COVID-19 symptoms are attenuated in atopic dermatitis patients treated with dupilumab Short running title: Reduced COVID-19 symptoms in dupilumab-treated AD

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Abstract

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. Since it is believed that Type 1/Th1immunity controls viral infections, and that there is a Th1/Th2 counter-regulation, we hypothesized that Th2 targeting with the IL-4Rα-antagonist, dupilumab, in patients with moderate-to-severe AD rebalances Th1/Th2 axis, potentially leading to attenuated COVID-19 symptoms. **Methods:** 1,237 moderate-to-severe AD patients 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 (n=498). Demographic and comorbid covariates were adjusted by multivariate 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=0.01) and on limited/no treatment (p=0.04), and less likely to experience any symptoms versus patients on other systemics (p=0.01). 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 to 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 AD patients.

Original Article

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ABSTRACT

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. Since it is believed that Type 1/Th1immunity controls viral infections, and that there is a Th1/Th2 counter-regulation, we hypothesized that Th2 targeting with the IL-4Rα-antagonist, dupilumab, in patients with moderate-to-severe AD rebalances Th1/Th2 axis, potentially leading to attenuated COVID-19 symptoms.

Methods: 1,237 moderate-to-severe AD patients 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 (n=498). Demographic and comorbid covariates were adjusted by multivariate 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=0.01) and on limited/no treatment (p=0.04), and less likely to experience any symptoms versus patients on other systemics (p=0.01). 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 to 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 AD patients.

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

Abbreviations:

AD: Atopic dermatitis

EUA: Emergency Use Authorization

BMI: Body mass index

IFN: Interferon

IL**:** Interleukin

TNF**:** Tumor necrosis factor

INTRODUCTION

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, due to extraordinary vaccine development efforts, the American Food and Drug Administration issued Emergency Use Authorizations (EUA) for three 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 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 (e.g., 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 (˜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. While 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] While 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 AD patients on dupilumab compared to other therapeutics.

The present study is the first large-scale, prospective evaluation of 1,237 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 to patients on other systemic treatments for AD.

METHODS

Patients

We performed a cross-sectional analysis of reported demographics, medical history, and medications from 1,237 moderate-to-severe AD patients enrolled from April 2nd 2020 through January 31st, 2021 in a prospec-

tive 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 ICD10 codes and each patient chart was reviewed to ensure 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 atopic dermatitis, 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 (i.e., 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 0-5: 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: "very severe disease" (required hospitalization, intubation, and other supportive measures); 5: "fatal."

One thousand two-hundred and thirty-seven patients were included in the final analysis, out of 1,357 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 to 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 TNFα and IL-23/IL-17 antagonists).

Statistical analysis

Demographic characteristics between groups were assessed using a two-sided Fisher exact test or ANOVA 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 incidence of any symptoms. Because of the potential for multiple confounders, we associated the presence of COVID-19-related symptoms with dupilumab treatment compared to other systemic treatments and with dupilumab treatment compared to 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, ACE-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

Twelve-hundred, thirty-seven 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 1A. No significant differences were found between groups in terms of age and race.

COVID-19 symptom severity

We calculated the distribution of COVID-19 symptom severity across groups in six categories: 0/"asymp-

tomatic," 1/"mild," 2/"moderate," 3/"severe," 4/"very severe," and 5/"fatal" (Table 1B). 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 1A),[32]we adjusted for known risk factors for increased COVID-19 morbidity (e.g., obesity, hypertension, etc.) using logistic regression models. We found that patients on dupilumab were less likely to experience moderate-to-severe symptoms compared to patients on other systemic treatments (OR=3.89; p=0.008, Table 2A). Furthermore, they were less likely to experience moderate-to-severe symptoms compared to those on limited/no treatments (OR=1.96; p=0.04; Table 2B). Additionally, BMI was significantly associated with moderate-to-severe symptoms across COVID-19 related patients treated with biologic and systemic therapies (p<0.001, Table 2A).

When evaluating the effects of various clinical variables on the presence of COVID-19-related symptoms, we found that non-biologic systemic treatment was significantly associated with symptomatology relative to treatment with dupilumab (OR=1.87; p=0.01, Table 2C). However, there were no differences in predicting symptomatology among patients on dupilumab relative to the limited/no treatment group (Table 2D).

