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MAJOR ARTICLE

Safety and Efficacy of Dupilumab for the Treatment of Hospitalized Patients With Moderate to Severe Coronavirus Disease 2019: A Phase 2a Trial

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Background. Based on studies implicating the type 2 cytokine interleukin 13 (IL-13) as a potential contributor to critical coronavirus disease 2019 (COVID-19), this trial was designed as an early phase 2 study to assess dupilumab, a monoclonal antibody that blocks IL-13 and interleukin 4 signaling, for treatment of inpatients with COVID-19.

Methods. We conducted a phase 2a randomized, double-blind, placebo-controlled trial (NCT04920916) to assess the safety and efficacy of dupilumab plus standard of care vs placebo plus standard of care in mitigating respiratory failure and death in those hospitalized with COVID-19.

Results. Forty eligible subjects were enrolled from June to November of 2021. There was no statistically significant difference in adverse events nor in the primary endpoint of ventilator-free survival at day 28 between study arms. However, for the secondary endpoint of mortality at day 60, there were 2 deaths in the dupilumab group compared with 5 deaths in the placebo group (60-day survival: 89.5% vs 76.2%; adjusted hazard ratio [HR], 0.05 [95% confidence interval {CI}, .004–.72]; $P = .03$). Among subjects who were not in the intensive care unit (ICU) at randomization, 3 subjects in the dupilumab arm were admitted to the ICU compared to 6 in the placebo arm (17.7% vs 37.5%; adjusted HR, 0.44 [95% CI, .09–2.09]; $P = .30$). Last, we found evidence of type 2 signaling blockade in the dupilumab group through analysis of immune biomarkers over time.

Conclusions. Although the primary outcome of day 28 ventilator-free survival was not reached, adverse events were not observed and survival was higher in the dupilumab group by day 60.

Clinical Trials Registration. NCT04920916.

Keywords. COVID-19; dupilumab; IL-13; SARS-CoV-2; type 2 immunity.

As in-hospital mortality from coronavirus disease 2019 (COVID-19) remains at 10%–26% [1, 2], paired with the ongoing threats of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, there remains a substantial need for additional therapeutics for those hospitalized with COVID-19. Current therapies against both the virus and with intention for immunomodulation have demonstrated variable and/or modest benefit. For example, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed a mortality reduction from 26% to only 23% with dexamethasone use in those hospitalized with COVID-19 respiratory failure, with the greatest mortality benefit seen in those requiring mechanical ventilation at randomization [3]. Clinical trials for remdesivir, an antiviral nucleoside analogue, have produced variable results, with the Adaptive COVID-19 Treatment Trial (ACTT)-1 demonstrating a 5-day reduction in clinical recovery time in those on supplemental oxygen [4]. Randomized controlled trials investigating interleukin (IL) 6 inhibitors have shown conflicting results, with some indicating a mortality benefit in those within 24 hours of intensive care unit (ICU) admission and others showing no difference in clinical outcomes between study groups [5, 6]. Janus kinase inhibitors initially showed only a 1-day improvement in clinical recovery time when combined with remdesivir, with later trials since showing reduced mortality from 13% to 8% when combined with usual

Received 17 June 2022; editorial decision 04 July 2022; accepted 25 July 2022; published online 27 July 2022

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https://doi.org/10.1093/ofid/ofac343

care in those requiring hospitalization and at least 1 elevated inflammatory marker [7, 8]. Findings from these studies suggest a need for improvement in treatment of those admitted with COVID-19 pneumonia.

We have discovered that COVID-19 patients with high plasma IL-13 levels have a significantly greater risk of needing mechanical ventilation [9]. IL-13, which signals through the receptor IL-4Rα along with the closely related cytokine IL-4, is involved in eosinophilic inflammation, mucous secretion, goblet cell metaplasia, and fibrosis, and has been regularly implicated in airway hyperresponsiveness and atopic disease [10]. We additionally found that neutralization of IL-13 in K18-hACE2 C57Bl/6J mice protected the animals from severe infection with SARS-CoV-2, as evidenced by reduced clinical score, weight loss, and mortality [9]. The association of IL-13 along with other effectors of type 2 immunity with respiratory failure from COVID-19 has also been demonstrated in other observation studies [11, 12]. These findings established mechanistic and biologic plausibility for IL-13 as a driver of pulmonary injury in COVID-19.

There are medications available to block IL-13 signaling: Dupilumab, a human immunoglobulin G4 subclass anti–IL-4Rα monoclonal antibody, was approved for treatment of moderate to severe atopic dermatitis by the United States (US) Food and Drug Administration in 2017. It reduces clinical severity in patients with allergic diseases including atopic dermatitis, asthma, and chronic rhinosinusitis [13]. The original clinical trials demonstrated minimal adverse events with dupilumab use, favoring it as a steroid-sparing therapy in atopic disease [14, 15]. Post hoc analysis of initial studies saw reduced incidence of respiratory viral infections with its use [16].

