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Anakinra or high-dose corticosteroids in COVID-19 pneumonia patients who deteriorate on low-dose dexamethasone: an observational study of comparative effectiveness

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Abstract

Objective: To assess whether escalating to high-dose corticosteroids or anakinra compared to continuing low-dose corticosteroids reduced mortality in patients with severe coronavirus disease 2019 (COVID-19) whose respiratory function deteriorated while receiving dexamethasone 6mg daily (DEXA6).

Methods: We conducted a retrospective cohort study between 3/1-12/31/2020 of hospitalized patients with confirmed COVID-19 pneumonia. In-hospital death was analyzed using logistic regression with inverse probability of treatment weighting of receiving anakinra, high-dose corticosteroid (dexamethasone >10mg daily) or remaining on low-dose corticosteroids on the day of first respiratory deterioration.

Results: We analyzed 6,671 patients whose respiratory status deteriorated while receiving DEXA6 for COVID-19 pneumonia, of whom 6265 stayed on low-dose corticosteroids, 232 were escalated to high-dose corticosteroids and 174 to anakinra in addition to corticosteroids. The propensity score-adjusted odds of death were higher in the anakinra (odds ratio [OR]=1.76, 95% CI=1.13-2.72) and high-dose corticosteroid groups (OR=1.53, 95% CI=1.14-2.07) compared with those who continued low-dose corticosteroids on the day of respiratory deterioration. The odds of hospital-acquired infections were also higher in the anakinra (OR=2.00, 95% CI=1.28-3.11) and high-dose corticosteroid groups (OR=1.43, 95% CI=1.00-2.04) compared with low-dose corticosteroid group.

Conclusion: Our findings do not support escalating patients with COVID-19 pneumonia who deteriorate on low-dose corticosteroids to high-dose corticosteroids or anakinra.

Keywords: corticosteroids; anakinra; COVID-19; mortality; infections

Introduction

Some patients with coronavirus disease 2019 (COVID-19) pneumonia display clinical and laboratory signs of a hyperinflammatory response including markedly elevated serum C-reactive protein (CRP) and ferritin levels, followed by rapid respiratory status decompensation and progression to multisystem organ failure. These observations led to use of varying doses of corticosteroids and targeted anti-cytokine agents, including anakinra, an anti-interleukin (IL)-1 treatment, early in the pandemic.

After a large, open label randomized controlled trial (RCT) showed a significantly lower 28-day mortality with 6mg dexamethasone daily (DEXA6) daily for up to 10 days compared to usual care (23.3% vs 26.2%) (Recovery Collaborative Group et al., 2021) in COVID-19 patients requiring supplemental oxygen, DEXA6 rapidly became standard of care. However, a sizeable proportion of patients' respiratory status deteriorate while treated with DEXA6. It is unknown whether intensifying immunosuppression with anakinra or high-dose corticosteroids improve survival compared to completing the DEXA6 protocol and practice remains varied. To our knowledge, these questions have not been addressed in RCTs or observational studies.

Evidence supporting the use of higher dose corticosteroids or anakinra compared to DEXA6 alone in newly hospitalized patients with COVID-19 pneumonia is inconclusive. A recently published RCT comparing dexamethasone 12mg (DEXA12) to DEXA6 in addition to oxygen support strategies found no difference in mortality between treatment groups regardless of severity of respiratory status at randomization (Bouadma et al., 2022). However, a pre-planned Bayesian analyses of a traditional RCT suggested that DEXA12 may be beneficial in patients with more severe respiratory impairment compared to DEXA6, although the difference

in mortality did not reach statistical significance in the primary analyses (Covid Steroid Trial Group et al., 2021).

In a randomized, open label adaptive platform trial (REMAP-CAP, 2021), anakinra plus corticosteroids had no effect on survival (REMAP-CAP, 2021) compared to patients predominantly treated with anti-IL6 inhibitors plus corticosteroids. In this trial, a high proportion of patients were mechanically ventilated at treatment start (37% in anakinra-treated patients and 32% in the comparison treatment arms) (National Institutes of Health, 2021). In contrast, a double blind RCT in patients with moderate respiratory impairment, anakinra plus DEXA6 compared to DEXA6 alone (SAVE-MORE) significantly reduced mortality (3.2% and 6.9%, respectively) and clinical worsening (Kyriazopoulou, Poulakou, et al., 2021).