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

Next, we compared the subgroup of patients comprised of 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 to 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 3; 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=0.002; Table 4A). Additionally, being on limited/no treatment was also significantly associated with moderate-to-severe symptoms relative to dupilumab (OR=2.44; p=0.05; Table 4B). BMI was a significant covariate of moderate-to-severe symptoms across all systemic treatment groups in this known infection/high-risk exposure group (p=0.005; Table 4A).

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=0.03, Table 4C). 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 4D).

DISCUSSION

The present study is the first large-scale 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 to 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 COVID-19 patients.[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] Since Type 1/Th1immunity 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-4Rα, 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 AD patients, compared to both other systemic treatments and to no systemic treatments. We found that patients treated with dupilumab were less likely to experience moderate-to-severe symptoms compared to patients on other systemics (p=0.01) as well as to patients on limited/no treatment (p=0.04). Patients treated with dupilumab were also less likely to experience any symptoms at all compared to patients on other systemics

(p=0.01). This effect holds true for patients with suspected COVID-19, as well as for patients with a confirmed COVID-19 diagnosis or a confirmed high-risk exposure. Those treated with dupilumab were less likely to experience moderate-to-severe symptoms compared to those on other systemics (p=0.002) as well as on limited/no treatment (p=0.05) and were less likely to experience symptoms at all compared to patients on other systemics (p=0.03).

The robust effect of dupilumab on COVID-19 symptomatology may be due to primary modulation of 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, asthma patients treated with the Th2 modulator omalizumab (anti-IgE) had a lower incidence of respiratory virus-induced asthma exacerbations and a more robust IFNα response in vitro to rhinovirus stimulation.[36]Similarly, our study found that COVID-19 symptoms and severity were reduced in dupilumab even when compared to 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 may account for the significant differences in clinical outcomes as compared to 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 (e.g. 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, since symptomatic patients are more likely to get tested. Additionally, 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 extends 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 timepoint. 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. Additionally, 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 to other treatments for AD in the context of COVID-19 infection. These findings have important implications, not only for the millions of moderate-to-severe AD patients 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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Table 1. Demographics and symptom severity for all patients and treatment groups.

1A.

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

1B. Percentage of patients by COVID-19 symptom severity score in each treatment group. 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."

	All patients n=1233	**Dupilumab n=631**	**Other systemics n=107**	**Limited/no treatment n=49**
Severity				

	All patients n=1233	Dupilumab n=631	Other systemics n=107	Limited/no treatment n=49
0 (n, %)	947 (77%)	492 (78%)	73 (68%)	382 (77%)
1 (n, %)	204 (16%)	110 (17%)	18 (17%)	76 (15%)
2 (n,%)	78 (6%)	29 (5%)	15 (14%)	34 (7%)
3 (n,%)	4 (0.3%)	0 (0%)	1 (1%)	3 (1%)
4/5 (n, %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 2. Logistic Regression Models Comparing Symptom Severity Among All Patients in Different Treatment Groups.

A. Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: Systemics vs Dupilumab as a predictor variable and adjusting for other clinical variables; **B** . Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: Limited/No-treatment vs Dupilumab as a predictor variable and adjusting for other clinical variables; **C** . Logistic regression model predicting asymptomatic versus symptomatic using treatment: Systemics vs Dupilumab as a predictor variable and adjusting for other clinical variables; **D** . Logistic regression model predicting asymptomatic versus symptomatic using treatment: Limited/No-treatment vs Dupilumab as a predictor variable and adjusting for other clinical variables. Log Odds Ratio is reported as the natural log of the odds ratio in the logistic regression model.

A

Outcome	Asymptomatic/mild versus moderate-to-severe symptoms	Asymptomatic/mild versus moder
	Log Odds Ratio	**Standard Error**
Intercept	-3.86	2.36
Systemics	1.36	0.51
Age	0.01	0.01
Asthma	-0.61	0.45
Gender	-0.35	0.45
Hypertension	-1.15	0.75
Diabetes	0.75	0.90
BMI	0.13	0.04
ACEi	0.55	1.91
Race	0.07	0.10

B

Outcome	Asymptomatic/mild versus moderate-to-severe symptoms	Asymptomatic/mild versu
	Log Odds Ratio	**Standard Error**
Intercept	-3.59	1.58
Limited/no treatment	0.67	0.33
Age	0.03	0.01
Asthma	0.26	0.33
Gender	-0.03	0.34
Hypertension	-0.96	0.58
Diabetes	-0.09	0.72
BMI	0.04	0.03
ACEi	0.83	1.09
Race	-0.07	0.08

