BRIEF REPORT

Use of Anakinra to Prevent Mechanical Ventilation in Severe COVID-19: A Case Series

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Objective. To report the clinical experience with anakinra in preventing mechanical ventilation in patients with coronavirus disease 2019 (COVID-19), symptoms of cytokine storm syndrome, and acute hypoxemic respiratory failure.

Methods. To be included in this retrospective case series, patients must have had severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), fever, ferritin levels >1,000 ng/ml with 1 additional laboratory marker of hyperinflammation, and acute hypoxemic respiratory failure. Acute hypoxemic respiratory failure was defined as requiring 15 liters of supplemental oxygen via a nonrebreather mask combined with 6-liter nasal cannula or use of ≥95% oxygen by high-flow nasal cannula. We excluded patients in whom there was suspicion of bacterial infection or who were receiving immunosuppressants. Subcutaneous anakinra was initiated at 100 mg every 6 hours and gradually tapered off completely. The primary outcome was the prevention of mechanical ventilation.

Results. Of the 14 patients who met the criteria, 11 patients received anakinra for a maximum of 19 days. Seven of the patients who started anakinra treatment ≤36 hours after onset of acute hypoxemic respiratory failure did not require mechanical ventilation, and all were discharged home. Four patients who started anakinra ≥4 days after onset of acute hypoxemic respiratory failure required mechanical ventilation. Of those, 3 patients were extubated (2 discharged home and 1 remained hospitalized), and 1 died. All 3 patients who met the criteria but did not receive anakinra required mechanical ventilation. Two patients were extubated (1 discharged home and 1 remained hospitalized), and 1 remained on mechanical ventilation.

Conclusion. Our data suggest that anakinra could be beneficial in treating COVID-19 patients with evidence of cytokine storm syndrome when initiated early after onset of acute hypoxemic respiratory failure. Our patient selection and treatment approach should be considered for investigation in a clinical trial to determine the safety and efficacy of anakinra in treating patients with COVID-19 and symptoms of cytokine storm syndrome.

INTRODUCTION

The clinical syndrome associated with infection from severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) is notable for its variability, ranging from asymptomatic infection to multiorgan failure and death (1). In a study describing the first 393 patients with coronavirus disease 2019 (COVID-19) at 2 New York City hospitals, 77.1% had fever, a symptom driven by interleukin-1 (IL-1) (2). The clinical presentation, along with transcriptomic analysis of whole blood from COVID-19 patients demonstrating IL-1α and IL-1β expression prior to the nadir of respiratory function, suggests that IL-1 may drive the pathophysiology of COVID-19 (3).

Cytokine storm syndrome has been observed in patients with COVID-19 and has been proposed to contribute to severe sequelae of disease, such as acute hypoxic respiratory failure and death (4). In distinct clinical settings, including macrophage

activation syndrome (MAS), elevated levels of proinflammatory cytokines and other laboratory indicators (including ferritin levels, C-reactive protein [CRP], D-dimer, and lymphopenia) have been observed (5). In systemic juvenile idiopathic arthritis (JIA), the prototypic disease for such syndromes, controlled clinical trials of an IL-1 inhibitor clearly demonstrated safety and efficacy (6).

Based on the experience of clinicians, particularly rheumatologists, IL-1 inhibition has been used in additional rare syndromes characterized by induction of hyperinflammation mediated by impaired regulation of the cytokine response (7,8). Anakinra, a recombinant IL-1 receptor antagonist approved by the US Food and Drug Administration for use in neonatal-onset multisystem inflammatory disease and rheumatoid arthritis, inhibits both IL-1α and IL-1β. Because it inhibits both IL-1 subtypes and has a short half life, anakinra could be a promising treatment for patients with severe COVID-19. The objective of this study was to describe a single-center preliminary experience using anakinra as part of clinical care to prevent progression to mechanical ventilation in patients with COVID-19 presenting with clinical and laboratory evidence of cytokine storm syndrome and acute hypoxic respiratory failure.

