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COVID-19 Symptoms Are Attenuated in Moderate-to-Severe Atopic Dermatitis Patients Treated with Dupilumab



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What is already known about this topic? Preliminary data suggest increased type 2 cytokines during the COVID-19 cytokine storm. However, it remains unclear how COVID-19 outcomes differ between patients with atopic dermatitis (AD) on type 2–targeting agents (dupilumab) and those treated with other systemics or topical treatments.

What does this article add to our knowledge? This is the first study to directly compare the severity of COVID-19 symptoms in patients with moderate-to-severe AD on different treatments, shedding important light on the treatment of patients with AD during the pandemic and beyond.

How does this study impact current management guidelines? Our results suggest that type 2 targeting with dupilumab may attenuate COVID-19 responses, supporting the safety of specific type 2–targeting agents in patients with AD during the COVID-19 pandemic, and potentially extending to other viral infections.

BACKGROUND: In the SARS-CoV-2/COVID-19 pandemic, we need to understand the impact of immunomodulatory medications on COVID-19 symptom severity in patients with inflammatory diseases, including the type 2/Th2 polarized skin disease, atopic dermatitis (AD).

OBJECTIVE: Because it is believed that type 1/Th1 immunity controls viral infections and that there is a Th1/Th2 counter-regulation, we hypothesized that Th2 targeting with the IL-4R α -antagonist, dupilumab, in patients with moderate-to-severe

AD would rebalance the Th1/Th2 axis, potentially leading to attenuated COVID-19 symptoms.

METHODS: A total of 1237 patients with moderate-to-severe AD in the Icahn School of Medicine at Mount Sinai Department of Dermatology were enrolled in a registry. Patients were screened for COVID-19-related symptoms and assigned a severity score (asymptomatic [0]-fatal [5]). Scores were compared among 3 treatment groups: dupilumab (n = 632), other systemic treatments (n = 107), and limited/no treatment

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Abbreviations used

AD- Atopic dermatitis

BMI- Body mass index

EUA- Emergency Use Authorization

OR- Odds ratio

PCR- Polymerase chain reaction

SD- Standard deviation

(*n* = 498). Demographic and comorbid covariates were adjusted by multivariate generalized logistic regression models.

RESULTS: The dupilumab-treated group showed reduced incidence and severity of COVID-19 symptoms versus other treatment groups. Dupilumab-treated patients were less likely to experience moderate-to-severe symptoms versus patients on other systemics (*P* = .01) and on limited/no treatment (*P* = .04), and less likely to experience any symptoms versus patients on other systemics (*P* = .01). This effect was seen in our entire cohort and in the subgroup of patients with verified COVID-19 or high-risk exposure.

CONCLUSIONS: Patients on dupilumab experienced less severe COVID-19 manifestations and lesser symptoms compared with patients on other systemics and on limited/no treatment. These results suggest that Th2 modulation with dupilumab may have a protective effect on anti-viral immune response in patients with AD. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:134-42)

Key words: Atopic dermatitis; Biologics; Dupilumab; COVID-19; SARS-CoV-2; Th2

As of July 2021, there have been more than 182 million cases of COVID-19 caused by the novel SARS-CoV-2 reported worldwide, leading to nearly 4 million deaths.¹⁻³ Recently, because of extraordinary vaccine development efforts, the American Food and Drug Administration issued Emergency Use Authorizations (EUA) for 3 vaccines.⁴⁻⁶ Despite the advent of these vaccines, effective treatments are still a target for research and development efforts, with several therapies having been granted EUA.⁷ Furthermore, the risk of patients with inflammatory skin diseases to develop more symptomatic COVID-19 infection is unknown, particularly in the context of immunomodulatory medications.

Previous research has shown that abnormally elevated Th2 cytokines may inhibit appropriate Th1 immune responses in the setting of viral exposure, impeding the reliance on Th1 signaling in initial responses to viral infections.⁸⁻¹¹ This is especially relevant for atopic dermatitis (AD), a disease characterized primarily by Th2 skewing,¹² with an increased susceptibility to viral infections.¹⁰ Moreover, elevated expression of Th2 cytokines in serum (eg, IL-4, IL-10, and IL-13) was reported in patients with COVID-19, especially during the cytokine storm.^{2,13-15}

