated cirAE			
Eczematous dermatitis	22 (41.5%)	N/A	
Bullous pemphigoid	14 (26.4%)	N/A	
Lichenoid dermatitis	7 (13.2%)	N/A	
Morbilliform drug eruption	5 (9.4%)	N/A	
Lichenoid dermatitis, bullous pemphigoid	1 (1.9%)	N/A	
Lichenoid dermatitis, eczematous dermatitis	1 (1.9%)	N/A	
Lichenoid dermatitis, morbilliform drug eruption	1 (1.9%)	N/A	
Radiation-induced morphea ICB exacerbated	1 (1.9%)	N/A	
Sclerodermoid reaction with morphea-profunda	1 (1.9%)	N/A	
ICB to the first cirAE, days			
Median (Q1, Q3)	63 (15, 198)	54.5 (21, 155)	0.395
ICB to the dupilumab-treated cirAE, days			
Median (Q1, Q3)	146 (21, 414)	N/A	
ICB to the dupilumab initiation, days			
Median (Q1, Q3)	352 (184, 585)	N/A	
Dupilumab duration, days			
Median (Q1, Q3)	230 (124, 418)	N/A	
Absolute eosinophil count before dupilumab			
Median (Q1, Q3)	0.39 (0.18, 0.76)	N/A	
Absolute eosinophil count after dupilumab			
Median (Q1, Q3)	0.16 (0.07, 0.26)	N/A	
CBC before dupilumab, days			
Median (Q1, Q3)	26 (18.5, 61)	N/A	
CBC after dupilumab, days			
Median (Q1, Q3)	140 (72.5, 219)	N/A	

CBC, complete blood count; CirAE, cutaneous immune-related adverse event; ICB, immune checkpoint blockade; N/A, not available; NOS, not otherwise specified; Q1, the first quartile; Q3, the third quartile.

Table 3 Treatments for cirAEs before dupilumab

Treatments for cirAEs before dupilumab*	The dupilumab group (N=53)	
Topical treatment alone	4 (7.5%)	53 (100%)
Topical and other treatments	49 (92.5%)	
Antihistamines	4 (7.5%)	12 (22.6%)
Antihistamines, anticonvulsants	2 (3.8%)	
Antihistamines, anticonvulsants, phototherapy	1 (1.9%)	
Antihistamines, IVIg	1 (1.9%)	
Antihistamines, IVIg, oral antibiotics, biologics	1 (1.9%)	
Antihistamines, phototherapy	2 (3.8%)	
Antihistamines, phototherapy, oral retinoid	1 (1.9%)	
Antihistamines, high-dose glucocorticoids	6 (11.3%)	25 (47.2%)
Antihistamines, high-dose glucocorticoids, anticonvulsants	5 (9.4%)	
Antihistamines, high-dose glucocorticoids, anticonvulsants, oral systemic	1 (1.9%)	
Antihistamines, high-dose glucocorticoids, anticonvulsants, Phototherapy	2 (3.8%)	
Antihistamines, high-dose glucocorticoids, biologics	1 (1.9%)	
Antihistamines, high-dose glucocorticoids, oral systemic, IVIg	1 (1.9%)	
Antihistamines, high-dose glucocorticoids, oral systemic	1 (1.9%)	
Antihistamines, high-dose glucocorticoids, phototherapy, oral retinoid	1 (1.9%)	
Antihistamines, low-dose glucocorticoids, anticonvulsants, oral antibiotics, oral vitamin	1 (1.9%)	
Antihistamines, low-dose glucocorticoids, anticonvulsants, phototherapy	1 (1.9%)	
Antihistamines, low-dose glucocorticoids	2 (3.8%)	
Antihistamines, low-dose glucocorticoids, oral retinoid	2 (3.8%)	
Antihistamines, low-dose glucocorticoids, phototherapy, opioid antagonist	1 (1.9%)	
High-dose glucocorticoids	2 (3.8%)	10 (18.9%)
High-dose glucocorticoids, anticonvulsants	1 (1.9%)	
High-dose glucocorticoids, anticonvulsants, oral systemic, hemorrhagic agents	1 (1.9%)	
High-dose glucocorticoids, oral antibiotics	1 (1.9%)	
High-dose glucocorticoids, oral retinoid	1 (1.9%)	
Low-dose glucocorticoids	3 (5.7%)	
Low-dose glucocorticoids, oral retinoid	1 (1.9%)	
Anticonvulsants	1 (1.9%)	1 (1.9%)
Phototherapy, oral retinoid	1 (1.9%)	1 (1.9%)

*All 53 patients in the dupilumab group received topical treatments that were not presented in all rows.
cirAEs, cutaneous immune-related adverse events.

significant decrease in absolute eosinophil count before and after dupilumab treatment (median: 0.39 vs 0.16, p<0.001) (table 2).

