European Review for Medical and Pharmacological Sciences 2020; 24: 4040-4047

Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience

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Abstract. – OBJECTIVE: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2)-related pneumonia, referred to as COVID-19 (Coronavirus Disease 19), is a public health emergency as it carries high morbidity, mortality, and has no approved specific pharmacological treatments. In this case series, we aimed to report preliminary data obtained with anti-complement C5 therapy with eculizumab in COVID-19 patients admitted to intensive care unit (ICU) of ASL Napoli 2 Nord.

PATIENTS AND METHODS: This is a case series of patients with a confirmed diagnosis of SARS-CoV2 infection and severe pneumonia or ARDS who were treated with up to 4 infusions of eculizumab as an off-label agent. Patients were also treated with anticoagulant therapy with Enoxaparin 4000 IU/day *via* subcutaneous injection, antiviral therapy with Lopinavir 800 mg/day + Ritonavir 200 mg/day, hydroxychloroquine 400 mg/day, ceftriaxone 2 g/day IV, vitamine C 6 g/day for 4 days, and were on Non-Invasive Ventilation (NIV).

RESULTS: We treated four COVID-19 patients admitted to the intensive care unit because of severe pneumonia or ARDS. All patients successfully recovered after treatment with

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eculizumab. Eculizumab induced a drop in inflammatory markers. Mean C Reactive Protein levels dropped from 14.6 mg/dl to 3.5 mg/dl and the mean duration of the disease was 12.8 days.

CONCLUSIONS: Eculizumab has the potential to be a key player in treatment of severe cases of COVID-19. Our results support eculizumab use as an off-label treatment of COVID-19, pending confirmation from the ongoing SOLID-C19 trial.

Key Words:
Coronavirus, CoVid-19, Treatment, Eculizumab.

Introduction

At the end of 2019, multiple cases of viral pneumonia of unknown origin were reported in China. The responsible virus has since then been identified as part of the severe acute respiratory syndrome coronaviruses species (SARS-CoVs) and named "SARS-CoV2", while the SARS-CoV-2-related pneumonia is commonly referred to as COVID-19[1].

The acute respiratory distress syndrome (ARDS) definition includes multiple immune-mediated pathologies, also observed in severe cases of coronavirus (CoV) infection[2]. It has been extensively demonstrated that complement activation, and especially C5a, is involved in the development of acute lung disease induced by pathogenic viruses[3,4].

Gralinski et al[4] evaluated activation of the complement system in a mouse model of CoV. They showed that, at day 1 post-infection, C3 activation products were detected in SARS-CoV MA15-infected mice, but not in control mice. Moreover, they highlighted C3 deposition in the lungs of infected wild type mice on day 2 and day 4 post-infection, while transgenic animals lacking C3 were protected from SARS-CoV-induced disease. In addition to a decreased weight loss, transgenic mice showed less inflammatory cells in the large airway and parenchyma, perivascular cuffing, thickening of the interstitial membrane, and low levels of intra-alveolar edema, an improved respiratory function, and lower levels of inflammatory cytokines or chemokines both in the respiratory system and in blood[4].

MERS-CoV causes a severe acute respiratory failure, burdened with a high mortality. Jiang et al[5] showed that MERS-related disease in mice is characterized by an elevated secretion of cytokines and chemokines. Moreover, in these infected mice they highlighted an excessive complement activation[5]. In particular, they detected increased concentrations of C5a and C5b-9, resulting from cleavage of C5, in sera and lung, respectively.

Therefore, a C5 inhibitor may be an effective therapeutic in coronavirus-mediated disease. Jiang et al[5] demonstrated that blocking C5a with a specific antibody against the C5a receptor (C5aR) reduces lung damage, due to a reduced alveolar macrophage infiltration and interferon (IF-N)-gamma receptor expression, accompanied by a decreased viral replication[5].

As the available evidence supports the role of C3 and the terminal complement complex in the pathogenesis of ARDS during viral infections, but not the alternative pathway, the inhibition of complement, specifically at the terminal complement node through inhibition of C5, may control the inflammatory processes.

