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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

International Society for Extracellular Vesicles and International Society for Cell and Gene Therapy statement on extracellular vesicles from mesenchymal stromal cells and other cells: considerations for potential therapeutic agents to suppress coronavirus disease-19

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STATEMENT: The International Society for Cellular and Gene Therapies (ISCT) and the International Society for Extracellular Vesicles (ISEV) recognize the potential of extracellular vesicles (EVs, including exosomes) from mesenchymal stromal cells (MSCs) and possibly other cell sources as treatments for COVID-19. Research and trials in this area are encouraged. However, ISEV and ISCT do not currently endorse the use of EVs or exosomes for any purpose in COVID-19, including but not limited to reducing cytokine storm, exerting regenerative effects or delivering drugs, pending the generation of appropriate manufacturing and quality control provisions, pre-clinical safety and efficacy data, rational clinical trial design and proper regulatory oversight.

First described in December 2019, the severe acute respiratory syndrome associated with coronavirus disease-19 (COVID-19) quickly evolved into a pandemic, with severe and increasing worldwide morbidity and mortality. Although most infected patients have mild to moderate symptoms or are even asymptomatic, older patients and those with pre-existing chronic diseases are at greater risk of developing serious complications, such as pneumonia or multiple organ failure. COVID-19 respiratory infection is marked by dysregulated immune responses leading to significant respiratory pathology as well as increased probabilities for multi-organ pathologies. While the inflammatory pathways are still being elucidated, notable components include increased circulating levels of pro-inflammatory cytokines and other mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10) and monocyte chemoattractant protein-1 (MCP-1) [4, 6, 41]. There are also significant alterations in circulating inflammatory cell populations, with initial lymphocytosis followed by severe lymphopenia, with increased ratios of helper to regulatory T cells [4, 6, 30]. Since dysregulated immune responses and the cytokine storm are triggers for development of acute respiratory distress syndrome, an increasing effort and current clinical trials are focused on immune therapeutic approaches, such as IL-1 blockade (anakinra), IL-6 receptor blockade (tocilizumab) and Janus kinase inhibition [22]. In parallel, there are a rapidly increasing number of cell-based therapy investigations, mostly utilizing mesenchymal stromal cells (MSCs) [12]. These are based on supporting pre-clinical data for use of MSCs delivered either systemically or intratracheally in pre-clinical models of acute lung injuries and on demonstration of safety of systemic MSC administration in recent trials for acute respiratory distress syndrome resulting from other etiologies [15, 21].

Among the cell-based therapy investigations for COVID-19, some registered clinical trials aim to utilize extracellular vesicles (EVs) prepared from MSC-conditioned media rather than the cells themselves. MSC-EVs will be administered intravenously (ChiCTR2000030484) or by inhalation (NCT04276987, ChiCTR2000030261). The rationale for these approaches is based on a relatively small but growing number of investigations in pre-clinical lung injury and sepsis models in which MSC-EV preparations were described as being as safe and effective as—if not more than—their parent cells [19, 40]. The approach is further supported by a growing body of literature on the therapeutic potential and mechanisms of EVs in a wide range of diseases, including recent positive results in a steroid-refractory graft-versus-host disease patient treated with MSC-EVs and in a single-center, randomized, placebo-controlled phase 2/3 clinical pilot study on chronic kidney disease patients treated with MSC-EVs [14, 25].

The mechanisms by which EVs exert their beneficial effects, as well as their site(s) of action, remain incompletely understood. Nonetheless, effects observed in a range of pre-clinical non-COVID-19 model systems suggest that they may also have efficacy against COVID-19. For example, systemic administration of MSC-EV preparations modulated immune responses such as elevated cytokine storms in relevant lung disease models, including acute lung injury and sepsis [17, 20, 23, 24, 27, 35, 38, 42]. Notably, in *Escherichia coli*-induced pneumonia mouse models, MSC-EV administration was found to enhance phagocytosis of bacteria [9, 23]. In a pig model, MSC-EVs were shown to attenuate influenza virus-induced acute lung injury, among other conditions, by inhibiting influenza virus replication [11]. Disease-attenuating effects on inflammatory immune responses following MSC-EV administration have also been observed in other disease models [2]. In an ischemic stroke model, for example, syste mic MSC-EV administration reduced stroke-induced lymphopenia and pro-inflammatory immune responses in the brain and periphery, resulting in overall improvement of disease symptoms [7, 37]. These preliminary observations support MSC-EV administration as a potential treatment option for COVID-19.

However, the specific scientific rationale for the administration of MSC-EV and other EV treatments in COVID-19 patients needs to be better understood and justified. For example, MSC-EVs do not necessarily suppress immune responses, but rather modulate them. Specifically, they seem to moderate acute immune responses toward regulatory responses, with the latter inducing tolerance and restoring homeostasis [43–45]. While tolerance induction in graft-versus-host disease and other non-infectious diseases may be beneficial, it might also have severe adverse effects in the presence of replicating pathogens. Although influenza and *E. coli* infections were attenuated in selected models [9, 11, 23], other viruses and bacteria might conceivably expand in an uncontrolled manner in induced tolerogenic environments.