The purpose of this study was to compare the effectiveness and safety of either intensifying immunosuppression or continuing the DEXA6 protocol in patients hospitalized for COVID-19 pneumonia who were not responding to DEXA6. To formulate this research question, we engaged with a panel of clinician stakeholders, consisting of hospitalists, intensivists, infectious disease and immunology specialists, who wanted to know whether escalating to high-dose corticosteroids or adding anakinra would be associated with lower in-hospital mortality or an increased risk of infections in patients whose respiratory status worsened or did not improve after starting DEXA6. Using granular electronic health record data from a large, population-based sample of patients who received care at one of 36 hospitals in the Kaiser Permanente Southern California (KPSC) and Northern California (KPNC) regions, we performed

a retrospective, observational study to generate real-world evidence to address these clinically important questions.

Methods

We performed this retrospective cohort study after receiving approval from the KPSC Institutional Review Board (#12396).

Study population. KPSC and KPNC provide care for >9 million members and operate 36 medical centers across California. To assemble the study cohort, we identified adults (aged ≥18 years) admitted between 3/1/2020-12/31/2020 with a positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction result in the 3 weeks before admission or during the hospitalization who met the following additional inclusion criteria: 1) received dexamethasone 6mg or equivalent dose of another corticosteroid, 2) required oxygen supplementation 12 hours before or after first dose of dexamethasone administration and 3) experienced respiratory deterioration after the first 6mg dose of dexamethasone (see below for definition) or had moderate, severe, or very severe respiratory impairment that persisted for 24 hours or more after first 6mg dose of dexamethasone (referred to as persistence hereafter). Exclusion criteria were as follows: 1) admission for labor and delivery; 2) not receiving corticosteroid treatment; 3) first corticosteroid dose was less than or greater than 6mg of dexamethasone or equivalent; 4) "do not intubate" (DNI) orders, comfort care status prior to initiation of dexamethasone; 5) no supplemental oxygen required within 12 hours of starting 6mg of dexamethasone; 6) not meeting our definition for respiratory deterioration or persistence; 7) receiving anakinra before starting dexamethasone 6mg; 8) escalation to anakinra or high-dose corticosteroids (>10mg of dexamethasone or equivalent) prior to

meeting our definition of respiratory status deterioration or persistence; or 9) not meeting our definition of anakinra use or high- or low-dose corticosteroid use within 48 hours of respiratory status deterioration or persistence. To minimize immortal time bias, an additional exclusion criterion was receiving the first dose of anakinra or high-dose corticosteroids within 24 hours of the first dose of dexamethasone 6mg in those patients with persistently moderate, severe or very severe respiratory impairment (**Figure 1**).

Data collection. We retrieved data from the KPSC Research Data Warehouse and the KPNC Virtual Data Warehouse on exposures, outcomes and covariates of interest, the latter of which included patient demographic characteristics, comorbidity burden as reflected by the Elixhauser comorbidity score, corticosteroid use in the 12 months prior to admission, body mass index (BMI), inpatient and emergency department utilization in the year prior to admission, other inpatient treatments (including anakinra, tocilizumab, convalescent plasma and hemodialysis) and selected inflammatory markers, including D-dimer and c-reactive protein values. We also calculated values for the Epic Deterioration Index (DI), a score based on inpatient vital signs and laboratory values that has been shown to predict hospital mortality in hospitalized patients with and without COVID-19 (Singh et al., 2021).

Respiratory status deterioration or persistence. To define respiratory status deterioration or persistence we categorized patients according to the intensity of respiratory support they required. The categories included six tiers: mild impairment A (>0--2 L/min via nasal cannula, mild impairment B (>2-4L/min via nasal cannula), mild impairment C (>4-6L via nasal cannula or <40% FiO2 via face mask), moderate (6-15 L/min via nasal cannula or 40-60% FiO2 via mask), severe (>15 L/min via nasal cannula or high flow system, >60% FiO2 via mask or non-invasive

ventilation), or very severe (invasive mechanical ventilation). We defined respiratory deterioration as the first progression from one level of respiratory support to a higher level of support for any duration of time and persistence as remaining in the moderate, severe or very severe group for at least 24 hours after initiation of DEXA6.

Corticosteroid Groups following respiratory deterioration or persistence. Low-dose corticosteroid use was defined as a total daily dose of 6-10mg of dexamethasone or equivalent doses of other corticosteroids. High-dose corticosteroid use was defined as a total daily dose of >10mg of dexamethasone or equivalent doses of other corticosteroids. We did not distinguish between oral or intravenous administration or whether doses were divided into two or more daily doses. Groups were defined based on the highest prescribed corticosteroid dose within 48 hours after respiratory deterioration or persistence.