C

Outcome	Asymptomatic versus symptomatic	Asymptomatic versus symptomatic	Asymptomatic vers
	Log Odds Ratio	**Standard Error**	**Z-score**
Intercept	-0.59	0.97	-0.60
Systemics	0.63	0.25	2.46
Age	-0.001	0.01	-0.28
Asthma	0.15	0.19	0.77
Gender	-0.05	0.19	-0.25
Hypertension	-0.24	0.30	-0.80
Diabetes	0.16	0.44	0.35
BMI	0.02	0.02	1.19
ACEi	-0.74	0.68	-1.08
Race	-0.11	0.04	-2.50

D

Outcome	Asymptomatic versus symptomatic	Asymptomatic versus symptomatic	Asymptoma
	Log Odds Ratio	**Standard Error**	**Z-score**
Intercept	-1.32	0.78	-1.70
Limited/no treatment	0.10	0.15	0.64
Age	0.001	0.00	0.15
Asthma	0.27	0.16	1.75
Gender	-0.09	0.16	-0.56
Hypertension	-0.38	0.26	-1.46
Diabetes	0.15	0.36	0.41
BMI	0.01	0.01	0.67
ACEi	-0.03	0.54	-0.06
Race	-0.08	0.04	-2.20

Table 3. 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)	<0.001
Gender				0.04
Male (n,%)	70 (43%)	9 (35%)	33 (28%)	
Female (n,%)	94 (57%)	17 (65%)	83 (72%)	
Race				0.51
American Indian/Alaska Native (n,%)	0 (0%)	0 (0%)	3 (3%)	
Asian (n,%)	28 (17%)	5 (19%)	13 (11%)	
Black or African American (n,%)	30 (18%)	5 (19%)	19 (16%)	
Mixed race (n,%)	5 (3%)	1 (4%)	5 (4%)	
Native Hawaiian or Other Pacific Islander (n,%)	2 (1%)	0 (0%)	0 (0%)	
Unknown (n,%)	6 (4%)	1 (4%)	9 (8%)	
White (n,%)	93 (57%)	14 (54%)	67 (58%)	
Comorbidities				
Hypertension	21 (13%)	6 (23%)	15 (13%)	0.35

	Dupilumab	Other systemics	Limited/no treatment	P-value
Diabetes	9 (5%)	1 (4%)	5 (4%)	0.91
Asthma	61 (37%)	11 (42%)	44 (38%)	0.89
Obesity (BMI>30)	27 (19%)	7 (30%)	19 (18%)	0.38
Other medications				
ACEi	5 (3%)	0 (0%)	2 (2%)	0.84
COVID exposure and testing				
Tested positive for COVID 19 (n,%)	39 (24%)	11 (42%)	37 (32%)	0.09
Exposure to positive COVID 19 (n,%)	76 (46%)	6 (23%)	46 (40%)	0.06
Exposure to COVID 19-like symptoms (n,%)	49 (30%)	9 (35%)	33 (28%)	0.84

Table 4. Logistic Regression Models Comparing Symptom Severity Among Patients with Confirmed Diagnosis or COVID-19 Exposure in Different Treatment Groups.

Within the population of patients with confirmed diagnosis or COVID-19 exposure: **A** . Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: Systemics vs Dupilumab as a predictor variable and adjusting for other clinical variables; **B** . Logistic regression model predicting asymptomatic/mild versus moderate-to-severe symptoms using treatment: Limited/No-treatment vs Dupilumab as a predictor variable and adjusting for other clinical variables; **C.** Logistic regression model predicting asymptomatic versus symptomatic using treatment: Systemics vs Dupilumab as a predictor variable and adjusting for other clinical variables; **D.** Logistic regression model predicting asymptomatic versus symptomatic using treatment: Limited/No-treatment vs Dupilumab as a predictor variable and adjusting for other clinical variables. Log Odds Ratio is reported as the natural log of the odds ratio in the logistic regression model.

