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Marc Joseph Buensalido

Jan Jorge Francisco

Jia An Bello

Alan Olavere

See next page for additional authors

Authors

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Michelle Joy De Vera[1,2], Marc Joseph Buensalido[1], Jan Jorge Francisco[1], Jia An Bello[1], Alan Olavere[1], Alma Calavera[1], Josephine Ramos[1], Norma Ona[1], Eyreka Escalambre[3], Marvin Delos Santos[3], Samuel Bernal[1,3] and Vasiliki E Kalodimou[4]*

[1]The Medical City, Pasig City, Philippines

[2]Ateneo de Manila School of Medicine and Public Health, Philippines

[3]Globetek Science Foundation, Makati, Philippines

[4]MCV CytoMed International Limited, Cyprus & National Hellenic Research Foundation (E.I.E), Greece

***Corresponding author:** Vasiliki E Kalodimou, MCV CytoMed International Limited, Cyprus & National Hellenic Research Foundation (E.I.E), Greece, Email: kalodimou@yahoo.gr

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Abstract

A proposed mechanism of severe Corona virus Disease-2019 (COVID-19) is a deregulated innate immune response to an infection with SARS-CoV-2 resulting in cytokine release syndrome (CRS). Mesencymal stem cells (MSC) have been shown to have immunomodulatory effects and may attenuate the CRS. We present 11 cases of severe COVID-19 pneumonia treated with umbilical cord-derived, non-HLA matched MSC administered as four separate intravenous doses, 5×105 cells/kg. Clinical symptoms, measurements of inflammatory mediators and cytokines (IL6, IL10, IFN-γ, TNF-α), and radiological results were recorded for each patient. Although there were large variations in baseline cytokine pattern elevation, all cytokine levels decreased in all patients after the 4 infusions of UC-MSC, albeit in different magnitudes. Seven patients eventually improved in terms of need for supplemental oxygen and/or mechanical ventilation, clinical symptoms, resolution of pneumonia on imaging, and were discharged. Three patients expired, 1 of whom expired before completing the full course of therapy. This limited series of patients showed that UC-MSC therapy down regulates the cytokine storm and may improve clinical status in patients hospitalized with severe COVID-19 pneumonia without any infusion related reaction.

Keywords: Umbilical Cord Mesencymal; Cytokine; COVID-19; Etiologies

Introduction

Worldwide more than 49 million individuals have been infected with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), the corona virus causing COVID-19. From the World Health Organization, as of November 6, 2020, a little over 1.2 million deaths have been reported globally [1] and yet to date, there are no current specific drugs or vaccines available to cure patients with COVID-19 infection. Hence, there is a large unmet need for a safe and effective treatment for COVID-19 infected patients, especially the severe cases.

Severe COVID-19 infection may be accompanied by an aggressive inflammatory response with rapid release of

large amounts of pro-inflammatory cytokines described as a "cytokine storm" [2-4]. This cytokine storm is marked by a sudden increase in circulating levels of pro-inflammatory cytokines, particularly IL-6, TNF-α, interferon-γ and G-CSF, MCP-1, MIP1A, IP10, IL-18, and IL-1. In turn, this cytokine release results in an acute influx of various immune cells including neutrophils, macrophages and T cells from the circulations into the tissue sites of infection [5,6]. This leads to a severe inflammatory process with impairment of the endothelial cell-cell interactions, disruption of vascular barriers, capillary damage and leakage, diffuse alveolar destruction, and acute lung injury that results in a severe form of ARDS, leading to low oxygen saturation levels [7,8]. Left unchecked, this cascade of inflammatory reactions results in multi-organ failure and death [9].

Mesenchymal stem cell (MSC)-based therapies have attracted much attention because of their powerful self-renewal capability and pluripotency [10,11]. One of the main functions of MSC is immune regulation, which can alleviate the inflammatory response in the body through immunosuppression [12-14]. MSC can inhibit the abnormal activation of T lymphocytes and macrophages, and induce their differentiation into regulatory T cell subsets and anti-inflammatory macrophages, respectively. It can also inhibit the secretion of pro-inflammatory cytokines, such as, IL-1, TNF-α, IL-6, IL-12, and IFN-γ, thereby reducing the occurrence of cytokine storms [15,16]. Safety and effectiveness have been documented in many clinical trials using MSC [17] especially those dealing with immune-mediated inflammatory diseases including acute lung injury/acute respiratory distress syndrome (ARDS) [18,19] associated with pro-inflammatory cytokine release similar to that of COVID-19. Furthermore, MSC-based therapies demonstrated promising effects in the experimental treatment of ARDS via inhibition of alveolar collapse and cell apoptosis in lung tissue, increased alveolar fluid clearance, regulation of pulmonary vascular endothelial permeability, and regeneration and repair of damaged lung tissues [20-22]. Those functions of MSC are expected to make it an effective method for the treatment of COVID-19. Recently, umbilical cord MSC were reported to be effective in the treatment of severe COVID-19 patients [2,23].

