Mesenchymal Stromal Cells (MSC) for Refractory Crohn’s Disease

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Diverse Manufacturing of CTTWA

Operates as:
• Tissue Bank, Human Heart Valves - national resource
• ABMDR collection centre - national/international

Local Health Service Provision
• Allo & auto HPC & TC (BM, PBSC, CB, DLI) - 3 Tx programs
• Culture expanded keratinocytes
• Serum eyedrops, auto & allo

Other Products
Pericardium

• Clinical Trial Products
  • BM-MSC
  • Dermal Fibs
Clinical Trial Studies

✓ MSC Therapy for Steroid Refractory GVHD
  2007-2009, Phase I, single site RPH, continuing under SAS

❖ MSC Therapy for Obliterative Bronchiolitis associated with Lung Transplant
  2008-ongoing, Phase I, double sited Australian

❖ MSC Therapy to Treat Biologic Refractory Crohn’s Disease
  2010-ongoing, Phase II study, multi-centred Australian

❖ MSC Therapy for Steroid-Naïve Acute GVHD
  2012 -ongoing, Phase II study, multi-sited Australian.

➢ Cranial Reconstruction using MSC with a Ceramic Carrier & Polymer Scaffold
  2011-, Phase II, Perth double sited, Ethics pending

➢ MSC Therapy for Treating Chronic Obstructive Pulmonary Disease (COPD)
  2011-, Phase I, single site, radioactive tracking of cells, Ethics pending.
Bone Marrow Donor

- Related/ Unrelated
- Recruited as relative or friend of trial subject
- Age preference: 18-30 years
- Consent
- Donor assessment as for blood and tissue donors (ARCBS)
- Infectious disease screening at time of donation
  - Mandatory testing on TGA platforms
    - HIV-1 (NAT)
    - HCV (NAT)
    - HBV (NAT)
    - Anti-HIV -1/2
    - Anti- Hep C
    - HBs Ag
    - HTLV-1/2
    - TPHA
  - Non mandatory testing
    - CMV
    - Hep B core Ab
Donor BM (10ml)

Density Gradient Sedimentation

MNC

Plated into culture vessels

MSC

Adhesive cells culture expanded/ Factories
DMEM /10% FCS
Multiple passages (p5), 80% confluence
Bovine proteins removed

Clinical MSC Product

100 x 10^6 cells, fresh or cryopreserved

Viability
Negative microbial contamination
MSC morphology & phenotype (ISCT 2006)
[Tri-lineage differentiation capability]
[Cytogenetic Analysis]

Infused Clinical Dose (Cryopreserved, passage 5)

Aim ~2 x 10^6 MSC/kg patient wt.
RESULTS of RPH MSC Therapy for Steroid Refractory GVHD

No adverse effects of MSC infusion (>110)

• Improvement or CR of clinical symptoms
  aGVHD: n=12, CR 7; PR 4
  cGHVD: n=7, CR 2; PR 2

• Additional patients (3) treated under SAS

• Phase II multi-centred, GVHD + steroids ± MSC
Crohn’s Disease

- Etiology unknown-environmental, immune mediated and genetic factors.
- Chronic remitting and relapsing course –inflammation
- Current treatment -systematic approach
  - Steroids, immunomodulators, biologics

- Despite advent of biologics in 1998, 23% still require surgery (Schnitzler et al, 2009)
  - Failure of induction, loss of response, adverse effects
  - Alternative non surgical therapies required
MSC study: phase II

- **Aims**
  - establish efficacy / safety of allogeneic MSC in infliximab / adalimumab refractory CD
  - evaluate immunopathological changes in mucosa and peripheral blood

- **Inclusion Criteria**
  - CDAI > 250
  - endoscopic activity
  - 4 week “wash-out”
  - stable dose steroids, immunomodulator
    - (exclude active sepsis, co-existent CMV, PHx malignancy)
MSC study: phase II

- weekly infusions (x4): $2 \times 10^6$ MSC / kg

- $1^\circ$ endpoint: clinical response (CDAI fall of $\geq 100$) at day 42

- $2^\circ$ endpoints at day 42
  - clinical remission (CDAI drop $<150$)
  - endoscopic improvement (CDEIS) and remission
  - Improved QoL (increase IBDQ)

- PB and colonic biopsies taken prior to and at day 42 post MSC infusions for laboratory studies (PB and mucosal flow cytometry, cytokine/chemokine receptor by RT-PCR, serum cytokines)

- Multicentre Australian, n=30.
Delivery of MSC
Crohn’s Disease Activity Index (CDAI) for initial 10 patients receiving MSC therapy

Primary endpoint: CDAI reduction by 100 points
Crohn’s Disease Activity Index (CDAI) for initial 10 patients receiving MSC therapy

![Graph showing mean CDAI over days of MSC infusions]

- Mean CDAI with standard error of the mean (SEM) is plotted over days of MSC infusions.
- The graph indicates a decrease in CDAI as the number of MSC infusions increases.
- The x-axis represents days of MSC infusions (0, 7, 14, 21, 28, 42).
- The y-axis represents CDAI (SEM), with values ranging from 0 to 450.
Results

- 11 patients recruited

- 10 patients completed (23-55 yrs, 3 male)
  - Infusions well tolerated with no adverse events

- 1\textsuperscript{st} endpoint
  - 9/10 clinical response (CDAI fall >100)
    Decrease CDAI 392 vs 198 ($p = 0.001$)

- 2\textsuperscript{nd} endpoint
  - 6/10 clinical remission (CDAI <150)
  - 5/10 endoscopic improvement (CDEIS)

- High correlation of CDAI and IBDQ ($p= 0.002$)
Conclusions

- Remarkable clinical response for initial patients that failed conventional treatment
- 5 patients, received additional MSC therapy
- MSC potential therapeutic option
  - major change in disease management and treatment
- Phase III trial?
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