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Commentary

The Path to FDA Approval of MSC Therapy Will be Accelerated by COVID-19

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Efficacy of mesenchymal stem cells (MSC) has been demonstrated in thousands of pre-clinical studies for a wide range of diseases and injuries that elicit an overpowering inflammatory response. The capacity of MSC to dramatically reduce inflammation forms a solid foundation to justify the ~1,000 clinical trials using MSC that have been registered at ClinicalTrials.gov [1]. Despite this large number of trials, over the past 17 years, clinical use of MSC has not yet been approved by the FDA. The urgent need to treat life-threating stages of COVID-19 may prove to be a turning point for FDA approval of MSC in various inflammatory disorders.

As of July 10th, 2020, greater than 130,000 people in the US have died from COVID-19 and the number of infections is at an all-time high. In ~5% of COVID-19 patients the infection generates a severe "cytokine storm" with highly elevated levels of pro-inflammatory cytokines (including IL-1β, IL-6, TNF-α and IFN-γ) and other inflammatory proteins (such as C-reactive protein and serum amyloid A proteins) similar to sepsis [2]. The primary organ target of COVID-19 is the lungs, which often leads to acute respiratory distress syndrome (ARDS) with morbidity and mortality. There are no specific FDA-approved treatments for these life-threatening conditions.

MSC respond to increased pro-inflammatory cytokine production by releasing anti-inflammatory cytokines including IL-1ra, IL-4, and IL-10 and prostaglandins e.g. PGE2, which suppress inflammation and cytokine storms [3]. Prior to the COVID-19 pandemic, several companies had major MSC clinical programs to treat inflammatory disorders in which cytokine storm plays a critical role. For example, Remestemcel is a MSC product isolated from human bone marrow by Mesoblast that has received marketing approved for clinical treatment of graft vs. host disease (GvHD) in Japan, and is effective in cases where other anti-inflammatory therapies have failed [4]. Athersys has reported preliminary clinical efficacy in ARDS for its MSC product called Multistem, reducing patient mortality, numbers of patient-days in intensive care units and dependence on ventilators in an as yet unpublished study and in stroke [5]. Pluristem has reported that its PLX MSC product improved muscle function following hip arthroplasty [6]. Overwhelming evidence indicate that MSC therapy is safe even at doses as high as 1,200 million cells/dose [5].

Like SARS and MERS, the severity and lethality of the COVID-19 corona virus is due primarily to cytokine storm often resulting in ARDS and organ failure (e.g. heart). Anti-viral drugs such as remdesivir appear to reduce disease progression in early phases of COVID-19 by blocking mRNA replication thereby reducing viral load, but it is unclear whether it is effective in treating cytokine storm once it has developed. Tocilizumab is a monoclonal antibody that reduces cytokine storm by blocking the receptor for IL-6 that is effective in many cases of cytokine storm in CAR-T and is currently being investigated in many clinical trials for COVID-19.

Cytokine storm is a key factor in the severity and lethality of COVID-19. For example, in-hospital death from COVID-19 is associated with age and notably upregulation of IL-6 is a significant correlate [7]. MSC efficacy in reducing the severity of COVID-19 disease and

rebalancing of cytokines (significantly reducing levels of pro-inflammatory TNFa and increasing anti-inflammatory IL-10) in COVID-19 patients has been reported in a trial with small numbers of patients [8]. Pluristem and Mesoblast initiated compassionate use of MSC in ventilator-dependent COVID-19 patients. They reported preliminary evidence in April 2020 that their respective MSC products had marked reduction in death and enabled patients to come off ventilators more frequently than in historical control patients. The potential therapeutic benefits of MSC is highlighted by the rapid registration of new trials at ClinicalTrials.gov (Table 1) by three major companies with well characterized MSC products. These include MSC derived from bone marrow and injected intravenously (Remestemcel at 2 x 10^6 MSC/kg of body weight with a second dose after 4 days, NCT04371393, and Multistem, NCT04367077) and placenta-derived cells injected intramuscularly (PLX at 300x10^6 cells [9] injected only once or with a no dose after 7 days, NCT04389450).

