BRIEF REPORT

OPEN

Plasma Interleukin-6 Predicts Clinical Decline After Completion of Dexamethasone Therapy in Severe COVID-19

F. Linzee Mabrey, MD[1,2]
Pavan K. Bhatraju, MD, MSc[1,2]
Eric D. Morrell, MD[1,2]
Leila R. Zelnick, PhD[3]
Neha A. Sathe, MD[1,2]
Nicholas G. O'Connor, BS[1]
Carmen Mikacenic, MD[1,2,4]
Thomas R. Martin, MD[1]
W. Conrad Liles, MD, PhD[1,2]
Mark M. Wurfel, MD, PhD[1,2]

OBJECTIVES: To identify and characterize clinical decline after completion of dexamethasone in severe COVID-19 and determine whether interleukin (IL)-6 and other inflammatory biomarkers predict the occurrence of clinical decline.

DESIGN: Prospective observational cohort.

SETTING: ICUs in three University of Washington affiliated hospitals between July 2020 and April 2021.

PATIENTS: Patients admitted to an ICU with COVID-19 who completed a course of dexamethasone.

MEASUREMENTS AND MAIN RESULTS: We identified 65 adult patients with severe COVID-19 who completed a 10-day course of dexamethasone, of whom 60 had plasma samples collected within 3 days of dexamethasone completion. We measured IL-6 with a clinical-grade electrochemiluminescent assay and a larger panel of inflammatory biomarkers (IL-8, Monocyte Chemoattractant Protein-1, Monocyte Inflammatory Protein-1 alpha, interferon gamma, C-X-C Motif Chemokine Ligand 10, WBC, bicarbonate) with a research immunoassay. We defined clinical decline by the occurrence of incident severe kidney injury, incident or escalating shock or fever, worsening hypoxemia, or death within 5 days of completion of dexamethasone. We estimated risk for clinical decline by standardized $\log_2$ transformed biomarker concentration using multivariable logistic regression. Clinical decline post-dexamethasone was common, occurring in 49% of patients ($n = 32$). Among all biomarkers, IL-6 levels were most strongly associated with clinical decline. After adjustment for age, sex, and study site, the odds of post-dexamethasone clinical decline were 7.33 times higher per one SD increase in log2 transformed IL-6 concentrations (adjusted odds ratio, 7.33; CI, 2.62–20.47; $p < 0.001$). The discriminatory power of IL-6 for clinical decline was high (cross-validated mean area under the receiver operating characteristic curve, 0.90; 95% CI, 0.79–0.95).

CONCLUSIONS: Clinical decline after completion of dexamethasone for severe COVID-19 is common. IL-6 concentrations obtained prior to completion of dexamethasone may have utility in identifying those at highest risk for subsequent worsening. If validated, future work might test whether plasma IL-6 could be used as a tool for a personalized approach to duration of dexamethasone treatment in severe COVID-19.

KEY WORDS: COVID-19; dexamethasone; interleukin-6; post-dexamethasone clinical decline

The COVID-19 pandemic has resulted in more than 6 million deaths worldwide (1). While rapid strides have been made to identify effective therapeutics, critically ill patients with severe respiratory failure experience high mortality of over 30% (2–4). Dexamethasone, a potent anti-inflammatory, has been shown to reduce risk of death in COVID-19 respiratory failure (2, 5). National Institute of Health guidelines recommend treatment

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KEY POINTS

Questions: What proportion of patient's experience clinical decline within 5 days of dexamethasone completion in severe COVID-19? Can inflammatory markers measured at the time of dexamethasone completion prospectively identify patients at risk for clinical decline?

Findings: Clinical decline after completion of dexamethasone for severe COVID-19 is common. Interleukin-6 (IL-6) concentrations obtained near completion of dexamethasone may have utility in identifying those at highest risk for subsequent worsening.

Meaning: Some patients with severe COVID-19 may require greater than 10 days of dexamethasone. Clinical trials may be warranted that test whether IL-6 can be used as a tool for a personalized approach to duration of dexamethasone treatment in severe COVID-19.

with 6 mg/d of dexamethasone for 10 days for severe COVID-19. While a significant proportion of patients remain severely ill at the end of dexamethasone treatment (2), currently, there is equipoise regarding whether dexamethasone or other immune modifiers should be continued if this occurs. Identification and characterization of the patients who exhibit clinical decline after completion of a standard course of dexamethasone have not been systematically described. The proportion of patients who exhibit clinical decline consistent with persistence or recurrence of severe systemic inflammation and the extent to which this might be related to outcome is also unknown. In this study, our primary objective was to identify and characterize clinical decline after completion of a standard course of dexamethasone for COVID-19.

