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BRIEF REPORT

Dupilumab Use Is Associated With Protection From Coronavirus Disease 2019 Mortality: A Retrospective Analysis

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We previously found that type 2 immunity promotes coronavirus disease 2019 (COVID-19) pathogenesis in a mouse model. To test relevance to human disease, we used electronic health record databases and determined that patients on dupilumab (anti-interleukin [IL]-4R monoclonal antibody that blocks IL-13 and IL-4 signaling) at the time of COVID-19 infection had lower mortality.

Keywords. COVID-19; dupilumab; type 2 immunity; infectious disease.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19) and is currently causing a devastating global pandemic. Many approaches to combat mortality involve targeting inflammation, such as with the corticosteroid dexamethasone [1] or the monoclonal antibody against interleukin-6 (IL-6), tocilizumab [2]. However, although these therapeutic options have been observed to reduce mortality in patients, protection is not complete. This was exemplified by mortality from the Delta variant being 12.6% during the fall 2021 surge [3]. More recently, in-hospital deaths from the Omicron variant dropped to 7.3% [3]; however, reported deaths still remain high and methods to reduce these numbers are warranted. Additionally, the emergence of novel variants such as Omicron, for which the vaccine is increasingly less effective, highlights the need for development of better therapeutic options in treating this disease.

Recently, we have uncovered a causal role of IL-13 in promoting severe outcomes caused by infection with SARS-CoV-2, suggesting that type 2 immune responses are pathogenic during COVID-19 [4, 5]. IL-13 is often associated with promoting pathology in asthma, allergies, and atopic dermatitis. In the lung, pulmonary responses potentiated by IL-13 include airway hyperreactivity, mucus production, smooth muscle contractility, recruitment of immune cells, and long-term airway remodeling [6–8]. In acute settings, this results in airway restriction causing breathing difficulty and wheezing, and can result in decreased lung capacity and function in the long term.

Dupilumab is a human monoclonal antibody that blocks signaling of the closely related cytokines IL-4 and IL-13 by targeting the shared alpha subunit of their receptors, IL-4Rα [9–11]. IL-4 and IL-13 are both primarily associated with type 2 responses that drive pathogenesis of asthma and atopic dermatitis, which dupilumab is approved to treat [9–11]. We were interested in whether dupilumab use in patients who were later diagnosed with COVID-19 was associated with protection from mortality because of its ability to block pathogenic IL-13 signaling. Earlier, we had performed a randomized, double-blind, placebo-controlled clinical trial of dupilumab for the treatment of moderate to severe COVID-19 in a small study of 40 hospitalized adults. Subjects randomized to receive dupilumab had lower mortality, again supporting the potential significance of IL-13 in COVID-19 [5].

Here, we report that in more than 2000 patients that dupilumab usage is associated with reduced mortality compared with matched-control patients. Our findings support the hypothesis that IL-13 signaling during COVID-19 is associated with more severe outcomes, and that pharmacological inhibition of this pathway may be a feasible therapeutic option for treating this disease.

METHODS

The National COVID Cohort Collaborative (N3C) data transfer to the National Center for Advancing Translational Sciences is performed under a John Hopkins University Reliance Protocol #IRB00249128 or individual site agreements with the National Institutes of Health. The N3C Data Enclave is managed under the authority of the National Institutes of Health; information can be found at https://ncats.nih.gov/n3c/resources.

Database and Inclusion Criteria

N3C

The N3C cohort was filtered to patients who were COVID-19 positive based on the presence of either a SARS-CoV-2

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polymerase chain reaction, antigen-positive test results, or a COVID-19 diagnosis code. The first instance of either indicator in the patient's record was used as the COVID-19 index date. To increase our confidence that dupilumab would have a biological effect in COVID-19 patients, a cutoff was made for dupilumab use within 61 days before the patients' index event to account for the pharmaceutical lifespan. Using these filters, the following 2 subcohorts were analyzed:

1. Controls: COVID-19-positive patients with no record of dupilumab use within 61 days of their index event.
2. Dupilumab (+): Any COVID-19 patient with recorded dupilumab use within the 61 days preceding their index event.

The incidence of COVID positivity in people on dupilumab [cohort definition 1/(definition 1 + 2)], along with 95% confidence intervals (CIs), was calculated.

TriNetX

Data were retrieved from the COVID-19 Research Network provided by TriNetX, comprising 80 million patients from 65 health care organizations in 11 countries (on December 7, 2021). COVID-19 patients were identified via the International Classification of Diseases-10 code U07.1 or the presence of a SARS-CoV-2-related RNA diagnosis within the past 2 years. Drug use was identified via RxNorm codes for dupilumab (1876376) and the laboratory value for C-reactive protein (9063); 1:1 matching was performed for age and sex.

Matching

N3C

A case-control design was used. Dupilumab (+) patients were matched to control patients in a 1:5 ratio, with exact matching on sex, race, and ethnicity; N3C site; asthma; and nearest matching on age. Asthma was included as additional matching criteria because it is an approved disease for which dupilumab is prescribed and primarily affects respiratory inflammation.

TriNetX

Analytical tools were used to obtain baseline characteristics, balance cohorts with propensity score matching, and analyze outcomes of interest in the final cohorts. Baseline characteristics, including demographics, diagnoses, procedures, and medication were obtained. Propensity score matching was used to balance cohorts. Propensity scores matched cohorts 1:1 using a nearest neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation.