Despite the greater risk for viral infections and the baseline Th2 polarization in AD, the risk for COVID-19 incidence and symptom severity in this common disease (approximately 7% of the adult US population)¹⁶ is still unknown. Determining COVID-19 risk profiles is particularly important in patients with moderate-to-severe AD on immunomodulatory medications. Although some society guidelines recommend continuing these medications, there remains a dearth of evidence.^{17,18} Recent case

series and studies on some inflammatory conditions suggest that immunomodulatory medications may not change the risk of infection or symptomatology.¹⁹⁻²¹ However, most of these reports were small-scale studies or did not include AD. Furthermore, direct comparisons of COVID-19 outcomes between specific immunomodulatory drugs are lacking, making it difficult to draw conclusions about the comparative effects of different immunomodulatory medications.

Dupilumab, which inhibits the key Th2 cytokines IL-4 and IL-13, is the first FDA-approved treatment for moderate-to-severe AD, and is also approved for asthma and chronic rhinosinusitis with nasal polyps.²²⁻²⁴ Although dupilumab has been shown to robustly modulate the Th2 pathway, it does not affect Th1 signaling.^{23,25} Preliminary reports have not shown increased SARS-CoV-2 infection rates among patients treated with dupilumab.²⁶⁻³¹ However, these limited studies did not compare dupilumab-treated patients with those on other treatments or not receiving systemic treatments. To date, no study has evaluated the effects of SARS-CoV-2 exposure and infection in patients with AD on dupilumab compared with other therapeutics.

The present study is the first large-scale, prospective evaluation of 1237 patients with moderate-to-severe AD treated with dupilumab, broad immunosuppressants, or those not receiving systemic treatments. This registry study aims to investigate whether targeting type 2 inflammation with dupilumab may protect against symptomatic SARS-CoV-2 infections in patients with AD. Our data show that patients on dupilumab were less likely to develop symptomatic COVID-19 infection compared with patients on other systemic treatments for AD.

METHODS

Patients

This study was reviewed and approved by the Institutional Review Board of the Department of Dermatology at the Icahn School of Medicine (approval protocols STUDY-20-00410 and STUDY 20-00682). We performed a cross-sectional analysis of reported demographics, medical history, and medications from 1237 patients with moderate-to-severe AD enrolled from April 2, 2020, through January 31, 2021, in a prospective registry related to COVID-19 in the Department of Dermatology at the Icahn School of Medicine at Mount Sinai. Patients were enrolled under institutional review board—approved consent, and the study was conducted according to the Declaration of Helsinki. The electronic medical record was queried for all related International Classification of Diseases (Tenth Revision) codes, and each patient chart was reviewed to ensure that inclusion criteria were met. Patients were enrolled at the time of clinical visit, when applicable, or enrolled over the phone. Inclusion criteria included being older than 9 years of age with a diagnosis of moderate-to-severe AD, defined as currently or previously being on systemic therapy (including dupilumab, phototherapy, or oral immunomodulatory medications), or as candidates for systemic therapy.

Patients were asked about past medical history, medications, demographics (ie, age, gender, and self-reported race), as well as the presence and duration of individual COVID-19-related symptoms, including objective or subjective fever, sore throat, cough, congestion, headache, fatigue, anosmia, dysgeusia, dyspnea, nausea, vomiting, diarrhea, anorexia, and skin changes. Based on the symptoms described, each patient was given a COVID-19 symptom severity score from 0 to 5: 0: “asymptomatic”; 1: “mild disease” (no fever, no dyspnea, resolving in <7 days, resembling a common cold); 2: “moderate disease” (some

TABLE I. Demographics and symptom severity for all patients and treatment groups

	All patients	Dupilumab	Other systemics	Limited/no treatment	P value
Sample size (n)	1237	632	107	498	
Age, mean (SD)		41.2 (19.1)	42.0 (19.4)	39.9 (18.9)	.39
Gender, n (%)					.001
Male	521 (42)	296 (47)	44 (41)	181 (36)	
Female	716 (58)	336 (53)	63 (59)	317 (64)	
Race, n (%)					.46
American Indian/Alaska Native	5 (0.4)	1 (0.2)	0 (0)	4 (1)	
Asian	216 (17)	126 (20)	21 (20)	69 (14)	
Black or African American	205 (17)	102 (16)	18 (17)	85 (17)	
Mixed race	40 (3)	21 (3)	3 (3)	16 (3)	
Native Hawaiian/Other Pacific Islander	4 (0.3)	2 (0.0001)	0 (0)	2 (0.0001)	
Unknown	95 (8)	44 (7)	7 (7)	44 (9)	
White	672 (54)	336 (53)	58 (54)	278 (56)	
Comorbidities, n (%)					
Hypertension		115 (18)	20 (19)	72 (14)	.21
Diabetes		37 (6)	7 (7)	26 (5)	.78
Asthma		250 (40)	38 (36)	169 (34)	.16
Obesity (BMI > 30)		112 (20)	14 (16)	85 (19)	.61
Other medications, n (%)					
ACEi		20 (3)	4 (4)	8 (2)	.16
COVID-19 infection, n (%)					
Laboratory confirmed COVID-19 infection	87 (7)	39 (6)	11 (10)	37 (7)	.26

