Compassionate use of C5 inhibitor, Nomacopan, potentially influenced the course and progression of disease in COVID-19 pneumonia

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Abstract

BACKGROUND: Nomacopan® is a first-in-class, dual inhibitor of leukotriene B4 (LTB4) and complement C5. It is currently in Phase-III clinical trials for bullous pemphigoid and HSCT-TMA. Nomacopan was used compassionately to treat 7 USA COVID-19 pneumonia patients. We compared them with the data from an observational study of biomarkers within a larger cohort of COVID-19 patients UK who had the same inclusion and exclusion criteria, where discriminating biomarkers were associated with worse outcomes.

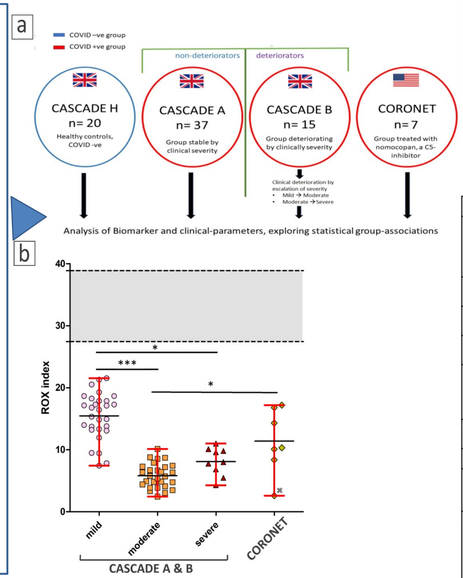
METHODS: The groups of patients in USA (CORONET study) and UK (CASCADE) healthy-controls and COVID-19 pneumonia patients summarised in Figure 1. Between-group comparisons in demographic, clinical and biomarker levels were carried out using Kruskal-Wallis and rank-Wilcoxon tests. 7 patients (six males and one female; 5 Cincinnati & 2 Ohio) in the CORONET study were treated with nomacopan (1st initial subcutaneous-dose: 45mg of nomacopan, 12-hourly for day 1. Subsequently, patients were administered 45mg, o.d. for 12 days. Antibiotic prophylaxis was co-administered.

RESULTS: ROX indices for patients at enrolment within the CASCADE and CORONET studies were lower than healthy controls, with SpO2 <93%, and were admitted to HDU/ICU with COVID-19 pneumonia. None were initially requiring invasive mechanical ventilation (IMV). In addition to the degree of respiratory failure we took biomarker data from our CASCADE study (UK) that was used to assess severity for the CORONET study (USA). Of the seven patients in the CORONET study, six survived, one (female) died where there was a three day delay to get nomacopan treatment. An independent Data Management and Safety Committee determined the use of the nomacopan in each patient

DISCUSSION: By combining the data in these groups of COVID-19 pneumonia patients we saw similar degrees of respiratory failure and a similar pattern of biomarkers. The treatment with nomacopan led to survival in 6 with early discharge from hospital and one death from the patient with delayed treatment. There were no treatment related adverse events.

Methods

Figure 1. Schematic summarising the participant groups in the CASCADE-CORONET studies. **(a)** Participants with COVID-19 were stratified according to degree of respiratory failure , (i) Mild: requiring low flow oxygen (FiO2≤0.4), (ii) Moderate: requiring FiO2>0.4 +/- NIV support (HFNO/CPAP), (iii) Severe: requiring mechanical ventilation. Combined nose and throat swabs for COVID-19 qPCR were taken from all participants and processed as per standard published protocols, with modifications. Biomarker levels were determined from blood samples with necessary containment procedures in place. **(b)** The ROX index is a clinical assessment of the degree of a patient's respiratory failure and need for intubation. Normal ROX indices were calculated with FiO_2 of 21%, respiratory rates between 12 & 18 bpm, and SpO_2 of 95-98%. The upper and lower limits shown in red bars represent the maximum and minimum data within that group. Black horizontal lines represent the average-ROX-index. CORONET patients treated with nomacopan, also had ROX indices below that of normal healthy individuals. The * indicate the p values.