PATIENTS AND METHODS

Patients and study design. This was a retrospective case series of patients with COVID-19, acute hypoxic respiratory failure, and signs and symptoms of cytokine storm syndrome. We evaluated patients with COVID-19 through the rheumatology inpatient consult service at New York-Presbyterian Hospital/Weill Cornell Medical Center and New York-Presbyterian Lower Manhattan Hospital from April 1 to June 2, 2020. Detailed inclusion and exclusion criteria used to guide the use of anakinra to treat cytokine storm syndrome in patients with COVID-19 are presented in Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41422/abstract. In summary, we required that patients have molecular documentation of SARS–CoV-2, fever (documented or historic), ferritin levels >1,000 ng/ml with 1 additional laboratory marker of hyperinflammation, and acute hypoxic respiratory failure. Acute hypoxic respiratory failure was defined as requiring either 15 liters of supplemental oxygen via a nonrebreather mask combined with 6-liter nasal cannula or ≥95% oxygen by high-flow nasal cannula. Patients on invasive mechanical ventilation at the time of evaluation were ineligible. Patients were considered for treatment with anakinra only after they were deemed ineligible for any ongoing clinical trial for patients with COVID-19. Verbal consent was obtained and documented in their electronic medical record for the off-label use of anakinra in the treatment of these patients. This study was approved by the Weill Cornell Medicine Institutional Review Board.

Treatment with anakinra. Only subcutaneous (SC) anakinra was available at our institution's pharmacy. Patients were started on 100 mg of SC anakinra every 6 hours; however,

while a uniform treatment plan and secure supply of medication was being established, the first 2 patients were initially treated with doses lower than the proposed 100 mg every 6 hours. The dosing frequency of anakinra was gradually decreased to every 8, 12, and 24 hours over a maximum treatment duration of 20 days. We tapered anakinra based on decreasing oxygen requirements and clinical improvement, or in response to elevated transaminase levels, cytopenia levels, concern for new bacterial infection (based on positive cultures, increase in procalcitonin to >0.6 ng/ml, or high clinical suspicion), or worsening renal function. We continued anakinra treatment in patients requiring mechanical ventilation with the goal that its use could facilitate extubation. There were 3 patients who met our eligibility criteria but were not given anakinra because it was either unavailable or the patient declined. We considered continuing anakinra treatment after discharge from the hospital based on clinical response and tolerability; in most cases, we discontinued anakinra because patients had improved significantly by that time, and the likelihood of further decompensation was low.

Background medications. We allowed background methylprednisolone, empiric antibiotics, and hydroxychloroquine, which were included in the clinical care protocols for COVID-19 at Weill Cornell Medical Center and New York-Presbyterian Lower Manhattan Hospital. Several patients were given anakinra together with methylprednisolone, as this was being considered for all patients with worsening respiratory failure at high risk for mechanical ventilation at our institution. None of these patients received remdesivir. We excluded patients with cancer who were receiving chemotherapy or immunotherapy and patients receiving other immunosuppressive biologics. Details regarding the exclusion criteria are provided in Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41422/abstract.

Monitoring. We monitored patients' vital signs, oxygen requirements, ferritin levels, complete blood cell count with differential cell count, comprehensive metabolic panels, erythrocyte sedimentation rates, CRP levels, lactate dehydrogenase levels, international normalized ratios, and prothrombin times.

Outcomes and timelines. The primary outcome was prevention of mechanical ventilation. Clinical response was defined as the patient being weaned off oxygen or to oxygen levels of 2 liters by nasal cannula. Failure to respond was defined as requiring mechanical ventilation. We used the ordinal scale of the World Health Organization trials for COVID-19 (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41422/abstract) to measure respiratory outcomes (9). The maximum use of anakinra in our

Table 1. Characteristics of patients with COVID-19 who met criteria for treatment with subcutaneous anakinra based on features of cytokine storm syndrome*