Dupilumab use was associated with greater survival from COVID-19 in retrospective analysis: Using the TriNetX international electronic medical record (EMR) database, we previously identified a cohort of 350 004 patients with COVID-19, of whom 81 had been prescribed dupilumab prior to their COVID-19 diagnosis [9]. Patients on dupilumab had a 12.3% absolute risk reduction in mortality compared to a propensity score–matched subcohort of 81 patients with COVID-19 not on dupilumab but with atopic diseases for which dupilumab is routinely used [9]. Dupilumab was also associated with reduced symptom severity and improved clinical outcomes in other observational studies utilizing large patient databases [17, 18].

The association of IL-13 with COVID-19 respiratory failure, the demonstration of survival benefit with IL-13 blockade in a mouse model, and the retrospective EMR analysis showing reduced COVID-19 mortality in those receiving dupilumab for atopic disease provided significant evidence for further exploration of dupilumab use for treatment of COVID-19. This, along with the safety of dupilumab and the potential for a targeted approach to therapy, led to the design of a clinical trial to test its use in patients hospitalized with COVID-19.

METHODS

Design

This was a randomized, double-blind, placebo-controlled trial designed as an early-phase study to assess the safety and efficacy of dupilumab use in 40 hospitalized patients with moderate to severe COVID-19 infection from a single center. It was approved by the University of Virginia (UVA) Institutional Review Board in June 2021 (NCT04920916). Eligible subjects were enrolled and randomized at a 1:1 ratio to receive either dupilumab or placebo, stratifying on disease severity measured by an oxygen requirement of ≤15 L/minute or >15 L/minute by nasal cannula. Included were those over the age of 18 who were hospitalized with a positive reverse-transcription polymerase chain reaction test (RT-PCR) for SARS-CoV-2 within the last 14 days and evidence of moderate to severe COVID-19 as defined by the National Institutes of Health (NIH) COVID-19 Severity Categorization [19]. Patients requiring mechanical ventilation at the time of enrollment were excluded. Both arms received standard of care management per current NIH COVID-19 treatment guidelines, including dexamethasone and remdesivir as deemed appropriate by their primary provider [19]. Subjects received a loading dose of dupilumab (600 mg, given as two 300-mg subcutaneous injections) or placebo on day 0, with additional maintenance doses of 300 mg or placebo given on days 14 and 28 if the subject remained hospitalized and was receiving active care [20]. Subjects were followed prospectively for 60 days.

Outcomes

The primary outcome of the study was the proportion of patients alive and free of invasive mechanical ventilation at day 28. Safety outcomes were assessed via determination of the cumulative incidence of adverse events, including those previously reported to occur with dupilumab use (ie, injection site reactions, eye/eyelid inflammation, conjunctivitis, herpes viral infection, eosinophilia) [20]. Additional clinical endpoints included all-cause mortality at day 28 and 60, proportion of patients alive and free of invasive mechanical ventilation at 60 days, hospital length of stay (LOS), ICU LOS, change in 8-point ordinal score, and change in partial pressure of oxygen or oxygen saturation to fraction of inspired oxygen ratio. Plasma inflammatory markers, including C-reactive protein (CRP), ferritin, and a 47-plex cytokine panel, were measured at various time points during the study. Additional type 2 inflammatory markers including TARC (CCL17), YKL40, eotaxin-3 (CCL26), arginase1 (Arg1), hyaluronan, soluble ST2, and total serum immunoglobulin E (IgE) were also measured. Ferritin, CRP, and IgE levels were measured at the UVA Clinical Laboratories while other biomarkers were measured by

multiplex immunoassays or enzyme-linked immunosorbent assays depending on the analyte. SARS-CoV-2 baseline nucleocapsid (N) protein level was measured from day 0, 2, 5, 7, and 14 available plasma of each subject using a microbead-based immunoassay, a highly sensitive detection method described in previous studies [21]. Day 0 nasopharyngeal swabs obtained for assessment of SARS-CoV-2 RNA positivity via RT-PCR underwent genomic sequencing to determine the SARS-CoV-2 lineage for samples with sufficient RNA using Artic version 3 primers on either MiSeq (Illumina) or MinIon (Oxford Nanopore) and categorized according to PANGOLIN and the World Health Organization [22, 23].

Statistical Analysis

COVID-19 hospitalization data from UVA between March 2020 and April 2021 showed that 79.5% of COVID-19 inpatients were alive and free of mechanical ventilation at 28 days under usual care. With a preselected sample size of 40 patients and $\alpha = .1$ (1-sided), we would be able to detect a difference of 17.7% in the proportion of subjects alive and free of mechanical ventilation at 28 days with 75% power.

Primary and secondary outcomes were analyzed under the intention-to-treat principle. Safety outcomes were analyzed in the as-treated population, including subjects who were enrolled and received at least 1 dose of study drug. Demographics and clinical and safety outcomes were analyzed initially with χ^2 or Fisher exact test for categorical measures and 2-sample *t* test or Wilcoxon rank-sum test for continuous measures, after assessment of normality. Treatment differences in ventilator-free survival proportions were analyzed via logistic regression. Mortality differences were evaluated by the log-rank test and further in the Cox regression for time-to-death outcome. Baseline patient characteristics and known risk factors for severe disease in COVID-19, including age, sex, body mass index (BMI), comorbidities, and COVID-19 vaccination status, were adjusted in regression models if initial analyses discovered imbalance in group characteristics [24]. Differences in the biomarkers between treatment groups were analyzed exploratively by *t* test or Wilcoxon rank-sum testing at each time point.