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index; SD, standard deviation.

TABLE II. Percentage of patients with COVID-19 symptom severity score in each treatment group

Severity	All patients (n = 1233)	Dupilumab (n = 631)	Other systemics (n = 107)	Limited/no treatment (n = 495)
0	947 (77)	492 (78)	73 (68)	382 (77)
1	204 (16)	110 (17)	18 (17)	76 (15)
2	78 (6)	29 (5)	15 (14)	34 (7)
3	4 (0.3)	0 (0)	1 (1)	3 (1)
4/5	0 (0)	0 (0)	0 (0)	0 (0)

COVID-19 symptom severity defined as a 5-level score: 0 “asymptomatic”; 1: “mild disease” (no fever, no dyspnea, resolving in <7 days, resembling a common cold); 2: “moderate disease” (some fever and/or cough, or other lower respiratory symptoms, resolving at home in 7-14 days); 3: “severe disease” (pneumonia, required hospitalization, but resolved without intubation); 4-5: “very severe disease” (required hospitalization, intubation, and other supportive measures) or “fatal.”

fever and/or cough, or other lower respiratory symptoms, resolving at home in 7-14 days); 3: “severe disease” (pneumonia, required hospitalization, but resolved without intubation); 4: “very severe disease” (required hospitalization, intubation, and other supportive measures); 5: “fatal.”

A total of 1237 patients were included in the final analysis, out of 1357 patients enrolled. In the final analysis, we excluded patients treated concomitantly with dupilumab and other systemic therapies (due to the hypothesis that dupilumab would reduce symptom severity compared with other systemic treatments), patients on dupilumab for <2 months (in order to allow for the proposed effects of dupilumab to manifest), and patients on additional immunomodulating therapies for other skin or extracutaneous indications besides AD (including TNF- α and IL-23/IL-17 antagonists).

Statistical analysis

We powered our study based on the range of estimates for the incidence of SARS-CoV-2-infected patients at Mount Sinai Hospital. We assumed a positivity rate of 21% among 600 Mount

Sinai Dermatology patients, with approximately n = 100 SARS-CoV-2-infected patients on dupilumab and n = 20 infected patients in the control group. Assuming an effect size of 25% (eg, 30% patients with symptoms in the control group and 5% in the dupilumab group), a sample size of at least n = 100 patients on dupilumab and n = 20 controls is enough to detect statistically significant differences between groups with 85% power using a 2-sided Fisher exact test with a type I error $\alpha = 0.05$. Assuming a sample size 5 times larger, such as n = 500 infected patients on dupilumab and n = 100 infected patients in the control group, would allow us to detect an effect size of 10% (eg, 15% patients with symptoms in the control group and 5% in the dupilumab group) with 90% power using a 2-sided Fisher exact test with a type I error $\alpha = 0.05$.

Demographic characteristics between groups were assessed using a 2-sided Fisher exact test or analysis of variance for categorical and continuous variables, respectively. The primary outcome for this report was the presence of moderate-to-severe COVID-19 symptoms in each treatment group, with the secondary outcome being the