Anakinra use following respiratory deterioration or persistence. Anakinra is a short-acting IL-1 inhibitor that is prescribed in combination with corticosteroids in the treatment of cytokine storm. It can be administered subcutaneously or intravenously although in our system the intravenous formulation was not available at the time of this study. Doses are adjusted in patients with renal failure. To account for variation in anakinra dosing based on clinicians preferences for high or low doses and to eliminate transient use that would not be expected to improve COVID-19-related cytokine storm, anakinra use following respiratory deterioration or persistence was defined as follows: 1) five or more consecutive days of treatment regardless of daily dose; 2) at least 3 consecutive days of high-dose anakinra (>=400mg per day or >=200mg per day for those with an estimated GFR of <80mL/min); or 3) at least one day of anakinra at any dose and discontinuation due to death.

Outcomes. The primary outcome was in-hospital death. Secondary outcomes were hospital length of stay, total duration of mechanical ventilation and infectious complications. We assessed the frequency of all hospital acquired infections as well as specific infections (bloodstream, urinary tract, soft tissue and pulmonary infections other than COVID-19) identified by using ICD-10 codes (**Appendix Table 1**) entered by professional medical coders on discharge.

Statistical analysis. We described continuous and categorical variables using means and standard deviations and counts and percentages, respectively. To reduce imbalance in demographic and clinical characteristics among the treatment groups, we fit propensity score models using multinomial regression to estimate the probability of receiving each treatment as a function of predictor variables that were plausibly associated with both exposure and outcome.(Imbens GW, 2000) Covariates included age (continuous), sex (male/female), race and ethnicity (categorical: white, Black, Hispanic, Asian or other/unknown), smoking (categorical: never, former, current), body mass index (categorical, normal/underweight, overweight, moderately obese or severely obese), episodes of inpatient, emergency department and urgent care utilization in the year prior to admission (continuous); Elixhauser comorbidity score (continuous), Epic DI (continuous), respiratory status (categorical: mild, moderate, severe or very severe), treatment with remdesivir, dialysis or convalescent plasma on or prior to day of deterioration/persistence (yes/no); steroid use 1 year prior to admission (yes/no); and month of admission (categorical). Patients with unknown BMI were not included in multivariable models (n=112 who continued 6mg of dexamethasone and n=2 in the high-dose corticosteroid escalation group).

We analyzed in-hospital mortality by fitting logistic regression models with inverse probability of treatment weights based on propensity scores. We used robust sandwich estimators to obtain appropriate standard errors of treatment effects, because the weighting induced a within-subject correlation in outcomes and an inflated sample size (Hernan, Brumback, & Robins, 2000; van der Wal WM, 2011; Xu et al., 2010). Propensity score adjusted odds ratios (OR) were reported with continuing low-dose corticosteroids following first deterioration/persistence as the reference group. To examine the effect of CRP levels at the time of deterioration/persistence, we conducted sensitivity analyses restricted to those patients with CRP values available within 24 hours prior to deterioration/persistence where the models described above were additionally adjusted for the highest CRP value within 24 hours of the time of deterioration/persistence.

All analyses were conducted using SAS 9.4 (Cary, NC). Two-tailed tests were used with the threshold of 0.05 for statistical significance.

Results

Among 28,035 patients with COVID-19 admitted between 3/1/2020-12/31/2020, 21,364 were excluded for a final study population of 6,671, of whom 2667 were from KPSC and 4004 were from KPNC. The main reasons for exclusion were lack of corticosteroid use; receiving high rather than low corticosteroid dose at initiation; oxygen requirements that did not worsen or remain persistently poor while on low-dose corticosteroids; or no supplemental oxygen requirements within 48 hours of low-dose corticosteroid initiation (**Figure 1**).

Most of the patients whose respiratory status deteriorated or remained persistently poor while being treated with low-dose corticosteroids remained on low-dose corticosteroids (n=6265, 93.9%), while 232 (3.5%) patients were escalated to high-dose corticosteroids and 174 (2.6%) were started on anakinra within 48 hours of the time of deterioration (**Table 1**). All anakinra-treated patients continued to receive concomitant corticosteroids. Following respiratory status deterioration, the median daily dose of dexamethasone or equivalent was 6 mg (interquartile range, IQR 6-6mg) in the low-dose group, 12mg (IQR 7.5-20mg) in the high-dose group and 6mg (IQR 6-15mg) in the anakinra group. The median duration of corticosteroid treatment was 6 days (IQR 4-9) in the low-dose group, 9 days (IQR 6-14) in the high-dose group and 9 days (IQR 6-14) in the anakinra group. The median duration of anakinra use was 8 days (IQR 5-10) and the median anakinra dose was 400 mg (400-400). Of the patients in the low-dose corticosteroid group, 10.3% (n=645) were later switched to high-dose corticosteroids (n=541) or anakinra (n=104) after a median of 9 days.

