Brief report

Clinical effectiveness and safety of dupilumab in patients with chronic obstructive pulmonary disease: A 7-year population-based cohort study

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Background: Previous randomized controlled trials have established the efficacy of dupilumab among patients with chronic obstructive pulmonary disease (COPD) treated with triple therapy over 52 weeks of follow-up.

Objective: This population-based cohort study aimed to explore the long-term safety and effectiveness of dupilumab in patients with COPD.

Methods: The study included US patients with COPD who were seen between April 2017 and August 2024. Patients initiating dupilumab and therapies that incorporated long-acting β_2-agonist (LABA) inhalers were included. Patients with asthma or lung cancer were excluded. The risk of outcomes occurring after initiation of dupilumab versus LABA-containing therapies was measured. For detailed methods, please see the Methods section in this article's Online Repository at www.jacionline.org.

Results: A total of 1521 dupilumab initiators and 1521 propensity score–matched patients who were receiving LABA-based therapies were included. Receiving dupilumab was associated with lower all-cause mortality (hazard ratio [HR] = 0.53, 95% CI = 0.43-0.65), fewer emergency department visits (HR = 0.78, 95% CI = 0.69-0.89), and lower acute exacerbation rates (HR = 0.59, 95% CI = 0.53-0.65). Dupilumab was also associated with reductions in the requirement for short-acting β_2-agonists (HR = 0.48, 95% CI = 0.43-0.52) and short-acting muscarinic antagonists (HR = 0.43, 95% CI = 0.37-0.49) for symptom control. Additionally, dupilumab decreased rates of subsequent pneumonia (HR = 0.65, 95% CI = 0.50-0.86), and COPD-relevant comorbidities, including new-onset heart failure (HR = 0.69, 95% CI = 0.53-0.90) and new-onset anxiety (HR = 0.70, 95% CI =0.53-0.93).

Conclusions: In patients with COPD, dupilumab was associated with a lower mortality rate, fewer emergency department visits, and a reduced risk of acute exacerbations, respiratory symptoms, and respiratory infections. More studies are needed to validate the efficacy of dupilumab among patients with COPD of various severities. (J Allergy Clin Immunol 2025;155:219-22.)

Key words: *COPD, anti–IL-4 receptor, anti–IL-13 receptor, acute exacerbations*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global concern; it was responsible for 3.23 million deaths in 2019.[1] Acute exacerbations (AEs) in COPD result in a significant decline in lung function, increased mortality, and a higher risk of subsequent AEs.[2] Previous trials of biologic agents, mainly targeting IL-5, have failed to demonstrate superiority.[3] Additionally, the recent COURSE trial, which explored anti–thymic stromal lymphopoietin (anti-TSLP) in treating patients with moderate-to-severe COPD, also did not achieve significance in reducing AEs compared with placebo.[4] In contrast, the BOREAS and NOTUS trials have shown that dupilumab, an anti–IL-4 receptor and anti–IL-13 receptor therapy, reduces the risk of AEs, improves lung function, and alleviates respiratory symptoms in patients with severe COPD undergoing triple therapy.[5,6] Due to various limitation during the coronavirus disease 2019 (COVID-19) pandemic, the BOREAS and NOTUS trials did not report key outcomes such as mortality and disease progression.[7] Therefore, the aim of this population-based cohort study was to investigate the long-term effectiveness of dupilumab among patients with COPD.

RESULTS AND DISCUSSION

A total of 336,337 patients with COPD met the study criteria; of those patients, 1,531 received dupilumab. Propensity score matching resulted in 1,521 matched pairs for further analysis, with pair members having comparable baseline characteristics, including no significant differences in rates of atopic dermatitis,

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Abbreviations used
AE: Acute exacerbation
COPD: Chronic obstructive pulmonary disease
HR: Hazard ratio
MUC5AC: Mucin 5AC, oligomeric mucus/gel-forming
TSLP: Thymic stromal lymphopoietin

prurigo nodularis, and chronic rhinosinusitis with nasal polyposis at baseline (Table I). The mean follow-up periods after propensity score matching were 80.1 ± 75.2 weeks for the dupilumab group and 134.6 ± 116.2 weeks for the active comparator group. The mean baseline absolute blood eosinophil count after matching was approximately 0.6 to 0.7 × 10^3/μL in both arms (Table I).