In COVID-19, it has been widely reported that biomarkers of systemic inflammation including baseline clinical laboratories, proinflammatory mediators, and antiviral mediators are associated with risk of worse outcomes (6–10). However, it remains unclear whether the levels of these biomarkers measured after having received an anti-inflammatory therapy like dexamethasone might be indicative of a successful or incomplete treatment course. Identification of "response biomarkers" that can prospectively identify patients at high risk for clinical decline after discontinuation of dexamethasone for COVID-19 could facilitate future trials testing whether extension of dexamethasone therapy beyond 10 days may be beneficial (11). Here, our secondary objective was to evaluate whether biomarkers of systemic inflammation measured around the time of completion of a standard course of dexamethasone for COVID-19 identifies patients who have had a suboptimal anti-inflammatory response and are at high risk of subsequent clinical decline.

MATERIALS AND METHODS

Clinical Data and Ascertainment of Outcomes

We selected a subset of adult patients admitted with COVID-19–related critical illness and hospitalized through completion of dexamethasone therapy who were previously enrolled in the COVID-19 Host Response and Clinical Outcomes (CHROME) study, a prospective cohort study of COVID-19 critical illness (University of Washington Institutional Review Board: 9763; study: CHROME; March 17, 2020) (12) (**Supplemental Fig. 1**, http://links.lww.com/CCX/B104). The study was conducted in accordance with University of Washington Institutional Review Board & Helsinki Declaration 1975 ethical standards, and patients were unrolled under IRB-approved waiver of informed consent.

We defined clinical decline after completion of dexamethasone in a way that recognized that in critically ill patients with respiratory failure, death frequently occurs because of multiple organ dysfunction (13). We defined post-dexamethasone clinical decline by the occurrence of at least one of the following: incident severe kidney injury, incident or escalating shock, incident or escalating fever, worsening hypoxemia, or death in the 5 days following completion of dexamethasone therapy. We defined each element of clinical decline as follows: Incident severe acute kidney injury (AKI)—greater than two-fold increase in serum creatinine compared with baseline or new need for renal replacement therapy; Incident fever—new temperature greater than 38°C not present within 48 hours of dexamethasone completion and escalating fever as rise of greater than 0.5°C if fever was already present; Incident shock—new norepinephrine requirement if not present within 48 hours of dexamethasone completion and escalating shock as a doubling or rise of greater than 0.1 μg/kg/min in the norepinephrine infusion rate or initiation of vasopressin

infusion if shock was already present; Worsening hypoxemia—an increase in Sequential Organ Failure Assessment (SOFA) respiratory score of greater than 1 point. Events were ascertained from data prospectively collected from the electronic medical record. We defined culture-verified secondary bacterial infections as presence of new positive cultures (blood, urine, respiratory) treated by the clinical team and identified within the time period spanning 48 hours before to 48 hours after completion of dexamethasone.

Plasma Biomarker Measurements

We measured "end-dexamethasone" biomarker concentrations in plasma samples obtained within 72 hours of completion of a 10-day course of dexamethasone (median 1 d before completion) (**Supplemental Table 1**, http://links.lww.com/CCX/B104). Interleukin (IL)-6 concentrations in plasma were measured using an U.S. Food and Drug Administration authorized clinical assay (14) (Roche Elecsys Immunoassay, Cobas e411 analyzer, Indianapolis, IN). Additional biomarker concentrations (IL-8, Monocyte Chemoattractant Protein-1 [MCP-1], Monocyte Inflammatory Protein-1 alpha [MIP-1α], interferon gamma [IFN-γ], C-X-C Motif Chemokine Ligand 10 [CXCL10]) were measured using electrochemiluminescence immunoassays (Meso Scale Diagnostics, Rockville, MD). In a repeated measures analysis, we used serial IL-6 measurements from samples collected within 72 hours of admission (admission IL-6), at the end of dexamethasone treatment (end-dexamethasone IL-6), and following completion of dexamethasone (post-dexamethasone IL-6—median 3 d, interquartile range [IQR]: 2–4 d, after completion of dexamethasone).