Eculizumab is a human monoclonal antibody (hmAb) designed to bind to the complement protein C5 with high affinity. It inhibits cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b-9, which is involved in cell lysis[6]. Interestingly, C5 blockade shows an indirect immunoprotective and immunoregulatory action by preserving early complement components (Figure 1).

Complement inhibition has been shown to be an effective therapeutic target in hematological and neuroinflammatory diseases[6-9]. Progressively more evidence shows that complement is also a key mediator of lung damage during viral infections, and especially during CoV infection[10]. Thus, it is possible that complement activation is also a key player in COVID-19 infection-related injuries and multi-organ failures (MOF).

Therefore, eculizumab (Soliris®, Alexion Pharma International, Zürich, Switzerland), an effective and extensively studied terminal complement inhibitor with a well-established safety profile, might work as an emergency therapy for the treatment of patients with severe pneumonia or ARDS associated with COVID-19 infection. As eculizumab completely inhibits C5-mediated terminal complement activity, we hypothesized that treatment with eculizumab could ameliorate COVID-19-induced lung injury, improving outcomes in patients with severe pneumonia or ARDS associated with COVID- 19 infection.

Here, we present four cases of COVID-19 related ARDS treated with eculizumab.

Patients and Methods

We report about the results obtained with the off-label use of eculizumab treated according to a treatment protocol established for internal use.

The treatment protocol consists of a screening period of up to 7 days, a treatment period lasting

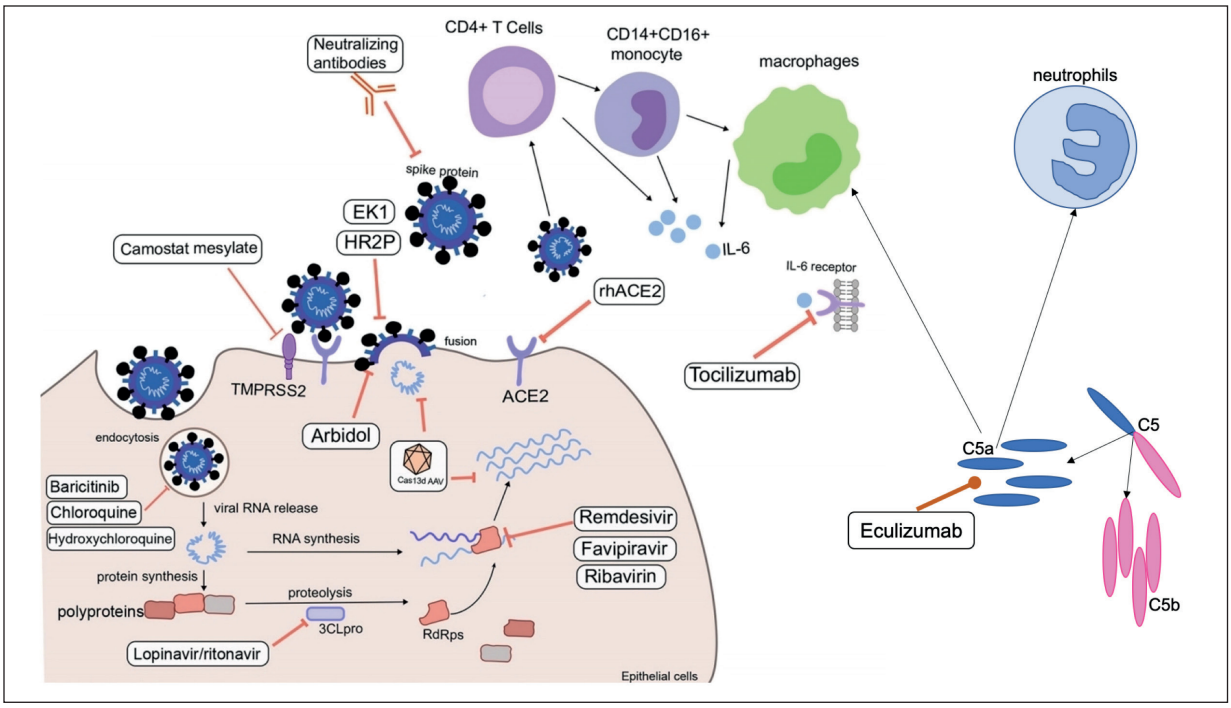

Figure 1. Pathogenesis and therapy targets.

up to 4 weeks, and the final assessment at day 29. Screening and the day 1 visits can occur on the same day if necessary if the subject has met all inclusion and none of the exclusion criteria.