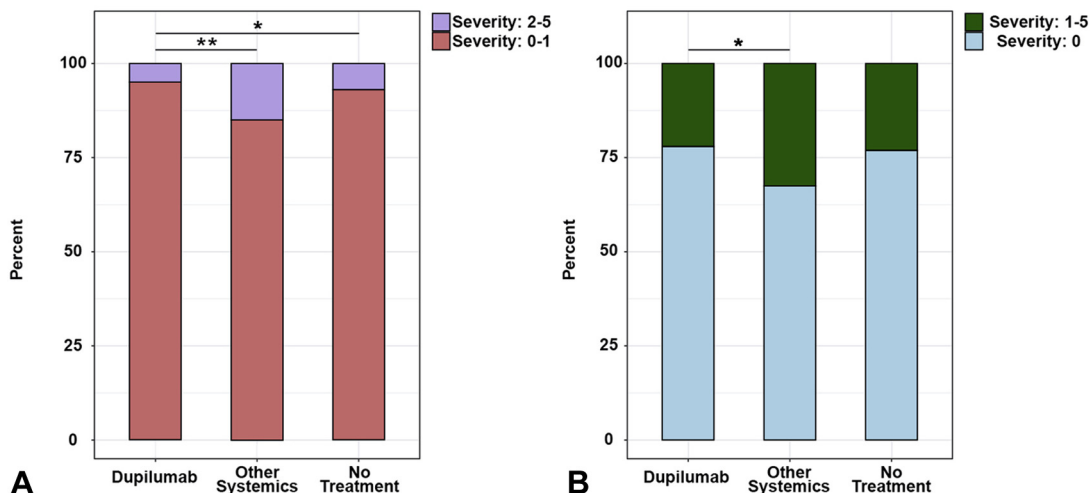


FIGURE 1. COVID-19 symptoms in whole patient cohort grouped by treatment. Whole patient cohort separated into treatment groups, dupilumab (n = 631), other systemics (n = 107), and limited/no treatment (n = 495), grouping symptom severity by (A) scores of 0-1 (asymptomatic or mild symptoms) and 2-5 (moderately symptomatic to fatal), and (B) scores of 0 (asymptomatic) or 1-5 (symptomatic). *P < .05; **P < .01.

TABLE III. Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: systemics versus dupilumab as a predictor variable and adjusting for other clinical variables

Asymptomatic/mild vs moderate-to-severe symptoms				
Outcome	Log odds ratio	Standard error	Z score	P value
Intercept	-3.86	2.36	-1.64	.10
Systemics	1.36	0.51	2.66	.008
Age	0.01	0.01	0.87	.39
Asthma	-0.61	0.45	-1.36	.17
Gender	-0.35	0.45	-0.78	.43
Hypertension	-1.15	0.75	-1.53	.12
Diabetes	0.75	0.90	0.83	.41
BMI	0.13	0.04	3.41	.001
ACEi	0.55	1.91	0.29	.77
Race	0.07	0.10	0.63	.53

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

TABLE IV. Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: limited/no treatment versus dupilumab as a predictor variable and adjusting for other clinical variables

Asymptomatic/mild vs moderate-to-severe symptoms				
Outcome	Log odds ratio	Standard error	Z score	P value
Intercept	-3.59	1.58	-2.28	.02
Limited/no treatment	0.67	0.33	2.04	.04
Age	0.03	0.01	2.46	.01
Asthma	0.26	0.33	0.79	.43
Gender	-0.03	0.34	-0.08	.94
Hypertension	-0.96	0.58	-1.67	.09
Diabetes	-0.09	0.72	-0.13	.90
BMI	0.04	0.03	1.55	.12
ACEi	0.83	1.09	0.76	.45
Race	-0.07	0.08	-0.85	.39

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

incidence of any symptoms. Because of the potential for multiple confounders, we associated the presence of COVID-19-related symptoms with dupilumab treatment compared with other systemic treatments and with dupilumab treatment compared with limited/no treatments using multivariate logistic regression models. We adjusted for known or suspected COVID-19-related comorbidities (age, gender, race, hypertension, diabetes, body mass index [BMI], asthma, angiotensin-converting enzyme inhibitor usage). Using a similar approach, we also associated the presence of COVID-19-related symptoms with AD treatments by stratifying our cohort into a set of higher COVID-19-related risk patients with confirmed positive SARS-CoV-2 polymerase chain reaction (PCR) or COVID-19 serological tests, exposure to COVID-19-positive patients (diagnosed via PCR or serology) or to a person with COVID-19-related symptoms.

RESULTS

Patients grouped by AD treatment

A total of 1237 patients with moderate-to-severe AD were included in the analysis (age range: 9-95 years). Patients were initially grouped based on their AD treatment: 632 patients on dupilumab, 107 patients on other systemic treatments, and 498 patients on limited or no treatment. The 107 patients on other systemics included 52 on phototherapy, 29 on oral JAK inhibitors, 14 on prednisone, 6 on methotrexate, 4 on cyclosporine, and 2 on mycophenolate mofetil. Among patients on limited or no treatment, 354 were on topicals and 153 had no treatment. Demographics, medication history, and comorbidities are listed in Table I. No significant differences were found between groups in terms of age and race.