As an exploratory analysis, we included mechanical ventilation as a time-varying variable in the Cox regression for further investigation of its influence on survivability. This allowed us to account for the significant change in mortality risk between pre- and postintubation when a patient was placed on mechanical ventilation. We additionally tested differences in the likelihood of ICU admission between the 2 groups by the log-rank test. Last, after assessment of normality, N-protein levels were split into quartiles and analyzed by treatment group for influence on mortality via log-rank test and Cox regression. Regression models were adjusted for additional medications that were most likely to influence viral load, including monoclonal antibodies and remdesivir. Longitudinal N-protein levels over the first 14 study days were evaluated by the treatment groups using the linear mixed-effects models to account for within-subject correlations.

RESULTS

Patient and Virus Characteristics

Forty patients were enrolled from 23 June 2021 through 11 November 2021 (21 in placebo and 19 in dupilumab; Supplementary Figure 1). The groups were well matched with regard to age, BMI, race, ethnicity, comorbidities, vaccination status, and days from COVID-19 symptom onset to enrollment (Table 1). Patients in the placebo arm were more likely to be male (16 of 21 subjects [76.2%]) compared to the dupilumab arm (7 of 19 subjects [36.8%]). There were no significant differences in nonstudy COVID-19 therapies received between the treatment groups (Table 1). Of those with nasopharyngeal samples available for SARS-CoV-2 sequencing, 30 of 31 (96.8%) subjects had the Delta variant and 1 subject in the placebo group had the Iota variant (Supplementary Table 1).

Safety

There were no significant differences in cumulative adverse events observed between the treatment groups (Table 2). In the dupilumab group, 5 of 19 subjects developed asymptomatic eosinophilia compared to 1 subject out of 21 in the placebo group (Fisher exact $P = .09$). There were no clinical consequences, including dermatologic, gastrointestinal, pulmonary, cardiac, or neurologic, attributed to the peripheral eosinophilia seen in these subjects.

Clinical Efficacy

There was no significant difference in the primary endpoint of proportion of patients alive and free of mechanical ventilation at day 28 between the 2 groups (15 of 19 in the dupilumab group vs 18 of 21 in the placebo group; Table 3). However, by the secondary endpoint at 60 days, 17 of 19 subjects (89.5%) in the dupilumab group were alive compared to 16 of 21 subjects (76.2%) in the placebo group, as no patients remained on mechanical ventilation by day 60 in either group (Table 3). Although the survival difference was not significant by log-rank test ($P = .25$), after adjustment for sex and mechanical ventilation as a time-varying predictor, the risk of death over the 60-day follow-up period was significantly lower in the dupilumab group compared to placebo (hazard ratio [HR], 0.05 [95% confidence interval {CI}, .004–.72]; $P = .03$; Table 3, Figure 1).

Among those who were not already admitted to the ICU at randomization (33 patients), numerically fewer subjects in the dupilumab group required ICU care (3 of 17 subjects [17.7%]) compared to the placebo group (6 of 16 subjects [37.5%]), though this difference was not statistically significant

Table 1. Patient Characteristics

Characteristic	Placebo (n = 21)	Dupilumab (n = 19)
Age, y, median (IQR)	63 (55–78)	59 (44–70)
Sex, male	16 (76.2)	7 (36.8)
BMI, kg/m^2, median (IQR)	32.3 (26–37)	33.6 (27–42)
Hispanic ethnicity	3 (14.3)	3 (15.8)
Race		
White	14 (66.7)	13 (68.4)
Black	6 (28.6)	4 (21.1)
Asian	0 (0.0)	1 (5.3)
Other	1 (4.8)	1 (5.3)
Comorbidities		
Obesity	15 (71.4)	14 (73.7)
Chronic kidney disease	7 (33.3)	3 (15.8)
Asthma	4 (19.1)	4 (21.1)
Respiratory disease (COPD, emphysema)	3 (14.3)	2 (10.5)
Diabetes	8 (38.1)	7 (36.8)
Coronary artery disease	6 (28.6)	3 (15.8)
Cardiac valvular disease	3 (14.3)	2 (10.5)
Hypertension	10 (47.6)	8 (42.1)
Congestive heart failure	5 (23.8)	2 (10.5)
Cardiac arrythmia	4 (19.1)	1 (5.3)
Depression or psychotic disorder	3 (14.3)	8 (42.1)
Malignancy	4 (19.1)	3 (15.8)
Autoimmune disease	2 (9.5)	2 (10.5)
Organ or stem cell transplant recipient	3 (14.3)	1 (5.3)
Other immunodeficiency	1 (4.8)	0 (0.0)
Smoking history		
Never	12 (57.1)	15 (79.0)
Current	3 (14.3)	0 (0.0)
Past	6 (28.6)	4 (21.1)
Days from symptom onset to study treatment, median (IQR)	8.0 (6.0–10)	7.0 (6.0–11)
Received COVID-19 vaccine		
Moderna	4 (19.1)	1 (5.3)
Pfizer	5 (23.8)	4 (21.1)
Johnson & Johnson	0 (0.0)	2 (10.5)
None	12 (57.1)	12 (63.2)
Other COVID-19 therapeutics received		
Steroids	20 (95.2)	19 (100)
Remdesivir	18 (85.7)	16 (84.2)
IL-6 inhibitor	0 (0.0)	0 (0.0)
Janus kinase inhibitor	4 (19.1)	1 (5.3)
Monoclonal antibodies	3 (14.3)	2 (10.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IL-6, interleukin 6; IQR, interquartile range.