Outcome Definitions

1. Hospitalized: The COVID-19 (+) test or diagnosis code occurred during a hospitalization (any consecutive series of visit encounters that include an inpatient stay).
2. Death: Death as recorded in a medical record system from contributing sites.

COVID Severity

Categorical variable with following levels:

1. Mild—outpatient
2. Moderate—hospitalized but no extracorporeal membrane oxygenation (ECMO) or intermittent mandatory ventilation (IMV)
3. Severe—hospitalized with ECMO or IMV
4. Death

Statistical Analysis

N3C

Statistical analyses were performed using R studio version 3.5.1. Conditional logistic regression, or exact tests in rare outcomes, was used to compare COVID-19 severity outcomes within the matched subset of COVID (+) patients.

TriNetX

Outcomes were defined as ventilation assist and death. Measures of association including risk differences with their respective 95% CIs were calculated. Time frame of follow-up for both groups was set to 365 days for Kaplan–Meier curves, which were generated for each analysis.

RESULTS

The N3C and TriNetX databases were independently queried. The N3C database as of August 27, 2021, included 1069 patients prescribed dupilumab, for which 220 were subsequently diagnosed with COVID-19 within 61 days of their dupilumab dose (infection rate, 20.6%; 95% CI, 18.2-23.1) (Table S1). We found that dupilumab use was associated with significantly fewer deaths than in the matched control group (0 vs 24 [2.2%]; odds ratio, 0.02) (Table 1). Sensitivity analyses that added matching by ECMO and IMV showed similar lower mortality rates in COVID+ patients who received dupilumab (95% CI, .010–.031; $P < .001$).

Next, to support the N3C findings that dupilumab was associated with protection from mortality, we used the TriNetX database and filtered for COVID-19 cases with (n = 2523) or without (n = 1.7 million) recorded use of dupilumab and performed 1:1 matching (Table S2). We found that dupilumab usage was associated with a lower risk of death (log-rank P value = .002) (Table 1) when compared with controls, similar to the results from our N3C cohort. Different from the N3C data, more hospitalizations were in the dupilumab group. We additionally tested for differences in bacterial pneumonia and in the use of other immunomodulator therapy, and found that only dexamethasone use was higher in the dupilumab

Table 1. Disease Outcomes in Patients Taking Dupilumab Compared With Matched Controls

	Controls (N = 1100)	Dupilumab (N = 220)	*P* Value
A. N3C	…	…	
Outcome			
Hospitalized	111 (10.1%)	22 (10.0%)	.97
Died	24 (2.2%)	0 (0.0%)	<.001
COVID-19 severity	…	…	
Mild	982 (89.3%)	198 (90.0%)	…
Moderate	83 (7.5%)	20 (9.1%)	…
Severe	<20[a]	<20[a]	…
B. TriNetX	…	…	
…	Controls (N = 2523)	Dupilumab (N = 2523)	*P* Value
Outcome	…	…	
Hospitalized	103	144	.007[b]
Died	*47*	32	.002
COVID-19 severity	…	…	
Ventilation	13	10	…
Bacterial pneumonia	10	11	…
COVID-19 treatments	…	…	
Dexamethasone	271	390[c]	…
Baricitinib or tofacitinib	10	10	…
Tocilizumab or sarilumab	10	10	…

Abbreviation: COVID-19, coronavirus disease 2019.

[a]To protect patient privacy, this suppressed in accordance with N3C download policy.

[b]Log-rank test on Kaplan–Meier.

[c]When separately matching the control and dupilumab groups for dexamethasone the Log-Rank Test on Kaplan-Meier remained significant with p = 0.017.

group (Table 1). When separately matching the control and dupilumab groups for dexamethasone the log-rank Test on Kaplan–Meier remained significant with $P = .017$.

DISCUSSION

Through utilization of 2 databases, we have found that prior dupilumab usage in COVID-19 patients was associated with improved survival compared with matched controls. Previous work by Ungar et al supported this finding, where, in atopic dermatitis patients, dupilumab use was also associated with a reduction in severe outcomes from COVID-19 [12]. We report these findings building off of in vivo work supporting a causal role for IL-13 in COVID-19 pathogenesis [4] and a small randomized clinical trial demonstrating a decreased mortality in subjects randomized to dupilumab [5]. Because of the mechanism of action of dupilumab, we hypothesize this protection, then, is mediated by blocking pathogenic IL-13 signaling.

Retrospective analyses, such as these, provide us with large-scale data that allow for smaller CIs than smaller prospective studies. However, there are limitations because of nonrandomized groups resulting in sampling biases, difficulty defining temporal boundaries, and not being able to infer causational relationships. The N3C database allowed for well-defined patient outcomes and temporal windows; however, small sampling size may limit the statistical power through this method. Supportive analysis by TriNetX allowed for larger cohort of dupilumab (+) cases, but was limited to lower matching criteria and at a 1:1 ratio. Utilization of both datasets, then, provides 2 analyses that supported our hypothesis.

Identification of dupilumab as being associated with reduction in death from COVID-19 may implicate this drug as a potential therapeutic option for patients. Future, large-scale clinical trials of dupilumab use during COVID-19 will be important for understanding the impact this drug may have on protecting patients from severe outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. W. P. and A. D. designed the study and wrote the manuscript with J. S. R. P. conducted the TriNetX analysis and I. M. and J. L. undertook the N3C analysis. All authors contributed to discussion regarding conceptualization and design of the reported studies. Authorship was determined using ICMJE recommendations.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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