LENZILUMAB TREATMENT IN COVID-19 PNEUMONIA REDUCES CIRCULATING CYTOKINES AND MARKERS OF SYSTEMIC INFLAMMATION

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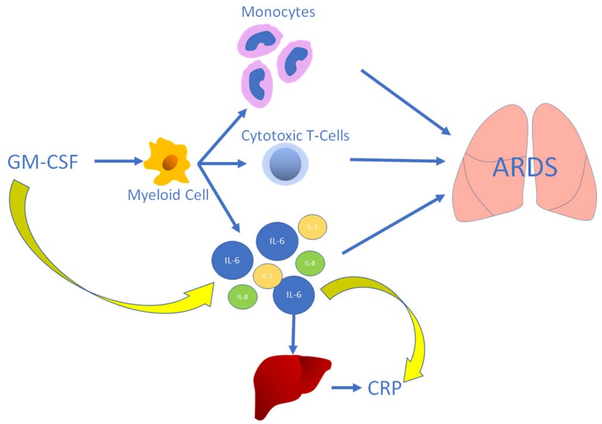
INTRODUCTION

GM-CSF is one of the early upstream mediators and orchestrators of the hyperinflammatory immune response following SARS-CoV-2 infection. The pro-inflammatory cytokine cascade observed in COVID-19 is consistent with GM-CSF orchestrated myeloid activation driving downstream effector cytokines production including IL-6. Subsequent elevation of CRP is driven by this elevation in IL-6. Baseline levels of GM-CSF and CRP have each been shown to correlate with COVID-19 disease progression. In the phase 3, randomized, double-blind, placebo-controlled LIVE-AIR study, GM-CSF neutralization with lenzilumab significantly improved the likelihood of survival without invasive mechanical ventilation (SWOV, primary endpoint, also referred to as ventilator-free survival) vs. placebo (HR:1.54; 95% CI, 1.02 to 2.32; p=0.040), which included standard supportive care including corticosteroids and remdesivir. This sub-analysis correlated levels of cytokines before and after lenzilumab treatment to characterize the relationship between GM-CSF, IL-6 and CRP and its impact on patient outcomes.

OBJECTIVE

The objective of this analysis was to highlight the correlation between the key inflammatory mediators, IL-6 and GM-CSF, and the widely used marker of inflammation, C-Reactive Protein (CRP). Additionally, the impact of baseline GM-CSF on the outcomes of hospitalized COVID-19 patients will be assessed.

The GM-CSF - IL-6 - CRP Axis



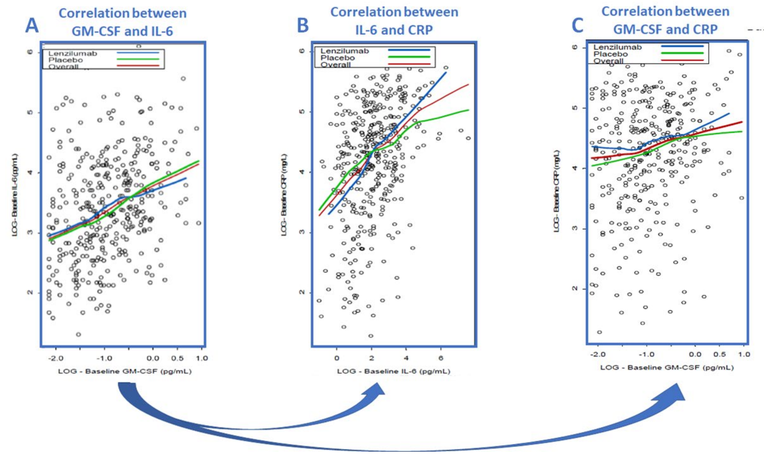
METHODS

LIVE-AIR was a phase 3, randomized, double-blind, placebo-controlled trial (NCT04351152). Patients hospitalized with COVID-19 pneumonia, requiring only supplemental oxygen, were randomized to receive lenzilumab (1800 mg in three equally divided doses of 600 mg, q8h) or placebo IV infusion, in addition to standard of care which included remdesivir and corticosteroids. Blood taken at baseline (BL) and times subsequent to treatment through day 10 (D10) were obtained and analyzed by high sensitivity enzyme immunoassay for GM-CSF, IL-6, and CRP.