A number of additional issues should be considered before administering MSC-EVs to COVID-19 patients. These include the source of MSC-EVs. MSCs are a heterogeneous cell entity that can be obtained from different tissues. Even if derived from the same tissues, they may display interindividual and possibly clone-specific functional differences [28, 29, 31, 36]. Indeed, side-by-side comparison of four MSC-EV preparations harvested from the conditioned media of different donor-derived bone marrow MSCs demonstrated significant variations in cytokine content [14]. Whether this correlates with therapeutic potency is not yet clear; however, in the example of the ischemic stroke model, it was demonstrated that MSC-EV preparations with comparable particle and protein contents can significantly differ in potency. While some preparations effectively suppressed stroke symptoms, others failed to exert therapeutic activities [37]. Furthermore, in an acute lung injury model, EVs from young, but not aged, MSCs alleviated lipopolysaccharide-induced acute lung injury [10].

Potentially, heterogeneity of EV potency due to different sources, preparations, aging and other factors could be resolved by generating immortalized clonal MSC lines that could be rigorously tested for EV production and potency [5]. Still, apart from their immunomodulatory capabilities, MSC-EVs apparently also control additional biological processes, some with approved therapeutic functions [1] and

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others that might trigger unforeseen side effects. Just recently, it was found that adipose-derived MSC-EVs had higher thrombogenic activity than bone marrow-derived MSC-EVs [3, 34]. Thus, the source of parental cells might increase thrombosis risk. Coupled with the finding that activation of complement pathways and an associated procoagulant state seem to result in catastrophic microvascular injury syndrome in a proportion of severe COVID-19 cases [18], MSC-EV administration could even be counterproductive in COVID-19.

To this end, it is imperative that stringent "identity" and "potency" parameters are defined and potential side effects addressed before MSC-EV or other EV preparations are released for therapeutic applications [16, 32, 39]. To date, many groups use in-house MSC-EV manufacturing and characterization strategies, mainly for pre-clinical studies [2]. Protocols fulfilling Good Manufacturing Practice (GMP) criteria are sparse, and just a few have been published [8, 26, 33]. For product candidates, studies focusing on safety and clinical pharmacology need to be performed. Results of such studies are mandatory to provide guidance for adjustment of manufacturing, storage, dosing and administration of EV-based therapeutics in specific target diseases.

We would like to refer to a recent statement by ISCT on the use of MSCs in COVID-19 [13] and one by the Italian STEMnet[1], as many of the same considerations apply to MSC-EVs or other EVs. Governmental organizations, health care providers and clinical investigators must take the lead by insisting that clinical uses of EVs follow appropriate scientific, regulatory and ethical guidelines and are approved only after a rigorous review by duly empowered agencies. The ethical guidelines produced by the World Health Organization are a useful baseline[2]. The urgency of the current outbreak does not justify administration of EVs in uncontrolled compassionate use settings and does not obviate the need to register clinical trials, obtain informed consent from patients or proxies and otherwise comply with good clinical practice. In particular, even limited compassionate use should employ well-characterized MSC-EV preparations produced through strict GMP conditions under the oversight of the relevant national regulatory entity. Additional outbreak-specific measures may be needed, including establishing simplified clinical protocols for hospitalized patients, such as the World Health Organization COVID-19 core protocol; minimizing risks to trial integrity[3]; and changing logistics of trial participant visits (e.g., implementation of remote assessments) as well as protocol changes for the sake of hazard minimization, which may need to be implemented and reported, in Europe, to the Institute for Research in Biomedicine Barcelona after the fact. Certainly, to foster developments, it is helpful to have regulatory flexibility and support from sources such as the US Food and Drug Administration special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program[4], the European Medicines Agency (EMA) COVID-19 Pandemic Task Force[5], the EMA guidance for medicine developers and companies on COVID-19[6] and the guidelines for clinical trials published by an EMA-coordinated group[7] or the Medicines and Healthcare Products Regulatory Agency[8], respectively. Most or all of the considerations covered for cell-based therapies are also applicable to EV investigations.

In conclusion, to mitigate the risk of potentially life-threatening side effects, ISCT and ISEV strongly urge that the potential benefits and risks in the use of MSC-EVs for COVID-19 be weighed carefully against available pre-clinical data in relevant animal models and clinical data from relevant MSC clinical trials and that any use of EVs be carefully evaluated through rational clinical trial design, employing well-characterized EV preparations produced under strict GMP conditions and under the proper regulatory oversight.

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Declaration of competing interest

JDA is the co-founder of an exosome therapeutics company called Somos Therapeutics, Inc. BG is a scientific advisory board member with Evox Therapeutics and Innovex Therapeutics SL. MG has a consulting and advisory role with MDimune. BLL has stock and other ownership interests with Tmunity Therapeutics; has received honoraria from Novartis, Terumo and AstraZeneca; and has a consulting or advisory role with Brammer Bio/ThermoFisher Viral Vector Services, Avectas, Immuneel, Ori Biotech and Vycellix. SKL is the founder of Paracrine Therapeutics and has a scientific advisory role with Ilias Biologics and ExoCo. SAM is the inventor of intellectual property licensed by BCH to United Therapeutics Corp.

Author contributions

Drafting the manuscript: VB, DJW, KWW, SKL, BG. All authors have approved the final article.

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