Statistical Analysis

We used multivariable logistic regression to test for associations standardized, $\log_2$-transformed end-dexamethasone measurements (IL-6, IL-8, MCP-1, MIP-1α, IFN-γ, CXCL10, WBC, bicarbonate) and post-dexamethasone clinical decline. The diagnostic accuracy of end-dexamethasone IL-6 and SOFA for predicting post-dexamethasone clinical decline was calculated by 10-K-fold cross validation. We tested for an interaction between time and post-dexamethasone clinical decline status in patients who had available plasma IL-6 measurements at three times (admission, end-dexamethasone, and post-dexamethasone) using a mixed effects model with a time × clinical decline interaction term.

RESULTS

We identified 65 patients who were followed through completion of dexamethasone therapy (duration: median: 10 d; IQR: 10–10; range, 7–11). Many of these patients remained severely ill after completion of dexamethasone (median end-dexamethasone SOFA: 6; IQR: 2–10) (**Table 1**). The primary outcome of post-dexamethasone clinical decline occurred in 32 of 65 patients (49%). Components of the outcome were overlapping with incident or worsening shock being the most common qualifying event (**Supplemental Fig. 2**, http://links.lww.com/CCX/B104). The overall in-hospital mortality was 38% (Table 1) and was significantly

TABLE 1.
Characteristics of the Cohort and Summary of Clinical Decline Events

Cohort Characteristics Parameter	
Baseline characteristics (*n* = 65)	
Age, median (IQR)	59 (50–70)
Male sex, *n* (%)	47 (72)
Acute respiratory distress syndrome, *n* (%)[a]	46 (71)
Transfer, *n* (%)	34 (52)
End-dexamethasone invasive mechanical ventilation, *n* (%)	30 (46)
End-dexamethasone Sequential Organ Failure Assessment, median (IQR)	6 (2–10)
In-hospital mortality, *n* (%)	25 (38)
Length of dexamethasone, median (IQR)	10 (10–10)
Treated with tocilizumab, *n* (%)	1 (1.5)
Post-dexamethasone clinical decline, *n* (%)	
Post-dexamethasone clinical decline (composite)	32 (49)
Incident severe acute kidney injury	6 (9)
Incident or escalating fever	18 (28)
Incident or escalating shock	25 (38)
Worsening hypoxemia	3 (5)
Death within 5 d	1 (2)

IQR = interquartile range.
[a]Acute respiratory distress syndrome adjudicated within 1 wk of admission using the Berlin criteria.
Categorical variables are presented as *n* (%).
Continuous variables are summarized with median (IQR).

higher in patients who experienced post-dexamethasone clinical decline (n = 21, 68%) than those who did not (n = 4, 12%) (Fisher exact $p < 0.001$).

Culture-verified bacterial infections arising within the time frame spanning 48 hours before to 48 hours after completion of dexamethasone occurred in 13 of 65 patients (20%). There were more infections in patients who experienced post-dexamethasone clinical decline (n = 11, 34% vs n = 2, 6%) (Fisher exact p = 0.005) (**Supplemental Table 2**, http://links.lww.com/CCX/B104).

Sixty participants had an available end-dexamethasone IL-6 measurement (median: 28 pg/mL; IQR: 13–111 pg/mL) (**Supplemental Table 3**, http://links.lww.com/CCX/B104). After adjustment for age, sex, and study site, the odds of post-dexamethasone clinical decline were 7.33 times higher per one SD increase in $\log^2$-transformed IL-6 concentration (adjusted odds ratio [aOR], 7.33; CI, 2.62–20.47; $p < 0.001$) (**Supplemental Table 4**, http://links.lww.com/CCX/B104). End-dexamethasone IL-6 was associated with increased odds of shock and AKI but, notably, not worsening hypoxemia (**Supplemental Table 5**, http://links.lww.com/CCX/B104). Standardized, $\log_2$-transformed IL-8, MCP-1, MIP-1α, and CXCL10 were also associated with post-dexamethasone clinical decline though the strengths of associations were less than that of IL-6. Concentrations of IL-8, IFN-γ, WBC, and bicarbonate were not associated with post-dexamethasone clinical decline (**Supplemental Table 6**, http://links.lww.com/CCX/B104). Given the strong association between end-dexamethasone IL-6 and clinical decline, we evaluated its discriminatory utility. Using 10-K-fold cross validation, we found that end-dexamethasone IL-6 was a robust predictor of post-dexamethasone clinical decline (cross-validated mean area under the receiver operating characteristic curve [cvMean AUC], 0.90; 95% CI, 0.79–0.95) and performed similarly to SOFA (cvMean AUC, 0.87; 95% CI, 0.68–0.92) (**Fig. 1*A***). End-dexamethasone IL-6 greater than 21.4 pg/mL (optimal cutpoint by Youden index) had a positive predictive value of 84% and a negative predictive value of 86%.

