Table S1. Summary of therapeutic benefits of MSCs in current preclinical models of experimental ARDS/ALI.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Article Source | Injury Model | MSC Source | MSC Delivery Method | Outcomes | Key Factors | References |
| *Am J Resp Cell Mol* | Mice bleomycin | MBMDMSC | Intravenous 6h after injury | Proinflammatory cytokines↓ | IFN-γ,IL-2,IL-1,IL-4 | **[1]** |
| *J Immunol* | Mice E.coli endotoxin | MBMDMSC | Intratracheal 4h after injury | Survival↑  BAL markers of inflammation↓ | TNF-ɑ,MIP-2 | **[2]** |
| *PLoS Med* | Mice LPS | MBMDMSC | Intravenous 30min after injury | BAL markers of inflammation↓ | Angiopoietin 1 | **[3]** |
| *Proc Natl Acad Sci USA* | Mice bleomycin | MBMDMSC | Intravenous after injury | BAL neutrophils and TNF↓ | IL-1ra | **[4]** |
| *Nat Med* | Mice CLP | MBMDMSC | Intravenous 24h before, during, or 1h after injury | Survival↑  Plasma proinflammatory cytokines↓ | PGE2,IL-10 | **[5]** |
| *Proc Nat Acad Sci USA* | Human endotoxin | HBMDMSC | Intratracheal 1h after injury | Lung water↓ | FGF7 | **[6]** |
| *Am J Respir Crit Care Med* | Mice CLP | MBMDMSC | Intravenous 6h after injury | Survival↑  Plasma proinflammatory cytokines↓ | IL-6,IL-1β,IL-10, KC,JE,CCL5 | **[7]** |
| *Blood* | Mice peritonitis | HBMDMSC | Intraperitoneal 15min after injury | Intraperitoneal inflammatory cell infiltrate↓ | TSG-6 | **[8]** |
| *Stem Cell Res Ther* | Mice OA LPS | HBMDMSC | OA 4h after injury | BAL inflammatory cells and proinflammatory cytokines↓ | TSG-6 | **[9]** |
| *Thorax* | Rat VILI | RBMDMSC | Intravenous immediately and 24h after injury | BAL inflammatory cells and proinflammatory cytokines↓ | TNF-ɑ,IL-10 | **[10]** |
| *Am J Respir Crit Care Med* | Human E.coli | HBMDMSC | Intravenous or intrabroncheal 1h after injury | Neutrophil influx↓ | TNF-ɑ,IL-10 | **[11]** |
| *Crit Care Med* | Mice LPS | BMDMSC | Intravenous 24h after injury | MMP-8↑  TIMP-1 and lung inflammation↓ | IL-1β,IL-6,IL-10,IFN-γ,MCP-1,MIP-1α | **[12]** |
| *Thorax* | Sheep P.aeruginosa | HBMDMSC | Intratracheal 1h after injury | Oxygenation↑  Pulmonary edema↓ | PaO2/FiO2 ratio | **[13]** |
| *J Immunol* | Mice E.coli endotoxin | HBMDMSC | Intratracheal 4h after injury | Survival↑  LXA4↑  BAL proinflammatory cytokines↓ | LXA4 | **[14]** |
| *Thorax* | Rat E.coli | HBMDMSC | Intravenous 0.5h after injury | Survival, IL-10 and KGF levels↑  IL-6↓ | IL-10,KGF,LL-37 | **[15]** |
| *Proc Natl Acad Sci USA* | Mice influenza H5N1 | HBMDMSCs | Intravenous 4 post infection | Survival, Ang-1 and KGF levels↑  Lung inflammation, pulmonary edema and permeability↓ | IL-1β,TNF-α,IFN-γ | **[16]** |
| *Crit Care Med* | Mice LPS | BMDMSC | Intravenous 12h after injury | Survival↑  Pulmonary vascular permeability↓ | PGE2,IL-1β,TNF-a, IL-10 | **[17]** |
| *Am J Respir Crit Care Med* | Mice LPS | HBMDMSC | Intravenous 4h after injury | Pro-inflammatory cytokines↑  TNF-α, IL-8↓ | TNF-α,IL-8,IFN-γ, IL-1β,IL-17 | **[18]** |
| *Crit Care Med* | Rat LPS | BMDMSC | Intravenous 48h after injury | KGF levels↑  TNF-α, IL-1β,KC, and TGF-β levels↓ | KGF,IL-1β,TNF-α, TGF-β | **[19]** |
| *Crit Care* | Rabbit LPS | BMDMSC | Intravenous 24h after injury | O2 saturation, IL-10 level↑  Lung inflammation, pulmonary  edema, IL-6 and TNF-α levels↓ | IL-10,IL-6,TNF-α | **[20]** |
| *Am J Respir Crit Care Med* | Mice HCl instillation,  VILI, or both | BMDMSC | Intravenous 48h after injury | Fibrosis in HCl model↑  Fibrosis in VILI model alone↓ | IL-10,IL-6 | **[21]** |
| *J Clin Med* | Rat E.coli | UCDMSC | Intravenous 1h after injury | Survival↑  Pro-inflammatory cytokines↓  Alveolar tissue↓ | IL-10,IL-6,TNFα, MPC-1 | **[22]** |
| *Thorax* | Mice E.coli | MSC-MVs | Intravenous 1h after injury | Alveolar fluid clearance↑  Lung protein permeability↓ | TNFα | **[23]** |
| *Stem Cell Res Ther* | Rat E.coli | UC-hMSC | Intravenous 30 min after injury | lung tissue airspace↑  lung microvascular permeability, total infiltrating cell count↓ | IL-1β,IL-6 | **[24]** |
| *Stem Cell Res Ther* | Mice LPS | HCMSC | Tail vein inject 4 h after injury | Inflammatory cell infiltration, alveolar wall thickening, edema↓ | TNF-α,IL-1β,IL-6 | **[25]** |
| *Stem Cell Res Ther* | Rat bleomycin | MSC-MVs | Intratracheal 2d after injury | apoptosis and inflammation↓ | IL-6,IL-8,TNF-α | **[26]** |