Patients escalated to high-dose corticosteroids had a greater comorbidity burden, higher EPIC DI scores and more severe respiratory impairment (>15L/min of oxygen or

mechanical ventilation) at the time of deterioration compared with patients who remained on low-dose corticosteroids (**Table 1**). Patients who escalated to anakinra treatment had slightly higher EPIC DI scores and CRP levels but similar severity of respiratory impairment at the time of deterioration and were more likely to be males and to have received convalescent plasma prior to deterioration compared with patients who remained on low-dose corticosteroids. All three groups were similar in age, BMI, race and ethnicity, smoking behavior, health care utilization in the 12 months prior to admission, and d-dimer levels at the time of deterioration. Treatment with remdesivir prior to deterioration was common while hemodialysis was rare, and neither differed significantly between groups.

Crude in-hospital mortality was higher among patients who received high-dose corticosteroids (41.9%, 95% CI 35.5-48.3%) or anakinra (32.8%, 95% CI 25.8-39.7%) compared with the low-dose group (26.2%, 95%CI 25.1-27.3%). These differences remained significant in the propensity score-adjusted models for both high-dose corticosteroids (OR= 1.53, 95% CI 1.14-2.07) and anakinra (OR= 1.76, 95% CI 1.13-2.72; **Table 2**). The average length of hospital stay was significantly longer in the anakinra and high-dose corticosteroid groups compared to the low-dose group in propensity score-adjusted models (4.8 and 2.3 days respectively; **Table 2**). There was no significant difference in ventilator days in either the high-dose or anakinra group compared to the low dose group following propensity score-adjustment (**Table 2**).

Treatment with anakinra (PS-adjusted OR= 2.00, 95% CI 1.28-3.11) or high-dose corticosteroids (PS-adjusted OR= 1.43, 95% CI 1.00-2.04) was associated with higher odds of hospital-acquired infections in crude and propensity-score adjusted models compared to continuing low-dose corticosteroids at the time of deterioration (**Table 2**). Bloodstream

infections and non-COVID-19 pneumonia were the most common hospital-acquired infections across all 3 groups. Anakinra use was associated with a significantly increased odds of bloodstream infections and hospital-acquired pneumonias in propensity score-adjusted models. High-dose corticosteroid treatment was associated with a significantly increased odds of bloodstream infections (**Table 2**).

The results of sensitivity analyses in which we adjusted for the highest CRP values within 24 hours of deterioration among the 4896 (73.4%) with such available CRP values yielded similar results. In these analyses, treatment with anakinra (adjusted OR= 1.94, 95% CI 1.22-3.07) or high-dose corticosteroids (adjusted OR= 1.71, 95% CI 1.20-2.44) was associated with higher odds of in-hospital mortality compared to continuing low-dose corticosteroids at the time of deterioration.

Discussion

We found that escalating immunosuppression with high-dose corticosteroids or anakinra in COVID-19 pneumonia patients whose respiratory function deteriorated or remained persistently poor while being treated with DEXA6 was not associated with reduced mortality. Both anakinra and high-dose corticosteroid treatment initiation on the day of deterioration were associated with higher odds of in-hospital death and hospital-acquired infections compared to those who remained on DEXA6. These findings add to the growing literature supporting DEXA6 as the dose of choice for COVID-19 pneumonia patients requiring supplemental oxygen (National Institutes of Health, 2022) and do not support intensifying immunosuppression in patients whose respiratory status deteriorates on DEXA6.

DEXA6 presumably improves survival in COVID-19 pneumonia patients by dampening lung inflammation as well as systemic inflammation in the subset of patients that exhibit signs and symptoms of cytokine storm (Mehta et al., 2020). Since early in the pandemic, many clinicians, including those at our hospitals (Langer-Gould et al., 2020), have treated patients with severe COVID pneumonia, particularly those with in-hospital respiratory status deterioration and rising inflammatory markers like CRP and ferritin, with high-dose corticosteroids, anakinra or tocilizumab, albeit with mixed results. Once DEXA6 became the standard of care, a common clinical challenge became how best to treat those that deteriorate or don't improve on this low dose of corticosteroids. Without evidence to guide them, some clinicians opted to intensify immunosuppression. The findings from this study, however, indicate that intensifying immunosuppression with high-dose corticosteroids or anakinra in these patients, does not lead to improved survival compared to continuing the DEXA6 protocol

for a full 10 days. We speculate that the lack of improvement we observed reflects the multiple non-hyperinflammatory pathophysiological processes that can lead to respiratory decompensation including direct viral damage, hypercoagulability, and/or secondary infections.