(log-rank $P = .23$; adjusted HR, 0.44 [95% CI, .09–2.09]; $P = .30$ for sex; Figure 2). There was no difference in additional secondary endpoints between the 2 treatment groups (Supplementary Table 2, Supplementary Figures 2 and 3).

Biomarker Analysis

In both treatment groups, CRP, ferritin, and IgE levels declined in the first 2 weeks, with no significant difference in the change in measures from day 0 to 14 between groups (Supplementary Figure 4). When looking at the change in absolute cell counts over time, there was an increase in eosinophils by day 14 in the dupilumab group compared to the placebo group ($P = .01$ by Wilcoxon rank-sum test; Supplementary Figure 5). Analysis of patient cytokine, chemokine, and growth factors in serum at various study time points showed a decreased monocyte chemoattractant protein 1 (MCP-1) at day 7 in the dupilumab treatment group compared to placebo ($P = .04$, Wilcoxon rank-sum test; Supplementary Figure 6). By day 14, there was a larger decrease in eotaxin-3 levels in the dupilumab

Table 2. Adverse Events Observed Throughout the Study Period, by Treatment Group

Adverse Event	No. (%)	
	Placebo (n = 21)	Dupilumab (n = 19)
Injection site reaction	0 (0.0)	0 (0.0)
Conjunctivitis	2 (9.5)	0 (0.0)
Bacterial pneumonia	1 (4.8)	2 (10.5)
Herpes viral infection	0 (0.0)	0 (0.0)
Eosinophilia[a]	1 (4.8)	5 (26.3)
Hyper-eosinophilic syndrome	0 (0.0)	0 (0.0)
Other infections	2 (9.5)	4 (21.1)
Cumulative	6	11

Other infections included *Clostridioides difficile* infection (1), bacteremia (2), urinary tract infection (2), and oral candidiasis (1).

[a]Eosinophilia was defined as an absolute eosinophil count >0.6 k/μL at ≥1 measurement throughout the study period. Difference between treatment groups was not statistically significant with Fisher exact $P = .09$.

Table 3. Primary and Key Secondary Endpoints, by Treatment Group

Endpoint	Placebo (n = 21)	Dupilumab (n = 19)	OR or HR (95% CI)	*P* Value
Proportion of patients alive and free of mechanical ventilation by day 28	18 (85.7)	15 (78.9)	Unadjusted OR: 1.60 (.31–8.30)	.57
			Adjusted OR: 2.45 (.40–15.10)	.34
Proportion of patients alive and free of mechanical ventilation by day 60	16 (76.2)	17 (89.5)	Unadjusted OR: 0.38 (.06–2.22)	.28
			Adjusted OR: 0.44 (.07–2.96)	.40
Mortality by day 28	3 (14.3)	1 (5.3)	Unadjusted HR: 0.35 (.04–3.32)	.36
			Adjusted HR: 0.06 (.003–1.59)	.09
Mortality by day 60	5 (23.8)	2 (10.5)	Unadjusted HR: 0.40 (.08–2.05)	.27
			Adjusted HR: 0.05 (.004–.72)	.03

Primary endpoint was ventilator-free survival by day 28. Secondary endpoints were ventilator-free survival by day 60, mortality by day 60, and mortality by day 28. Proportions are listed as No. (%). The differences in the ventilator-free survival proportions were evaluated using logistic regression, adjusted for sex. Differences in mortality risk were evaluated in the Cox regression, adjusted for sex and time-varying mechanical ventilation.

