Patients diagnosed with COVID-19 and treated with anakinra: a real-world study in the USA
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Summary
Anakinra, a recombinant, non-glycosylated human interleukin (IL)-1 receptor antagonist, has been used in real-world clinical practice to manage hyperinflammation in coronavirus disease 2019 (COVID-19). This retrospective, observational study analyses US hospital inpatient data of patients diagnosed with moderate/severe COVID-19 and treated with anakinra between 1 April and 31 August 2020. Of the 119 patients included in the analysis, 63.9% were male, 48.6% were of black ethnicity, and the mean (standard deviation [SD]) age was 64.7 (12.5) years. Mean (SD) time from hospital admission to anakinra initiation was 7.3 (6.1) days. Following anakinra initiation, 73.1% of patients received antibiotics, 55.5% received antithrombotics, and 91.0% received corticosteroids. Overall, 64.7% of patients required intensive care unit (ICU) admittance, and 28.6% received mechanical ventilation following admission. Patients who did not require ICU admittance or who were discharged alive experienced a significantly shorter time between hospital admission and receiving anakinra treatment compared with those admitted to the ICU (5 vs. 8 days; \( P = 0.002 \)) or those who died in hospital (6 vs. 9 days; \( P = 0.01 \)). Patients with myocardial infarction or renal conditions were six times (\( P < 0.01 \)) and three times (\( P = 0.01 \)), respectively, more likely to die in hospital than be discharged alive. A longer time from hospital admission until anakinra treatment was associated with significantly higher mortality (\( P = 0.01 \)). Findings from this real-world study suggest that a shorter time from hospital admission to anakinra treatment is associated with significantly lower ICU admissions and mortality among patients with moderate/severe COVID-19.

Graphical Abstract

Keywords: anakinra, COVID-19, database studies, interleukin-1 receptor antagonist protein, real-world evidence

Abbreviations: CCI, Charlson comorbidity index; CCPA, California Consumer Privacy Act; CDM, charge description master; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DAMPs, danger-associated molecular patterns; HIPAA, Health Insurance Portability and Accountability Act; ICU, intensive care unit; IL-1, interleukin-1; IL-1Ra, IL-1 receptor antagonist; IL-6, interleukin-6; MI, myocardial infarction; NA, not applicable; OR, odds ratio; Ref, reference level; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation; SoC, standard of care; SRF, severe respiratory failure; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

Introduction
The first human cases of the coronavirus disease 2019 (COVID-19) were reported in China in December 2019 and the disease subsequently spread across the world. According to country-level data, the USA is among the countries with the highest reported number of infections and deaths [1]. COVID-19 is characterized by a range of symptoms that typically appear 2–14 days after exposure to the virus, including...
fever, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea [2].

Older adults (>65 years) and people with severe underlying medical conditions, such as heart or lung disease, or diabetes, appear to be at a higher risk for serious complications such as acute respiratory distress and multiple organ failure from COVID-19 [2]. In addition, it has been reported that males are three times more likely to require ICU (intensive care unit) admittance compared with females [3]. The USA reported a cumulative hospitalization rate of 188.2 per 100 000 population at the beginning of October 2020, with the median length of hospitalization among survivors ranging from 10 to 13 days [4]. Overall, published data studying the clinical characteristics of patients in China report that around 30% of all hospitalized patients diagnosed with COVID-19 were admitted to the ICU with the median time from onset of symptoms to ICU admission ranging from 10 to 12 days [5–7].

COVID-19 is thought to be driven by the replication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and as such, provides a rationale for the potential use of antiviral therapies early in the course of the disease [8, 9]. Anti-inflammatory and immunomodulatory therapies are more likely to be beneficial in the later stages of the disease, where a hyperinflammatory response may lead to cytokine release syndrome and multi-organ failure [9]. Some patients experience worsening of respiratory symptoms as a result of a cytokine storm and current evidence suggests that the interleukin (IL)-1/IL-6 pathway is highly upregulated in patients with severe COVID-19 [10, 11]. Immunomodulation therapy aimed at reducing hyperinflammation includes agents that target pro-inflammatory cytokines [11–13]. Drugs under consideration for patients with moderate/severe COVID-19 include tocilizumab, siltuximab, sarilumab, and tofacitinib, which target the IL-6 pathway, and anakinra, a recombinant soluble IL-1 receptor antagonist (IL-1Ra) that competitively inhibits the binding of both IL-1α and -1β to their receptor (IL-1 type I) [14–18]. Anakinra is currently approved in the USA for rheumatoid arthritis, for deficiency of the IL-1Ra, which is a very rare genetic autoinflammatory syndrome, and for cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease [18]. In Europe, anakinra is indicated for rheumatoid arthritis, periodic fever syndromes, Familial Mediterranean Fever, and Still’s disease [19].

