Mesenchymal stromal stem cell (MSC) immunotherapy for experimental septic shock: systematic review and meta-analysis with trial sequential analysis of mortality.

Amit Patel1, 2, Shaman Jhanji3, Jiri Pavlu4, Michael Laffan2, Mark Ethell5, Anne Bradshaw6, Eduardo Olavarria7, Kevin Harrington1, Jane Apperley2, Stephen Brett8

1Targeted Therapy, Institute of Cancer Research, 2Centre for Haematology, Imperial College London, 3Critical Care Unit, The Royal Marsden NHS Foundation Trust, 4Imperial College Healthcare NHS Trust, 5Haemat-oncology Unit, The Royal Marsden NHS Foundation Trust, 6John Goldman Centre for Cellular Therapy, 7Centre for Haematology, 8Centre for Perioperative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, London, United Kingdom

Introduction: Septic shock is a life-threatening form of an inappropriate host response to severe infection, with impaired survival in patients with cancer. Mortality is 60-75% for patients with haematological or solid cancer - 1/3 higher than patients without cancer. Cellular immunotherapy with allogeneic MSCs is a promising multi-targeted inflammation and bacteria responsive personalised treatment, which may address this unmet clinical need. We hypothesised that MSC immunotherapy might improve survival in experimental septic shock models.

Material (or patients) and methods: We performed a systemic review and meta-analysis as described previously1 with the research question: what is the safety and efficacy of MSC immunotherapy for experimental septic shock. We chose mortality at the longest follow-up as the primary outcome measure in wild-type animals. Unmodified MSC groups from any source were compared to non-MSC groups.

Results: All 21 included studies were assessed as either unclear or high risk of bias, using the Cochrane Risk of Bias Assessment Tool. This was mainly because of poor reporting: possible selection bias (due to poorly reported random sequence generation and allocation concealment) and performance bias (due to the lack of blinding). The overall pooled effect size was in favour of MSC immunotherapy, using a random effects model: RR 0.59, 95% CI 0.48-0.73; P=0.0001; I²=82%. The large effect size was robust to sensitivity and meta-regression analyses, including adjustments for baseline mortality (60%) and co-treatments (fluids and antibiotics). Egger's regression did not detect publication bias (P=0.20). To ensure our meta-analysis was sufficiently large and adequately powered, and to test the robustness of the finding of MSC benefit, we subjected it to trial sequential analysis1. The cumulative z score crossed the conventional boundary of benefit (alpha of 0.05) and the constructed trial sequential boundary (Figure 1), correcting for repetitive testing of the same hypothesis. Furthermore, the z score also crossed the 95% power boundary demonstrating that our meta-analysis was sufficiently large to be confident of the result.

Figure 1. Trial sequential analysis. The cumulative z score of 21 studies, ordered by year, are indicated in blue. The conventional alpha (0.05) significance boundaries are indicated by parallel horizontal red lines. The curved red lines indicate the trial sequential corrected boundaries of benefit (upper half) and harm (lower half). The inner wedge to the right of the graph indicates the boundary of futility. The red vertical boundary indicates the information size for 95% power. The cumulative z score crosses the conventional boundary of benefit, the trial sequential boundary of benefit, and the 95% power boundary indicating after accounting for bias there remains robust evidence of the efficacy of MSC immunotherapy for experimental septic shock.

Image / Graph:
Conclusion: We robustly demonstrate a 41% relative reduction in death with MSC immunotherapy, representing a number needed to treat of just 4. This compelling experimental evidence requires clinical translation in patients with haematology cancer suffering from septic shock.


Disclosure of Interest: None Declared

Keywords: immunotherapy , Mesenchymal stromal stem cell , MSC, Sepsis, septic shock