Here, we report the use of umbilical cord MSC (UC-MSC) in patients with severe COVID-19, describing their clinical course, laboratory findings and response to UC-MSC treatment.

Materials and Methods

This case series was on 11 patients with COVID-19 infected pneumonia given UC-MSC treatment at The Medical City Hospital, Manila, Philippines from April 2020 to September 2020. All enrolled patients were confirmed by the real-time reverse transcription polymerase chain reaction (RTPCR) assay of HCoV-19 RNA done at The Medical City Hospital. Criteria for eligibility included age of 18 years and older, clinical findings consistent with severe COVID-19 defined by Clinical classification of COVID-19 released by the National Commission of China [24] and clinical diagnosis of cytokine storm/cytokine response syndrome Grade 2 or higher (ASTCT, CTCAE, or Lee criteria) [25]. We excluded patients who had known allergies to stem cell preparations and their components, had expected death within 48 hours, were diagnosed with HIV and active malignancy, and who were pregnant. Informed consents were secured from the patients and the treatment was approved by The Medical City Hospital Ethics Subcommittee on Cellular Therapy.

The source of MSC were isolated from human umbilical cord Wharton's Jelly, minced into tiny fragments and digested with collagenase and trypsin. UC-MSC were expanded in vitro and characterized by flow cytometry and confocal microscopy, with the ISCT-recommended cell surface marker expression of CD105, CD73 and CD90, and lack of CD34, CD45, CD14, CD11b, CD79a, CD19 and HLA-DR [26,27]. UC-MSC was screened for blood borne infectious agents such as HIV, hepatitis B and C, EBV, CMV and syphilis. Aliquots of MSC cells were also cultured to detect contamination by bacterial and fungal microorganisms. UC-MSC was not HLA-matched between donor and recipient.

UC-MSC was initially suspended in 100 ml D5LR before intravenous infusion. Dose was calculated at 0.5 x106 cells/kg body weight per infusion and given on days 1, 3, 5 and 7, with duration of 40 minutes (40 drops/min).23 Patients were closely monitored during the entire time of infusion.

We observed the patients during their entire stay in the hospital after UC-MSC infusion. Clinical symptoms, laboratory tests including measurements of inflammatory mediators and cytokines (IL6, IL10, IFN-γ, TNF-α), and radiological results were recorded for each patient. Cytokine levels were measured by ELISA with each sample run in triplicate.

Description of Cases

We treated 11 patients with COVID-19 pneumonia with UC-MSC. The Median age was 58 years (range 37-89). There were 8 males and 3 females. Table 1 shows the baseline characteristics, treatments and clinical outcomes of patients with COVID-19 treated with UC-MSC therapy. Two patients did not complete the 4 doses of MSC. One expired after the second dose, while the other patient developed arrhythmia after the second dose. Although it was unclear what the etiology of the arrhythmia was, the medical team decided to discontinue the remaining doses of MSC for this patient. In terms of other treatments given, the proportion

of treatment with oxygen was the highest (100%), followed by dexamethasone (10/11 patients) and remdesivir (9/11 patients). All patients also received different kinds of antimicrobials depending on the decision of their medical team.

