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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Editorial

An International Society for Cell and Gene Therapy Mesenchymal Stromal Cells Committee editorial on overcoming limitations in clinical trials of mesenchymal stromal cell therapy for coronavirus disease-19: time for a global registry

Coronavirus disease 2019 (COVID-19)-related respiratory failure is a significant cause of morbidity, mortality and health care utilization. Further, long-term respiratory consequences including fibroproliferative changes and chronic respiratory dysfunction remain an unclear but a growing problem. Vaccinations including boosters have decreased the incidence of COVID-19 severe respiratory disease, but significant numbers remain unvaccinated. In addition, some patients remain particularly vulnerable to severe acute respiratory syndrome coronavirus 2 infection regardless of vaccine and booster administration. For instance, patients with significant immunosuppression continue to have significantly greater rates of symptomatic COVID-19 infection and mortality [1–7].

While the main tool in combating the pandemic is prevention, drug-discovery pipelines are still required, especially when vaccine development and deployment are slower than the appearance of new variants. Current therapies including remdesivir, corticosteroids and immunotherapies such as tocilizumab and baricitinib have only partially decreased the incidence, severity and sequelae of respiratory disease [8,9]. Two new antiviral treatments available, molnupiravir [10] and a combination of nirmatrelvir and ritonavir (Paxlovid), may continue to lessen respiratory sequelae [11]. However, molnupiravir may result in mutagenic activities [12] for the host, whereas nirmatrelvir/ritonavir can interfere with a number of commonly used drugs [7,13]. In addition, specific antibodies against severe acute respiratory syndrome coronavirus 2 have shown efficacy in tempering respiratory symptoms and preventing major complications only when administered in the very early phases of infection and for not all the viral variants [14].

In this setting, cell-based therapy approaches using systemic administration of mesenchymal stromal cells (MSCs) and their derived products have a strong mechanistic rationale and pre-clinical track record [15]. A number of case series and uncontrolled trials of both academic and industry sponsorship have demonstrated safety of systemic MSC administration in patients with COVID-19 with different degrees of respiratory severity [16]. This has provided a platform for a growing number of randomized, blinded, placebo-controlled trials of systemic MSC administration [17]. MSC administration has consistently been found safe without significant infusional toxicities or attributable serious adverse events. Importantly, a growing number of studies, although not all, have demonstrated efficacy [18–21]. Of note, the published trials to date are from academic centers. Despite suggestive results in press releases, industry-sponsored, randomized, blinded, placebo-controlled trials have not yet undergone peer-reviewed publication.

These trials have been reviewed in several recent systematic reviews and meta-analyses. Overall, these have demonstrated safety and positive end points, including reduction of mortality rate [22–24]. They are, however, limited by the relatively small numbers of patients studied to date. The meta-analyses have also highlighted significant issues and lack of consensus on critical study parameters including but not restricted to the source of MSCs. Of the 11 clinical investigations included in the recent systematic reviews, including open label non-randomized or non-controlled trials, eight used MSCs derived from cord blood or umbilical cord tissue whereas others used MSCs derived from menstrual blood or bone marrow mononuclear cells. Another variable included differences in critical process parameters used to manufacture the MSCs including medium supplementation (some studies used fetal bovine serum [25], some used different types of platelet lysate [18,21], another used serum free medium [26]). Passage numbers varied between studies [26,27] as well as the cryopreservant used, reported in only one study [18]. Two studies reported infusing freshly thawed MSCs, whereas others lacked these details in the methods [18,21]. Other variables downstream of manufacturing included dose typically trials used $1–3 \times 10^6$/kg, although one trial used 240 million MSCs over 3 doses [21] and dosing (one to four infusions), time of administration, patient population, symptom heterogeneity, illness severity, and outcome measures.

Overall, these investigations support that use of MSCs as a treatment option for COVID-19 appears to be promising; however, potential risk of bias was detected in all studies. Although the latest meta-analyses demonstrated reduced mortality (relative risk of death 28 days after treatment 0.19; 95% confidence interval 0.05–0.78), outcome measures were not reported consistently and pooled estimates were not calculated. MSC administration tended to improve radiographic findings, pulmonary function (lung compliance, tidal volumes, arterial oxygen partial pressure/fractional inspired oxygen, alveolocapillary injury), and inflammatory biomarker levels. Circulating interleukin-6 level was the most commonly reported cytokine and were consistently decreased compared with controls at early but not later time points [22]. However, no comparisons were made between MSCs of different sources within any trial. There is further heterogeneity, as demonstrated by one recently published study from France using umbilical cord–derived MSCs (not included in the most-recent meta-analyses) [23]. This study showed that among the

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45 enrolled patients, arterial oxygen partial pressure/fractional inspired oxygen did not change between day 0 and day 7 as well as between MSC and placebo groups. Repeated MSC infusions were not associated with any serious adverse events.

In short, the optimal approaches for MSC administration and potential approval by regulatory agencies remain uncertain. On the one hand, this prompts for investigations toward deeper fundamental understanding on potential mechanisms of MSC actions, as a basis to precisely define required MSC attributes and to design rational clinical investigations, particularly those identifying patients more likely to respond [15]. On the other hand, this is in part due to the relatively limited numbers of patients involved in the published trials to date, which limits the power of observations on potential efficacy. To this end, a combined global registry of all patients enrolled in these trials, both academic and industry-sponsored, will provide an invaluable tool to better understand and apply MSC-based cell therapies to patients with COVID-19 respiratory disease [28–30]. Data in the registry could include information on patient phenotypes and inflammatory status, in addition to other clinical outcome measures, as these are increasingly recognized to influence potential MSC actions and efficacy. In addition, a registry approach provides the opportunity to collect information on critical process parameters used to manufacture the MSCs, and characterization data which can be harmonized to reflect MSC critical quality attributes. These data will support efforts such as "living systematic reviews" that are updated in real-time to provide researchers, patients and decision-makers with the most up-to-date information [31,32]. Moreover, a registry would facilitate individual patient data meta-analysis, which will help identify patient, disease and cell product characteristics that may modify MSC efficacy. Notwithstanding the logistics of collating and managing a registry and the need for buy-in from the wide range of investigators, the critical nature of the COVID-19 pandemic is a strong impetus for the biomedical community to join forces [33].

As the leading organization promoting development and application of MSC-based cell therapies, the International Society for Cell and Gene Therapy is well situated as an unbiased neutral agency to coordinate with comparable interested organizations, funding agencies and regulatory agencies globally to develop plans to manage the database and to serve as a central source for communication between the investigative groups. With focus on COVID-19–associated acute respiratory distress syndrome investigations, this will be a pilot endeavor that can serve as a basis for larger more broad ranging databases. To this end, we call upon all investigators and the International Society for Cell and Gene Therapy to join in this endeavor and strive to help make MSC-based approaches for COVID-19 respiratory diseases an effective therapy.

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