In patients with COVID-19, selective cytokine blockade with anakinra leads to a reduced need for mechanical ventilation, fewer days in the ICU, and a reduction in C-reactive protein levels [20–22]. Additionally, a meta-analysis of aggregate data from 1185 patients enrolled in nine studies reported a significantly lower mortality in patients treated with anakinra compared with patients receiving standard of care (SoC) with or without placebo (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.3, 0.5) [23]. The efficacy of anakinra to treat patients with moderate or severe COVID-19 at risk of progression to severe respiratory failure (SRF) has also been demonstrated in a phase 3 randomized controlled trial (SAVE-MORE; NCT04680949), which used clinical features and a biomarker (soluble urokinase plasminogen activator receptor, suPAR) to predict the risk to progress to SRF [24]. It was found that among patients with moderate or severe COVID-19 and levels of suPAR ≥6 ng/ml (N = 594), early treatment with anakinra plus SoC resulted in an approximately 3-fold improvement in overall clinical status at Day 28 compared with SoC plus placebo, as measured by the 11-point World Health Organization ordinal Clinical Progression Scale (OR 0.4, 95% CI 0.3, 0.5) [24].

Despite the growing clinical evidence demonstrating a benefit of anakinra in patients with COVID-19, there is a paucity of evidence in the real-world clinical setting. Real-world studies describing patient demographics, clinical characteristics, treatment patterns, and clinical outcomes of patients treated with anakinra are lacking. This current study aimed to address these evidence gaps by analysing real-world hospital inpatient data related to patients in the USA diagnosed with COVID-19 and treated with anakinra, as well as the time to treatment with anakinra, between 1 April and 31 August 2020.

Materials and methods

Data source
Data from a Charge Description Master (CDM) database were analysed for this study [25]. The database contains inpatient data for all billable items charged during a hospital visit (e.g. hospital services, medical devices, medical procedures, equipment fees, supplies, and diagnosis) from nearly 400 major hospitals and more than 37 million patients/year in the USA. The HealthVerity platform, which hosted the data set, complies with privacy laws such as California Consumer Privacy Act of 2018 (CCPA), General Data Protection Regulation (GDPR), Health Insurance Portability and Accountability Act of 1996 (HIPAA), among others [25].

Study population and design
This was a retrospective, observational study based on secondary use of data from a CDM database. The source population for this study was adult patients with COVID-19 treated with anakinra as part of routine clinical care between 1 April and 31 August 2020 in the USA. Patients who fulfilled the following criteria were eligible for inclusion in the study: ≥18 years of age at baseline, with at least one ICD-10 diagnosis code for COVID-19 (U071; disease diagnosis of COVID-19 confirmed by laboratory testing) listed as the primary or secondary reason for their inpatient hospital admission, and receiving at least one dose of anakinra during the same hospitalization. There were no exclusion criteria. Baseline was defined as the date of hospital admission.

Objectives
The primary objective was to describe the demographics and comorbidities of patients diagnosed with COVID-19 and treated with anakinra, in addition to the hospital characteristics where these patients were hospitalized.

The secondary objectives were to describe the following during hospitalization: COVID-19-related treatment patterns; patients with clinically relevant outcomes (mechanical ventilation inside and outside the ICU, ICU admission with or without mechanical ventilation, death, and hospital discharge); time to clinical outcomes from hospital admission and anakinra treatment initiation; and duration of stay in the hospital, in the ICU and/or on mechanical ventilation.
Exploratory objectives were to compare patient demographics, comorbidities, and time from hospital admission to anakinra treatment initiation between patients who were discharged alive and those who died in hospital, and between those who were and were not admitted to the ICU during hospitalization. Additionally, the association between the duration of time from hospital admission to anakinra treatment initiation and mortality were explored.

Statistical analysis
All analyses were conducted using SAS software version 9.4. Summary statistics were used to describe the overall patient population. Results are reported as means and standard deviations (SDs) for quantitative variables, whilst categorical variables are reported with frequencies and percentages. Differences in categorical variables were evaluated using the Chi-square test or Fisher’s exact test (if more than 20% of subcategories had frequencies lower than five). Differences in continuous variables were evaluated using the unpaired t-test for normally distributed variables or the Mann–Whitney–Wilcoxon test for non-normally distributed variables. Descriptive statistics for the time from baseline or time from anakinra initiation to clinical outcomes were presented using mean and SD. Patients were followed up until discharge or death.