Our findings do not exclude the possibility that initiation of anakinra upon hospitalization in COVID-19 patients *without* severe respiratory impairment is beneficial as indicated by previous studies (Kyriazopoulou, Huet, et al., 2021; Kyriazopoulou, Poulakou, et al., 2021). A meta-analysis of primarily observational studies suggested that anakinra may be effective when administered to COVID-19 pneumonia patients early in the disease course and in those with elevated CRP (>100), ferritin or soluble urokinase plasminogen activator receptor (SuPAR) levels (Kyriazopoulou, Huet, et al., 2021). These findings led to a double blinded RCT of anakinra plus DEXA6 compared to DEXA6 alone (Kyriazopoulou, Poulakou, et al., 2021) initiated within 2-3 days of hospitalization in COVID-19 pneumonia patients without very severe respiratory impairment and with elevated SuPAR levels and median CRP levels of 50 (Kyriazopoulou, Poulakou, et al., 2021). This RCT, the SAVE-MORE trial, showed overall low mortality rates, but a significant reduction in mortality in the anakinra-treated group compared to DEXA6 alone (3.2% and 6.9%, respectively). The two open-label RCTs (CORIMUNO-19 Collaborative group, 2021; REMAP-CAP, 2021) that reported no difference in survival in anakinra-treated patients compared to standard of care (corticosteroids and anti-IL-6 treatments in one trial and supportive care in the other) both included a large fraction of patients with severe respiratory impairment and populations with much higher mortality rates, as was the case in this observational study, in contrast to the SAVE-MORE trial (Kyriazopoulou, Poulakou, et al., 2021). We excluded 207 patients that were started on anakinra following

DEXA6 initiation but prior to meeting our definition of respiratory status deterioration or persistence. This raises the possibility that these patients were escalated due to rising inflammatory markers, as we previously recommended (Langer-Gould et al., 2020). Whether anakinra reduces mortality without increasing the risk of hospital-acquired infections in patients with early or mild COVID-19 pneumonia is not addressed in the current study. Thus, the results of these RCTs as well as the findings reported herein and in our previous observational study (Langer-Gould et al., 2020) could be viewed as consistent if early administration of anakinra is indeed critical.

We also cannot exclude the possibility that escalating immunosuppression with anakinra or high-dose corticosteroids in COVID-19 pneumonia patients who do not respond to DEXA6 is harmful. That anakinra and high dose corticosteroid treatments can increase the risk of infections, as we observed, is an anticipated adverse event. It is plausible that either through increasing the risk of secondary infections or augmenting viral damage by inhibiting immune-mediated viral clearance mechanisms, intensifying immunosuppression later in the disease course increases mortality. Alternatively, our findings of increased odds of in-hospital infections and mortality, particularly in anakinra-treated patients, may be explained by unmeasured confounders, the main limitation of this study. Such potential unmeasured confounders include rising inflammatory markers and laboratory or other indices of (multi) organ failure. While we did not find any decreased odds of death with intensified immunosuppression, it is very possible that residual confounding by indication with those patients judged to be at highest risk of death treated most aggressively explains the increased odds of mortality among anakinra or high-dose corticosteroid treated patients we observed.

Other limitations of this study are the relatively small number of patients escalated to high-dose corticosteroids or anakinra following respiratory status deterioration/persistence, precluding subgroup analyses stratified by severity of respiratory impairment or CRP levels on the day of deterioration. Lastly, whether these results can be extrapolated to vaccinated populations where far fewer patients experience severe respiratory impairment or to the omicron variant, or any future strain, is uncertain.

Strengths of this study include the importance of the question and restricting the analysis to patients who were escalated to high-dose corticosteroids or anakinra only after deteriorating or failing to improve following initiation of DEXA6. This approach minimizes confounding by indication and the influence of potentially unmeasured changes in COVID-19 pneumonia care around the same time DEXA6 became standard of care.

Interpretation

Our findings, taken together with those from previous studies (Bouadma et al., 2022; Covid Steroid Trial Group et al., 2021; Langer-Gould et al., 2022), support DEXA6 for up to 10 days as the dose of choice for COVID-19 pneumonia patients requiring supplemental oxygen (National Institutes of Health, 2022) and do not support intensifying immunosuppression with high-dose corticosteroids or adding anakinra in patients whose respiratory status deteriorates after initiating DEXA6.

Conflicts of Interest/Disclosures: KB has received research support unrelated to this study from Moderna/Pfizer. LCM has received research support unrelated to this study from Boehringer Ingelheim. GJE has received research support unrelated to this study from Astra Zeneca. The other authors have no conflict of interest.