TABLE I. Baseline characteristics of patients with COPD treated with dupilumab and LABA-containing treatments

	Before propensity score matching			After propensity score matching		
Characteristic	**Dupilumab (n = 1,531)**	**LABA-containing therapy (N = 334,806)**	**SMD**	**Dupilumab (n = 1,521)**	**LABA-containing therapy (n = 1,521)**	**SMD**
Age at index (y), mean ± SD	67.0 ± 13.3	68.4 ± 11.2	0.115	66.9 ± 13.3	67.0 ± 12.4	0.07
Demographic group, no. (%)						
White	1,135 (74.1)	264,299 (76.7)	0.058	1,130 (74.3)	1,168 (76.8)	0.058
Black or African American	197 (12.9)	33,013 (9.6)	0.104	195 (12.8)	165 (10.8)	0.061
Hispanic or Latino	38 (2.5)	8,798 (2.6)	0.004	38 (2.5)	39 (2.6)	0.004
Asian	39 (2.5)	4,569 (1.3)	0.089	38 (2.5)	30 (2)	0.036
Smoking						
Current tobacco use, no. (%)	331 (21.6)	51,137 (14.8)	0.177	331 (21.8)	327 (21.5)	0.006
Sex						
Female, no. (%)	693 (45.3)	159,865 (46.4)	0.022	689 (45.3)	665 (43.7)	0.032
Male, no. (%)	780 (50.9)	172,033 (49.9)	0.021	775 (51)	784 (51.5)	0.012
Body mass index (kg/m^2), mean ± SD*	28.6 ± 7.4	28.8 ± 8.0	0.029	28.6 ± 7.4	28.9 ± 7.7	0.044
Comorbidity, no. (%)						
Type 2 diabetes mellitus	520 (34)	88,873 (25.8)	0.18	514 (33.8)	516 (33.9)	0.003
Hypertensive disease	1,079 (70.5)	206,157 (59.8)	0.226	1,071 (70.4)	1,094 (71.9)	0.033
Cerebrovascular disease	344 (22.5)	51,897 (15.1)	0.191	340 (22.4)	349 (22.9)	0.014
Transient cerebral ischemic attack	74 (4.8)	10,163 (2.9)	0.098	73 (4.8)	80 (5.3)	0.021
Ischemic heart diseases	603 (39.4)	112,322 (32.6)	0.142	595 (39.1)	620 (40.8)	0.034
Acute myocardial infarction	171 (11.2)	31,002 (9)	0.072	169 (11.1)	169 (11.1)	<0.001
Heart failure	358 (23.4)	81,771 (23.7)	0.008	354 (23.3)	348 (22.9)	0.009
Peripheral vascular disease	265 (17.3)	38,092 (11)	0.18	263 (17.3)	258 (17)	0.009
Dementia	38 (2.5)	10,547 (3.1)	0.035	38 (2.5)	39 (2.6)	0.004
Solid tumor	45 (2.9)	3,698 (1.1)	0.133	44 (2.9)	40 (2.6)	0.016
Hematologic malignancies	66 (4.3)	7,287 (2.1)	0.125	65 (4.3)	64 (4.2)	0.003
Chronic kidney disease	250 (16.3)	34,203 (9.9)	0.191	246 (16.2)	251 (16.5)	0.009
Connective tissue disorders	139 (9.1)	10,473 (3)	0.255	138 (9.1)	142 (9.3)	0.009
Depressive disorder	517 (33.8)	73,145 (21.2)	0.284	513 (33.7)	551 (36.2)	0.052
Atopic dermatitis	482 (31.5)	1,938 (0.6)	0.93	350 (23)	318 (20.9)	0.051
Chronic rhinosinusitis with nasal polyposis	76 (5)	1,117 (0.3)	0.292	64 (4.2)	80 (5.3)	0.05
Eosinophilic esophagitis	23 (1.5)	188 (0.1)	0.165	23 (1.5)	36 (2.4)	0.062
Prurigo nodularis	175 (11.4)	1,159 (0.3)	0.485	134 (8.8)	122 (8)	0.028
Medication, no. (%)						
Theophylline	16 (1)	3,157 (0.9)	0.013	16 (1.1)	15 (1)	0.007
Arformoterol	24 (1.6)	1,664 (0.5)	0.108	24 (1.6)	22 (1.4)	0.011
Formoterol	324 (21.2)	28,583 (8.3)	0.369	321 (21.1)	344 (22.6)	0.037
Olodaterol	56 (3.7)	1,140 (0.3)	0.24	51 (3.4)	59 (3.9)	0.028
Salmeterol	280 (18.3)	34,138 (9.9)	0.243	278 (18.3)	296 (19.5)	0.03
Vilanterol	320 (20.9)	41,668 (12.1)	0.239	318 (20.9)	329 (21.6)	0.018
Aclidinium	10 (0.7)	2,850 (0.8)	0.02	10 (0.7)	10 (0.7)	<0.001
Glycopyrronium	260 (17)	26,058 (7.6)	0.29	256 (16.8)	253 (16.6)	0.005
Tiotropium	354 (23.1)	57,045 (16.5)	0.166	349 (22.9)	362 (23.8)	0.02
Umeclidinium	287 (18.7)	29,852 (8.7)	0.297	285 (18.7)	293 (19.3)	0.013
Revefenacin	10 (0.7)	417 (0.1)	0.086	10 (0.7)	10 (0.7)	<0.001
Beclomethasone	37 (2.4)	4,417 (1.3)	0.084	37 (2.4)	34 (2.2)	0.013
Budesonide	407 (26.6)	45,990 (13.3)	0.336	402 (26.4)	431 (28.3)	0.043
Laboratory data						
Blood eosinophil count, 10^3/μL†	0.7 ± 5.3	0.5 ± 5.1	0.029	0.7 ± 5.3	0.6 ± 5.6	0.017