Logistic regression models were used to describe the association between time from hospital admission to anakinra initiation and death, adjusting for patients demographics (age, gender, and ethnicity), Charlson comorbidity index (CCI), and oxygen use. Univariate logistic regression models were used to analyse the associations between each of these covariates and death as well as between each covariate and ICU admission status. ORs with 95% CIs were reported.

Results
Patient demographics, hospital characteristics, comorbidities, and time to anakinra initiation
A total of 119 patients met the eligibility criteria and were included in the study. Overall, patients were most likely to be male and of black ethnicity, with a mean (SD) age of 64.7 (12.5) years and a mean (SD) CCI score of 4.7 (3.9) (Table 1). Overall, 85.7% of patients had more than one comorbidity and over half of all patients had one of the three most common comorbidities and the most common comorbidity was hypertension. Over half of the patients had diabetes and pulmonary diseases (Table 1). All patients included in the study were treated in urban hospitals, and the mean (SD) time from hospital admission to anakinra initiation was 7.3 (6.1) days (Table 1).

COVID-19-related treatment patterns
Number of additional COVID-19-related treatments
The mean (SD) number of COVID-19-related treatments prescribed to patients during their hospital stay was 5.8 (2.1), with four or more additional treatments prescribed to 89.9% of patients (Supplementary Table 1). The mean (SD) number of different types of antibiotics, antithrombotics, and immunomodulators prescribed to patients during their hospital stay were 3.1 (1.5), 0.7 (0.7), and 2.0 (0.9), respectively (Supplementary Table 1).

The mean (SD) number of additional COVID-19-related medications prescribed after anakinra initiation was 3.8 (2.1), with four or more additional treatments prescribed to 46.2% of patients (Supplementary Table 1). The need
for additional COVID-19-related treatments after anakinra initiation reduced in nearly all treatment classes except for antithrombotics. The mean (SD) number of different types of antibiotics, antithrombotics, and immunomodulators prescribed to patients after anakinra initiation up to discharge or death was 1.8 (1.7), 0.6 (0.7), and 1.4 (0.8), respectively (Supplementary Table 1).

Patients receiving additional COVID-19-related treatments

The types of COVID-19-related treatments and the number of patients who were prescribed these treatments either during their hospital stay (from hospital admission until hospital discharge or death in hospital) or following anakinra initiation (until hospital discharge or death in hospital) are described in Supplementary Table 2. The mean (SD) daily dose of anakinra received was 272.2 (83.4) mg. All patients were prescribed antibiotics during their hospital stay, with 73.1% of patients being prescribed them following anakinra initiation. Azithromycin and ceftriaxone were the most prescribed antibiotics during hospitalization. More than half of all patients were prescribed antithrombotics during their hospitalization, with aspirin being the most prescribed antithrombotic.

Corticosteroids were prescribed to most patients, with methylprednisolone and prednisone being the most common corticosteroids during hospitalization. A total of 43.7% patients were prescribed tocilizumab during their hospital stay and 17.6% following anakinra initiation. Few patients were prescribed antivirals during their hospital stay, and no patients were prescribed immune-based therapies.

Clinical outcomes

During hospital stay

Overall, 64.7% of patients were admitted to the ICU during their hospitalization (Supplementary Table 3), and 28.6% received mechanical ventilation after being admitted to the ICU. Nearly a third of all patients received mechanical ventilation during hospitalization either inside or outside the ICU (Supplementary Table 3). Over a third of patients died in hospital, whilst nearly two-thirds were discharged alive (Supplementary Table 3). The mean (SD) time patients spent on mechanical ventilation was 14.9 (9.1) days, whilst the mean (SD) time patients spent in the ICU and the hospital was 18.8 (11.1) and 20.5 (13.5) days, respectively (Supplementary Table 3).

Of the patients requiring ICU admission, nearly two-thirds were admitted on the day of hospital admission. Nearly a quarter of patients requiring mechanical ventilation received this on the day of hospital admission (Supplementary Table 4). The mean (SD) time from hospital admission to ICU admission, receiving mechanical ventilation, or death was 2.0 (3.9), 7.9 (9.4), and 21.2 (9.5) days, respectively (Supplementary Table 4).