Patient/age/sex	Race/ethnicity	Medical history	Days from COVID-19 symptom onset to respiratory decompensation	Documented temperature at evaluation, °C†	Ferritin, ng/ml	Lymphocyte count, µl	LDH, units/liter	D-dimer, µg/ml FEU	CRP, mg/dl
Patients treated with anakinra									
1/61/M	White	T2DM, asthma, obesity, CAD	6	38.2	1,288	1,200	–	270	0.0
2/48/M	Hispanic	Obesity	10	38.2	1,576	–	955	718	30.8
3/60/F	Asian	COPD	10	36.5	2,255	500	746	923	1.2
4/74/M	Hispanic	HTN, GERD, T2DM, HLD	10	38.0	1,482	–	212	1,200	–
5/63/M	Asian	Hypothyroidism	4	37.5	1,629	–	873	2,079	2.6
6/81/F	White	GERD, β-thalassemia	15	36.5	1,388	900	360	691	4.3
7/62/M	Hispanic	HTN, obesity, pre-T2DM, HLD, BPH	6	37.1	1,479	500	924	2,760	14.2
8/66/M	Hispanic	None	15	38.6	1,736	700	479	814	27.4
9/65/M	Asian	HTN, T2DM, BPH, CVA	10	37.9	1,536	1,100	424	929	5.9
10/43/M	Asian	None	15	38.0	2,273	800	542	221	15.7
11/42/M	Asian	T2DM	15	37.0	>1,650	1,400	451	341	15.6
Patients not treated with anakinra but meeting criteria									
12/63/M	Hispanic	T2DM, HTN	14	37.6	1,055	600	878	>20	22.2
13/59/F	Hispanic	None	5	37.5	1,855	800	533	364	28.2
14/56/M	Hispanic	HTN, BPH	11	37.2	2,360	1,200	586	450	28.6

* COVID-19 = coronavirus disease 2019; LDH = lactate dehydrogenase; FEU = fibrinogen equivalent unit; CRP = C-reactive protein; T2DM = type 2 diabetes mellitus; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HTN = hypertension; GERD = gastroesophageal reflux disease; HLD = hyperlipidemia; BPH = benign prostatic hyperplasia; CVA = cerebrovascular accident.
† Fever could be historic and only occurred before hospital admission or evaluation.

protocol was 20 days. Patients were followed up until they were able to wean off oxygen or until discharge.

RESULTS

Fourteen patients met our criteria for cytokine storm syndrome in the setting of severe COVID-19 pneumonia and acute hypoxic respiratory failure (Table 1). Of those patients, 11 received anakinra. The first 2 patients treated were initially given a lower dose of anakinra; once we established a treatment guideline and had adequate supply of the medication, the remaining patients were treated in a standardized way. The majority of the patients who did not meet our criteria for acute hypoxic respiratory failure had a less severe form of COVID-19 and improved gradually over time on their own (data not shown).

The doses of anakinra and background medications received by each patient, including the dosage and duration of methyl-prednisolone, are shown in Table 2. Patients treated with anakinra within 36 hours of meeting our oxygen supplementation threshold for eligibility (early initiation) did not require mechanical ventilation (patients 1, 2, 3, 6, 8, and 11) or avoided recurrent mechanical ventilation (patient 9). All patients who did not require mechanical ventilation were discharged home. Patients whose oxygen requirements met our criteria for acute hypoxic respiratory failure for ≥4 days prior to initiating anakinra treatment (late initiation) required mechanical ventilation (patients 4, 5, 7, and 10). We continued anakinra in all late-initiation patients to facilitate extubation. Two patients developed infections (patients 4 and 7), prompting discontinuation of anakinra. Three of the 4 late-initiation patients were extubated, and 2 were discharged home (patients 7 and 10). One remains in the hospital (patient 4). For those intubated, the duration of mechanical ventilation ranged from 7 to 19 days. For patient 5, anakinra was initiated before blood culture results were available; once a bacterial infection was identified, anakinra was discontinued, but the patient died weeks later. Three of the 14 patients who met the cytokine storm syndrome criteria did not receive anakinra (patients 12, 13, and 14); all required mechanical ventilation and then received an IL-6 antagonist after documentation of elevated IL-6 levels. IL-6 levels were elevated only in these 3 patients; 1 was extubated and discharged home (patient 13) and 2 remained in the hospital. Of the 2 patients remaining in the hospital, 1 was still intubated as of June 2, 2020 (patient 14) and the other initially failed extubation but was successfully extubated 7 days later (patient 12) (Table 2).

