HSC Public Health Agency
Research and Development

HSC R&D Division Award Details

HSC R&D File Reference	COM/5596/20
HSC R&D Funding Scheme	Needs-Led Commissioned Research Award
Project Title	The REALIST Study (Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration): Re-purposed to recruit patients with ARDS secondary to COVID-19
Award Holder Name	Professor Danny McAuley (Queen's University Belfast)
Host Research Organisation	Queen's University Belfast
Award Start Date	01.04.20
Award End Date	01.03.22

Evidence Brief

Why did we start? (The need for the research and/or Why the work was commissioned)	Acute respiratory distress syndrome (ARDS) is characterised by acute hypoxaemic respiratory failure with bilateral radiographic opacities that is not fully explained by cardiac failure. Incidences of ARDS in hospitalised patients with COVID-19 between 17% to 68% have been reported. Mesenchymal stromal cells (MSCs) are a potential novel therapeutic in ARDS due to their pleiotropic immunomodulatory and reparative properties. The REALIST study was initially set up (with funding from the Wellcome Trust) prior to the COVID-19 pandemic to conduct a phase 1/2 clinical trial to investigate a novel MSC product (ORBCEL-C) in patients with moderate to severe ARDS. At the outset of the COVID-19 pandemic in March 2020, the phase 2 study was ready to commence recruitment at five clinical sites across the UK. Similarities between ARDS due to COVID-19, and ARDS due to other causes were recognised and there was a rationale to investigate MSCs as a therapeutic agent in ARDS due to COVID-19. The funding from HSC R&D facilitated the repurposing of the REALIST study to recruit a cohort of patients with ARDS due to COVID-19.
What did we do? (Methods)	The REALIST-COVID study was a multicentre randomised, double-blind, allocation concealed, placebo-controlled trial of ORBCEL-C MSCs in patients with ARDS due to COVID-19. It was conducted at 12 clinical sites across the UK. Patients were randomised to receive a single intravenous infusion of ORBCEL-C (400 x 106 cells) or placebo (Plasma-Lyte 148). The primary safety outcome was the incidence of serious adverse events (SAEs). The primary efficacy outcome was oxygenation index (OI) at day 7. Secondary outcomes included OI at day 4 and 7; respiratory compliance, driving pressure, PaO2/FiO2 ratio and Sequential Organ Failure Assessment score (SOFA) on days 4, 7, and 14; and clinical outcomes including extubation, reintubation, ventilator-free-days (VFDs) to day-28, duration of ventilation, length of intensive care unit (ICU), and hospital stay, as well as 28- and 90-day mortality. Adverse events were reported to day-90.
What answer did we get? (Findings)	60 participants were recruited from 2nd April until 4th December 2020 (with the final analysis including 30 patients in the ORBCEL-C group and 29 patients in the placebo group as one patient in the placebo group withdrew consent). ORBCEL-C MSCs were found to be safe and well tolerated. There was no difference between groups in the primary safety outcome, the incidence of SAEs (there were 6 SAEs in the ORBCEL-C and 3 in the placebo group, RR 2.9 (95% confidence interval (CI) 0.6 to 13.2), p=0.25). There was no difference in the primary efficacy outcome of OI at day 7 between groups (mean [SD] ORBCEL-C 98.3 [57.2], placebo 96.6 [67.3]; mean difference 1.8; 95% CI 30.7 to 34.4; p=0.91). There were also no differences between the groups in secondary surrogate outcomes of pulmonary and non-pulmonary organ function. 28-day mortality was 17% (n=5) in the ORBCEL-C and 21% (n=6) in the placebo group. 90-day mortality was also similar between groups (ORBCEL-C n=7 (23.3%), placebo n=8 (27.6%), risk ratio 0.8, 95% confidence intervals 0.4 to 2.0, p=0.71).
What should be done now? (Practice/Policy Implications and/or Recommendations)	This phase 2 study demonstrated that ORBCEL-C MSCs were safe and well tolerated in a population of patients with moderate to severe ARDS due to COVID-19. The MSC product was feasible to deliver to critically ill patients within existing NHS infrastructure. This phase 2 study did not demonstrate improvements in surrogates of pulmonary or non-pulmonary organ dysfunction in patients with COVID-19 related ARDS. This evidence does not support the routine administration of MSCs to patients with moderate to severe COVID-19 ARDS, and at this time there are no recommendations for change to clinical practice/policy. The REALIST research programme is ongoing and currently investigating ORBCEL-C MSCs in a cohort of patients with ARDS unrelated to COVID-19. Long-term follow up of patients in the COVID-19 study cohort to 2 years is ongoing and will provide important information regarding the long-term safety profile of MSCs.