TABLE V. Logistic regression model predicting asymptomatic versus symptomatic using treatment: systemics versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic vs symptomatic			
	Log odds ratio	Standard error	Z score	P value
Intercept	-0.59	0.97	-0.60	.55
Systemics	0.63	0.25	2.46	.01
Age	-0.001	0.01	-0.28	.78
Asthma	0.15	0.19	0.77	.44
Gender	-0.05	0.19	-0.25	.80
Hypertension	-0.24	0.30	-0.80	.42
Diabetes	0.16	0.44	0.35	.72
BMI	0.02	0.02	1.19	.23
ACEi	-0.74	0.68	-1.08	.28
Race	-0.11	0.04	-2.50	.01

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

TABLE VI. Logistic regression model predicting asymptomatic versus symptomatic using treatment: limited/no treatment versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic vs symptomatic			
	Log odds ratio	Standard error	Z score	P value
Intercept	-1.32	0.78	-1.70	.09
Limited/no treatment	0.10	0.15	0.64	.52
Age	0.001	0.00	0.15	.88
Asthma	0.27	0.16	1.75	.08
Gender	-0.09	0.16	-0.56	.58
Hypertension	-0.38	0.26	-1.46	.15
Diabetes	0.15	0.36	0.41	.68
BMI	0.01	0.01	0.67	.51
ACEi	-0.03	0.54	-0.06	.95
Race	-0.08	0.04	-2.20	.03

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

COVID-19 symptom severity

We calculated the distribution of COVID-19 symptom severity across groups in 6 categories: 0/"asymptomatic," 1/"mild," 2/"moderate," 3/"severe," 4/"very severe," and 5/"fatal" (Table II). Our initial analysis focused on the entire cohort of patients, agnostic to laboratory evidence of COVID-19 infection. Treatment groups were compared to determine the proportions of patients in each symptom category (Figure 1). Given the potential for multiple confounders and risk factors for symptomatic infection (Table I),³² we adjusted for known risk factors for increased COVID-19 morbidity (eg, obesity, hypertension, etc) using logistic regression models. We found that patients on dupilumab were less likely to experience moderate-to-severe symptoms compared with patients on other systemic treatments (odds ratio [OR] = 3.89; $P = .008$, Table III). Furthermore, they were less likely to experience moderate-to-severe symptoms compared with those on limited/no treatments (OR = 1.96; $P = .04$, Table IV). In addition, BMI was significantly associated with moderate-to-severe symptoms across

COVID-19-related patients treated with biologic and systemic therapies ($P < .001$, Table III).

When evaluating the effects of various clinical variables on the presence of COVID-19-related symptoms, we found that nonbiologic systemic treatment was significantly associated with symptomatology relative to treatment with dupilumab (OR = 1.87; $P = .01$, Table V). However, there were no differences in predicting symptomatology among patients on dupilumab relative to the limited/no treatment group (Table VI).

Symptom severity in patients with confirmed COVID-19 diagnosis or exposure

Next, we compared the subgroup of patients comprising those with a laboratory confirmed COVID-19 infection history based on PCR testing, or other antibody testing performed in a clinical context, or those with high-risk COVID-19 exposures, including individuals with documented COVID-19 infection or with symptoms highly suspicious for COVID-19 infection ($n = 164$ for dupilumab, $n = 26$ for other systemics, $n = 116$ for limited/no treatment; Table VII, Figure 2). Similar to the previous logistic regression model results, non-dupilumab systemic treatment was significantly associated with moderate-to-severe symptoms relative to treatment with dupilumab (OR = 13.79; $P = .002$, Table VIII). In addition, being on limited/no treatment was also significantly associated with moderate-to-severe symptoms relative to dupilumab (OR = 2.44; $P = .05$, Table IX). BMI was a significant covariate of moderate-to-severe symptoms across all systemic treatment groups in this known infection/high-risk exposure group ($P = .005$, Table VIII).