LABA, Long-acting β2 agonist; *SMD*, standardized mean difference.
*Body mass index at baseline available for 73.7% and 56.3% of dupilumab- and LABA-treated patients before propensity score matching and 73.6% and 76.7% after propensity score matching.
†Blood eosinophil count at baseline available for 70.2% and 54.3% of dupilumab- and LABA-treated patients before propensity score matching and 70.0% and 73.7% after propensity score matching.

TABLE II. Comparison of outcomes in patients with COPD receiving dupilumab versus LABA-containing treatments

	Before propensity score matching					After propensity score matching				
	Dupilumab (n = 1,531)	LABA-containing therapy (n = 344,807)			Adjusted log-rank *P* value*	Dupilumab (n = 1,521)	LABA-containing therapy (n = 1,521)			Adjusted log-rank *P* value*
Outcome	Events	Events	HR	95% CI		Events	Events	HR	95% CI	
General medical outcome										
All-cause mortality	130	71,284	0.533	(0.449-0.633)	<.001	129	362	0.527	(0.430-0.647)	<.001
Emergency visit	414	123,385	0.834	(0.757-0.919)	<.001	409	623	0.781	(0.688-0.886)	<.001
Hospitalization	36	10,815	0.840	(0.605-1.165)	.328	35	60	0.721	(0.473-1.100)	.169
COPD-related outcome										
AE	652	202,824	0.668	(0.618-0.721)	<.001	646	999	0.585	(0.530-0.646)	<.001
Acute upper respiratory infection	63	21,336	1.018	(0.795-1.304)	.932	63	109	0.805	(0.586-1.105)	.222
Pneumonia	85	41,592	0.569	(0.460-0.704)	<.001	85	164	0.654	(0.501-0.855)	.005
Acute respiratory failure	92	45,462	0.511	(0.416-0.626)	<.001	92	202	0.570	(0.443-0.732)	<.001
ARDS	21	14,561	0.422	(0.275-0.648)	<.001	20	81	0.355	(0.216-0.583)	<.001
Medication for symptom control										
SABA	654	237,730	0.494	(0.457-0.533)	<.001	651	1,115	0.475	(0.431-0.523)	<.001
SAMA	311	157,335	0.410	(0.367-0.458)	<.001	307	717	0.427	(0.373-0.489)	<.001
Methylxanthine	39	14,080	0.710	(0.518-0.972)	.04	38	78	0.586	(0.396-0.866)	.013
Mucolytic agent	41	18,775	0.554	(0.408-0.753)	<.001	40	80	0.627	(0.426-0.922)	.026
Other comorbidity										
Heart failure	85	34,844	0.649	(0.524-0.802)	<.001	85	171	0.687	(0.526-0.896)	.011
Anxiety	75	32,898	0.705	(0.562-0.885)	.003	75	150	0.703	(0.530-0.932)	.023
Sleep disorder	78	33,421	0.782	(0.626-0.976)	.04	78	133	0.859	(0.646-1.142)	.295
Obstructive sleep apnea	47	20,850	0.669	(0.502-0.891)	.009	47	85	0.801	(0.558-1.151)	.269
Overweight and obesity	77	23,990	0.998	(0.798-1.248)	.982	77	97	1.182	(0.870-1.607)	.295
Adverse effect										
Hypereosinophilic syndrome	10	97	12.281	(4.508-33.455)	<.001	≤10	≤10	5.110	(0.570-45.786)	.149
Blood level of eosinophils per 100 leukocytes > 4%	68	41,328	0.639	(0.504-0.811)	<.001	68	155	0.666	(0.498-0.890)	.012
Blood level of eosinophils per100 leukocytes > 6%	60	26,028	0.831	(0.645-1.070)	.178	59	110	0.832	(0.602-1.150)	.294