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

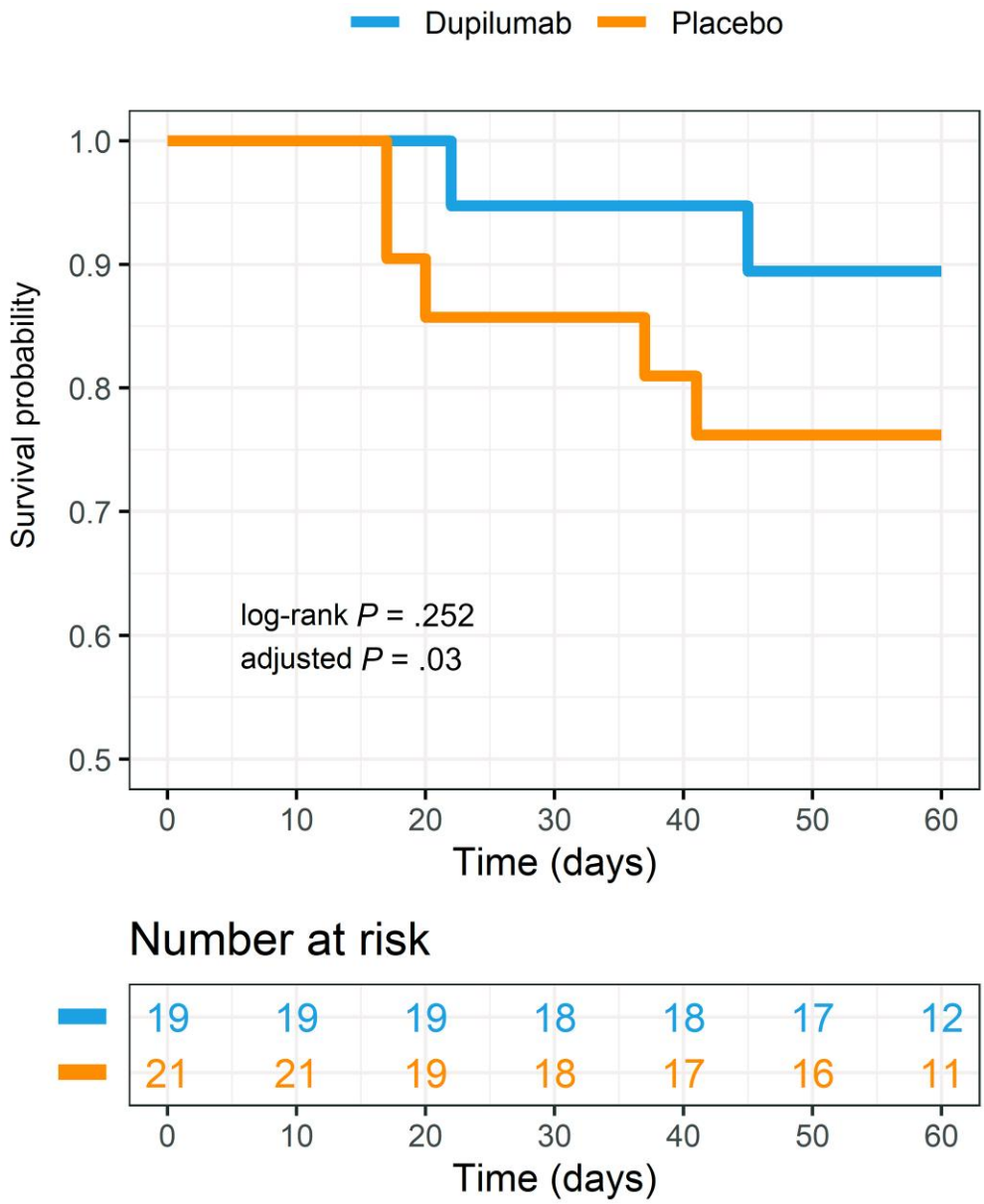

Figure 1. Kaplan-Meier survival curves depicting 60-day mortality between the 2 treatment groups. Adjusted *P* value indicative of adjustment for sex and time-varying ventilation in the Cox regression. Patient study visits occurred within an allotted range of exact study days, and therefore the number at risk in the table is representative of patient data availability up until those exact days (ie, if study visit was conducted on day 59 and no event had occurred, then the subject was included in the at-risk pool up until day 59 but not in that for day 60).

group compared to placebo ($P = .08$, Wilcoxon rank-sum test; Supplementary Figure 6). Additionally, there was a trend toward decreased levels of YKL40 in the dupilumab group compared to placebo by day 14 ($P = .26$, Wilcoxon rank-sum test; Supplementary Figure 6).

There was no statistically significant difference in baseline N-protein levels in the dupilumab group compared to the placebo group (median, 671 ng/mL vs 580 ng/mL, respectively; $P = .75$ by Wilcoxon rank-sum test). When comparing the top quartile vs the bottom 3 quartiles (ie, bottom 75th percentile) of baseline N-protein level within each treatment group, we found significant survival difference among the 4 groups (log-rank $P = .022$; Supplementary Figure 7). The 60-day mortality risk for those in the top quartile of baseline N-protein was 3.8 times of those in the bottom 3 quartiles after adjusting for treatment group, remdesivir use, and monoclonal antibody use (95% CI, .78–18.7; $P = .098$). N-protein levels in log-scale declined significantly from baseline to day 14 levels ($P < .0001$); however, no difference was found in the rate of decline between the 2 treatment groups ($P = .17$).