Patient	1	2	3	4	5	6	7	8	9	10	11
Age	57	49	37	70	64	70	52	58	58	64	89
Sex	M	F	M	M	F	M	M	M	M	M	F
Co-morbidities	Dys-lipidemia, BPH	Myasthenia gravis, hyper-tension	Type 2 DM	Type 2 DM; Renal Cell Carcinoma (S/P Nephrec-tomy, Right)	Type 2 DM, Non Obstructing Coronary Artery Disease	Type 2 DM, Dys-lipidemia, History of Renal Cell CA (2005)	Essential Thrombo-cytosis Hyper-tension	None	None	Hyper-tension COPD	None
Treatments given											
1. Oxygen	High flow O2	Mechanical ventilation 4th HD	High flow O2	Mechanical ventilation 4th HD then BIPAP by 25th HD	O2 by nasal cannula	O2 by nasal cannula	O2 by nasal cannula	Mechanical ventilation 1st HD	O2 by nasal cannula	Mechanical ventilation 15th HD	Mechanical ventilation 1st HD
2. Anti-virals: Remde-sivir	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
3. Anti-microbials	Meropenem	Ceftriaxone	Ceftriaxone	Ceftriaxone Azithro-mycin Piperacillin-tazobactam Meropenem Levofloxacin	Azithro-mycin	Meropenem	Azithro-mycin	Piperacillin-Tazobactam Meropenem Ceftazidime Avibactam Vancomycin Levofloxacin Ampicillin Polymixin B	Piperacillin-Tazobactam Meropenem Ceftazidime Avibactam Vancomycin Levofloxacin Ampicillin Polymixin B	Azithro-mycin Ceftriaxone Piperacillin-Tazobactam Levofloxain Meropenem Amikacin Fluconazole Cotri-moxazole	Piperacillin-Tazobactam Clindamycin Vancomycin Meropenem
	Azithro-mycin Levofloxacin	Meropenem	Piperacillin-Tazobactam	Cefixime Clindamycin	Piperacillin-Tazobactam	Ceftriaxone	Ceftriaxone	Fluconazole Anidula-fungin Amikacin Tigecycline			
	Aztreonam	Fluconazole				Piperacillin-tazobactam					
4. Steroids dexame-thasone	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		10 days	5 days	10 days	10 days	10 days	10 days	10 days	10 days	10 days	10 days
5. Hydroxy-chloroquine	Yes	No	No	No	No	No	No	No	No	No	No
6. CRRT	No	No	No	No	No	No	No	Yes	Yes	No	Yes
7. Others		IVIG									
UC-MSC											
Timing	6th HD	6th HD	5th HD	31st HD	1st HD	8th HD	3rd HD	4th HD	2nd HD	9th HD	2nd HD
Doses given	4	4	4	4	4	2	4	4	4	2	4
Chest x-ray findings											

Pre-MSC	New onset pneumonia, bilateral	Consider bilateral pneumonia	Pneumonia, bilateral, with interval increase	Pneumonia, bilateral	Bilateral pneumonia	bilateral infiltrates	Consider pneumonia, left	Consider pulmonary edema with interval regression in the RIGHT and interval progression in the LEFT.	Consider interval development of bibasal pneumonia	Bilateral pneumonia	Consider bilateral pneumonia
Post-MSC	Unchanged bilateral pneumonia	Bilateral pneumonia with consolidation; regressing in the right and unchanged in the left	Regressing bilateral pneumonia		Resolving pneumonia, bilateral	Regressing bilateraL pneumonia	Pneumonia, bilateral, with decrease on the left and onset on the right	Pneumonia, bilateral, with interval regression	No significant change in the bilateral pneumonia	Regressing pneumothorax, left	Resolving pneumonia, bilateral
PaO_2/FiO_2											
Pre-MSC	94	195.4	121.25	125.58	289	105	427	234	125	97.5	227.2
Post-MSC	308.75	166.2	ND	ND	465	ND	ND	252	178.8	54	214
Inflammatory markers											
1. CRP											
Pre-MSC	66.73	336	270	85.94	1.47	94.95	41.37	251.7	66.5	381	57.21
Post-MSC	2.07	119.3	4.9	ND	0.47	ND	2.23	109.5	12.64	53.51	46.59
2. Ferritin											
Pre-MSC	3770	864	3079	2310	3102	845	1090	1380	3970	1400	1350
Post-MSC	789	776	979	ND	773	ND	718	22000	1500	867	388
3. D Dimer											
Pre-MSC	0.25	1.77	0.14	ND	ND	2.37	0.19	0.71	0.46	0.77	2.51
Post-MSC	0.82	3.3	0.59	ND	ND	ND	ND	ND	ND	1.62	ND
4. LDH	ND										
Pre-MSC	738	543	381	579	451	1482	210	468	598	299	481
Post-MSC	218	784	193	ND	335	ND	207	1379	396	249	312
Other Outcomes: Days from MSC infusion to:											
1. Off mech ventilation	NA	34	NA	NA	NA	Expired	NA	Expired	NA	Still on mechanical ventilation	Expired
2. Off oxygen	14	On O2 until discharge	7	9	8	Expired	6	Expired	9	NA	Expired
3. Improved chest imaging	16	11	11	7	9	Expired	5	Expired	7	NA	7
4. Negative COVID RT-PCR	27	Positive until discharge	10	ND	12	Expired	10	Expired	ND	ND	Expired
5. Discharge	23	49	13	13	14	Expired	8	Expired	13	Still admitted	Expired
Mortality	No	No	No	No	No	Yes 12th HD	No	Yes 51st HD	No	No	Yes 23rd HD