Up to 4 weekly infusions of eculizumab at 900 mg were administered. Eculizumab is formulated at pH 7 and each 30 mL vial contains 300 mg of eculizumab, polysorbate 80 (6.6 mg) (vegetable origin), sodium chloride (263.1 mg), sodium phosphate dibasic (53.4 mg), sodium phosphate monobasic (13.8 mg), and water for injection, USP. Eculizumab has to be administered *via* IV infusion *via* gravity feed, a syringe-type pump, or an infusion pump, and has been diluted to a final concentration of 5 mg/mL before administration. The diluted eculizumab has been IV administered over approximately 35 minutes. The patients have been monitored for at least 1 hour following the infusion for signs or symptoms of an infusion reaction. The duration of each patient's treatment with eculizumab was a minimum of 8 days and a maximum of 22 days.

Patients could be treated with: 1. Confirmed severe COVID-19 requiring hospitalization; 2. Symptomatic, bilateral pneumonia confirmed by CT or X-ray at screening or within the 7 days prior to screening; 3. Severe pneumonia requiring oxygen supplementation (WHO 2020); 4. ≥18 year of age at the time of providing informed consent/assent; 5. willing and able to give written informed consent. Exclusion Criteria: 1. confirmed mild to moderate COVID-19, even if the patient is hospitalized; 2. the patient is not expected to survive > 24 hours.

Supportive therapy during treatment with eculizumab consisted in:

- anticoagulant therapy with Enoxaparin 4000 IU/day *via* subcutaneous injection;
- antiviral therapy with Lopinavir 800 mg/day + Ritonavir 200 mg/day;
- hydroxychloroquine 400 mg/day;
- ceftriaxone 2 g/day IV;
- vitamin C6 g/day for 4 days;
- CPAP (non-invasive ventilation).

All chest CT examinations were performed with a Philips Ingenuity 64 scanner located in the "red" COVID area.

Patients were examined in a supine position, wrapped in a waterproof sheet, with arms raised in respiratory apnea, if possible. Scanning range from the apex to the base. The scan parameters adopted were as follows: helical scan mode; tube voltage, 120 kV; mAs 30-200 mAs; matrix, at least 512 x 512; 1 mm thick reconstruction algorithm with high spatial frequency (for lung or bone); CT analysis: two radiologists have analyzed the CT images independently with lung window (width,

1500 HU; level, -700 HU) and mediastinal (width, 350 HU; level, 40 HU). In case of discrepancy, an agreement was reached through discussion. For each patient, the initial CT scans were evaluated for the following high-resolution CT feature: (a) distribution of lesions in lung (peripheral, central, peripheral and central), (b) number of lobes involved (one, two or three, four or five); (c) shape of lesions (patchy, nodular); (d) appearance of lesions (ground-glass opacity (GGO),consolidation, ground-glass opacity with consolidation); (e) specific signs of outbreak (vascular thickening, crazy paving pattern-defined as GGO area associated with thickening interlobular and intralobar septa-, air bronchogram sign, halo sign, fibrosis); (f) size of the single largest lesion – cm-(<1 cm, 1-3 cm, >3 cm); (g) associated manifestations (emphysema, neoplasm, fibrosis); (h) extrapulmonary manifestations (presence of thoracic lymphadenopathy defined as lymph node size of ≥10 mm in short-axis dimension, pleural effusion or pleural thickening); (i) other anomalies (cavitation, cross linking, calcification, bronchiectasis). Each of the five lung lobes was assessed for degree of involvement and classified as minimal [<5 %: score 1, mild (6-25%: score 2), moderate (26%-50%: score 3), severe (51-75%: score 4), very severe (>75%: score 5) and an overall lung "total severity score" was calculated by summing the five lobe scores (range of possible scores, 0-25)][11].

The patients underwent follow-up chest CT during the study time window. These scans were also evaluated to assess for change or progression over time, with a consensus approach by two of the radiologists (G.D.C and AG.T.).

