Successful Outpatient Treatment of Refractory Crohn’s Disease Using Adult Mesenchymal Stem Cells

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Data was presented at the October 2006 American College of Gastroenterology conference

**Protocol/Methods**

**Mesenchymal Stem Cells**
- Generally quiescent in bone marrow
- Immunoregulatory effects
- Home to sites of injury
- Capable of:
  - Tissue regeneration
  - Blood vessel formation
  - Prevention of scarring

**Prochymal™**
- Ex vivo cultured mesenchymal stem cells from marrow of screened, healthy volunteers
- No donor-recipient matching required
- Cells frozen and thawed at site of use
- Typical outpatient infusion: 20-70 min

**Rationale**
- Ability of MSCs to:
  - Home to damaged GI tract tissue
  - Regenerate epithelial cells
  - Down-regulate TNF-α
  - Exert immunomodulatory effects

- Evidence from single-patient* and phase II studies of Prochymal™ in GI-GvHD demonstrating rapid healing of gut mucosa


**Study Design**
- Primary endpoint:
  - Clinical response (reduction in CDAI ≥ 100 points) by Day 28

- Secondary endpoints:
  - Clinical remission (CDAI < 150) by Day 28
  - Improved QOL (increase in IBDQ) by Day 28

**Methods**
- Eligible subjects:
  - 18-70 years of age
  - Failed steroids and immunomodulators
  - Endoscopic and/or radiographic evidence of active disease
  - CDAI score ≥ 220
  - CRP ≥ 5 mg/L
  - Previous Infliximab allowed if last dose > 90 days prior to enrollment

**Study Design**
- Open-label, phase II pilot study
- Aim: Evaluate the safety and efficacy of two Prochymal™ stem cell infusions in patients with treatment-refractory moderate-to-severe Crohn’s disease

**Study Design**
- Randomized to low (2 million cells/kg) or high (8 million cells/kg) dose IV Prochymal™

**Prochymal™ Infusion**

**CDAI**

**IBDQ**
Results

- 10 patients randomized; one lost to follow-up after Day 7
- Concomitant medications:
  - Mesalamine: 2
  - AZA/6-MP: 3
  - Corticosteroids (≤20mg/d): 2
  - Antibiotics: 3 (Cipro: 2, Metronidazole: 1)
  - Methotrexate: 1
- 8 patients had prior Infliximab

CDAI Scores

- Decrease CDAI in all 9 evaluable subjects by Day 28
- Mean decrease CDAI=105 (341 vs. 236, p=0.004)
- Clinical response in 3 of 9 subjects
  - 2 by Day 7, all 3 by Day 14
  - One in clinical remission by Day 7
  - All 3 had previously lost response to Infliximab

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Low Dose n=5</th>
<th>High Dose n=5</th>
<th>All Patients n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs): Mean (SD)</td>
<td>41 (14)</td>
<td>45 (12)</td>
<td>43 (12)</td>
</tr>
<tr>
<td>Male (n)</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>Disease duration (yrs): Mean (SD)</td>
<td>16 (10)</td>
<td>12 (10)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Race (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0/5</td>
<td>1/5</td>
<td>1/10</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4/5</td>
<td>4/5</td>
<td>8/10</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/5</td>
<td>0/5</td>
<td>1/10</td>
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Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low Dose n=5</th>
<th>High Dose n=5</th>
<th>All Patients n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB + colonic dz</td>
<td>3/5</td>
<td>4/5</td>
<td>7/10</td>
</tr>
<tr>
<td>Prior GI surgery</td>
<td>4/5</td>
<td>4/5</td>
<td>8/10</td>
</tr>
<tr>
<td>CDAI: Mean (SD)</td>
<td>323 (81)</td>
<td>378 (68)</td>
<td>351 (76)</td>
</tr>
<tr>
<td>IBDQ: Mean (SD)</td>
<td>103 (25)</td>
<td>110 (38)</td>
<td>107 (31)</td>
</tr>
</tbody>
</table>

Change in CDAI Scores

LOW DOSE

HIGH DOSE

Data was presented at the October 2006 American College of Gastroenterology conference
Results

Dose Response Trend

Mean change CDAI score at Day 28: -137 vs. -65, high vs. low dose, p=0.39

Change in IBDQ Scores

IBDQ Scores

- Significant increase in mean IBDQ by Day 28 (113 vs. 146, p=0.008)
- IBDQ ≥ 170 in 3 subjects
- Trend toward association between mean change IBDQ and clinical response at Day 28 (p=0.07)

Quality of Life

Adverse Events

- No infusion reactions
- 1 SAE (anemia), unrelated
- 5 subjects with non-serious adverse event(s), all mild or moderate in severity
Conclusions

• Prochymal™ induced clinical response in 3 of 9 subjects with treatment-refractory moderate-to-severe Crohn’s disease
• Response rapid (within 7-14 days)
• Significant decrease in mean CDAI and increase mean IBDQ by Day 28
• Infusions were well tolerated

Future Directions

• Prochymal™ may have a role in treatment of Infliximab failures
• Dose optimization, larger, placebo-controlled studies are in preparation

Acknowledgments

• This study was sponsored by Osiris Therapeutics, Baltimore, MD
• Investigators/sites:
  - W. Michael Pandak, MD, Richmond, VA
  - John Hanson, MD, Charlotte, NC
  - Paul Lebovitz, MD, Pittsburgh, PA
  - Robert Bé, MD, Baton Rouge, LA