A

Outcome	Asymptomatic/mild versus moderate-to-severe symptoms	Asymptomatic/mild versus moder
	Log Odds Ratio	**Standard Error**
Intercept	-16.59	1455.40
Systemics	2.62	0.86
Age	0.04	0.02
Asthma	-1.25	0.77
Gender	-0.26	0.66
Hypertension	-2.06	1.15
Diabetes	1.91	1.32
BMI	0.22	0.08
ACEi	12.09	1455.40
Race	-0.11	0.16

B

Outcome	Asymptomatic/mild versus moderate-to-severe symptoms	Asymptomatic/mild versu
	Log Odds Ratio	**Standard Error**
Intercept	-19.95	1606.87
Limited/no treatment	0.89	0.46
Age	0.04	0.02
Asthma	0.10	0.46
Gender	0.11	0.49

Outcome	Asymptomatic/mild versus moderate-to-severe symptoms	Asymptomatic/mild versu
Hypertension	-0.97	0.79
Diabetes	-0.87	1.14
BMI	0.08	0.04
ACEi	16.70	1606.87
Race	-0.05	0.11

C

Outcome	Asymptomatic versus symptomatic	Asymptomatic versus symptomatic	Asymptomatic vers
	Log Odds Ratio	**Standard Error**	**Z-score**
Intercept	0.86	1.86	0.46
Systemics	1.09	0.51	2.12
Age	-0.001	0.01	-0.05
Asthma	0.12	0.34	0.34
Gender	0.23	0.34	0.68
Hypertension	0.02	0.54	0.03
Diabetes	1.00	0.93	1.07
BMI	-0.03	0.03	-1.06
ACEi	-1.40	1.44	-0.97
Race	-0.09	0.08	-1.22

D

Outcome	Asymptomatic versus symptomatic	Asymptomatic versus symptomatic	Asymptoma
	Log Odds Ratio	**Standard Error**	**Z-score**
Intercept	-0.54	1.41	-0.38
Limited/no treatment	0.31	0.27	1.18
Age	0.01	0.01	1.13
Asthma	0.44	0.27	1.60
Gender	0.09	0.28	0.32
Hypertension	-0.41	0.45	-0.92
Diabetes	0.72	0.66	1.08
BMI	-0.03	0.02	-1.14
ACEi	-0.58	0.98	-0.58
Race	-0.05	0.06	-0.75

Figure Legends

Figure 1A. Whole patient cohort separated into treatment groups, dupilumab (n=631), other systemics (n=107), and limited/no treatment (n=495), grouping symptom severity in each treatment group by scores of 0-1 (asymptomatic or mild symptoms) and 2-5 (moderately symptomatic to fatal). *P<0.05. **P<0.01.**1B.** Whole patient cohort separated into treatment groups, dupilumab (n=631), other systemics (n=107), and limited/no treatment (n=495), grouping presence of symptoms in each treatment group by a score of 0 (asymptomatic) or 1-5 (symptomatic). *P<0.05. **P<0.01.

Figure 2A. 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 in each treatment group by scores of 0-1 (asymptomatic or mild symptoms) and 2-5 (moderately symptomatic to fatal). *P<0.05. **P<0.01. **2B.** 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 presence of symptoms in each treatment group by a score of 0 (asymptomatic) or 1-5 (symptomatic). *P<0.05. **P<0.01.

Figure 1

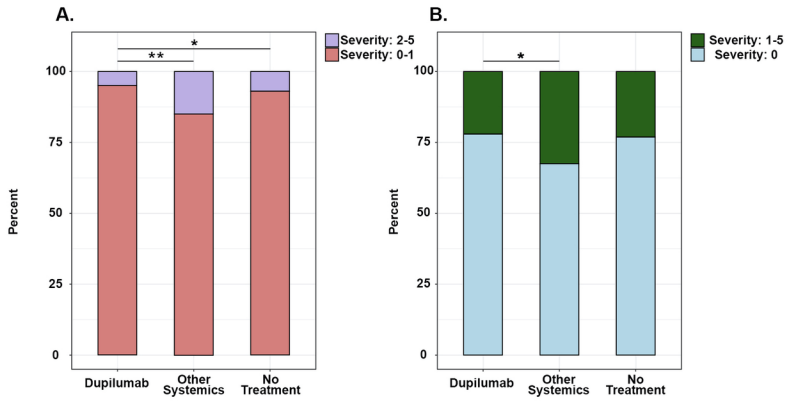

Figure 2