Case Reports

First Case

Female, 54 years old, COVID-19 diagnosis on 22 march 2020. She was admitted to Sub-Intensive Care Unit (Sub-ICU) on 25 march 2020 for fever, cough, dyspnoea, respiratory failure. No comorbidity on clinical history. The test results on hospital admission demonstrated leukocytosis with neutrophilia and lymph cytopenia, anemia, lower PT rate, upper CRP, Lactate, D-Dimer values. Liver and renal function were normal. Chest CT scan revealed bilateral ground glass opacities with main mantellar distribution, small areas of consolidation in lower lobes and in right middle lobe, septal thickening and vascular enlargement. The treatment scheme was: lopinavir 800 mg/day + ritonavir 200 mg/day, vitamin C6 g/day for 4 days + hydroxychloroquine 400 mg/day + eculizumab 900 mg 2 doses, enoxaparin 4000 IU/day subcutaneous, CPAP (NIV) + ceftriaxone 2 g/day IV. At discharge, all laboratory tests were better. Chest CT scan showed slight reduction of consolidation in the lower lobes (Figure 2) and evolution of the GGO in consolidation areas in the upper lobes with septal thickening. The duration of illness was 15 days.

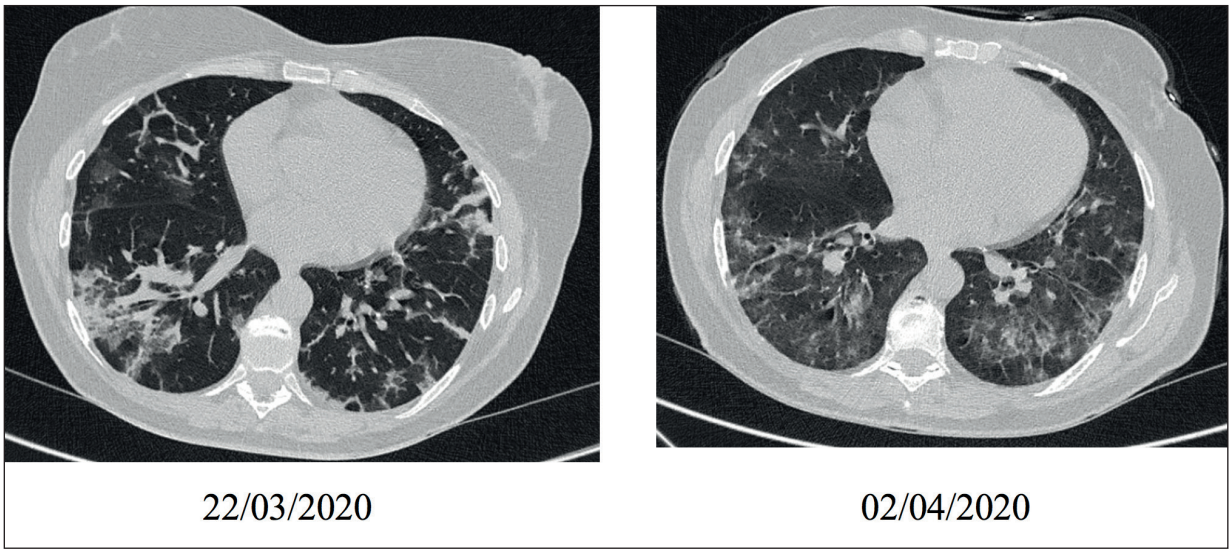

Figure 2. CT-scan patients 1.

Second Case

Male, 73 years old, medical history of hypertension. COVID-19 diagnosis on 15 march 2020. He was admitted to Sub-Intensive Care Unit (Sub-ICU) on 23 march 2020 for fever, dyspnoea, respiratory failure. Test results on hospital admission demonstrated leukocytosis with neutrophilia and lymph cytopenia, lower PT rate, upper CRP, Lactate, D-Dimer values. Liver and renal functions were normal. Chest CT scan showed the presence of multiple bilateral areas of confluent consolidations, associated with hazy ground glass areas, consisting with interstitial bilateral pneumonia. The treatment scheme was: lopinavir 800 mg/day + ritonavir 200 mg/day, vitamin C6 g/day for 4 days + hydroxychloroquine 400 mg/day + eculizumab 900 mg 2 doses, enoxaparin 4000 IU/day subcutaneous, CPAP (NIV) + ceftriaxone 2 g/day IV. At discharge, all laboratory tests were better. Chest CT scan revealed slight reduction of consolidations and appearance of large septal thickening. The duration of illness was 6 days.