ARDS, Acute respiratory distress syndrome; *LABA*, long-acting β_2 agonist; *SABA*, short-acting β_2 agonist; *SAMA*, short-acting muscarinic antagonist.
*Log-rank test *P* values adjusted using the Benjamini-Hochberg method.

During follow-up, dupilumab was associated with significantly lower risks of all-cause mortality (hazard ratio [HR] = 0.53 [95% CI = 0.43-0.65]), emergency visits (HR = 0.78 [95% CI = 0.69-0.89), AEs (HR = 0.59 [95% CI = 0.53-0.65]), new-onset pneumonia (HR = 0.65 [95% CI = 0.50-0.86]), and new-onset acute respiratory failure (HR = 0.57 [95% CI = 0.44-0.73]). There was also a significant reduction in the development of new-onset acute respiratory distress syndrome (HR = 0.36 [95% CI = 0.22-0.58]).

Those who initiated dupilumab therapy also experienced significantly fewer respiratory conditions and required less use of rescue and symptomatic therapies, including short-acting β_2 agonists (HR = 0.48 [95% CI = 0.43-0.52]), short-acting muscarinic antagonists (HR = 0.43 [95% CI = 0.37-0.49]), and mucolytic agents (HR = 0.63 [95% CI = 0.43-0.92]). Additionally, dupilumab initiators demonstrated a reduction in subsequent COPD-relevant comorbidities, including new-onset heart failure (HR = 0.69 [95% CI = 0.53-0.90]) and new-onset anxiety (HR = 0.70 [95% CI = 0.53-0.93]) (Table II). In our study, dupilumab was not associated with higher rates of new-onset hypereosinophilic syndromes. Moreover, initiation of dupilumab therapy was associated with a lower subsequent incidence of eosinophil counts (eosinophils/100 leukocytes in blood) higher than 4% (HR = 0.67 [95% CI = 0.50-0.89]).

This population-based cohort study demonstrated that dupilumab treatment was associated with better clinical outcomes, including lower all-cause mortality, fewer emergency department visits, and reduced rates of AEs, respiratory infections, and acute respiratory failure, as well as fewer symptoms. Our study showed dupilumab to be associated with a 41% reduction in the risk of AEs, comparable to the 30% reduction reported in the BOREAS and NOTUS trials. In the BOREAS trial, patients treated with dupilumab showed a trend toward lower rates of respiratory tract infections compared to those on triple therapy (7.9% and 9.8%, respectively). This aligns with our finding that dupilumab is associated with a reduced risk of pneumonia.

The recent COURSE trial, a phase IIa clinical trial, failed to demonstrate clinical benefits in reducing AE rates in patients with moderate-to-severe COPD and blood eosinophil counts higher than $0.30 \times 10^3/\mu L$ who received with the anti-TSLP therapy tezepelumab versus with placebo over 52 weeks (HR = 0.46 [95% CI = –15 to 75]). Prior studies have shown that IL-13 can stimulate the expression of mucin 5AC (oligomeric mucus/gel-forming [MUC5AC]), leading to increased mucus production in the airways.[8] Dupilumab, by directly blocking the IL-13 receptor, effectively reduces airway inflammation and limits sputum impaction, thereby contributing to lower rates of respiratory infections, respiratory symptoms, and exacerbations. Reduced mucus

production and retention may explain the greater clinical efficacy of anti–IL-13 receptor therapy compared to anti-TSLP in alleviating airway hypersensitivity in patients with COPD. Additionally, the significantly reduced risk of subsequent heart failure in dupilumab-treated patients may result from fewer occurrences of hypoxia and a reduced inflammatory response, due to better control of COPD symptoms and fewer AEs.[9,10] Prior studies have shown that COPD exacerbations are associated with impaired cardiac function.[11] Because dupilumab significantly decreased the numbers of AEs in patients with COPD, it may also reduce the subsequent risk of heart failure. Further randomized controlled trials focusing on long-term COPD-related comorbidities, especially cardiovascular comorbidities, are warranted to confirm these results.