Table 1: Patient Characteristics and Outcomes Measures.

Eight patients were not receiving invasive mechanical ventilation when US-MSC was administered; with 1 eventually needing mechanical ventilation and 1 expiring. Of the 3 patients who were already on mechanical ventilation before UC-MSC treatment, 2 eventually expired, while the third patient did not finish the complete course of treatment and is still admitted in the hospital.

Seven patients eventually improved in terms of need for supplemental oxygen and/or mechanical ventilation, clinical symptoms, resolution of pneumonia on imaging, and were discharged. C-reactive protein (CRP) and ferritin levels were the most consistent inflammatory markers measured for all the patients. In all patients, CRP decreased after UC-MSC treatment. Likewise for ferritin, except for 1 patient whose ferritin levels increased even more after UC-MSC. This patient later expired. Three patients expired, 1 of whom expired before completing the full course of therapy.

Figure 1 shows cytokine levels measured pre- and post-UC-MSC treatment. We were not able to do cytokine measurements on the 2 patients who did not complete the full course of therapy. The specific cytokine that were mainly elevated in each patient were either IL-6 (5 patients) or IFN-γ (4 patients). Regardless, all cytokine levels decreased for all patients after the 4 infusions of UC-MSC, albeit in different magnitudes.

All patients who received the UC-MSC treatment had no adverse reactions such as rash, allergic reaction, or febrile reaction during or after infusion.

