Dupilumab use is associated with protection from COVID-19 mortality: A retrospective analysis

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Running title: Dupilumab-associated protection in COVID

Abstract:

We previously found that type 2 immunity promotes 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-IL-4Rα 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

Introduction: 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 IL-6, tocilizumab [2]. However, while these therapeutic options have been observed to reduce mortality in patients, protection is not complete. This was exemplified by mortality due to the delta variant being 12.6% during the fall 2021 surge [3]. More recently, in-hospital deaths due to 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 Interleukin (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 long-term can result in decreased lung capacity and function.

Dupilumab is a human monoclonal antibody which 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 which drive pathogenesis of asthma and atopic dermatitis, for 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 due to 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 for over two thousand patients that dupilumab usage is associated with reduced mortality compared to 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 N3C data transfer to NCATS is performed under a John Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

Database and Inclusion Criteria:

N3C: The N3C (National COVID Cohort Collaborative) cohort was filtered to patients who were COVID-19 positive based on the presence of either a SARS-CoV-2 PCR or 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 prior to the patients' index event to account for the pharmaceutical lifespan. Using these filters, there were two sub cohorts that 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 above / (definition 1 + 2)], along with 95% confidence intervals, 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 (for database access on 12/07/2021). COVID-19 patients were identified via the ICD-10 code U07.1 or the presence of a SARS-CoV-2-related RNA diagnosis within the last two years. Drug use was identified via RxNorm codes for dupilumab (1876376) and the lab 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 gender, race and ethnicity, N3C site, asthma and nearest matching on age. Asthma was included as additional matching criteria since 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 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% CI's 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 27th 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%). We found that dupilumab use was associated with significantly fewer deaths than in the matched control group (0 vs 24 (2.2%); OR: 0.02) (**Table 1**). Sensitivity analyses that added matching by ECMO and IMV showed similar lower mortality rates in COVID+ patients who received Dupilimab (95% CI: 0.010-0.031, p<.001).

Next, to support the N3C findings that dupilumab was associated with protection from mortality, we utilized 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. We found that dupilumab usage was associated with a lower risk of death (log-rank p-value = 0.002) (**Table 1**) when compared to 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 group (Table 1). When separately matching the control and dupilumab groups for dexamethasone the Log-Rank Test on Kaplan-Meier remained significant with p = 0.017.

Discussion:

Through utilization of two databases, we have found that prior dupilumab usage in COVID-19 patients was associated with improved survival compared to matched controls. Previous work by Ungar et al., 2022 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]. Due to 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 confidence intervals than smaller prospective studies. However, there are limitations due to non-randomized groups resulting in sampling biases, difficulty defining temporal boundaries, and not being able to infer causational relationships. The

N3C database used 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 two analyses which supported our hypothesis.

Identification of dupilumab as a being associated with reduction in death due to 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.

NOTES

Author contributions: WP and AD designed the study and wrote the manuscript with JS, RP conducted the TriNetX analysis and IM and JL the N3C analysis. All authors contributed to discussion regarding conceptualization and design of the reported studies. Authorship was determined using ICMJE recommendations.

Attribution:

This research was possible because of the patients whose information is included within the data and the organizations and scientists who have contributed to the on-going development of this community resource https://doi.org/10.1093/jamia/ocaa196.

Funding Sources:

AD, JS, and WP were supported by grants to WP from the Manning Family Foundation, Ivy Foundation, Henske Family, and NIH R01 AI124214.

Analyses performed by IM and JL were conducted with data or tools accessed through the NCATS N3C Data Enclave https://covid.cd2h.org and N3C Attribution & Publication Policy v1.2-2020-08-25b, and supported by NCATS U24 TR002306. Support for project planning and analysis was also provided by the integrated Translational Health Research Institute (iTHRIV) with funding support from NCATS UL1 TR003015. RP was supported by Deutsche Forschungsgemeinschaft (DFG KFO339, DFG TRR295).

Competing interests: William A. Petri, Jr. receives research funding from Regeneron, Inc. which is the maker of dupilumab. Indika Mallawaarachi reports grants or contracts

from iTHRIV NCATS Award: UL1TR003015 (institutional award). Johanna J. Loomba reports grants or contracts from iTHRIV NCATS Award: UL1TR003015 (institutional award) and NCATS U24 TR002306 (institutional award). Robert Preissner reports grants or contracts from SFB TRR295 (Deutsche Forschungsgemeinschaft – DFG). Jennifer M. Sasson reports grants or contracts from NIH R01 AI124214 and patents from TYPE 2 CYTOKINES AS PREDICTORS OF DISEASE SEVERITY AND/OR AS THERAPEUTIC TARGETS FOR COVID-19; PCT/US21/37912; 17JUN2021. Alexandra N. Donlan and William A. Petri, Jr. reports patents from Donlan AN, Petri WA Jr. United States Provisional Patent Application Serial No. 63/073,234r DUAL NEUTRALIZATION OF IL-4 AND IL-13 TO TREAT TYPE 2 INFLAMMATION IN COVID-19 (Filed September 9, 2020.). The other authors declare no competing interests.

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Table 1. Disease outcomes in patients taking dupilumab compared to matched controls.

A. N3C			
	Controls (N=1100)	**Dupilumab (N=220)**	**P-value**
Outcome			
Hospitalized	111 (10.1%)	22 (10.0%)	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*	<20*	(-)
B. TriNetX			
-	**Controls (N=2523)**	**Dupilumab (N=2523)**	**P-value**
Outcome			
Hospitalized	103	144	0.007**
Died	*47*	32	0.002
COVID-19 Severity			
Ventilation	13	10	(-)
Bacterial Pneumonia	10	11	(-)
COVID-19 Treatments			
Dexamethasone	271	390***	(-)
Baracitinib or tofacitinib	10	10	(-)
Tocilizumab or sarilumab	10	10	(-)

*To protect patient privacy, suppressed in accordance with N3C download policy.
**Log-Rank Test on Kaplan-Meier

***when separately matching the control and dupilumab groups for dexamethasone the Log-Rank Test on Kaplan-Meier remained significant with p = 0.017

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