Despite significant findings from the BOREAS and NOTUS trials, there were notable limitations. Recruitment of African American patients was low (around 0.5% of the total population). It was also reported that the COVID-19 pandemic significantly impacted the conduct of the trials as well as patient behaviors, leading to a lower observed incidence of AEs and respiratory infections.[5,6] This limited the ability of the trials to measure long-term outcomes following dupilumab treatment. The present study adds to the literature with a sample including 12.9% African American patients and a follow-up period exceeding 7 years. Although dupilumab has been approved by the US Food and Drug Administration for COPD, it may not be prescribed for that purpose in this study. Instead, our participants could have received dupilumab for conditions such as atopic dermatitis,[12,13] chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis. More studies are warranted to determine whether these results can be extrapolated to patients with COPD who do not have these comorbidities.

The BOREAS and NOTUS trials established the short-term efficacy of dupilumab in patients with COPD and type 2 inflammation who are at high risk of exacerbation despite maximum triple therapy. It was hypothesized that by alleviating type 2 inflammation, dupilumab could decrease mucus secretion, reduce airway resistance, and improve lung function.[5,6] Our study suggests that patients with various severity levels of COPD may also benefit from the broader inhibition of type 2 inflammation by dupilumab. However, this finding should be interpreted with caution, as we did not compare dupilumab with standard treatments for different stages of COPD due to limited sample size.

Despite rigorous efforts, our study has several limitations. First, not all patients had data on pulmonary function test results, and there was a lack of standardized measures of symptoms and quality of life. Second, data on economic status were limited, and some confounding factors may not have been fully balanced. Finally, data on inhaler compliance and technique were unavailable. To our knowledge, this is the first population-based cohort study to explore the safety and effectiveness of dupilumab in patients with COPD across various severity levels. Further prospective studies are needed to validate our results.

In summary, dupilumab was associated with lower risks of all-cause mortality, emergency visits, AEs, respiratory failure, and respiratory infections in patients with COPD. More studies are warranted to validate these findings.

DISCLOSURE STATEMENT

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Clinical implications: Clinical benefits of dupilumab for COPD include a lower risk of mortality, fewer exacerbations, and reduced rates of respiratory infections.

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METHODS

This population-based cohort study included patients with COPD recruited from multiple health care organizations in the United States (TriNetX LLC, Cambridge, Mass) between April 2017 and August 2024. The study was exempt from institutional review board approval and adhered to the STROBE reporting guideline. Patients who initiated dupilumab therapy after a diagnosis of COPD were included. The active comparator arm comprised patients with COPD receiving long-acting β_2-agonist–containing therapy. Patients with a diagnosis of asthma or lung cancer during the observation period were excluded. The index date was defined as the initiation date of either dupilumab or a long-acting β_2-agonist–containing bronchodilator.

Propensity score matching was conducted based on variables including age, sex, smoking status, ethnicity, comorbidities, inhalation therapy, and absolute blood eosinophil counts. We assessed the balance of confounding variables using standardized mean differences, with a threshold of 0.10 as a predefined criterion. The primary outcome was all-cause mortality; secondary outcomes included emergency department visits, acute exacerbations, new-onset pneumonia, new-onset acute respiratory failure, use of medications for symptom relief, and COPD-related comorbidities (eg, new-onset heart failure, new-onset anxiety, and new-onset sleep disorders). For outcome analyses involving events including emergency visits, hospitalizations, acute exacerbations, and symptom-control medication use, patients with a prior history of these events before the index date were not excluded. For all other outcomes, only the first new-onset event per patient occurring after the index date was counted. An intention-to-treat approach was applied; Cox proportional hazards regression models were used to obtain HRs with 95% CIs, and the log-rank test was used to evaluate the effect of dupilumab on outcomes over time.