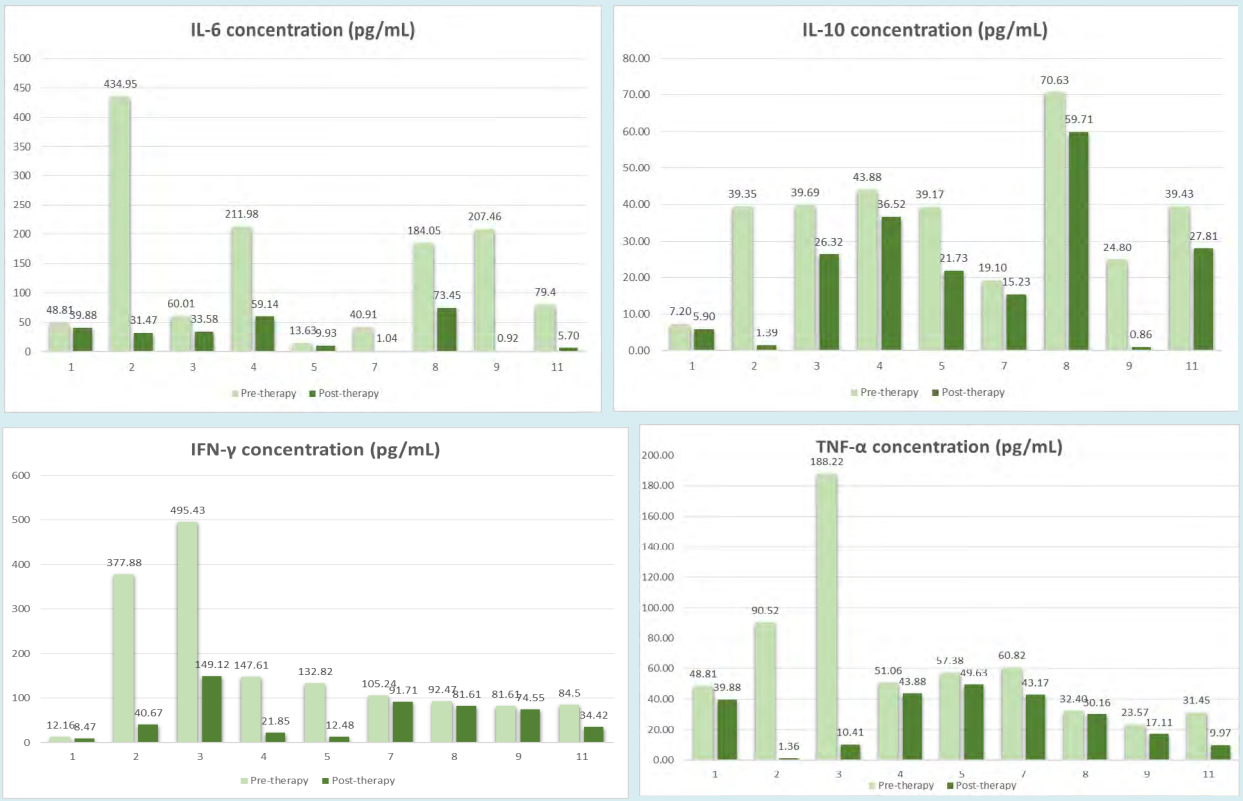

Figure 1: Cytokine levels pre and post UC-MSC therapy.

Discussion

MSC has a positive impact in its use in cytokine release syndromes (CRS) from various etiologies because it has been shown to suppress excessive immune system activation by reducing the release of inflammatory factors mediated by immunomodulation [28-32]. As CRS plays a prominent role in the pathophysiology of COVID-19, using MSC to attenuate this syndrome makes it a promising candidate as a treatment of severe disease.

In this case series, we showed that although there were large variations in baseline cytokine pattern elevation all cytokines measured decreased rapidly after UC-MSC infusion. The extent of reduction of specific cytokines also differed, but in general, the higher the pre-MSC level of a specific

cytokine, the greater the reduction of that cytokine; with reductions post-MSC treatment of up to > 90% compared to pre-MSC treatment levels in some patients. With this decrease in cytokine levels, there was likewise a decrease in other inflammatory markers, such as CRP and ferritin.

With the cytokine storm noted in patients with late-stage COVID-19 infection typically implicated as the primary cause of death [33] recognition of inflammatory markers or other cytokine-directed treatments obviously have important implications for treatment selection. Tocilizumab, a recombinant monoclonal antibody against the IL-6 receptor, which has been shown to mitigate the CRS associated with chimeric antigen receptor (CAR) T-cell therapy, has been used as a potential therapy for the cytokine storm associated with severe COVID-19 pneumonia [34,35]. However, it is important to emphasize the difference in cytokine profiles of the patients. Our series clearly shows that cytokines other than IL-6, such as IFN-γ and TNF-α are also strongly associated with the inflammatory reaction and CRS in severe COVID-19 patients. Patients, in which case tocilizumab might not be expected to completely control the CRS in these patients. And so alternatives for dampening the overwhelming cytokine release are required, and the need for cytokine assays might be critical in personalized care and planning for future therapeutic options for COVID-19.

Similar to results from other centers, we also found that after UC-MSC infusions, there were no obvious side effects observed, indicating that the MSC were very well tolerated, even in severely ill patients.

As this is a case series, there are obvious limitations. We definitely cannot draw causal inferences because of inherent known and unknown confounders. The consequence of the decrease in cytokine levels to the clinical course of the patients is difficult to determine. The course of each patient was extremely varied. Although the majority of patients improved and were eventually discharged, the time for an individual patient to achieve these milestones were very different. We were unable to determine if there was an association on when and which cytokines decreased with the timing of clinical improvements for each patient. Even those patients who expired had marked decreases in the cytokine levels. We could also not observe a pattern in terms of effects on the timing on UC-MSC administration with noted decreases in cytokine levels, clinical improvement or mortality.

Our patients were a very heterogeneous group, especially in the other therapies that they received. Aside from MSC, these patients also received other off-label medications for COVID-19 pneumonia, such as antibiotics, remdesivir, dexamethasone, and hydroxychloroquine. Therefore, specific contributions of each therapy to the clinical improvement of the patients would be difficult to ascertain. However, unlike these other agents, MSC has been shown to have an immunomodulatory effect which could directly attenuate CRS. The cytokine data seen in our patients is therefore crucial.

Conclusion

Our experience showed that UC-MSC therapy down regulates the cytokine storm and may improve the clinical status in patients hospitalized with severe COVID-19 pneumonia without any infusion related reaction. Other current multiple center, prospective trials that are on-going will hopefully further elucidate the role of MSC in the treatment of COVID-19.

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