CELLULAR IMMUNOTHERAPY FOR SEPTIC SHOCK: CISS Phase I Trial

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Disclosures

- Funding for CISS related work
  - Stem Cell Network
  - CIHR
  - Ontario Institute for Regenerative Medicine
  - Ontario Research Fund
Why study use of mesenchymal stromal cells for septic shock?

- 20% of all ICU admissions
- Mortality rate of 20 - 40%
- Long-term morbidity associated with physical, cognitive, and emotional dysfunction for survivors
- Estimated costs in USA: $24 billion/year

Rationale for MSCs in Septic Shock

MSCs inject IL-10 and PGE2 into the body, which inhibits IDO and reduces the concentration of Neutrophils and NK Cytotoxicity, increasing the activity of Macrophage M2. This leads to the synthesis of antibacterial peptides (LL-37 Hepcidin) and increased phagocytic activity. PGE2 also stimulates mitochondrial transfer. MSCs regulate the balance of pro-inflammatory cytokines (IL-2, TNFa, IL6, IL17, IL12) to maintain homeostasis. The reduced bacterial load decreases tissue inflammation, leading to lower organ failure and mortality. MSCs also modulate the inflammatory phase intensity.

Laroye et al, Stem Cells, 2017
Mei et al. AJRCCM, 2010; 182(8): 1047-57

**Odds Ratio (OR) Calculations**

- OR < 1 favors MSCs as compared to controls

**Graphical Representation**

- Time (hours) vs. % Survival
- Comparison between CLP only and CLP + MSCs
- p < 0.05

**Reference**

We performed an open label single-centre Phase I dose-escalation trial of freshly cultured adult allogenic bone marrow-derived MSCs in patients with septic shock to examine the safety and tolerability of MSCs in this clinical setting

CISS framed as a ‘rescue’ intervention
CISS Observational Arm
n = 21

CISS eligibility met within 24 hours of ICU admission (additional 6 hours to enrolment)

CISS Interventional Arm
n = 9

CISS eligibility met within 24 hours of ICU admission (additional 6 hours to enrolment)

Consent Obtained

≥ 1 hour of pulmonary and hemodynamic stability

Low Dose (n = 3)
0.3 x 10^6 cells/kg

Mid Dose (n = 3)
1.0 x 10^6 cells/kg

High Dose (n = 3)
3.0 x 10^6 cells/kg

* DSMC review after completion of each dose panel or as required

Serial blood for inflammation
At baseline, 1, 4, 12, 24, and 72 hours

Record adverse events

Maximum Tolerated Dose Established for Phase II Trial

L McIntyre et al, published online AJRCCM, Sept 29, 2017
Eligibility Criteria

- **Main inclusion criteria:**
  - Receipt of antibiotics and source control
  - Adequate resuscitation endpoints (CVP ≥ 8 mmHg; ScVO₂ ≥ 70%)
  - Cardiovascular failure and
  - At least 1 persistent or worsening organ failure or organ hypoperfusion

- **Main exclusion criteria:**
  - Another dominant form of shock
  - Severe chronic morbidities
  - Immunesuppression
  - History of malignancy in previous 2 years
  - Non commitment to aggressive care (family/treating physician)
Safety Outcomes

- MSC infusion events
  - Life threatening hemodynamic or pulmonary instability up to 30 minutes post MSC infusion

- “Expected” serious adverse events
  - Nosocomial infection
  - Arrhythmias
  - Acute coronary syndrome
  - Bleeding
  - Pulmonary embolism
  - Death 28/90 days
  - Re-admission to ICU

- Serious unexpected adverse events

- Malignancy
Safety: Trial Suspension Criteria*

- Life threatening hemodynamic or pulmonary instability up to 30 minutes post MSC infusion OR
- Death within 24 hours after cessation of MSC infusion OR
- Serious unexpected adverse event

* Event considered possibly/related to the study drug/protocol
## CISS Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Observational Cohort (n = 21)</th>
<th>Interventional Cohort (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>61 (23-95)</td>
<td>71 (38-91)</td>
</tr>
<tr>
<td>Sex, (female), No (%)</td>
<td>12 (57)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>APACHE II Score*</td>
<td>26 (17-32)</td>
<td>25 (11-28)</td>
</tr>
<tr>
<td>MODS score</td>
<td>5 (1 – 15)</td>
<td>5 (3 – 10)</td>
</tr>
<tr>
<td>Qualifying Organ Failure No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>15 (71)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Hematologic Failure</td>
<td>4 (19)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>8 (38)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Organ Hypoperfusion</td>
<td>15 (71)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Baseline Organ Support No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasoactive agents</td>
<td>21 (100)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Ventilation</td>
<td>21 (100)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>4 (19)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