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Ethical Approval Statement: We performed this retrospective cohort study after receiving approval from the KPSC Institutional Review Board (#12396).

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Figure Legend

Figure 1. Consort diagram of cohort derivation

Abbreviations: SARS-CoV2=SARS corona virus 2, KPSC=Kaiser Permanente Southern California, KPNC=Kaiser Permanente Northern California, DEXA6=dexamethasone 6mg daily, DNI=do not intubate, O2=oxygen, Td=time of deterioration/persistence

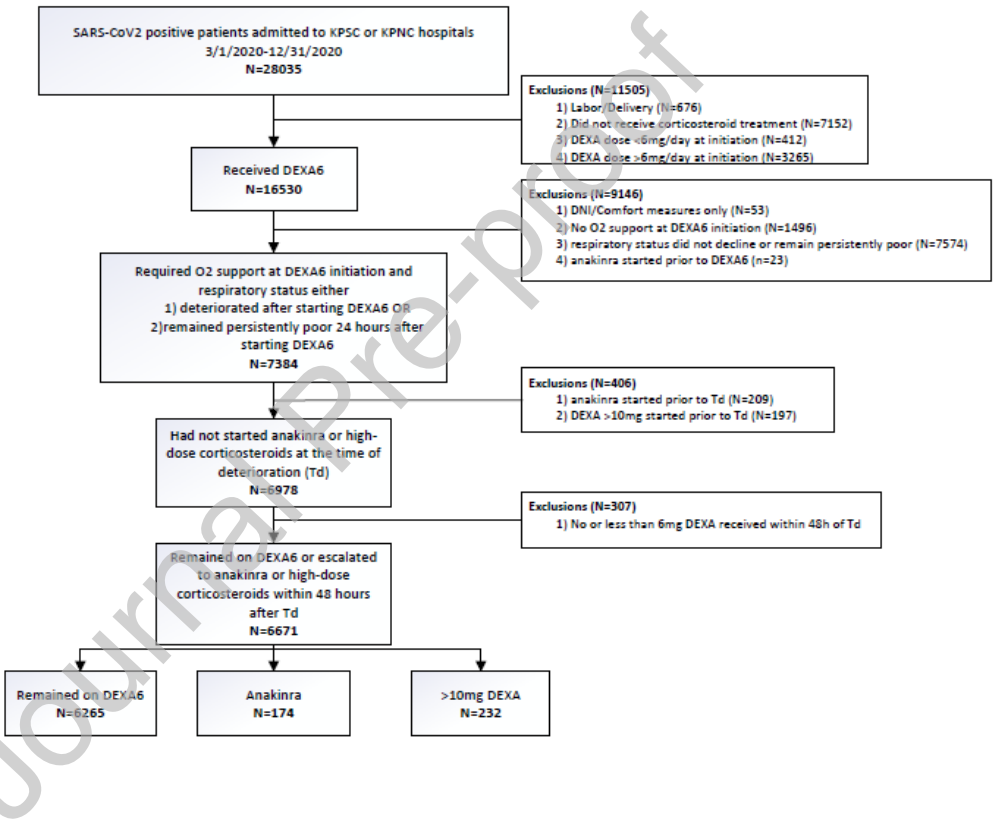

Table 1. Patient Characteristics on Day of Deterioration

	>10mg DEXA (N=232)	Anakinra (N=174)	Remained on DEXA6 (N=6265)	Total (N=6671)
Age, mean (SD), y	61.8 (15.7)	59.9 (15.3)	61.4 (15.3)	61.4 (15.3)
Male gender, n (%)	144 (62.1%)	127 (73.0%)	3825 (61.1%)	4096 (61.4%)
Race and ethnicity, n (%)				
Asian	31 (13.4%)	19 (10.9%)	723 (11.5%)	773 (11.6%)
Black	16 (6.9%)	12 (6.9%)	486 (7.8%)	514 (7.7%)
Hispanic	128 (55.2%)	109 (62.6%)	3540 (56.5%)	3777 (56.6%)
White	45 (19.4%)	23 (13.2%)	1177 (18.8%)	1245 (18.7%)
Other[a]	12 (5.2%)	11 (6.3%)	336 (5.4%)	362 (5.4%)
BMI categories, n (%)				
Underweight	1 (0.4%)	0 (0.0%)	46 (0.7%)	47 (0.7%)
Normal	22 (9.5%)	23 (13.2%)	701 (11.2%)	746 (11.2%)
Overweight	66 (28.4%)	62 (35.6%)	1740 (27.8%)	1868 (28.0%)
Moderate Obese	101 (43.5%)	68 (39.1%)	2678 (42.7%)	2847 (42.7%)
Severe Obese	40 (17.2%)	21 (12.1%)	988 (15.8%)	1049 (15.7%)
Unknown	2 (0.9%)	0 (0.0%)	112 (1.8%)	114 (1.7%)
Smoking, n (%)				
Never/Passive	125 (53.9%)	92 (52.9%)	3441 (54.9%)	3658 (54.8%)
Quit	82 (35.3%)	45 (25.9%)	1806 (28.8%)	1933 (29.0%)
Active	5 (2.2%)	4 (2.3%)	135 (2.2%)	144 (2.2%)
Unknown	20 (8.6%)	33 (19.0%)	883 (14.1%)	936 (14.0%)
Oral corticosteroids in the past 12 months, n (%)	48 (20.7%)	26 (14.9%)	973 (15.5%)	1047 (15.7%)
Elixhauser comorbidities, median (IQR)	5.0 (3.0, 7.0)	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)
Healthcare utilizations in the past 12 months				
Inpatient visit count, n (%)				
0 visit	205 (88.4%)	156 (89.7%)	5604 (89.4%)	5965 (89.4%)