In patients with known COVID-19 infection or high-risk exposure, being on non-dupilumab, systemic therapies was significantly associated with symptomatology relative to being on dupilumab (OR = 2.97; $P = .03$, Table X). Similar to the entire cohort, there were also no differences in predicting symptoms among high-risk exposure patients on dupilumab relative to the limited/no treatment group (Table XI).

DISCUSSION

The present study is the first large-scale, prospective evaluation of COVID-19 symptomatology in patients with moderate-to-severe AD, aiming to understand the effect of specific Th2 modulation with dupilumab compared with other systemic immunomodulators and topical or no treatment. Understanding COVID-19 symptomatology in patients with moderate-to-severe AD in the context of immunomodulatory treatment is crucial, due to the long-term health consequences of SARS-CoV-2 infection, which are more substantial with moderate-to-severe symptomatology,³³ as well as the massive economic burden on the United States hospital system from treating patients with COVID-19.³⁴ Patients with moderate-to-severe AD are also particularly important to study in this context due to their increased susceptibility to viral infections and their robust type 2/Th2 activation.^{10,35} As type 1/Th1 immunity is considered to control viral responses, and there is a Th1/Th2 counter-regulation, we hypothesized that specific Th2 antagonism in patients with moderate-to-severe AD with the anti-IL-4R α , dupilumab, may rebalance the Th1/Th2 axis, potentially leading to attenuated COVID-19 symptomatology.

Our study found that dupilumab reduces both the incidence and severity of COVID-19 symptoms among patients with AD, compared with both other systemic treatments and no systemic

TABLE VII. Patient demographics in patients with confirmed diagnosis or COVID-19 exposure

	Dupilumab	Other systemics	Limited/no treatment	P value
Sample size (n)	164	26	116	
Age, mean (SD)	37.1 (16.7)	42.8 (16.5)	37.6 (15.9)	<.001
Gender, n (%)				.04
Male	70 (43)	9 (35)	33 (28)	
Female	94 (57)	17 (65)	83 (72)	
Race, n (%)				.51
American Indian/Alaska Native	0 (0)	0 (0)	3 (3)	
Asian	28 (17)	5 (19)	13 (11)	
Black or African American	30 (18)	5 (19)	19 (16)	
Mixed race	5 (3)	1 (4)	5 (4)	
Native Hawaiian or Other Pacific Islander	2 (1)	0 (0)	0 (0)	
Unknown	6 (4)	1 (4)	9 (8)	
White	93 (57)	14 (54)	67 (58)	
Comorbidities, n (%)				
Hypertension	21 (13)	6 (23)	15 (13)	.35
Diabetes	9 (5)	1 (4)	5 (4)	.91
Asthma	61 (37)	11 (42)	44 (38)	.89
Obesity (BMI > 30)	27 (19)	7 (30)	19 (18)	.38
Other medications, n (%)				
ACEi	5 (3)	0 (0)	2 (2)	.84
COVID exposure and testing, n (%)				
Tested positive for COVID-19	39 (24)	11 (42)	37 (32)	.09
Exposure to positive COVID-19	76 (46)	6 (23)	46 (40)	.06
Exposure to COVID-19-like symptoms	49 (30)	9 (35)	33 (28)	.84

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index; SD, standard deviation.