Results

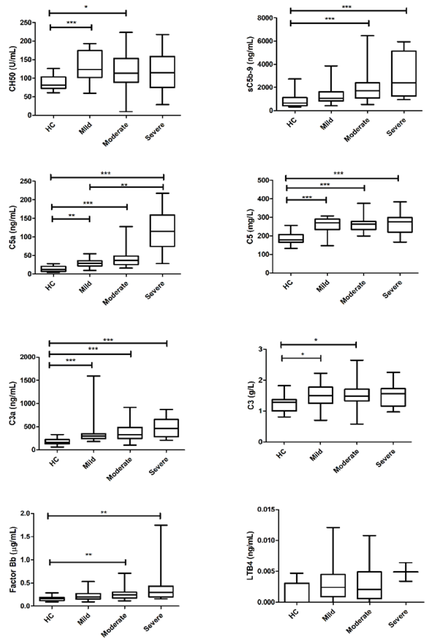


Figure 2. Levels of complement components and LTB4 in healthy controls compared to COVID-infected patients. CH50, sC5b-9, C5, C5a, C3a, and LTB4 levels were all elevated in CASCADE patients. Not all the biomarker levels assessed in CASCADE were measured in CORONET patients.

Figure 3. CORONET patients summarised by clinical outcomes and CH50 levels, and CRP measurements. The Biomarkers of subset of CASCADE patients remained clinically stable and those who deteriorated during their hospital stay were compared with the same biomarkers from 5 of the CORONET patients from Cincinnati. The biomarker levels in the deteriorators in CASCADE were the same as the CORONET patients.

CORONET CAMPASSIONATE USE OF NOMACOPAN

	Age (yr)	Gender	qPCR test	Date of admission	O2 flow rate /min for SpO2> 93%	Outcome: survival or death	Number of day to recover	CH50 at 3days UL < 40u/mL	Highest CRP/UL <10mg/ml	Discharge/death
Cincinnati Patients										
1.	68	Male	+ve	09/20	8L NC	Survived	11	<17u/mL	40.5mg/mL	Normoxia on air
2.	56	Male	+ve	11/20	2L NC	Survived	3	22u/mL	199mg/mL	Normoxia on air
3.	45	Male	+ve	01/21	6L NC	Survived	5	21u/mL	116mg/mL	Normoxia on air
4.	44	Male	+ve	02/21	6L NC	Survived (IMV) 4 days)	22	20u/mL	193mg/mL	4L O2 with rest
5.	41	Male	+ve	04/21	4L NC	Survived	5	15u/mL	109.3mg/L	Normoxia on air
Ohio Patients										
1.	62	Male	+ve	7/2020	4L NC	Survival	6	<10	154.18 mg/L	Normoxia on air
2.	28	Female Delayed nomacopan 3 days	+ve	7/2020	IMV 7 days after admission	IMV for 7 days	N/A	>60 prior to nomacopan	274.65 mg/L	Died 14 days after admission