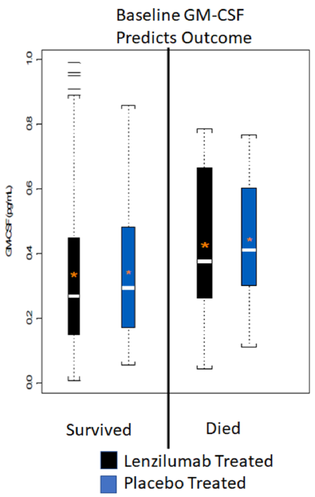
RESULTS

Correlation between GM-CSF, IL-6 and CRP

Elevation of CRP is driven by IL-6, a downstream pro-inflammatory effector cytokine of hyperinflammatory immune response whose production is driven in part by GM-CSF. The graph below displays the evident correlation between GM-CSF levels and IL-6 levels(A) and the resultant correlation between IL-6 and CRP levels (B). Despite CRP production being downstream of GM-CSF, it appears that a correlation between GM-CSF and CRP remains (C). This suggests the utility of using CRP as a biomarker for emerging hyperinflammatory immune response driven by upstream GM-CSF.



Higher baseline GM-CSF associated with increased mortality

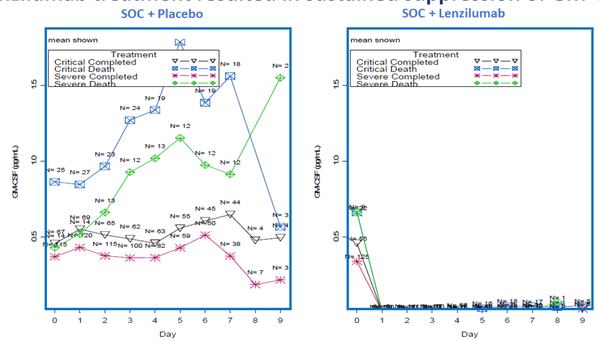


Baseline GM-CSF were measured using ultra-high sensitivity Simoa assay.

The pro-inflammatory cytokine cascade observed in COVID-19 is consistent with GM-CSF orchestrated myeloid activation. Previous research has demonstrated that increasing levels of circulating GM-CSF have been associated with progression and increasing severity of disease. This analysis further validates this observation, demonstrating that baseline GM-CSF appears to identify patients who pose the greatest mortality risk.

However, it must also be noted that, even in the inflammatory state, GM-CSF levels are in the pg/ml quantities and remain difficult to measure.

Lenzilumab treatment resulted in sustained suppression of GM-CSF

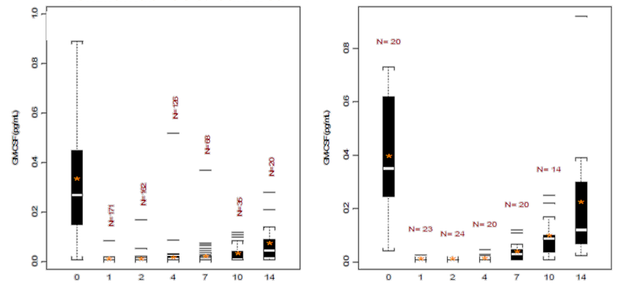


Lenzilumab treatment resulted in sustained reduction in GM-CSF levels regardless of outcome. In patients treated with placebo, a continued rise in GM-CSF levels was observed in patients who died (Critical Death and Severe Death). In patients who survived, GM-CSF levels remained level before reducing from Day 6-7.

Lenzilumab treatment suppressed IL-6 and CRP

	GM-CSF (fg/ml)			IL-6 (pg/ml)			CRP (mg/L)		
	BL	D1	D10	BL	D1	D10	BL	D1	D10
Placebo (n=247)	460 ±30	530 ±430	840 ±100	29.7 ±9.7	23.1 ±3.1	76.5 ±25.5	91.6 ±4.5	68.8 ±4.0	70.1 ±11.2
Lenzilumab (n=233)	400 ±30	10 ±10	50 ±10	23.0 ±3.7	13.9 ±2.0	40.7 ±12.1	100.0 ±5.3	73.5 ±4.7	50.8 ±10.2

Rebound in GM-CSF in lenzilumab treated patients who died



In patients treated with lenzilumab who subsequently died, not only did these patients have a higher baseline GM-CSF, but they also experienced a rebound in GM-CSF from Day 7. This may suggest that patients with higher GM-CSF levels may benefit from a second dose of lenzilumab if they continue to progress despite and an initial lenzilumab dose. Future studies are required to confirm this therapeutic approach.

CONCLUSION

- There appears to be a correlation between IL-6 and GM-CSF, IL-6 and CRP as well as GM-CSF and CRP suggesting that using CRP as a biomarker for emerging hyperinflammatory immune response driven by upstream GM-CSF may have clinical utility
- Lenzilumab produced marked and sustained suppression of GM-CSF, a key initiator of the downstream hyperinflammatory response
- In placebo patients who died, GM-CSF levels continue to rise from baseline
- In patients treated with lenzilumab who subsequently died, a rebound in GM-CSF was observed, suggesting that repeat dosing of lenzilumab may be of some benefit