

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

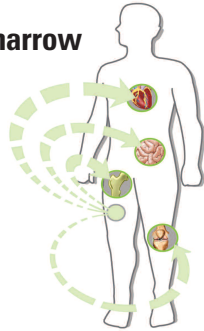
Jane Onken, MD; Dianne Gallup, MS; John Hanson, MD; Michael Pandak, MD; Linda Custer, PhD*, Duke Clinical Research Institute, Durham NC and *Osiris Therapeutics, Baltimore MD

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-patient¹ and phase II studies of Prochymal™ in GI-GvHD demonstrating rapid healing of gut mucosa**

¹LeBlanc K, et al. Lancet 2004;363:1439.

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

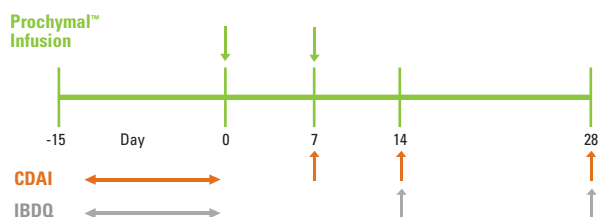
- **Primary endpoint:**
 - Clinical response (reduction in CDAI \geq 100 points) by Day 28
- **Secondary endpoints:**
 - Clinical remission (CDAI $<$ 150) by Day 28
 - Improved QOL (increase in IBDQ) by Day 28

Methods

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

Study Design

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



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Results

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

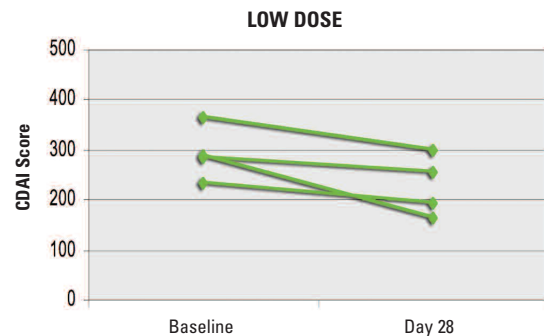
CDAI Scores

- 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

	Low Dose n=5	High Dose n=5	All Patients n=10
Age (yrs): Mean (SD)	41 (14)	45 (12)	43 (12)
Male (n)	5/5	5/5	10/10
Disease duration (yrs): Mean (SD)	16 (10)	12 (10)	14 (10)
Race (n)			
African American	0/5	1/5	1/10
Caucasian	4/5	4/5	8/10
Hispanic	1/5	0/5	1/10

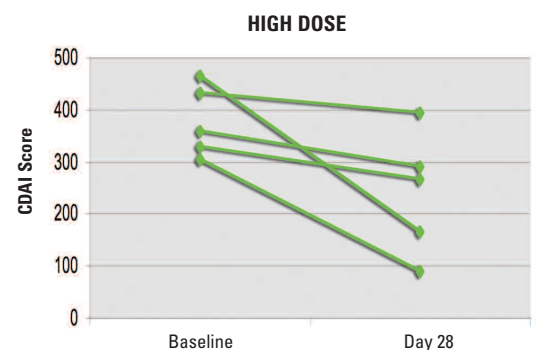
Change in CDAI Scores



Baseline Characteristics

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

Change in CDAI Scores



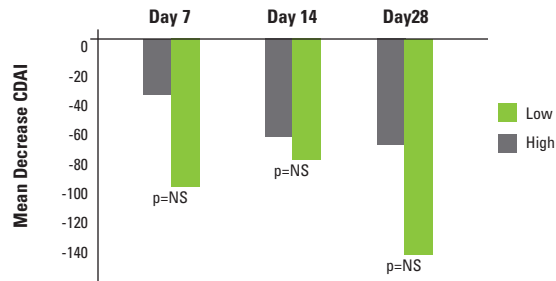
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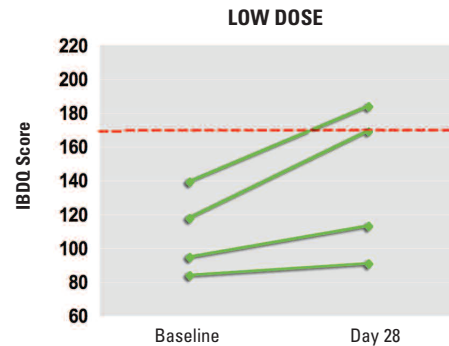
Results

Dose Response Trend



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

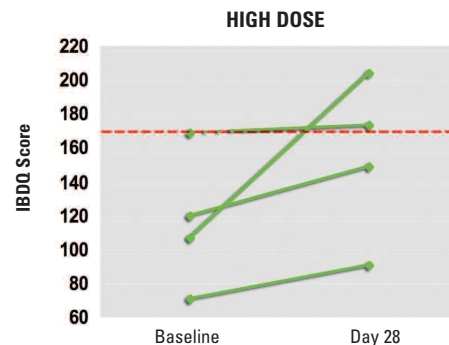
Change in IBDQ Scores



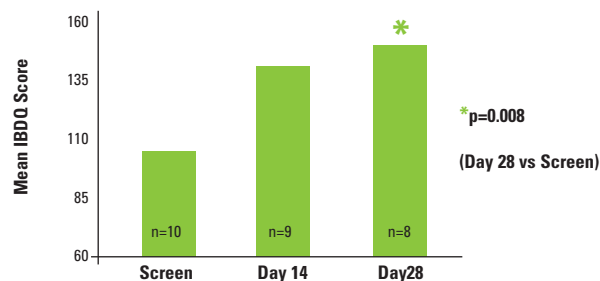
IBDQ Scores

- 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)

Change in IBDQ Scores



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

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Summary/Conclusion

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

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- Investigators/sites:
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