* Median (Range)
CISS Baseline Characteristics

<table>
<thead>
<tr>
<th>Infectious Source No (%)</th>
<th>Observational Cohort (n = 21)</th>
<th>Interventional Cohort (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>8 (38)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>6 (29)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>2 (10)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (19)</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

| Time to Enrolment*      | 19 (5 – 28)                   | 24 (11 – 28)                  |

<table>
<thead>
<tr>
<th>Dose of MSCs Received (range)</th>
<th>Observational Cohort</th>
<th>Interventional Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (0.3 x 10^6 cells/kg)</td>
<td>--</td>
<td>19 – 30</td>
</tr>
<tr>
<td>Mid dose (1.0 x 10^6 cells/kg)</td>
<td>--</td>
<td>80 – 86</td>
</tr>
<tr>
<td>High dose (3.0 x 10^6 cells/kg)</td>
<td>--</td>
<td>132 – 250</td>
</tr>
</tbody>
</table>

* Median (Range)

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Safety Outcomes

- No MSC infusion related serious adverse events or deaths in first 24 hours post MSC infusion

- No serious unexpected adverse events

- No safety signals for physiological measures first 72 hours
  - Mean arterial pressure
  - Heart rate
  - P/F ratios
  - Oxygenation index
  - MODS scores first 7 days
## Expected Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Observational Cohort (n = 21)</th>
<th>Interventional Cohort (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>No (%: 95%CI)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nosocomial bacterial infection</td>
<td>10 (48: 24-71)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>Nosocomial fungal infection</td>
<td>5 (24: 4-44)</td>
<td>3 (33: 0-72)</td>
</tr>
<tr>
<td>Clinically important bleeding</td>
<td>3 (14: 0-31)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2 (10: 0-23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tachy/bradyarrythmias</td>
<td>3 (14: 0-31)</td>
<td>4 (44: 4-85)</td>
</tr>
<tr>
<td>Pulmonary embolism (PE)</td>
<td>2 (10: 0-23)</td>
<td><strong>0(0)</strong></td>
</tr>
</tbody>
</table>

* Events monitored for first 28 days  
** 1 event occurred 32 days post MSC infusion

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## Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Observational Cohort (n = 21)</th>
<th>Interventional Cohort (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temperature (post-pre) Infusion</strong>*</td>
<td>0 (-1 to 0.8)</td>
<td>0 (-0.9 to 0.7)</td>
</tr>
<tr>
<td><strong>Mortality No (%: 95%CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>4 (19: 1-37)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>90 days</td>
<td>4 (19: 1-37)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td><strong>ICU length of stay (survivors)</strong>*</td>
<td>13 (4-50)</td>
<td>12 (7-30)</td>
</tr>
<tr>
<td><strong>Hospital length of stay (survivors)</strong>*</td>
<td>21 (4-100)</td>
<td>29 (10-58)</td>
</tr>
<tr>
<td><strong>ICU re-admission No (%)</strong></td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Median (Range)

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Conclusion

• Infusion of MSCs into participants with septic shock to a dose of 3 million cells/kg appears safe

• Recruitment into trial is feasible 0.6 to 1.0 patients per month

• Logistical challenges having freshly cultured product

• Funding secured to initiate a Canadian multi-centre phase II RCT
Acknowledgements

• CISS Executive Committee
  – Duncan Stewart
  – Dean Fergusson
  – Shirley Mei
  – David Courtman
  – John Marshall
  – Keith Walley
  – Brent Winston
  – Claudia dos Santos
  – John Granton
  – Shane English
  – Alies Maybee

• Canadian Critical Care Trials Group
• Canadian Critical Care Translational Biology Group
• Michael Matthay
CISS MSCs

• Bone marrow derived, allogeneic, freshly cultured MSCs
• 1 bone marrow donor
• Characterized for identity (tri-lineage differentiation, cell surface marker expression), sterility, genetic stability, potency
• Pre-specified release criteria
• Viability of final cell product ranged from 89.4% to 96.3%

L McIntyre et al, published online AJRCCM, Sept 29, 2017
Time Course Plasma Cytokine Levels

- IL-1β
- IL-6
- TNF-α
- RAGE
- ANGPT2
- IL-10

Hours after Enrollment