Third Case

Female, 82 years old, medical history of hypertension, chronic ischemic heart disease, chronic obstructive bronchopathy. Covid-19 diagnosis on 12 march 2020. She was admitted to Sub-Intensive Care Unit (Sub-ICU) on 19 march 2020 for fever, cough, dyspnoea, respiratory failure. Test results on hospital admission demonstrated leukocytosis with neutrophilia and lymph cytopenia, anemia, lower PT rate, upper CRP, D-Dimer values. Liver and renal function were normal. First chest CT scan found in the upper lobes bilateral, peripheral ground glass opacities with rare and small consolidation areas, while in the lower lobes predominate confluent consolidations with septal thickening. The treatment scheme was: lopinavir 800 mg/day + ritonavir 200 mg/day, vitamin C6 g/day for 4 days + hydroxychloroquine 400 mg/day + eculizumab 900 mg 2 doses, enoxaparin 4000 IU/day subcutaneous, CPAP (NIV) + ceftriaxone 2 g/day IV. At discharge, all laboratory tests were better. Chest CT scan revealed mild increase of consolidations, with volume loss of the lower lobes. Duration of illness was 16 days.

Fourth Case

Male, 53 years old, medical history of hypertension. COVID-19 diagnosis on 22 march 2020. He was admitted to Sub-Intensive Care Unit (Sub-ICU) on 29 march 2020 for fever, cough, dyspnoea, respiratory failure. The test results on hospital admission demonstrated leukocytosis with neutrophilia and lymph cytopenia, anemia, lower PT rate, upper CRP, Lactate, D-Dimer values. Liver and renal function were normal. Chest CT scan revealed diffuse ground glass and small areas of consolidation, both peripheral and centrally located, mainly distributed in the in the right lung. The treatment scheme was: lopinavir 800 mg/day + ritonavir 200 mg/day, vitamin C6 g/day for 4 days + hydroxychloroquine 400 mg/day + eculizumab 900 mg 2 doses, enoxaparin 4000 IU/day subcutaneous, CPAP (NIV) + ceftriaxone 2 g/day IV. At

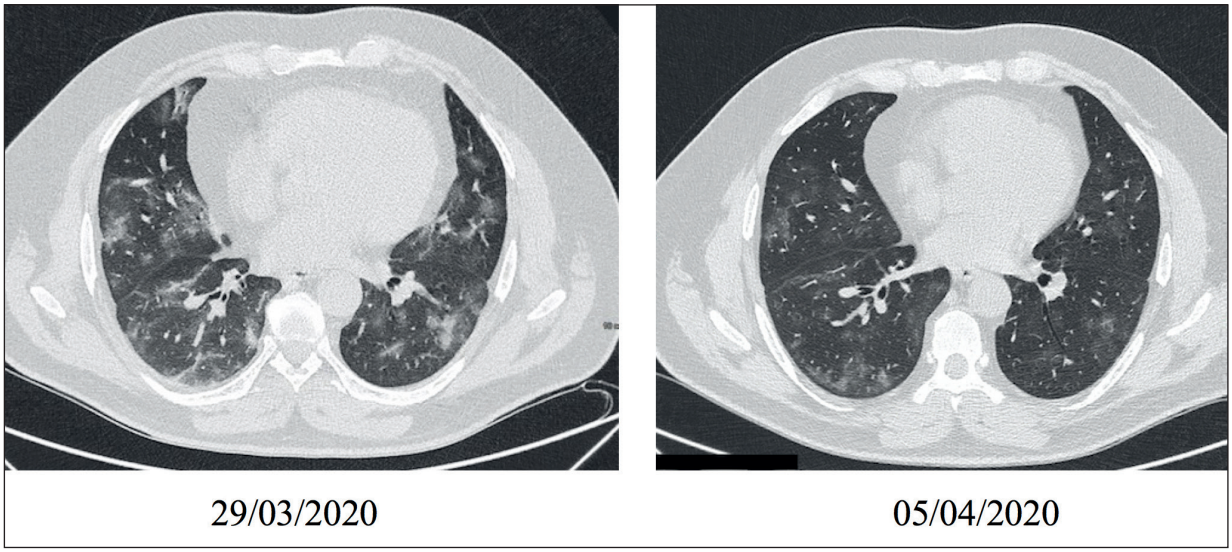

Figure 3. CT-scan patients 4.