1-2 visits	23 (9.9%)	16 (9.2%)	557 (8.9%)	596 (8.9%)
3 or more visits	4 (1.7%)	2 (1.1%)	104 (1.7%)	110 (1.6%)
Emergency department visit count, n (%)				
0 visit	139 (59.9%)	117 (67.2%)	3933 (62.8%)	4189 (62.8%)
1-2 visits	72 (31.0%)	49 (28.2%)	1922 (30.7%)	2043 (30.6%)
3 or more visits	21 (9.1%)	8 (4.6%)	410 (6.5%)	439 (6.6%)
Urgent care visit count, n (%)				
0 visit	180 (77.6%)	108 (62.1%)	4767 (76.1%)	5055 (75.8%)
1-2 visits	44 (19.0%)	50 (28.7%)	1214 (19.4%)	1308 (19.6%)
3 or more visits	8 (3.4%)	16 (9.2%)	284 (4.5%)	308 (4.6%)
COVID severity on day of deterioration				
Time from DEXA6 initiation to day of deterioriation, median (IQR), d	1.0 (0.8, 1.7)	1.0 (0.8, 1.3)	1.0 (0.9, 1.4)	1.0 (0.9, 1.4)
Epic deterioration index[b], median (IQR)	51.8 (15.2)	49.4 (13.3)	48.5 (15.0)	48.6 (14.9)
Respiratory impairment, n (%)				

Mild A (>0 and <2 l/min via N/C)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mild B (>2 and <4 l/min via N/C)	28 (12.1%)	28 (16.1%)	1297 (20.7%)	1353 (20.3%)
Mild C (>4 and <6 l/min via N/C or 40% FiO2 via mask)	29 (12.5%)	31 (17.8%)	902 (14.4%)	962 (14.4%)
Moderate (6-15 l/min via N/C or 40%-60% via mask)	39 (16.8%)	35 (20.1%)	1089 (17.4%)	1163 (17.4%)
Severe (high flow, NIV, >15 l/min via N/C or >60% via mask)	94 (40.5%)	69 (39.7%)	2447 (39.1%)	2610 (39.1%)
Invasive mechanical ventilation	42 (18.1%)	11 (6.3%)	530 (8.5%)	583 (8.7%)
Other treatments on or prior to day of deterioration				
Remdesivir, n (%)	147 (63.4%)	103 (59.2%)	4311 (68.8%)	4561 (68.4%)
Convalescent Plasma, n (%)	15 (6.5%)	22 (12.6%)	310 (4.9%)	347 (5.2%)
Tocilizumab, n (%)	0 (0.0%)	0 (0.0%)	4 (0.1%)	4 (0.1%)
Dialysis, n (%)	1 (0.4%)	3 (1.7%)	98 (1.6%)	102 (1.5%)
Selected laboratory values on day of deterioration[c]				
C-reactive protein, n	180	157	4559	4896
Median (IQR), mg/L	123.4 (68.0, 193.4)	150.4 (79.6, 205.6)	118.0 (63.4, 184.0)	119.0 (64.2, 185.7)
D-Dimer, n	169	162	4278	4609
Median (IQR), mcg FEU/mL	0.9 (0.6, 1.5)	1.0 (0.7, 2.0)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)

[a]Other race/ethnicity includes multiple, native American Alaskan, Pacific Islander, other, unknown