All patients who received dupilumab had failed prior first-line therapy for the management of their cirAE. Table 3 presents the details of treatments patients received before starting dupilumab for managing cirAEs. In the dupilumab group, 100% (53 patients) received topical treatments, 69.8% (37 patients) were treated with antihistamines, and 66.0% (35 patients) received high-dose (24 patients) or low-dose (11 patients) systemic glucocorticoids for managing cirAEs before the initiation of dupilumab therapy. In the multivariable time-varying Cox proportional hazards models (table 4), the overall survival of the dupilumab group was not significantly different from control group 1 (HR=0.74, 95% CI: 0.35 to 1.60, p=0.5) or control group 2 (HR=0.70, 95% CI: 0.32 to 1.51, p=0.4). The use of high-dose systemic glucocorticoids within 2 years following ICB initiation was associated with poorer overall survival (HR=2.03, 95% CI: 1.04 to 3.96, p=0.039) in the regression comparing the dupilumab group to the control group one and (HR=2.21, 95% CI: 1.25 to 3.91, p=0.006) in the regression comparing the dupilumab group to the control group 2. Cox modeling assumptions held globally and separately for each covariate in the two models (p>0.05). After further adjusting for ICB interruption (online supplemental table S4) and duration (online supplemental table S5), dupilumab exposure did not significantly increase the risk of mortality as in the primary analyses, with the coefficient tending toward a protective effect.

Table 4 Time-varying cox proportional hazards models for overall survival

	Comparison 1*			Comparison 2†		
	HR	95% CI	P value	HR	95% CI	P value
Dupilumab	0.74	0.35 to 1.60	0.5	0.70	0.32 to 1.51	0.4
Systemic glucocorticoid	2.03	1.04 to 3.96	0.039	2.21	1.25 to 3.91	0.006
Age at ICB initiation	1.03	0.99 to 1.06	0.11	1.01	0.98 to 1.03	0.6
CCS	1.10	0.96 to 1.27	0.2	1.18	1.06 to 1.32	0.003
Cancer stage at ICB‡						
IV	—	—		—	—	
III and other	0.75	0.37 to 1.54	0.4	0.74	0.38 to 1.42	0.4
Cancer type						
Melanoma	—	—		—	—	
Genitourinary	2.13	0.95 to 4.77	0.066	1.32	0.57 to 3.07	0.5
Head and neck	1.98	0.69 to 5.65	0.2	3.11	1.29 to 7.47	0.011
Thoracic	1.49	0.55 to 3.98	0.4	2.04	0.81 to 5.13	0.13
Other	2.67	0.77 to 9.22	0.12	3.01	1.20 to 7.56	0.019
ICB type						
Combination	—	—		—	—	
PD-1/PD-L1	0.89	0.44 to 1.81	0.8	0.69	0.39 to 1.22	0.2
Race						
White	—	—		—	—	
Other	1.66	0.65 to 4.24	0.3	1.56	0.62 to 3.92	0.3
Sex						
Female	—	—		—	—	
Male	0.66	0.35 to 1.22	0.2	1.24	0.69 to 2.23	0.5

*Comparison 1: comparison between the dupilumab group and the control 1 group.
†Comparison 2: comparison between the dupilumab group and the control 2 group.
‡Other includes the cases where the corresponding cancers were not staged based on AJCC criteria. Due to sample size, we combined them with patients with stage III cancers at ICB initiation in the models.
AJCC, American Joint Committee on Cancer; CCS, Charlson Comorbidity Score; ICB, immune checkpoint blockade; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