All eligible patients had ferritin levels >1,000 ng/ml for 1–2 days before consultation (Figure 1A). Ferritin levels trended down, but only 2 patients achieved levels <500 ng/ml by the study's conclusion. Most of the patients also had lymphocyte counts <1,200/μl at the time of consultation, and 5 patients had lymphocyte counts >1,500/μl by the end of follow-up (Figure 1B). Nearly all patients had a CRP level >5 mg/dl, which trended down or normalized in all but 1 patient, who developed a superimposed

infection (Figure 1C). In patients 12, 13, and 14, the ferritin levels and lymphocyte counts were similar to those in the patients who received anakinra, and they did not fluctuate over the course of the disease and our observation period; CRP levels normalized within 2 days of receiving an anti–IL-6 biologic (data not shown).

DISCUSSION

This case series suggests that anakinra confers the greatest benefit in the treatment of COVID-19 with features of cytokine storm syndrome when patients require high levels of supplemental oxygen for <2 days and before intubation. Our treatment strategy involved giving high doses of anakinra soon after the development of acute hypoxic respiratory failure, followed by a slow tapering over a maximum of 20 days, guided by clinical response and tolerability. The goal of treating patients at risk for mechanical ventilation was to prevent organ damage, morbidity, and, in the setting of a rapidly progressing pandemic, depletion of health care resources such as ventilators. Our data demonstrate that patients in whom anakinra treatment was initiated early did not require mechanical ventilation and were discharged home. This early aggressive treatment was likely key in decreasing the patients' risk of requiring mechanical ventilation without major risk of complications. For patients requiring mechanical ventilation, anakinra should be used with caution due to the risk of complications such as superimposed bacterial infection.

To date, there are several reports from Europe regarding the use of anakinra in patients with COVID-19. Unlike our study, they did not require that patients have severe respiratory failure in order to initiate anakinra (10–12). Such an approach increases the possibility of overestimating the medication's efficacy and confers potentially unnecessary risk of medication side effects. Our criteria for initiating anakinra included severe respiratory failure to avoid treating patients who are more likely to improve without immunosuppression. We defined a specific phenotype of patients with COVID-19, which allowed us to examine the clinical response in a group of patients with similar clinical presentation.

Of those patients who fit this phenotype, 3 did not receive anakinra and instead received an IL-6 antagonist after documentation of elevated IL-6 levels. Two patients were successfully extubated. Since IL-1 can induce IL-6, it is possible that anakinra could have prevented mechanical ventilation in those 3 patients. The possibility that anakinra may have improved outcomes in those patients is also supported by the presence of fever, a symptom mediated by IL-1 (13). Thus, even in the setting of IL-6 elevation, anakinra could be considered in patients with acute hypoxic respiratory failure.

This case series captures the heterogeneity in the US population. Half of our patients were Hispanic, 5 were Asian, and 2 were white. This diversity makes it challenging to apply results from more homogeneous populations, which makes our study distinct from those reported from Europe. Anakinra is not available

Table 2. Concomitant therapies and clinical outcomes in the COVID-19 patients treated with anakinra*