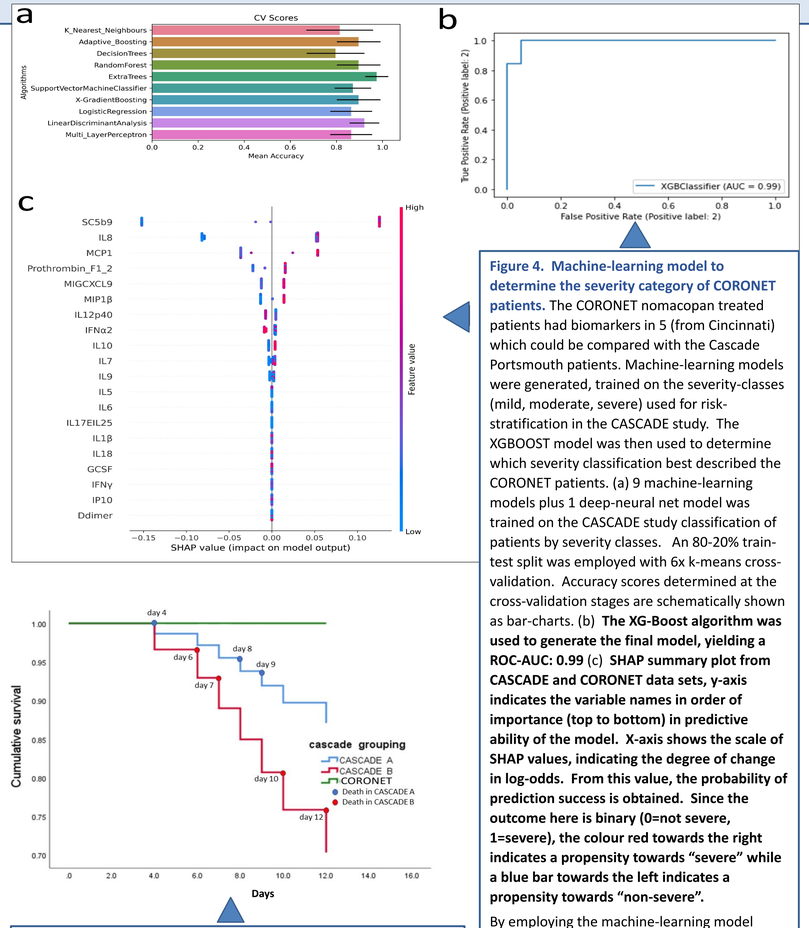


Figure 4. Machine-learning model to determine the severity category of CORONET patients. The CORONET nomacopan treated patients had biomarkers in 5 (from Cincinnati) which could be compared with the Cascade Portsmouth patients. Machine-learning models were generated, trained on the severity-classes (mild, moderate, severe) used for risk-stratification in the CASCADE study. The XGBOOST model was then used to determine which severity classification best described the CORONET patients. (a) 9 machine-learning models plus 1 deep-neural net model was trained on the CASCADE study classification of patients by severity classes. An 80-20% train-test split was employed with 6x k-means cross-validation. Accuracy scores determined at the cross-validation stages are schematically shown as bar-charts. (b) **The XG-Boost algorithm was used to generate the final model, yielding a ROC-AUC: 0.99** (c) **SHAP summary plot from CASCADE and CORONET data sets, y-axis indicates the variable names in order of importance (top to bottom) in predictive ability of the model. X-axis shows the scale of SHAP values, indicating the degree of change in log-odds. From this value, the probability of prediction success is obtained. Since the outcome here is binary (0=not severe, 1=severe), the colour red towards the right indicates a propensity towards "severe" while a blue bar towards the left indicates a propensity towards "non-severe".**

By employing the machine-learning model trained on CASCADE severity classifications, the CORONET 5 Cincinnati patients with biomarkers showed the same "severe" pattern as the CASCADE cohort deteriorators

Figure 5. Survival and deaths in CASCADE A, CASCADE B and CORONET studies. Kaplan-Meier curve analysis, showing comparative survival and deaths. One patient, who was not treated timely in the CORONET study, was not included in this survival curve plot.

Discussion

The 6 patients (Cincinnati and Ohio) were treated with nomacopan in the CORONET study recovered. One patient unfortunately succumbed to the disease where there was a delay in starting treatment. A critique of this compassionate programme is its small size and that patients in the CORONET study could be of a milder phenotype than deteriorators in CASCADE and would have made a recovery regardless of the treatment with nomacopan. To address this, our machine-learning model of biomarkers classified the 5 Cincinnati patients (incomplete set of biomarkers in both Ohio pts.) comparatively as severe according to the classification system used in the CASCADE (UK) study (poster 11486). Thus retrospectively, the CORONET study patients would have been classified as having the same deteriorating phenotype as in CASCADE. Our analysis showed that these patients also had high levels of sC5b-9, of the terminal complement pathway. A randomised/controlled and double blinded study would be needed to confirm that nomacopan is an effective treatment. No treatment emergent adverse effects were seen with nomacopan.

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