discharge, all laboratory tests were better. Chest CT scan performed after 7 days showed marked reduction of extension and density of the ground glass areas and consolidations (Figure 3).

In Table I, we reported about one patient affected by β-thalassemia but not taking any drug and three affected by arterial hypertension treated with angiotensin-converting enzyme (ACE)-inhibitors.

Discussion

We presented four cases of COVID-19 pneumonia, with ARDS, treated with eculizumab. These cases show the heterogeneity of the patients affected by COVID-19.

SARS-CoV-2, similarly to SARS-CoV and MERS-CoV, causes a progressively and rapidly worsening pneumonia, with diffuse alveolar damage occurring during an early phase of the infection[5]. Both SARS-CoV and MERS-CoV also induce a substantial cytopathic effect and dysregulation of host immune responses[5]. Zhang et al[12] also reported about a cytokine release syndrome (CRS) in COVID-19, with a massive release of interleukin (IL)-6. IL-6 plays a key role in the so-called "cytokine storm", which is commonly reported during autoimmune diseases and viral infections[12].

Therefore, they studied the use of an IL-6 receptor (IL-6R) inhibitor to counteract CRS in COVID-19 patients, with encouraging results. These anecdotal data have paved the way for clinical testing of tocilizumab in COVID-19 patients. Despite pending results from ongoing clinical trials, tocilizumab is now considered one of the key drugs for the treatment of severe COVID-19.

SARS-CoV and MERS-CoV are also characterized by a dysregulation of the innate immune system, with a massive activation of the complement system[4,5]. Given the differences and similarities between these viruses and SARS-CoV-2, including the pathogenesis of the disease, it was possible to hypothesize that SARS-CoV-2 also caused an inappropriate activation of the complement system[13].

Eculizumab is an inhibitor of the activated residue of C5 (C5a). It is a hmAb used for the treatment of complement-mediated thrombotic microangiopaties and acute neuromuscular diseases, such as myasthenia gravis[14,15].

High levels of C5a have been found in bronchoalveolar lavage fluid (BALF) of individuals affected by viral-mediated acute lung injury (ALI) but not in BALF from recovered patients with ARDS[3]. COVID-19 patients, like SARS patients, show an increased alveolar infiltrate of macrophages. Moreover, C5a mediates neutrophil attraction, aggregation, activation, and endothelial damage[3]. Therefore, an increased activation of the complement system, and especially of the terminal activated factor C5a, might lead to a rapidly worsening ALI with a consequent ARDS. These observations provide a strong biological rationale for clinical testing of eculizumab in COVID-19 patients with severe respiratory syndrome.

As a matter of fact, despite our patients showed a rapidly worsening respiratory function, with a ground-glass bilateral lung infiltrate highlighted at a chest CT-scan, all of them showed a marked clinical improvement within the first 48 hours after the first administration of eculizumab, including an elder woman with arterial hypertension, COPD and cardiovascular disease.

Several studies showed that COVID-19 is deadly in elder people, even more when affected by more than one comorbidity[16,17].

We note that the elder woman, for whom mechanical ventilation was contra-indicated, showed a rapid, marked and clear response to eculizumab, and fully recovered despite a severe lung injury.

Conclusions

Our preliminary data collected in four cases show that eculizumab may be a key player in the treatment of severe cases of COVID-19. Our results support eculizumab use as an off-label treatment of severe COVID-19, pending confirmation from the ongoing SOLID-C19 trial.

Participants

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Acknowledgements

The authors are grateful to Verduci Editore for fast evaluation of the manuscript and to M.B., M.C. and G.N, for scientific infectious disease support.