**Abbreviation:** MSC mesenchymal stem (stromal) cell, AB antibody, Ang angiopoietin, BAL bronchoalveolar lavage, CLP caecal ligation and puncture, E.coli Escherichia coli, P.aeruginosa Pseudomonas aeruginosa, HBMDMSC human bone marrow-derived MSCs, HCMSC human chorionic villi-derived MSC, UC-hMSC umbilical cord-human MSCs, MBMDMSC murine bone marrow-derived MSCs, RBMDMSC rat bone marrow-derived MSCs, LPS lipopolysaccharide, MSC-CM MSC-conditioned media, OA oral aspiration, PGE2 prostaglandin E2, IL Interleukin, IL-1ra Interleukin 1 receptor antagonist, TNF tumour necrosis factor, VILI ventilator-induced lung injury, IFN Interferon, LXA4 lipoxin A4, KC murine IL8 homolog, JE murine MCP-1 homolog, CCL5 murine Rantes homolog, TIMP tissue inhibitor of metalloproteinase, MMP metalloproteinase, MVs Microvesicles, FGF7 fibroblast growth factor7, NA not applicable, h hour, min minute, d day.

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Table 2. Ongoing and new studies of mesenchymal stem cell-based therapies in COVID-19 pneumonia.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Registry Numbers | Country | | Phase | | Status | MSC Source | Delivery Method | Estimated Enrolment | Start Date | End Date | Main outcomes |
| ChiCTR2000029990 | China | | / | | Completed | BMDMSC | Intravenous 1x106cells/kg | 10 | January 23,2020 | February 16,2020 | Improved the inflammation situation in severe COVID-19; improved outcomes. |
| Ongoing | |  | |  | |  |  |  |  |  |  |
| NCT04315987 | Brazil | | 1 | | Not yet recruiting | UC-MSCs | Intravenous 2x107cells/kg | 66 | April  2020 | June  2020 | / |
| NCT04313322 | Jordan | | 1 | | Recruiting | WJ-MSCs | Intravenous 1x10e6/kg | 5 | March 16, 2020 | September 30, 2020 | / |
| NCT04333368 | France | | 1/2 | | Recruiting | UC-MSCs | Intravenous 1 Million/kg | 60 | April 6, 2020 | July 31,  2021 | / |
| NCT04339660 | China | | 1/2 | | Recruiting | UC-MSCs | Intravenous 1 x10E6 cells/kg | 30 | February 1,  2020 | June 30,  2020 | / |
| NCT04352803 | / | | 1 | | Not yet recruiting | AA-MSCs | Intravenous 500,000/kg | 20 | April  2020 | April  2026 | / |
| NCT04371601 | China | | 1 | | Active, not recruiting | UC-MSCs | Intravenous 106/kg | 60 | March 1, 2020 | December 31, 2022 | / |
| NCT04361942 | Spain | | 2 | | Recruiting | Allogenic-MSCs | Intravenous 1 million cells/kg | 24 | April  2020 | December 31, 2020 | / |
| NCT04252118 | China | | 1 | | Recruiting | MSCs | Intravenous 3.0 x 10E7 cells/kg | 20 | January 27,2020 | December, 2021 | / |
| NCT04273646 | China | | / | | Not yet recruiting | UC-MSCs | Intravenous 5.0 x 10E6 cells/kg | 48 | April 20, 2020 | February 15,2022 | / |
| NCT04269525 | China | | 2 | | Recruiting | UC-MSCs | Intravenous 3.3 x 107 cells/50ml | 10 | February 6,  2020 | September 30, 2020 | / |

**Abbreviation:** WJ-MSCs Wharton's Jelly-Mesenchymal Stem Cells, UC-MSCs umbilical cord-derived MSCs, AA MSCs Autologous Adipose Derived Mesenchymal Cells.