Patient	Concomitant medications	Time from initiation of maximum supplemental O_2 (NRB 15L + NC 6L or HFNC) to initiation of anakinra	Anakinra dose titration	Number of days receiving anakinra	Current clinical status†	Observations	Adverse reactions while taking anakinra
Patients treated with anakinra							
1	None	16 hours	↓ to 100 mg SC daily on day 8, discontinued on day 9	9	1	Discharged from hospital, no limitation on activities‡	None
2	None	36 hours	↑ to 100 mg SC q6h on day 2, ↓ to 100 mg SC q8h on day 6, ↓ to 100 mg SC q12h on day 10, ↓ to 100 mg SC daily on day 13	19	1	Discharged from hospital, no limitation on activities; received anakinra 100 mg daily for 5 days as outpatient‡	Elevation of AST/ALT (also on scheduled acetaminophen), injection site reaction on last 2 days of treatment
3	Methylprednisolone 25 mg q12h 4 days prior to starting anakinra, tapered after 10 days (total 14 days)	24 hours	↓ to 100 mg SC q8h on day 3, ↓ to 100 mg SC q12h day 5, ↓ to 100 mg SC daily day 8, discontinued day 12	12	1	Discharged from hospital, no limitation on activities‡	None
4	Methylprednisolone 40 mg q12h x 3 days prior to starting anakinra (total 3 days)	4 days	↓ to 100 mg SC q8h on day 4, ↓ to 100 mg SC q12h day 10, discontinued day 12	12	3	Hospitalized without oxygen support; required MV for 19 days§	Bacterial infection
5	Methylprednisolone 30 mg q12h x 3 days prior to starting anakinra (total 3 days)	4 days	Discontinued on day 2	2	8	Death Anakinra discontinued after 8 doses due to bacterial infection¶	Bacterial infection#
6	Methylprednisolone 30 mg q12h x 4 days prior to starting anakinra (total 4 days)	24 hours	↓ to 100 mg SC q8h on day 4, ↓ to 100 mg SC q12h day 9, ↓ to 100 mg SC daily day 11, discontinued day 12	12	1	Discharged from hospital, no limitation on activities‡	Elevation of AST/ALT and leukopenia
7	Methylprednisolone 50 mg q12h x 4 days prior to starting anakinra (total 5 days)	7 days	↓ to 100 mg SC q8h on day 5, ↓ to 100 mg SC q12h day 7, ↑ to 100 mg SC q6h day 8, discontinued day 9	9	2	Discharged from hospital, with limitation on activities; hospitalized, required invasive MV for 16 days; intubated after 1 dose of anakinra§	Bacterial infection
8	Methylprednisolone 40 mg q12h x 1 day, tapered during following 7 days (while remaining on anakinra)	18 hours	↓ to 100 mg SC q8h on day 3, ↓ to 100 mg SC q12h day 15, ↓ to 100 mg SC daily day 16, discontinued day 17	17	2	Discharged from hospital, with limitation on activities‡	None

(Continued)

Table 2. (Cont'd)

Patient	Concomitant medications	Time from initiation of maximum supplemental O$_2$ (NRB 15L + NC 6L or HFNC) to initiation of anakinra	Anakinra dose titration	Number of days receiving anakinra	Current clinical status†	Observations	Adverse reactions while taking anakinra
9	Methylprednisolone 60 mg daily × 5 days (2 weeks prior to anakinra), then methylprednisolone 40 mg q12h for 5 days (simultaneous with the first 5 days of anakinra)	4 days after extubation	↓ to 100 mg SC q8h on day 4, ↓ to 100 mg SC q12h day 9, ↓ to 100 mg SC daily day 12, discontinued day 17	17	2	Discharged from hospital, with limitation on activities; required MV for 5 days; met criteria for CSS before and after extubation but consulted for anakinra treatment only after extubation‡	None
10	Methylprednisolone 40 q12h × 1 day (prior to anakinra)	24 hours	↓ to 100 mg SC q8h on day 6, discontinued on day 7	7	1	Discharged from hospital, no limitation on activities; required MV for 7 days; patient was intubated on day 1 of anakinra§	High suspicion for bacterial infection
11	None	24 hours	↓ to 100 mg SC q8h on day 2, discontinued day 4	4	1	Discharged from hospital, no limitation on activities; no anakinra on discharge‡	Elevation of AST/ALT; high suspicion for bacterial superinfection
Patients not treated with anakinra but meeting criteria							
12	Received tocilizumab and glucocorticoids	Not applicable	Anakinra not available in the hospital	0	4	Hospitalized, requiring supplemental 6L NC oxygen, O$_2$ saturation 98%; required MV for 15 days, failed extubation, and required MV again for 6 more days; now extubated§	Not applicable
13	Received sarilumab and glucocorticoids	Not applicable	Anakinra not available in the hospital	0	1	Discharged from hospital, no limitation on activities§	Not applicable
14	Received sarilumab and glucocorticoids	Not applicable	Patient declined anakinra	0	6	Hospitalized requiring invasive MV with tracheostomy; 41 days on MV as of June 2, 2020**	Not applicable