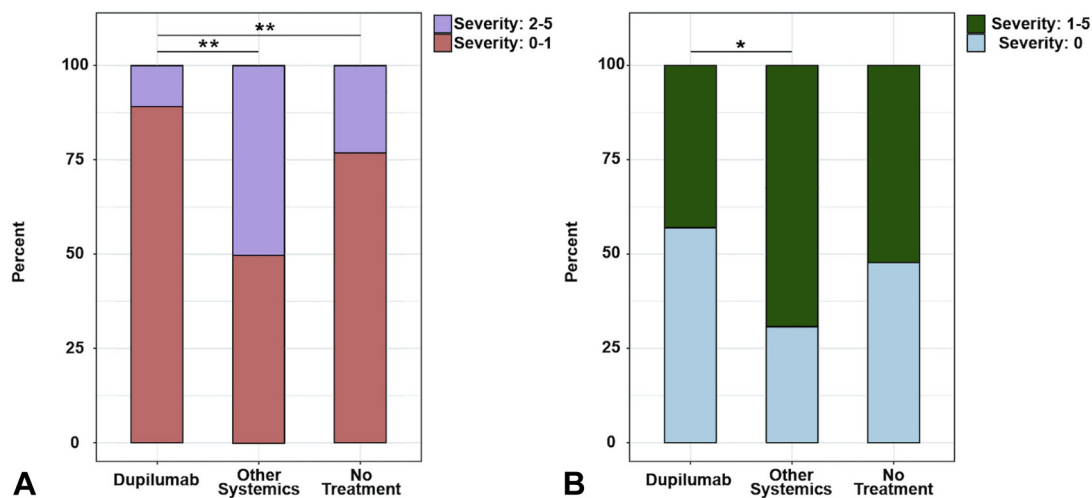


FIGURE 2. COVID-19 symptoms in exposed patient cohort grouped by treatment. Cohort of patients with known infection or high-risk COVID-19 exposures, separated into treatment groups, dupilumab (n = 164), other systemics (n = 26), and limited/no treatment (n = 116), grouping symptom severity by (A) scores of 0-1 (asymptomatic or mild symptoms) and 2-5 (moderately symptomatic to fatal), and (B) scores of 0 (asymptomatic) or 1-5 (symptomatic). **P* < .05; ***P* < .01.

treatments. We found that patients treated with dupilumab were less likely to experience moderate-to-severe symptoms compared with patients on other systemics (*P* = .01) as well as with patients on limited/no treatment (*P* = .04). Patients treated with dupilumab were also less likely to experience any symptoms at all compared with patients on other systemics (*P* = .01). This

relationship holds true for patients with suspected COVID-19, as well as for patients with a serologically confirmed COVID-19 diagnosis or a confirmed high-risk exposure. Those treated with dupilumab were less likely to experience moderate-to-severe symptoms compared with those on other systemics (*P* = .002) as well as on limited/no treatment (*P* = .05) and were less likely to

TABLE VIII. Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: systemics versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic/mild vs moderate-to-severe symptoms			
	Log odds ratio	Standard error	Z score	P value
Intercept	-16.59	1455.40	-0.01	.99
Systemics	2.62	0.86	3.05	.002
Age	0.04	0.02	1.55	.12
Asthma	-1.25	0.77	-1.62	.11
Gender	-0.26	0.66	-0.40	.69
Hypertension	-2.06	1.15	-1.80	.07
Diabetes	1.91	1.32	1.44	.15
BMI	0.22	0.08	2.84	.005
ACEi	12.09	1455.40	0.01	.99
Race	-0.11	0.16	-0.70	.48

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

TABLE IX. Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: limited/no treatment versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic/mild vs moderate-to-severe symptoms			
	Log odds ratio	Standard error	Z score	P value
Intercept	-19.95	1606.87	-0.01	.99
Limited/no treatment	0.89	0.46	1.94	.05
Age	0.04	0.02	2.73	.006
Asthma	0.10	0.46	0.22	.83
Gender	0.11	0.49	0.23	.82
Hypertension	-0.97	0.79	-1.22	.22
Diabetes	-0.87	1.14	-0.76	.45
BMI	0.08	0.04	1.91	.06
ACEi	16.70	1606.87	0.01	.99
Race	-0.05	0.11	-0.43	.67

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

experience symptoms at all compared with patients on other systemics ($P = .03$).

The robust effect of dupilumab on COVID-19 symptomatology may be due to primary modulation of the Th2 pathway, without downregulation of Th1 immunity. This relationship between Th2 modulation and Th1/innate immune responses has been demonstrated in other atopic disease states, such as asthma.³⁶ In one study, patients with asthma treated with the Th2 modulator omalizumab (anti-IgE) had a lower incidence of respiratory virus-induced asthma exacerbations and a more robust IFN- α response *in vitro* to rhinovirus stimulation.³⁶ Similarly, our study found that COVID-19 symptoms and severity were reduced in dupilumab even when compared with limited/no treatment, suggesting that Th2 suppression may normalize the Th1/Th2 imbalance. Unlike dupilumab, broad-acting immunosuppressants downregulate Th1 and other immune axes in addition to the pathogenic Th2 axis,^{23,37-39} which

TABLE X. Logistic regression model predicting asymptomatic versus symptomatic using treatment: systemics versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic vs symptomatic			
	Log odds ratio	Standard error	Z score	P value
Intercept	0.86	1.86	0.46	.64
Systemics	1.09	0.51	2.12	.03
Age	-0.001	0.01	-0.05	.96
Asthma	0.12	0.34	0.34	.73
Gender	0.23	0.34	0.68	.50
Hypertension	0.02	0.54	0.03	.98
Diabetes	1.00	0.93	1.07	.28
BMI	-0.03	0.03	-1.06	.29
ACEi	-1.40	1.44	-0.97	.33
Race	-0.09	0.08	-1.22	.22