ClinicalTrials.Gov	Cell Type or Tissue source	Phase	Max Dose	Repeat Dose	Total Dose	# Patients (Controls)
NCT04315987	NestaCell	1	20	1,3,5,7 d	80	45, (45)
NCT04252118	UC	1	30	0,3,6	90	10, (10)
NCT04336254	Dental pulp	1,2	30	1,4,7 d	90	10, (10)
NCT04273646	UC	1,2	35	1,3,5,7 d	140	24, (24)
NCT04352803	Adipose	1	35		35	20
NCT04293692	UC		35	X4	140	24, (24)
NCT04288102	UC	2	40	X3	120	50, (50)
NCT04390152	Wharton's Jelly	1,2	50	X2	100	20, (20)
NCT04313322	Wharton's Jelly	1	70	0,3,6 d	210	5
NCT04346368	BM	1,2	70		70	10, (10)
NCT04361942		2	70		70	12, (12)
NCT04333368	Wharton's Jelly	1,2	70		70	20, (20)
NCT04371601		1	70	4X4 d	280	30, (30)
NCT04367077	Multistem BM					
NCT04416139	UC	2	70		70	5, (5)
NCT04302519	Dental Pulp	1	70	1,3,7 d	210	24
NCT04339660	UC	1,2	70		70	15, (15)
NCT04390139	Wharton's Jelly	1,2	70	1,3 d	140	15, (15)
NCT04398303	UC	1,2	70		70	70
NCT04429763	UC	2	70		70	15, (15)
NCT04366323	Adipose	1,2	80	X2	160	13, (13)
NCT04400032	BM	1	90	1,1,1	75, 150, 270	3,3,3
NCT04269525	UC	2	99	1,3,5,7 d	396	10
NCT04366063		2,3	100	0,2 d	200	40, (20)
NCT04355728	UC	1,2	100		100	12, (12)
NCT0434560		1	100		100	30
NCT04345601	BM	1	100		100	30
NCT04399889	Cord Tissue	1,2	100	X3	300	20, (10)
NCT04362189	Adipose	2	100	0,3,7,10 d	400	50, (50)
NCT04348461	Adipose	2	105	X2	210	50, (50)
NCT04371393	Remestemcel (BM)	3	140	0,4 d	280	150, (150)

NCT04366830			140	X2	280	
NCT04348435	Adipose	2	200	0,2,6,14 d	1000	75, (25)
NCT04428801	Adipose	2	200	X3	600	100, (100)
NCT04392778	UC	1,2	210	0,3,6 d	630	10, (20)
NCT04389450	PLX Pad	2	300	0,4 d	300/600	140
NCT03042143	UC	1,2	400		400	75
NCT04349631	Adipose	2		X5		56
NCT04366271	UC	2				53, (53)
NCT04382547	Olfactory Mucosa	1,2				20, (20)
NCT04377334	BM	2				20, (20)
NCT04397796	BM	1				45

Table 1: *Doses indicated for COVID-19 trials listed at ClinicalTrials.gov. Doses are reported in millions of cells. Doses reported as number of cell/kg were calculated using an adult weight of 70 kg to obtain an estimate of the dose. Umbilical cord (UC), bone marrow (BM). Days (d). Six trials that are single case studies have been omitted. All trials indicated IV injection except for NCT04389450, which is intramuscular.*

IV injection of MSC results in their rapid accumulation in the lungs where they may secrete anti-inflammatory paracrine factors, which mitigate cytokine storm and ARDS in lungs of COVID-19 patients. However, this effect may only be transient insofar as most IV-injected MSC are cleared rapidly from the lungs. To extend the treatment period, repeat injections of MSC are often performed at intervals of 3 - 7 days (Table 1).