Table I. Patient clinical characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis (yrs)	54	73	82	53
Sex	F	M	F	M
Chronic medical illness or history of	β-thalassemia	Hypertension	Hypertension	Hypertension
Exposure and setting	Professional exposure; Sub-ICU	Family exposure; Sub-ICU	Family exposure; Sub-ICU	Family exposure; Sub-ICU
Duration of illness (days)	15	18	16	13
Diagnosis date	22/3/20	15/3/20	12/03/20	22/3/20
Symptoms	Fever, cough, dyspnoea, respiratory failure	Fever, cough, respiratory failure	Fever cough dyspnoea, respiratory failure	Fever cough dyspnoea, respiratory failure
TEST RESULTS ON HOSPITAL ADMISSION				
WBC (cells/μL)	13800	12300	7100	12800
Neutrophils (cells/μL)	11300	9300	5900	10400
Lymphocytes (cells/μL)	1000	2800	1000	1800
Hb (g/dL)	8.6	10.8	10	16
PLTS (#/μL)	460000	482000	300000	196000
PT (sec)	**68%**	**76%**	**73%**	**65%**
D-dimer (ng/ml)	**405**	**2933**	**601**	**213**
CPK (UI/L)	141	33	92	72
ALT (UI/L)	25	92	19	63
AST (UI/L)	46	164	31	19
Total bilirubin (mmol/L)	0.8	0.9	0.8	0.8
Sodium (mmol/L)	132	139	137	135
Potassium (mmol/L)	4.4	3.5	3.4	3.2
Creatinine (mg/dL)	0.65	0.94	1.22	0.98
CRP (mg/dL)	**18.4**	**18.1**	**20.2**	**15.5**
Lactate (UI/L)	1.3	1.2	1	2.3
Chest CT scan findings	Bilateral mantellar GGO and small consolidation with vascular thickening	Multiple bilateral consolidations with hazy GGO	Bilateral GGO in upper lobes and bilateral consolidations in lower lobes	Diffuse GGO and small consolidation areas (right lung > left lung)
Admission to Sub-ICU	25/3/20	23/03/20	19/03/20	29/3/20
TEST RESULTS AFTER 48 HOURS SINCE ECULIZUMAB INITIATION AT DISCHARGE				
WBC (cells/μL)	7000	8600	6600	7600
Neutrophils (cells/μL)	4800	5300	4200	5400
Lymphocytes (cells/μL)	1200	3200	1300	1300
Hb (g/dL)	7.9	11.3	9.8	14.4
PLTS (#/μL)	353000	461000	240000	225000
PT (sec)	**74%**	**77%**	**87%**	**72%**
D-dimer (ng/ml)	**506**	**1891**	**572**	**277**
CPK (UI/L)	54	38	54	106
ALT (UI/L)	21	75	25	19
AST (UI/L)	31	134	34	25
Total bilirubin (mmol/L)	0.4	0.8	0.5	0.9
Sodium (mmol/L)	136	135	142	140
Potassium (mmol/L)	4.3	4.0	4.7	3.9
Creatinine (mg/dL)	0.49	0.74	0.54	0.82
CRP (mg/dL)	**4**	**8.1**	**2.2**	**0.3**
Lactate (UI/L)	1.8	1.0	1	1.1
Chest CT scan findings	Slight reduction of consolidation in the lower lobes, evolution of the GGO in consolidation areas in the upper lobes	Slight reduction of consolidation areas and appearance of large septal thickening	Mild increase of consolidations, with volume loss of the lower lobes	Marked reduction of extension and density of the ground glass areas and consolidations

Author Contributions

F.D., F.G.N., G.P, M.B., M.C, G.N and G.F conceived the study; F.D, F.G.N, C.B and G.F. and developed the study design; F.D., F.G.N., G.P, M.B., M.C, G.N., S.M., A.R., E.A., G.B., C.S., S.S.L.M., P.M., U.D.V., I.S., A. C., M.F., I.D., S.C., F.C., L.B., A.F., A.M., M.D.A., M.V., A.D.A. and G.F. oversaw the study; F.D., F.G.N., G.P, M.B., M.C, C.B., G.N, A.R., P.D.N., C.D.G., A.P. and G.F. drafted the manuscript; M.C., G.F. and C.B. analysed the data. All authors have read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

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