Following anakinra initiation

A total of seven patients were initiated on anakinra prior to being admitted to the ICU, and 16 were initiated on anakinra prior to receiving mechanical ventilation (Supplementary Table 5). Among these patients, the mean (SD) time from anakinra initiation to ICU admission and mechanical ventilation was 4.4 (5.7) and 6.6 (7.6) days, respectively (Supplementary Table 5). More patients received anakinra after being admitted to the ICU (n = 67) than before ICU admission (n = 7), and slightly more patients received anakinra after mechanical ventilation (n = 18) than before (n = 16).

Predictors of ICU admission

When comparing patient demographics, hospital characteristics, and comorbidities according to whether or not patients were admitted to the ICU, the time to anakinra treatment following hospital admission was significantly shorter in duration in those patients who did not require ICU admittance than those who were admitted to the ICU (5 vs. 8 days, respectively, P = 0.002; OR 1.1, 95% CI 1.0, 1.2; Table 2).

Patients with pulmonary diseases were approximately twice as likely to be admitted to the ICU than not be admitted (P = 0.03; OR 2.4, 95% CI 1.1, 5.2) and those with myocardial infarction were approximately five times more likely to require ICU admittance than not (P = 0.03; OR 4.8, 95% CI 1.1, 22.3; Table 2). Overall, patients with higher CCI scores (≥3) were significantly more likely to be admitted to the ICU than those with lower scores (<3) (P = 0.007; OR 4.3, 95% CI 1.3, 13.6; Table 2). The mean (SD) number of supplemental oxygen therapies administered to patients was higher in those admitted to the ICU than in those who were not admitted (12.1 [12.7] vs. 2.7 [5.2], respectively; Table 2). No other significant differences in patient demographics, hospital characteristics, or specific comorbidities were found between those who were and were not admitted to the ICU.

Predictors of mortality

A longer time from hospital admission until the initiation of anakinra treatment was associated with a significantly higher likelihood of mortality (P = 0.01; OR 1.1, 95% CI 1.0, 1.2), even after adjusting for confounders (P = 0.011; OR 1.1, 95% CI 1.0, 1.2; Table 3). When comparing patient demographics, hospital characteristics, and comorbidities according to whether patients were discharged alive or died in hospital, those who were discharged alive experienced a significantly shorter duration of time between hospital admission and receiving anakinra treatment compared with those who died in hospital (6 vs. 9 days, respectively, P = 0.01; OR 1.1, 95% CI 1.0, 1.2; Table 3). Patients with myocardial infarction were six times more likely to require ICU admittance than not (P = 0.01; OR 2.4, 95% CI 1.1, 5.2) and those with renal conditions were three times more likely to die in hospital (OR 5.8, 95% CI 1.9, 17.8; P < 0.01) and those with renal conditions were three times more likely to die in hospital than be discharged alive (OR 2.8, 95% CI 1.3, 6.0; P = 0.01; Table 3). No other significant differences between patient demographics, hospital characteristics, specific comorbidities, or overall CCI score were observed between those who were discharged alive or those who died in the hospital (Table 3).