* All except patients 8 and 11 received hydroxychloroquine. All patients had discontinued anakinra by the end of the case series. COVID-19 = coronavirus disease 2019; NRB = nonrebreather; HFNC = high-flow nasal cannula; SC = subcutaneously; q6h = every 6 hours; AST = aspartate amino transferase; ALT = alanine aminotransferase; CSS = cytokine storm syndrome.
† Clinical status graded on 9-point ordinal scale suggested by the World Health Organization (9).
‡ Never required mechanical ventilation (MV).
§ Required mechanical ventilation but was successfully extubated.
¶ Deceased.
# Patient's blood culture was drawn before anakinra was initiated and results were pending when the medication was started. Once the results were positive, anakinra was discontinued.
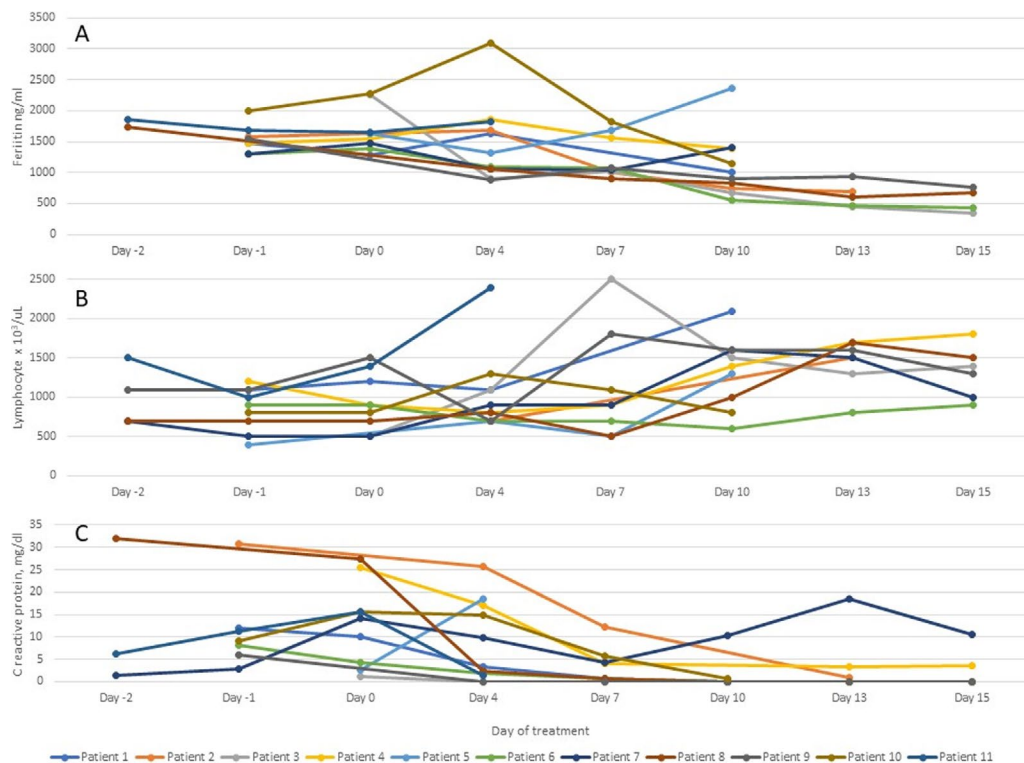** Required mechanical ventilation.