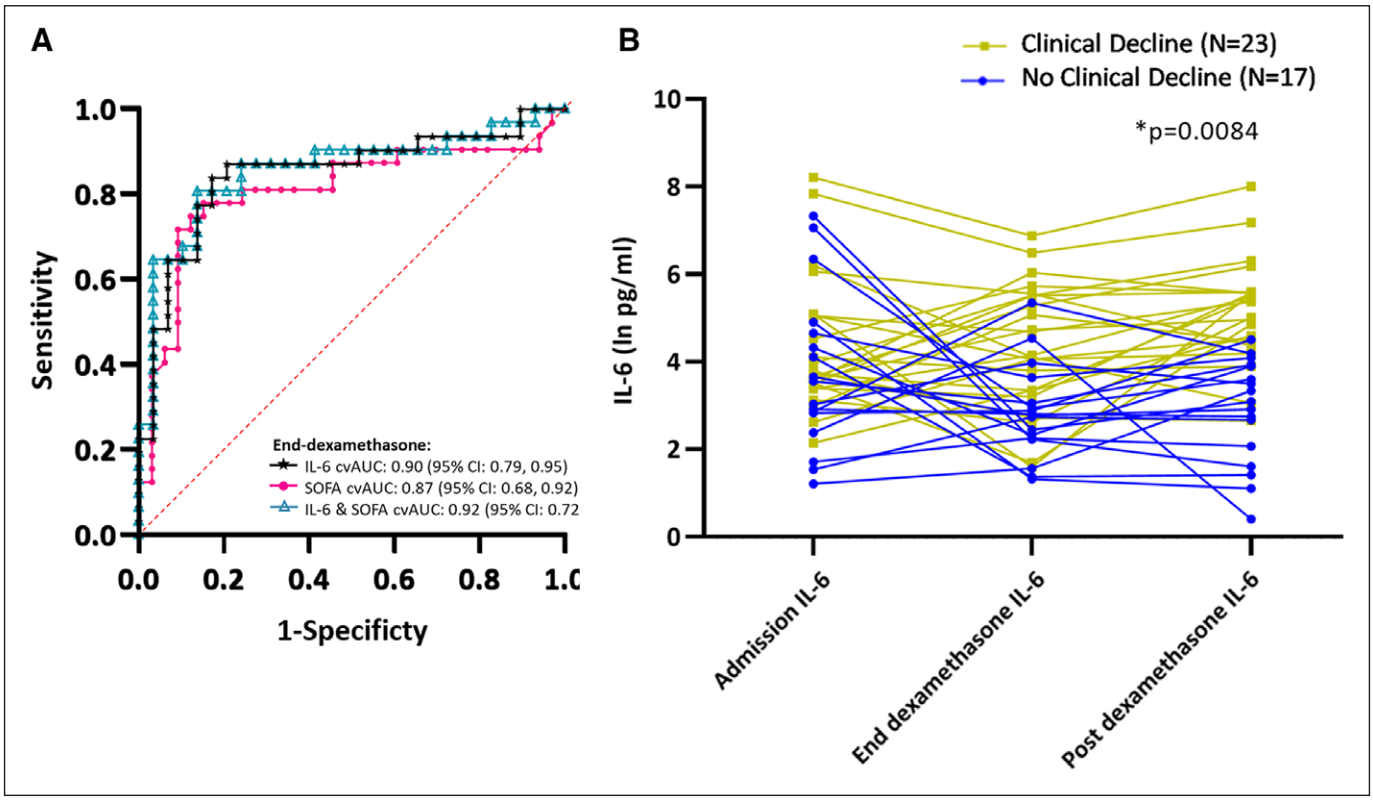

Figure 1. End-dexamethasone IL-6 predicts subsequent clinical decline. **A**, Receiver operating characteristic curves for end-dexamethasone interleukin-6 (IL-6) concentrations, end-dexamethasone Sequential Organ Failure Assessment (SOFA) scores, end-dexamethasone IL-6 concentrations + SOFA scores as predictors of post-dexamethasone clinical decline using logistic regression and k-fold cross-validation (CV). **B**, *Spaghetti plot* showing IL-6 concentrations at three time points for 40 individuals with available data. *Lines* connect measurements for individual patients. The displayed p value is for the significant interaction between time point and post-steroid clinical decline in a mixed-effects model. cvAUC = cross-validated area under the receiver operating characteristic curve.