Discussion

This retrospective study analysed existing real-world data to describe the patient demographics, comorbidities, treatment patterns, clinical outcomes, and predictors of ICU admission and mortality among hospitalized patients diagnosed with COVID-19 and treated with anakinra in the USA. This study adds to the evidence base by exploring the association between time from hospital admission to anakinra treatment initiation and ICU admission and mortality in these patients.
| Time from hospital admission to anakinra initiation, mean (SD) days | No (n = 42) | Yes (n = 77) | Unadjusted OR [95% CI] | P-value |
|---|---|---|---|---|
| 5.2 (4.6) | 8.4 (6.5) | 1.1 [1.0, 1.2] | 0.002 |
| Gender, n (%) | | | | |
| Female | 14 (32.6) | 29 (67.4) | 1.2 [0.5, 2.7] | 0.64 |
| Male | 28 (36.8) | 48 (63.2) | Ref | |
| Age, mean (SD) years | 62.4 (12.6) | 65.9 (12.3) | 1.0 [1.0, 1.1] | 0.14 |
| Ethnicity, n (%) | | | | |
| Black | 11 (30.6) | 25 (69.4) | Ref | 0.84 |
| Hispanic | 5 (26.3) | 14 (73.7) | 1.2 [0.4, 4.3] | |
| White | 3 (21.4) | 11 (78.6) | 1.6 [0.4, 7.0] | |
| Mixed | 2 (40.0) | 3 (60.0) | 0.7 [0.1, 1.5] | |
| Missing | 21 (46.7) | 24 (53.3) | | |
| Area of location, n (%) | | | | |
| Rural | 0 (0.0) | 0 (0.0) | | |
| Urban | 42 (35.3) | 77 (64.7) | | |
| Hospital size, n (%) | | | | |
| <500 beds | 1 (20.0) | 4 (80.0) | Ref | 0.66 |
| ≥500 beds | 41 (36.0) | 73 (64.0) | 0.5 [0.1, 4.1] | |
| Hospital teaching type, n (%) | | | | |
| Major teaching | 41 (34.7) | 77 (65.3) | | |
| Non-teaching | 1 (100) | 0 (0.0) | | |
| Oxygen use [count], mean (SD) | 2.7 (5.2) | 12.1 (12.7) | 1.2 [1.1, 1.3] | <0.0001 |
| Anakinra initiated before ICU | | | | |
| No | 42 (37.5) | 70 (62.5) | | 0.05 |
| Yes | 0 (0.0) | 7 (100) | | |
| Number of comorbidities | 0 | 3 (60.0) | 2 (40.0) | Ref | 0.36 |
| 1 | 7 (58.3) | 5 (41.7) | 1.1 [0.1, 9.0] | |
| 2 | 10 (40.0) | 15 (60.0) | 1.3 [0.3, 16.0] | |
| ≥3 | 22 (40.0) | 55 (60.0) | 3.8 [0.6, 24.0] | |
| Types of comorbidities | | | | |
| Hypertension | 32 (34.8) | 60 (65.2) | 1.1 [0.5, 2.7] | 0.83 |
| Diabetes | 22 (33.8) | 43 (66.2) | 1.1 [0.5, 2.5] | 0.72 |
| Pulmonary diseases | 15 (25.4) | 44 (74.6) | 2.4 [1.1, 5.2] | 0.03 |
| Obesity | 14 (38.9) | 22 (61.1) | 0.8 [0.4, 1.8] | 0.59 |
| Renal conditions | 14 (28.6) | 35 (71.4) | 1.7 [0.8, 3.7] | 0.20 |
| Congestive heart failure | 9 (25.7) | 26 (74.3) | 1.9 [0.8, 4.5] | 0.16 |
| COPD | 3 (17.6) | 14 (82.4) | 2.9 [0.8, 10.7] | 0.10 |
| MI | 2 (11.8) | 15 (88.2) | 4.8 [1.1, 22.3] | 0.03 |
| Liver disease | 3 (30.0) | 7 (70.0) | 1.3 [0.3, 5.3] | 1.00 |
| Cerebrovascular disease | 1 (11.1) | 8 (88.9) | 4.8 [0.6, 39.4] | 0.16 |
| Peripheral vascular disease | 2 (33.3) | 4 (66.7) | 1.1 [0.2, 6.3] | 1.00 |
| Rheumatologic autoimmune conditions | 0 (0.0) | 1 (100) | | |
| CCI score, mean (SD) | 4.1 (4.4) | 5.0 (3.7) | 1.1 [1.0, 1.2] | 0.07 |
| CCI score, categorical n (%) | | | | |
| 0 | 9 (60.0) | 6 (40.0) | Ref | 0.007 |
| 1 | 12 (57.1) | 9 (42.9) | 1.1 [0.3, 4.3] | |
| 2 | 2 (20.0) | 8 (80.0) | 6.0 [0.9, 38.6] | |
| ≥3 | 19 (26.0) | 54 (74.0) | 4.3 [1.3, 13.6] | |

CCI, Charlson comorbidity index; CI, Wald confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; Ref, reference level. OR [95% CI]: odds ratio with 95% confidence interval from logistic regression model of ICU admission. P-value: Student’s t-test for continuous variables and Chi-square test for categorical variables. P-value in italic: Mann–Whitney test for continuous variables and Fisher’s exact test for categorical variables.