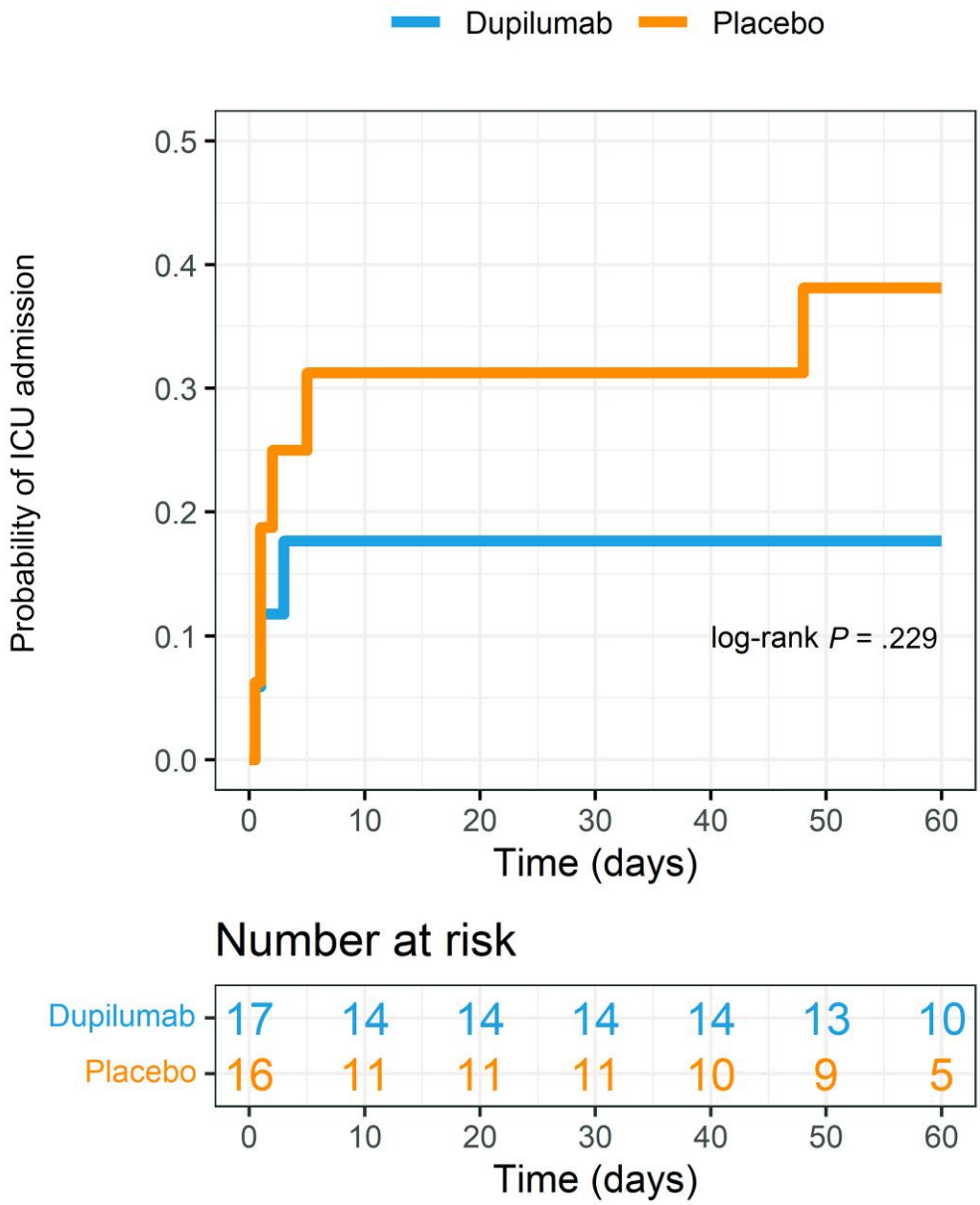

Figure 2. Kaplan-Meier curve depicting need for escalation to intensive care over the 60-day study period. Patients already admitted to the intensive care unit on day of enrollment (n = 7) were excluded from analysis. Patient study visits occurred within an allotted range of exact study days and therefore the number at risk in the table is representative of patient data availability up until those exact days (ie, if study visit was conducted on day 59 and no event had occurred, then the subject was included in the at-risk pool up until day 59 but not in that for day 60).

DISCUSSION

In this randomized double-blind, placebo-controlled trial, although there was no difference between study groups regarding the primary endpoint of 28-day ventilator-free survival, the secondary endpoint of increased 60-day survival in the dupilumab group was achieved. Additionally, there were no safety signals seen with dupilumab use.

Although most deaths occurred in the placebo arm (5 of 21 subjects) compared to dupilumab (2 of 19 subjects), the overall mortality of subjects enrolled in this study (17.5%) was higher than expected, suggesting enrollment of a population with relatively higher disease severity. ICU mortality was 20% in the dupilumab group vs 36% in placebo, and ventilator mortality was 50% in the dupilumab group compared to 100% in placebo. Severity of illness seen in our study reflected that enrollment occurred during the Delta surge and that the majority of those enrolled were unvaccinated, consistent with national data at the time [25]. For example, the National Hospital Care Survey data from the US Centers for Disease Control and Prevention showed 11.9%–13.1% in-hospital mortality in select hospitals

throughout the US during the month of August 2021 with ventilatory mortality rates ranging from 47.9% to 74.1%, a time period during which this study enrolled subjects [26]. Furthermore, baseline N-protein levels were the same between the 2 groups and comparable to baseline N-protein levels of patients enrolled in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-3 trials [27]. As high N-protein levels are predictive of COVID-19 disease progression, a finding also demonstrated in this study, this suggests that patients enrolled in our study were of comparable baseline disease severity [27].