End-dexamethasone IL-6 remained a strong predictor of clinical decline even after: 1) limiting to participants without severe AKI, fever, or shock at the time of measurement (Supplemental Table 5, http://links.lww.com/CCX/B104); 2) excluding participants with plasma samples collected greater than 1 day after completion of dexamethasone (**Supplemental Table 7**, http://links.lww.com/CCX/B104); and 3) excluding those with bacterial infections (**Supplemental Table 8**, http://links.lww.com/CCX/B104).

We then examined whether ICU admission IL-6 levels or the trajectory of IL-6 levels were associated with post-dexamethasone clinical decline. Admission IL-6 levels were not associated with clinical decline (aOR, 1.10; 95% CI, 0.51–2.37; $p = 0.81$), which remained true when excluding outside hospital transfers ($p = 0.90$). In a repeated measures analysis using enrollment, end-dexamethasone, and post-dexamethasone IL-6 levels, we identified a significant interaction between time and post-dexamethasone clinical decline ($p = 0.0084$). Among those who experience post-dexamethasone clinical decline, post-dexamethasone IL-6 was 2.21-fold higher (95% CI, 1.10–4.46; adjusted $p = 0.024$) than end-dexamethasone IL-6 suggesting that withdrawal of steroids precedes an increase in inflammation (**Fig. 1*B***; and **Supplemental Fig. 3**, http://links.lww.com/CCX/B104).

In an exploratory analysis of 36 participants enrolled prior to publication of the Randomised Evaluation of COVID-19 Therapy Trial trial of dexamethasone in COVID-19 who were hospitalized through day 7 and "not" treated with dexamethasone, 13 (36%) met criteria for subsequent clinical decline between days 8 and 12 (zero deaths, eight fever, six shock, one AKI, one worsening hypoxemia). Among those with available measurements ($n = 25$), day 7 IL-6 was not associated with subsequent clinical decline (OR, 1.11; $p = 0.53$).

DISCUSSION AND CONCLUSIONS

Our study demonstrated that immediate clinical decline, often with worsening organ dysfunction, is common after completion of a standard course of dexamethasone for COVID-19 and associated with subsequent mortality. We showed that end-dexamethasone IL-6 in plasma, a measurement available in most clinical laboratories, was a robust predictor of post-dexamethasone clinical decline. In contrast, IL-6 measured at ICU admission did not predict post-dexamethasone clinical decline. This suggests that the end-dexamethasone IL-6 levels reflect a response to therapy rather than just a difference in baseline severity. In looking at the trajectory of IL-6 after completion of therapy, we observed a rise in IL-6 levels among those who experienced clinical decline that was not seen in those who did not exhibit clinical decline. Taken together, our findings suggest that end-dexamethasone IL-6 levels may have utility as a dexamethasone response biomarker, identifying those with suboptimal response to treatment who are at risk for subsequent organ injury and who exhibit a potentially modifiable rise in inflammation. Recently, a pilot study showed that a biomarker-guided strategy to determine the duration of dexamethasone was feasible, and future studies might test whether IL-6 can be used as a response biomarker to guide the duration of dexamethasone treatment in COVID-19 (11).

Our study has some limitations. First, it is limited to a single modest cohort and will require validation. Second, there was some variation in plasma collection times relative to dexamethasone completion, which could have contributed bias. However, the distribution of sampling times were similar between groups, and a sensitivity analysis limiting to only patients sampled less than or equal to 1 day after completion of dexamethasone showed similar results. Finally, it is possible that secondary infections could be confounding the relationship between IL-6 elevation and clinical decline. However, in a sensitivity analysis, the association between end-dexamethasone IL-6 and subsequent clinical decline was strong irrespective of whether patients were diagnosed with a secondary infection.

In conclusion, clinical decline after dexamethasone treatment for severe COVID-19 is common and may be related to ongoing systemic inflammation. If validated, future trials might test whether IL-6 measurements could be used as a simple response biomarker tool to guide a personalized approach to duration of dexamethasone treatment in severe COVID-19.

1 *Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA.*

2 *Sepsis Center of Research Excellence-UW (SCORE-UW), University of Washington, Seattle, WA.*

3 *Kidney Research Institute (KRI), Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA.*

4 *Translational Research, Benaroya Research Institute, Seattle, WA.*

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For information regarding this article, E-mail: mflinzee@uw.edu

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