*aComorbidities included: diabetes, hypertension, pulmonary diseases, heart diseases (any of MI, congestive heart failure, peripheral vascular disease, cerebrovascular disease), renal diseases, liver diseases, obesity.*
| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| Discharged alive (n = 77) | 6.1 (4.9) | 9.4 (7.4) | 1.1 [1.0, 1.2] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |
| Deceased (n = 42) | Ref | Ref | 1.0 [0.9, 1.0] | 0.30 | 0.8 [0.9, 1.0] | 0.06 |

**Time from hospital admission to anakinra initiation, mean (SD) days**

| Gender, n (%) | Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|---------------|------------------|------------------------|---------|------------------------|---------|
| Female | 29 (67.4) | 14 (32.6) | 0.8 [0.4, 1.8] | 0.64 | 0.6 [0.3, 1.5] | 0.283 |
| Male | 48 (63.2) | 28 (36.8) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |

**Age, mean (±SD) years**

| Ethnicity, n (%) | Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------|------------------------|---------|------------------------|---------|
| Black | 21 (58.3) | 15 (41.7) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |
| Hispanic | 11 (57.9) | 8 (42.1) | 1.0 [0.3, 3.1] | 0.1 | 0.6 [0.3, 1.5] | 0.283 |
| White | 8 (57.1) | 6 (42.9) | 1.1 [0.3, 3.7] | 0.1 | 0.6 [0.3, 1.5] | 0.283 |
| Mixed | 3 (60.0) | 2 (40.0) | 0.9 [0.1, 6.3] | 0.1 | 1.1 [0.1, 9.1] | 0.919 |
| Missing | 34 (75.6) | 11 (24.4) | 0.5 [0.2, 1.5] | 0.229 |

**Area of location, n (%)**

| Hospital size, n (%) | Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|----------------------|------------------|------------------------|---------|------------------------|---------|
| Rural | 0 (0.0) | 0 (0.0) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |
| Urban | 77 (64.7) | 42 (35.3) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |

**Hospital teaching type, n (%)**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| Major teaching | 76 (64.4) | 42 (35.6) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |
| Non-teaching | 1 (100) | 0 (0.0) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |

**Oxygen use [count], mean (SD)**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| ICU admission | 39 (50.6) | 38 (49.4) | 9.3 [3.0, 28.5] | 0.0001 |

**Number of comorbiditiesd**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| 0 | 3 (60.0) | 2 (40.0) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.011 |
| 1 | 10 (83.3) | 2 (16.7) | 0.3 [0.0, 3.1] | 0.1 | 0.6 [0.3, 1.5] | 0.283 |
| 2 | 18 (72.0) | 7 (28.0) | 0.6 [0.1, 4.3] | 0.01 | 1.1 [0.1, 9.1] | 0.919 |
| ≥3 | 46 (60.0) | 31 (40.0) | 1.0 [0.2, 6.4] | 0.229 |

**Comorbidities**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| Hypertension | 59 (64.1) | 33 (35.9) | 1.1 [0.5, 2.8] | 0.81 |
| Diabetes | 45 (69.2) | 20 (30.8) | 0.7 [0.3, 1.4] | 0.26 |
| Pulmonary diseases | 36 (61.0) | 23 (39.0) | 1.4 [0.7, 2.9] | 0.4 |
| Obesity | 28 (77.8) | 8 (22.2) | 0.4 [0.2, 1.0] | 0.01 |
| Renal conditions | 25 (51.0) | 24 (49.0) | 2.8 [1.3, 6.0] | 0.01 |
| Congestive heart failure | 22 (62.9) | 13 (37.1) | 1.1 [0.5, 2.6] | 0.79 |
| COPD | 12 (70.6) | 5 (29.4) | 0.7 [0.2, 2.2] | 0.58 |
| MI | 5 (29.4) | 12 (70.6) | 5.8 [1.9, 17.8] | <0.01 |
| Liver disease | 4 (40.0) | 6 (60.0) | 3 [0.8, 11.5] | 0.16 |
| Cerebrovascular disease | 4 (44.4) | 5 (55.6) | 2.5 [0.6, 9.7] | 0.28 |
| Peripheral vascular disease | 4 (66.7) | 2 (33.3) | 0.9 [0.2, 5.2] | 1.00 |
| Rheumatologic autoimmune conditions | 0 (0.0) | 1 (100) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.186 |

**CCI score, mean (±SD)**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| 0 | 4.2 (3.8) | 5.5 (4.1) | 1.1 [1.0, 1.2] | 0.07 |
| 1 | 10 (66.7) | 5 (33.3) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.186 |
| 2 | 17 (81.0) | 4 (19.0) | 0.5 [0.1, 2.2] | 0.31 |
| ≥3 | 7 (70.0) | 3 (30.0) | 0.9 [0.2, 4.8] | 0.01 |