The success of clinical trials with MSC may also depend on various parameters including cell dose. There may be differences in the efficacy of different types of MSC depending on their origin and production procedures, which may limit the validity of direct comparisons. However, given that MSC have common anti-inflammatory actions to resolve cytokine storm, one can assume as a first approximation, that effective doses will be similar using different types of MSC. A recent study using this approach suggested that minimal effective adult IV doses were ~70 - 190 million for MSC derived from bone marrow and umbilical cord [1]. Doses lower than ~70 million cells did not show efficacy. Higher doses of ~300 million MSC were either no more effective or were less effective than the minimal effective dose. Doses of Multistem were found to be safe ranging from 400 - 1,200 million cells/dose. Efficacy of Multistem was reported in phase 2a and phase 2 trials with doses of 900 million in ARDS (NCT02611609) and 1,200 million cells (ischemic stroke), respectively, but the results failed to meet their primary outcomes with these relatively high doses [10] albeit the ARDS trial consisted of only 10 subjects/group and was not powered for efficacy outcomes. Would lower doses be more effective?

We have analyzed MSC doses in trials to treat COVID-19 that have been registered so far at ClinicalTrial.gov (Table 1). In this group of 42 trials injecting MSC by IV, 8 indicated doses below 70 million/patient, which are below the threshold for efficacy and 12 indicated doses of ~70 million/patient, which are at levels that were effective in some but not all trials [1]. Another 6 did not indicate any dose. Thus > 60% of the listed trial doses were unknown or may only have weak or no MSC effects in COVID-19 clinical trials. The remaining 16 trials are in a range that has demonstrated efficacy in previous clinical trials for other indications. Especially at this time of COVID-19 crisis, it is important that every trial disclose the dose(s) they are using, and additional information should be made available (e.g. on cell characterization) to give the field the best chance to identify potential treatments by comparing results among the many trials ongoing and being registered at a rapid pace. Cell dose-dependence should also be performed when possible to optimize dosing for each MSC product.

The IV remestemcel dose of 2 million cells/kg (~140 million for an adult assumed weight of 70 Kg) for the COVID-19 trial is being used clinically to treat GvHD [11]. The IV Multistem COVID-19 trial did not indicate a dose (NCT04367077) and one can only assume it would

be 900 million as used previously for ARDS. After IV injection, MSC rapidly accumulate in the lungs where secretion of anti-inflammatory paracrine factors may be advantageous by acting locally to mitigate cytokine storm in COVID-19. However, this effect will only be transient insofar as most of the MSC are cleared rapidly from the lungs. To extend the treatment period, repeat injections of MSC are often performed at intervals of 3 - 7 day (Table 1). All trials in table 1 use IV injections except for NCT04389450, which uses intramuscular injection of PLX cells that allow longer and more robust survival than after IV injection at least in mice (Racheli Ofir, Pluristem, personal communication). Long-term (6 - 8 weeks) survival and efficacy of MSC in pre-clinical studies has been achieved after injection of MSC encapsulated in alginate microspheres, which protects the cells from direct interactions with the host while allowing permeability of cytokines across the microspheres [12]. Thus, encapsulation of MSC provides extended release of anti-inflammatory cytokines that have systemic effects through the circulation.

Patients with ARDS and COVID-19 frequently develop bacterial infections in the lungs that are associated with high morbidity and mortality. In addition to reducing cytokine storm, MSC also reduce bacterial infections by secreting small proteins including lipocalins [13], which have potent anti-bacterial effects that should provide added benefit of MSC therapy [14].

The rapid development of MSC trials for COVID-19 will yield much data in the near term. The positive responses observed so far within ~2 weeks with MSC in COVID-19 patients, if confirmed, combined with the urgent need for an effective ARDS therapy for advanced COVID-19, and the excellent safety profile for MSC, is likely to enable the FDA to act as quickly as possible to evaluate MSC therapies for clinical approval in COVID-19. If the data warrants approval of MSC to treat COVID-19, the path for consideration of MSC for other indications that are being investigated will likely to be accelerated. Thus, clinical efficacy of MSC in COVID-19 trials will accelerate the path for FDA approval of MSC for treatment of other related and unrelated diseases with severe cytokine storms.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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