[b]Epic deterioration index score missing in 5 patients who remained on DEXA6

[c]In patients with multiple values within 24 hours of deterioration, the highest value was recorded

Abbreviations: DEXA=dexamethasone; DEXA6=6mg dexamethasone; SD=standard deviation; y=years; BMI=body mass index; d=days; IQR=interquartile range; l/min=liters per minute; N/C=nasal cannula; FiO2=fraction of inspired oxygen; NIV=non-invasive ventilation; mg/L=milligrams per liter; mcg=microgram; FEU/mL=fibrinogen equivalent units per milliliter

Table 2. Anakinra or high-dose corticosteroids on day of deterioration while treated with dexamethasone 6mg and primary and secondary outcomes

	Treatment		
	Remained on DEXA6	Anakinra	>10mg DEXA
N	6,107	174	229
Mortality, n (%)	1,599 (26.2)	57 (32.8)	96 (41.9)
Unadjusted, OR (95% CI)	Reference	1.37 (1.00 to 1.90)	2.04 (1.56 to 2.66)
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	1.76 (1.13 to 2.72)	1.53 (1.14 to 2.07)
Hospital LOS, mean (SD)	12.1 (12.4)	16.4 (12.8)	15.6 (12.6)
Unadjusted mean difference	Reference	4.4 (2.5 6.3)	3.6 (1.9 5.2)
Propensity score adjustment (IPTW) with robust standard errors, mean difference[a]	Reference	4.8 (2.5 7.1)	2.3 (0.6 3.9)
Ventilator days, mean (SD)	4.3 (10.3)	5.6 (9.8)	7.5 (12.0)
Unadjusted mean difference	Reference	1.3 (-0.2 2.8)	3.2 (1.6 4.8)
Propensity score adjustment (IPTW) with robust standard errors, mean difference[a]	Reference	0.9 (-0.5 2.4)	1.4 (-0.0 2.8)
Hospital acquired infection (%)	14.2	25.3	23.1
Unadjusted, OR	Reference	2.05 (1.45 2.91)	1.83 (1.33 2.50)
Propensity score adjustment (IPTW) with robust standard errors, OR[a]	Reference	2.00 (1.28 3.11)	1.43 (1.00 2.04)
Bloodstream infection (%)	10.6	19.5	19.2
Unadjusted, OR	Reference	2.06 (1.40 3.02)	2.01 (1.44 2.83)
Propensity score adjustment (IPTW) with robust standard errors, OR[a]	Reference	1.99 (1.22 3.27)	1.60 (1.10 2.33)
Pulmonary infection (%)	5.2	10.9	8.3
Unadjusted, OR	Reference	2.24 (1.37 3.66)	1.65 (1.02 2.68)
Propensity score adjustment (IPTW) with robust standard errors, OR[a]	Reference	2.31 (1.29 4.14)	1.13 (0.65 1.98)
Soft tissue infection (%)	0.1	0.0	0.0
Urinary tract infection (%)	2.3	5.2	3.1
Unadjusted, OR	Reference	2.34 (1.17 4.68)	1.35 (0.63 2.93)
Propensity score adjustment (IPTW) with robust standard errors, OR[a]	Reference	2.14 (0.95 4.80)	1.39 (0.58 3.35)

[a]The propensity score model for all outcomes included age, gender, race and ethnicity, smoking, body mass index, Elixhauser comorbidity index, Epic DI score, severity of respiratory impairment and dialysis on day 1 of admission; remdesivir, convalescent plasma, or anakinra use on day 1 of admission; and inpatient, outpatient and urgent care utilizations and corticosteroid use in the 12 months prior to admission.

Abbreviations: DEXA= dexamethasone or equivalent corticosteroid dosing; DEXA6= 6mg daily of dexamethasone; mg=milligram; OR=odds ratio; CI=confidence interval; IPTW=inverse probability of treatment weights; SD=standard

deviation

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Appendix Table 1. List of International Classification of Disease-10 codes

Outcome	*Codes*
Bloodstream infection	A40.3, A40.8, A40.9, A41.01, A41.02, A41.1, A41.2, A41.3, A41.50, A41.51, A41.52, A41.53, A41.59, A41.81, R78.81, T80.211A
Urinary tract infection	N30.00, N30.90, N30.91, N39.0, T83.510A
Soft tissue infection	A48.0, L03.011, L03.012, L03.031, L03.032, L03.113, L03.114, L03.115, L03.116, L03.211, L03.221, L03.311, L03.313, L03.317
Pulmonary infection	B44.0, B44.1, J13, J14, J15.0, J15.1, J15.20, J15.211, J15.212, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9, J18.1, J95.851