**CCI score, categorical n (%)**

| Mortality status | Unadjusted OR [95% CI] | P-value | Adjusted OR [95% CI]a | P-valueb |
|------------------|------------------------|---------|------------------------|---------|
| 0 | 43 (58.9) | 30 (41.1) | 1.4 [0.4, 4.5] | 0.01 |
| 1 | 10 (66.7) | 5 (33.3) | Ref | I [Ref] | 0.01 | 1.1 [1.0, 1.2] | 0.186 |
| 2 | 17 (81.0) | 4 (19.0) | 0.5 [0.1, 2.2] | 0.31 |
| ≥3 | 7 (70.0) | 3 (30.0) | 0.9 [0.2, 4.8] | 0.01 |

CCI, Charlson comorbidity index; CI, Wald confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; Ref, reference level. OR [95% CI]: odds ratio with 95% confidence interval from logistic regression model of death in hospital. P-value: Student's t-test for continuous variables and Chi-square test for categorical variables. P-value in italic: Mann–Whitney test for continuous variables and Fisher’s exact test for categorical variables.

aAdjusted for time from hospital admission to anakinra initiation, age, gender, ethnicity, oxygen use, and CCI score.

bP-value: Student’s t-test for continuous variables and Chi-square test for categorical variables.

cIncludes patients with discordant ethnicity information between the two consumer data sources (Acxiom and Epsilon).

dComorbidities included: diabetes, hypertension, pulmonary diseases, heart diseases (any of MI, congestive heart failure, peripheral vascular disease, cerebrovascular disease), renal diseases, liver diseases, obesity.
According to published research, between 26% and 32% of hospitalized patients diagnosed with COVID-19 are admitted to the ICU and the median time from onset of symptoms to ICU admission ranges from 10 to 12 days [5, 6, 26]. The current study demonstrated that a shorter duration of time from hospital admission to anakinra initiation resulted in patients being significantly less likely to be admitted to the ICU or die in hospital. In line with this, in a retrospective single center study, the administration of anakinra to patients with severe/moderate COVID-19 soon after hospital admission led to improved respiratory parameters and provided rapid resolution of systemic inflammation. Although the sample size was limited (N = 5), the preliminary findings demonstrated the potential efficacy of early anakinra treatment in patients with COVID-19 [27]. Consistent with these findings, in a meta-analysis of four observational studies, anakinra was associated with a significantly lower overall mortality (P < 0.0001) and a significantly lower risk of need for mechanical ventilation (P < 0.0001) compared with the control group [28].

The demographics of patients treated with anakinra in the current analysis are similar to those of previously published studies. The age of patients is in alignment with an observational study by Yang et al. in Wuhan, China of critically ill patients with COVID-19 [6]. Yang et al. observed that deceased patients were older and more likely to have received mechanical ventilation compared to those who survived. The present study did not observe any significant differences in the age of patients who were discharged alive compared to those who died in the hospital. The slightly higher proportion of male patients in this study is similar to findings of a meta-analysis in which males with COVID-19 were three times more likely to require ICU admittance [29]. When assessed for an association between gender and mortality after anakinra initiation, the present study did not find the patient’s gender to be associated with an increased likelihood of mortality or ICU admission, which is consistent with a previous case series where differences in survival were not related to the gender of the patient [30].

Patients initiated on anakinra treatment presented with hypertension and diabetes as the two most common comorbidities. Published data highlight an association between the presence of underlying diseases with an increase in ICU admittance and mortality in patients with severe COVID-19 [5, 6]. Consistent with these findings, this study reported almost a 6-fold increase in the odds of dying in hospital compared to being discharged alive for patients with myocardial infarction.

The descriptive nature of the present study did not allow patient subgroups to be analysed based on additional treatments received; however, a previous patient-level meta-analysis found significant survival benefit for patients receiving anakinra without the corticosteroid dexamethasone (OR 0.2, 95% CI 0.1, 0.4) when compared with dexamethasone co-administration (OR 0.7, 95% CI 0.4, 1.4) [23]. Antibiotics and corticosteroids were the most prescribed treatment types in COVID-19-associated hospitalizations in this current study and were used throughout hospitalization. The present research reported that antithrombotics were prescribed to over 50% of all patients studied. This frequent use of antithrombotics (particularly antiplatelet agents such as aspirin and clopidogrel) is in line with a review of clinical trials evaluating antithrombotics, which suggests a high incidence of thromboembolic events in patients diagnosed with COVID-19, with the risk of such events highest in patients with severe disease [31].