The detection of survival and mechanical ventilation differences at 60 days rather than at 28 days is consistent with reports of immunologic dysfunction from COVID-19 extending out to 8 months for mild to moderate COVID-19, with deaths from severe COVID-19 occurring out to 12 months [28, 29]. Although the small size of our study limits broad conclusions about the mortality benefit of dupilumab, these findings combined support a late clinical benefit of blockade of a type 2 immune process in COVID-19. The response to dupilumab in asthma is also protracted, with improvements in forced expiratory volume in 1 second (FEV_1) first being observed 2 weeks after initiation of treatment [30]. Thus, the time to clinical effect of dupilumab in the acute COVID-19 setting may have limited our ability to see early clinical differences between the treatment groups. For example, subjects in our study who ultimately required mechanical ventilation did so within the first 8 days of the study, some within 1-2 days of enrollment, during a time in which drug concentration may have been lower, particularly in the context of a rapidly evolving clinical process.

Although biomarker trends seen in both groups were likely influenced by the steroids that almost all subjects received, we did see a reduction of the type 2 immune markers YKL40 and eotaxin-3 in the dupilumab arm when compared to the placebo arm, indicative of the IL-4Rα blockade with inhibition of downstream mediators of the type 2 immune response. Increased peripheral eosinophil counts in the dupilumab group occurred by day 14, consistent with previous observations of dupilumab use in patients with atopic disease, likely due to decreased eosinophil uptake in tissue [30, 31]. While we did not see IgE decrease at 2 weeks of dupilumab treatment, this is consistent with prior studies showing gradual decline of IgE levels compared to other biomarkers after dupilumab initiation [31]. We also saw reduction in MCP-1, a potent chemoattractant molecule of monocytes/macrophages, in the dupilumab group, high levels of which have been associated with COVID-19 disease severity [32, 33]. Last, although recent invitro studies have shown that high IL-13 levels are associated with reduction in angiotensin-converting enzyme 2 receptor expression and decreased SARS-CoV-2 viral load, this is inconsistent with our study, which shows similar rates of decline in N-protein levels in those who received IL-4Rα blockade compared to placebo [34].

This was a small study, designed as an early-phase trial to assess the relative performance of dupilumab vs placebo in hospitalized patients with COVID-19. The study had several limitations. These included the lack of achievement of the primary endpoint of proportion of patients alive and free of mechanical ventilation at day 28, and the wide CIs in the survival benefit of dupilumab at day 60. The insignificant results were more likely due to small sample size. Additional limitations included unequal sex distribution between groups (also due to small sample size), that patients were almost exclusively infected by the Delta variant of SARS-CoV-2, and a higher-than-expected overall mortality rate.

Nevertheless, for the purpose of hypothesis generating, this early-phase study had several notable strengths including having as a foundation the preclinical data on the mechanism of disease exacerbation by IL-13 in COVID-19, originality in the study of type 2 immune inhibition, the use of a prospective placebo-controlled randomized and double-blind design, and demonstration of the safety of dupilumab. Importantly, there was evidence for mortality reduction and reduced ICU escalation with dupilumab use as we had predicted from animal models and retrospective human studies, despite sample size limitations. In light of the ongoing need for additional therapies for COVID-19–associated respiratory failure and the modest clinical benefits seen with other antiviral and immunotherapies currently being used, the results of this study advance dupilumab as a promising treatment option for people hospitalized with COVID-19.

Supplementary Data

Supplementary materials are available at *Open Forum 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

Acknowledgments. We thank the patients who consented to enroll in this study in an effort to help others with coronavirus disease 2019 (COVID-19), and the nursing staff and providers on the COVID-19 units for their assistance with the trial. We thank Jennifer White for institutional review board (IRB) protocol preparation; Amy Warren and Lori Elder for IRB protocol preparation and Investigational New Drug (IND) preparation/submission; and the staff at the investigational drug pharmacy at the University of Virginia (UVA). We also thank Mary Young and William Petri and the Biorepository and Tissue Research Facility at UVA who collected, organized, and analyzed research samples. Last, we thank Helene Highbarger, Perrine Lallemand, and Jeroen Highbarger of the Virus Isolation and Serology Laboratory, Frederick National Laboratory (FNL), and Ashley McCormack of the Laboratory of Human Retrovirology and Immunoinformatics, FNL, for their technical support on the nucleocapsid protein project.

Patient consent. Approval for this study was obtained through the US Food and Drug Administration IND application in April 2021. Approval through the UVA IRB was obtained in June 2021. The trial is registered

at ClinicalTrials.gov (NCT04920916). Consent forms were IRB-approved. Each participant was approached with written consent and provided a verbal explanation of the study purposes, study procedures, potential risks of the study, and their rights as research participants, which was suited to each participant's comprehension. Participants had the opportunity to carefully review the written consent form, discuss with family or surrogates, and ask questions prior to signing.