DISCUSSION

This multi-institutional retrospective cohort study suggests that dupilumab is an effective treatment modality for recalcitrant cirAEs of various morphologies and that its use does not adversely impact mortality among ICB recipients. Notably, the survival trend associated with dupilumab was protective of mortality but did not reach statistical significance in this study due to insufficient sample size of the dupilumab population to demonstrate this protective effect. Interestingly, a recent study has suggested that dupilumab may enhance response to ICB treatment in ICB-resistant cancers; in six patients with non-small cell lung cancer with progressive disease while on PD-1 or PDL-1 receptor inhibiting immunotherapy, patients were given adjunct dupilumab in addition to their continued ICB regimens.[29] One of the six patients experienced near-complete response following the addition of dupilumab.[29] Similarly, though not reaching statistical significance, our results suggest that the use of dupilumab for cirAE management may be associated with a protective mechanism in the ICB population. Additional prospective randomized clinical trials with larger cohorts are necessary to further elucidate this potential relationship. Our study demonstrates that dupilumab does not increase the risk of mortality in this population and adds valuable data to aid oncologists and dermatologists in guiding their therapeutic selection and counseling patients about the long-term implications of dupilumab use in the setting of ICB therapy. Additionally, this is the largest study of dupilumab efficacy in the ICB-treated population and the first study to explicitly explore its long-term safety profile in an ICB-treated population.

The utility of dupilumab in the management of cirAEs has previously been reported, and our conclusions confirm these findings.[8] Our results demonstrated an 88.7% response rate to dupilumab therapy among ICB recipients across a broad range of cirAE morphologies, demonstrating that this therapeutic strategy is highly effective. Prior studies have reported an 87% cirAE response rate to dupilumab use,[8] which our findings

independently validate in a larger multi-institutional cohort. We also further stratified responders by cirAE morphology and found that although dupilumab is effective for the management of multiple different morphologies of cirAEs, its efficacy varies across morphologies. For instance, among individual morphologies of cirAEs, dupilumab demonstrated the highest non-response for the management of bullous eruptions and the highest complete response rate for the management of maculopapular drug eruptions (though our sample size is limited and further studies into this population are necessary), followed by eczematous eruptions. Interestingly, all patients with lichenoid and other eruptions achieved partial or complete response with a 90% rate of complete response in patients with mixed morphologies. It is important to note that morbilliform drug eruption is equivalent to maculopapular rash. As a result, this study suggests that the use of dupilumab in the treatment of lichenoid, other, and mixed morphologies could also be useful and that clinicians should consider broadening the indications for which they use dupilumab, despite the current absence of these morphologies in the NCCN guidelines for the management of irAEs.[1]

Additionally, these results suggest that the use of high-dose systemic glucocorticoid immunosuppression within 2 years of immunotherapy initiation may be associated with detrimental effects on overall survival, which previous studies have also reported, though prospective randomized clinical trials are necessary to further explore this association.[5 30] It is important to note that, unlike other classes of biologics such as tumor necrosis factor (TNF) inhibitors or interleukin 17 and 23 inhibitors,[31–33] dupilumab is considered a more targeted form of immunosuppression and does not require the same degree of laboratory monitoring as the aforementioned biologic classes.[34] Additionally, dupilumab has been approved for use in children as young as 6 months of age.[35] Our findings also indicate a significant delay from the time of dupilumab-treated cirAE start to dupilumab initiation of 206 days. We suspect that this delay may be due to several issues, including time to dermatology referral and insurance approval of dupilumab. Based on these findings, we encourage early referral to dermatology for patients experiencing cirAEs.

Our study suggests that dupilumab can be used in the management of treatment-refractory cirAEs) without impacting survival. Clinicians should consider using dupilumab in treating cirAEs not responsive to topical therapies as a safer alternative to the more commonly used systemic glucocorticoid immunosuppression and can counsel patients that this therapeutic strategy does not adversely impact their ICB outcomes. Additionally, this study demonstrates a favorable response to dupilumab treatment across several cirAE morphologies, including non-specific morphologies, and clinicians should discuss this treatment option with their cirAE patients with difficult-to-classify rashes. This study provides further support for the need to shift the paradigm of irAE management from reliance on systemic glucocorticoid immunosuppression, which may dampen the desired immune response in the setting of ICB treatment, toward more targeted forms of immunomodulation, with the goal of uncoupling toxicity from the therapeutic effect of ICBs. Additional studies exploring the use of other biologic and targeted immunosuppressive treatment modalities for the management of cirAEs and irAEs more broadly are necessary.

Limitations of this study include its retrospective nature and limited sample size of the dupilumab-treated cohort. However, this is the largest study of dupilumab-treated cirAEs to date and the first to include robust comparator cohorts to investigate the impact of dupilumab on mortality in the ICB population. Future studies should confirm these findings among larger cohorts of ICB recipients and investigate the optimal time, dosing, and frequency for dupilumab therapeutic intervention in this population.

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