Considering the findings of this real-world study it may be hypothesized that IL-1 blockade by anakinra reduces mortality due to hyperinflammation. Severe COVID-19 is known to have similarities with hyperinflammation seen in IL-1-mediated autoimmune or autoinflammatory conditions; while features of hyperinflammation such as macrophage activation syndrome, a type of secondary haemophagocytic lymphohistiocytosis syndrome, or a cytokine storm are also known to occur in patients with severe COVID-19 [32, 33]. Studies with anakinra as a treatment for the hyperinflammatory phase of COVID-19 have demonstrated reduced mortality and the need for invasive mechanical ventilation among patients with severe form of the disease, while high-dose intravenous anakinra has been shown to be well-tolerated and resulted in improvements in respiratory function in patients with COVID-19 and acute respiratory distress syndrome [20, 21].

It has been suggested that some patients have a predisposition for an excessive inflammatory response resulting in a severe form of the disease upon infection [34]. Elevated ferritin and IL-6 levels have been reported in non-survivors as compared with survivors in a retrospective study [35]. In contrast, a cohort study found that IL-1, but not IL-6, inhibition was associated with a significant reduction in mortality in patients hospitalized with COVID-19 who had respiratory insufficiency and hyperinflammation [36]. A recent study by van Deuren et al. reported the impact of genetic variants on IL-1-mediated immunological cascades [37]. The framework used in the study may not only provide insight into the impact of genetic variations on the IL-1 pathway and cytokine response among patients but importantly could potentially be applied for use in understanding inter-individual immune response differences among patients with COVID-19.

Data relating to biomarkers indicative of disease severity were not available in this real-world secondary database. The SAVE-MORE trial, however, reported that early start of treatment with anakinra guided by levels of the biomarker suPAR is associated with reducing mortality by 55% and the median time to ICU discharge by 4 days in patients with COVID-19 pneumonia at risk of progressing to SRF [24]. The study used suPAR as a tool to predict progression to SRF in patients with severe pneumonia caused by SARS-CoV-2 infection [24], with clinical evidence suggesting that early increase of suPAR is associated with an excess release of danger-associated molecular patterns (DAMPs), such as calprotectin and IL-1α [38, 39]. Results from the proof-of-concept trial (SAVE; NCT04357366), obtained on a cohort of 130 patients with lower respiratory tract infection and suPAR levels ≥ 6 ng/mL, demonstrated that early suPAR-guided anakinra treatment reduced the incidence of SRF and resulted in a lower 30-day mortality, and a shorter duration of stay in the ICU compared with a matched cohort receiving SoC [40]. Collectively, results from the present real-world study add to the evidence that early initiation of anakinra treatment following hospital admission is associated with fewer ICU admissions and a lower risk of mortality.

This study has several limitations; patients included in the database may not be representative of all patients with COVID-19 hospitalized in the USA as the hospitals
Real-world study of anakinra for COVID-19, 2022, Vol. 207, No. 2

225

included were not selected at random. Data relating to stage and severity of disease, inflammatory burden, route of anakinra administration, SoC therapies, or biomarkers were not available in this real-world secondary database and therefore could not be analysed. As this is a descriptive study, comparison of the baseline characteristics of patients receiving anakinra with those receiving other medications was beyond the scope of the current study. Due to limitations in the sample size, exploring differences in anakinra dose according to time from hospital admission to anakinra treatment (early vs. late) in patients with COVID-19 was not possible; however, it would be interesting for future research. Only data relating to events that occurred during hospitalization are available; therefore, events such as death that occurred outside the hospital setting were not captured. Data relating to ethnicity were also missing for 38% of patients, which could explain a potential ethnic disparity in the outcomes of interest. All patients included in the study were admitted to urban hospitals, and infer-ences regarding the effect of facility characteristics on pa-tient characteristics and treatment patterns are not possible. Furthermore, as this is a descriptive study without a control arm, a direct association between anakinra and study out-comes cannot be made.

In summary, findings from this real-world study suggest that a shorter duration of time from hospital admission to treatment with anakinra is associated with significantly lower ICU admissions and mortality, which lends support for the shorter duration of time to use of anakinra treatment following hospital admission as an effective treatment in moderate/severe COVID-19, potentially reducing mortality and hospital resource burden.

Supplementary data
Supplementary data are available at Clinical and Experimental Immunology online.

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Conflict of interest
K.J. and F.D. are employees of Creativ-Ceutical, a consultancy company that was contracted by Sobi to design and conduct this analysis. C.R., D.E., F.D., and J.N. are employees of Sobi.

Author contributions
All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Ethical approval
This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology, STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki. The data collected did not include any direct identifiers.

Data availability
The data set used and analysed during the current study are available from the corresponding author on reasonable request.

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