Figure 1. Ferritin levels (**A**), absolute lymphocyte count (**B**), and C-reactive protein levels (**C**) over time in patients with coronavirus disease 2019, severe respiratory failure, and features of cytokine storm syndrome treated with anakinra.

in China; 5 patients with Asian ancestry were included in this case series, providing valuable insight into the effect of anakinra in this population. The Hispanic population has experienced high mortality rates due to COVID-19 in New York City and is underrepresented in other research studies (14). Probing differences in COVID-19 outcomes across ethnic groups in the US is crucial, as it can help us understand the role of genetic and environmental factors that could contribute to a more severe clinical presentation of this disease. There are data linking genetic mutations associated with decreased natural killer cell function to fatal infections in patients with H1N1 (15). These mutations can trigger syndromes like MAS/cytokine storm syndrome in the setting of a viral infection; thus, future studies analyzing patients' genetic predisposition to develop severe COVID-19 should be pursued.

Mechanical ventilation is a known risk factor for developing bacterial pneumonia. Both of the patients who continued treatment with anakinra after requiring mechanical ventilation developed superimposed bacterial infection, which suggests anakinra may have augmented this risk. However, for patients who did not require mechanical ventilation, anakinra was well tolerated without the development of major infections. Elevation in transaminase levels was the most frequently observed laboratory abnormality in patients while they were receiving anakinra. It is possible that these changes were caused by cytokine storm syndrome itself; in all cases, the enzyme levels improved after lowering the anakinra dosage, so discontinuation was not necessary. All patients were

able to tolerate 100 mg of anakinra every 6 hours for 2–6 days before we decided to lower the dosage. The most common reasons for decreasing the dosage were clinical improvement or elevation of transaminase levels. Only 1 patient receiving anakinra experienced an injection site reaction, and this was the patient with the longest duration of treatment (19 days). Some studies of MAS used intravenous (IV) anakinra, while our study used the SC form (11). The pharmacokinetics of the medication could be affected by SC administration leading to slowed absorption, especially in obese patients. Still, our study provides insight into the use of SC anakinra when the IV form is not available.

To our knowledge, our study is the first report in the US to examine the use of anakinra in patients with COVID-19 and features of cytokine storm syndrome. A strength of our study is that we defined a narrow phenotype, which enabled us to both target a specific group of patients most likely to benefit from anakinra and avoid risks of immunosuppression in patients most likely to recover on their own. Whereas previous studies in MAS primarily examined IV administration of anakinra, our study showed a benefit with SC anakinra.

Our study has several limitations, including a small sample size and the absence of controls. We were still able to examine the relevance of our selection criteria by documenting clinical progression in 3 patients who did not receive anakinra.

Our experience provides insight regarding the use of anakinra in treating patients with COVID-19 with severe acute hypoxic

respiratory failure and features of cytokine storm syndrome. We identified a specific patient phenotype with COVID-19 that may benefit most from treatment with anakinra. It also provides guidance on a treatment strategy that employs high doses of anakinra for a minimum of 3–4 days followed by a slow taper based on clinical response and side effects, such as elevation of transaminase levels. The results of this study suggest that anakinra should be used cautiously in patients requiring mechanical ventilation, as those patients developed superimposed bacterial infection. This phenotype and treatment approach should be considered for examination in ongoing clinical trials (ClinicalTrials.gov identifiers: NCT04366232, NCT04412291, NCT04364009, NCT04324021, NCT04341584, and NCT04330638) and future clinical trials aimed at determining the safety and efficacy of anakinra in patients with COVID-19 and features of cytokine storm syndrome.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Navarro-Millán had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Navarro-Millán, Sattui, Lakhanpal, Zisa, Siegel, Crow.
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Analysis and interpretation of data. Navarro-Millán, Sattui, Lakhanpal, Zisa, Siegel, Crow.

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