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Financial support. This work was supported by grants from the Virginia Biosciences Health Research Corporation; by PBM C19 Research (a COVID-19 research entity of PBM Capital, a local healthcare-focused investment firm); by the Henske Family Foundation (a local foundation); and by the National Institutes of Health (NIH) (grant/award numbers R01 AI124214 and T32 AI007496 to A. D., T32 DK072922/TL1 DK132771 to J. S., and UL1TR003015 and KL2TR003016 to J. M. S. and J. Z. M.). The nucleocapsid protein project has been funded in whole or in part with federal funds from the National Cancer Institute, NIH (contract number 75N91019D00024).

Potential conflicts of interest. The authors: No reported conflicts of interest.

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.

References

1. Macedo A, Gonçalves N, Febra C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol **2021**; 57:14–21.
2. Gray WK, Navaratnam AV, Day J, et al. Variability in COVID-19 in-hospital mortality rates between national health service trusts and regions in England: a national observational study for the getting it right first time programme. EClinicalMedicine **2021**; 35:100859.
3. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med **2021**; 384:693–704.
4. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med **2020**; 383:1813–26.
5. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med **2021**; 384:1503–16.
6. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med **2021**; 384:1491–502.
7. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med **2021**; 384:795–807.
8. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med **2021**; 19:1–12.
9. Donlan AN, Sutherland TE, Marie C, et al. IL-13 is a driver of COVID-19 severity. JCI Insight **2021**; 6:e150107.
10. Wynn TA. IL-13 effector functions. Annu Rev Immunol **2003**; 21:425–56.
11. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature **2020**; 584:463–9.
12. Liang Y, Ge Y, Sun J. IL-33 in COVID-19: friend or foe? Cell Mol Immunol **2021**; 18:1602–4.
13. Thibodeaux Q, Smith MP, Ly K, Beck K, Liao W, Bhutani T. A review of dupilumab in the treatment of atopic diseases. Hum Vaccin Immunother **2019**; 15: 2129–39.
14. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet **2016**; 388:31–44.
15. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet **2017**; 389:2287–303.
16. Geng B, Bachert C, Busse WW, et al. Respiratory infections and anti-infective medication use from phase 3 dupilumab respiratory studies. J Allergy Clin Immunol Pract **2022**; 10:732–41.
17. Ungar B, Glickman JW, Golant AK, et al. COVID-19 symptoms are attenuated in moderate-to-severe atopic dermatitis patients treated with dupilumab. J Allergy Clin Immunol Pract **2022**; 10:134–42.
18. Mahroum N, Damiani G, Watad A, et al. Higher rates of COVID-19 but less severe infections reported for patients on dupilumab: a big data analysis of the World Health Organization VigiBase. Eur Rev Med Pharmacol Sci **2021**; 25: 5865–70.
19. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. **2020**. Available at: https://covid19treatmentguidelines.nih.gov. Accessed 1 January 2021.
20. US Food and Drug Administration. Dupixent package insert. **2020**. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed 1 January 2021.
21. Shan D, Johnson JM, Fernandes SC, et al. N-protein presents early in blood, dried blood and saliva during asymptomatic and symptomatic SARS-CoV-2 infection. Nat Commun **2021**; 12:1931.
22. World Health Organization. Tracking SARS-CoV-2 variants. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed 1 January 2021.
23. Baker DJ, Aydin A, Le-Viet T, et al. CoronaHiT: high-throughput sequencing of SARS-CoV-2 genomes. Genome Med **2021**; 13:21.
24. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature **2020**; 584:430–6.
25. Centers for Disease Control and Prevention. Rates of laboratory-confirmed COVID-19 hospitalizations by vaccination status. Available at: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination. Accessed 15 January 2022.
26. Centers for Disease Control and Prevention. In-hospital mortality among hospital confirmed COVID-19 encounters by week from selected hospitals. Available at: https://www.cdc.gov/nchs/covid19/nhcs/hospital-mortality-by-week.htm. Accessed 15 January 2022.
27. Lundgren JD, Grund B, Barkauskas CE, et al. Responses to a neutralizing monoclonal antibody for hospitalized patients with COVID-19 according to baseline antibody and antigen levels. Ann Intern Med **2022**; 175:234–43.
28. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol **2022**; 23:210–6.
29. Mainous AG 3rd, Rooks BJ, Wu V, Orlando FA. COVID-19 post-acute sequelae among adults: 12 month mortality risk. Front Med **2021**; 8:778434.
30. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med **2018**; 378:2475–85.
31. Hamilton JD, Harel S, Swanson BN, et al. Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases. Clin Exp Allergy **2021**; 51:915–31.
32. Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interf Cytokine Res **2009**; 29:313–26.
33. Chen Y, Wang J, Liu C, et al. IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. Mol Med **2020**; 26:97.
34. Morrison CB, Edwards CE, Shaffer KM, et al. SARS-CoV-2 infection of airway cells causes intense viral and cell shedding, two spreading mechanisms affected by IL-13. Proc Natl Acad Sci U S A **2022**; 119:1–12.