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

TABLE XI. Logistic regression model predicting asymptomatic versus symptomatic using treatment: limited/no treatment versus dupilumab as a predictor variable and adjusting for other clinical variables

Outcome	Asymptomatic vs symptomatic			
	Log odds ratio	Standard error	Z score	P value
Intercept	-0.54	1.41	-0.38	.70
Limited/no treatment	0.31	0.27	1.18	.24
Age	0.01	0.01	1.13	.26
Asthma	0.44	0.27	1.60	.11
Gender	0.09	0.28	0.32	.75
Hypertension	-0.41	0.45	-0.92	.36
Diabetes	0.72	0.66	1.08	.28
BMI	-0.03	0.02	-1.14	.25
ACEi	-0.58	0.98	-0.58	.56
Race	-0.05	0.06	-0.75	.46

Log odds ratio is reported as the natural log of the odds ratio in the logistic regression model.

ACEi, Angiotensin-converting enzyme inhibitor; BMI, body mass index.

may account for the significant differences in clinical outcomes as compared with dupilumab, which reduces incidence and severity of symptoms in COVID-19. These results hold even when adjusting for a number of clinical and demographic variables that may affect COVID-19 severity, including race, age, and BMI.³² Older age and higher BMI were significantly associated with more frequent and more severe symptoms, consistent with prior knowledge.³²

The main analysis in our study included all patients with a likely COVID-19 diagnosis, regardless of a laboratory-confirmed COVID-19 diagnosis. Thus, we acknowledge that some patients who reported probable COVID-19 symptoms may have had other infections (eg, respiratory or gastrointestinal). However, we believe that this approach is crucial for several reasons, primarily, because there are likely many COVID-19 cases undiagnosed by formal testing in our cohort; testing was unreliable early on, and even now laboratory screening for asymptomatic cases is not routinely performed. Further, including all subjects may contribute to eliminating biases in testing behavior, because symptomatic

patients are more likely to get tested. In addition, although the impetus for this study was to evaluate the impact of immunomodulatory drugs specifically on COVID-19 symptomatology, these data showing that Th2 modulation potentially ameliorates COVID-19 symptoms extending beyond the current era. Our findings may thus have implications for other common viral infections, such as influenza, and for possible future pandemics.

In the setting of the current COVID-19 pandemic, despite the advent of vaccination and increasing efforts to widely distribute vaccines to the population, it remains crucial to understand the impact of immunomodulatory medications in patients with chronic inflammatory diseases; many people may be unable or unwilling to get vaccines, the long-term protection offered by vaccines is still unknown, and the efficacy and duration of immune response to vaccination in the setting of immunomodulatory medications remains unknown. Because of this, we also performed an analysis focused on outcomes in patients with confirmed laboratory evidence of COVID-19 infection or with significant known COVID-19 exposures, and the results in this subset were even more significant than those found in the entire cohort.

We acknowledge some limitations in this study. Primarily, there are inherent limitations to a registry-based study, including sampling bias, recall bias, and patients being enrolled at a single time point. Our study was also limited by the fact that we could not obtain laboratory confirmation (via serology testing) of COVID-19 infection in many patients. Additional testing will provide even more evidence for the relevance of these findings to confirmed COVID-19 infection.

Future studies are needed to understand the implications of our findings for other specific viral conditions. Furthermore, biomarker-based studies may provide added support for the proposed mechanism by which Th2 blockade might produce the results seen in this study. In addition, understanding the immune response to COVID-19 vaccination in patients on immunomodulatory medications will be crucial as vaccination becomes increasingly widespread. Lastly, further studies in other inflammatory conditions commonly treated with immunomodulatory medications will be needed as well. The present study is the first to demonstrate the significant protection potentially offered by Th2 targeting with dupilumab in reducing symptom incidence and severity compared with other treatments for AD in the context of COVID-19 infection. These findings have important implications, not only for the millions of patients with moderate-to-severe AD in this country exposed to COVID-19 and other viral infections, but potentially for patients with chronic atopic and other conditions on immunomodulatory medications.

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